Food and Chemical Toxicology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester, CAS Registry Number 76649-17-7

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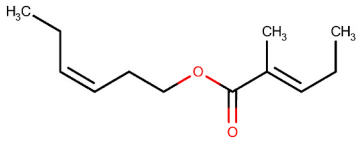
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 051721. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 2-Pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester CAS Registry Number: 76649-17-7

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Abbreviation/Definition List:

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

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https://doi.org/10.1016/j.fct.2021.112497
Received 20 May 2021; Accepted 7 August 2021
Available online 11 August 2021

(*continued*)

AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
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.

2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs *cis*-3-hexenol (CAS # 928-96-1) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1) show that 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from analog 2-hexenoic acid, 2-methyl-, methyl ester, (2E)- (CAS # 16493-96-2) provided 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester a NESIL of 1100 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2014c; RIFM, 2014b; RIFM, 2014d; RIFM, 2014a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 1100 μg/cm^2.	RIFM (2010)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 3.2 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 382.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 2.08 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 2.08 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00208 μg/L	

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2-Pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester
2. **CAS Registry Number:** 76649-17-7
3. **Synonyms:** 2-Pentenoic acid, 2-methyl-, (3Z)-3-hexenyl ester (9CI); 2-Pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester
4. **Molecular Formula:** $C_{12}H_{20}O_2$
5. **Molecular Weight:** 196.29
6. **RIFM Number:** 569
7. **Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 253.72 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.42 KOWWIN v1.68 (EPI Suite)
4. **Melting Point**: 2.27 °C (EPI Suite)
5. **Water Solubility:** 7.69E+00 mg/L, at 25 °C, WSKOW v1.42 in (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 2.97 Pa at 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} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrances**: 0.014% (RIFM, 2016)
2. **Inhalation Exposure***: 0.00035 mg/kg/day or 0.024 mg/day (RIFM, 2016)
3. **Total Systemic Exposure****: 0.0012 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 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; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

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

6.2. Analogs Selected

a. **Genotoxicity:** *cis*-3-Hexenol (CAS # 928-96-1) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2-Hexenoic acid, 2-methyl-, methyl ester, (2E)-(CAS # 16493-96-2)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across Justification

See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References

None.

8. Natural occurrence

2-Pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is not reported to occur in food by the VCF*.

*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

Pre-registered for 2010; no dossier available as of 05/17/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.085
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.51
4	Products related to fine fragrances	0.47
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.12
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.12
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.12
6	Products with oral and lip exposure	0.28
7	Products applied to the hair with some hand contact	0.96
8	Products with significant ano-genital exposure (tampon)	0.050
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.92
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.3
10B	Aerosol air freshener	3.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.8
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester, the basis was a skin sensitization NESIL of 1100 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester; however, read-across can be made to, *cis*-3-hexenol (CAS # 928-96-1) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1) (see Section VI).

The mutagenic activity of *cis*-3-hexenol 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 *cis*-3-hexenol in solvent 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 metabolic activation (S9) (RIFM, 2014c). Under the conditions of the study, *cis*-3-hexenol was not mutagenic in the Ames test, and this can be extended to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester.

The mutagenic activity of 2-methylpent-2-en-1-oic acid 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 2-methylpent-2-en-1-oic acid in 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, 2014b). Under the conditions of the study, 2-methylpent-2-en-1-oic acid was not mutagenic in the Ames test, and this can be extended to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester.

The clastogenic activity of *cis*-3-hexenol 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 *cis*-3-hexenol in DMSO at concentrations up to 1002 μg/mL in the presence and absence of S9 for 3 h and in the absence of S9 for 24 h *cis*-3-Hexenol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels/the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2014d). Under the conditions of the study, *cis*-3-hexenol was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester.

The clastogenic activity of 2-methylpent-2-en-1-oic acid 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 2-methylpent-2-en-1-oic acid in DMSO at concentrations up to 1150 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h 2-Methylpent-2-en-1-oic acid 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, 2014a). Under the conditions of the study, 2-methylpent-2-en-1-oic acid was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester.

Based on the available data, *cis*-3-hexenol and 2-methylpent-2-en-1-oic acid do not present a concern for genotoxic potential, and this can be extended to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/28/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester or any read-across materials. The total systemic exposure to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester (1.2 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: 04/29/21.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester or on any read-across materials. The total systemic exposure to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester (1.2 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: 04/29/21.

11.1.4. Skin sensitization

Based on the existing data and the read-across material 2-hexenoic acid, 2-methyl-, methyl ester, (2E)- (CAS # 16493-96-2), 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is considered a skin sensitizer with a defined NESIL of 1100 μg/cm^2.

11.1.4.1. Risk assessment. No skin sensitization studies are available for 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester. Based on the existing data and read-across material 2-hexenoic acid, 2-methyl-, methyl ester, (2E)- (CAS # 16493-96-2; see Section VI), 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material 2-hexenoic acid, 2-methyl-, methyl ester, (2E)- was found to be sensitizing with an EC3 value of 38.3% (9575 μg/cm^2) (RIFM, 2007). In a Confirmation of No Induction in Humans test (CNIH) with 1% or 1181 μg/cm^2 of read-across material 2-hexenoic acid, 2-methyl-, methyl ester, (2E)- in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 107 volunteers (RIFM, 2010).

Based on the available data on read-across material 2-hexenoic acid, 2-methyl-, methyl ester, (2E)-, summarized in Table 1, 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester is considered to be a weak skin sensitizer with a defined NESIL of 1100 μg/cm^2.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020).

Table 1
Data Summary for 2-hexenoic acid, 2-methyl-, methyl ester, (2E)- as read-across material for 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester.

LLNA Weighted Mean EC3 Value $\mu g/cm^2$ (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) $\mu g/cm^2$	NOEL-HMT (Induction) $\mu g/cm^2$	LOEL[b] (Induction) $\mu g/cm^2$	WoE NESIL[c] $\mu g/cm^2$
9575 (1)	Weak	1181	N/A	NA	1100

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/17/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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 et al., 2009). Based on the lack of absorbance, 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester. Based on the Creme RIFM Model, the inhalation exposure is 0.024 mg/day. This exposure is 58.3 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: 05/04/21.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester 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, 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

Biodegradation. No data available.

Ecotoxicity. No data available.

Other available data. 2-Pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester has been pre-registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.42	4.42
Biodegradation Factor Used	0	0
Dilution Factor	3	3

(continued on next page)

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.08			1000000	0.00208	

(*continued*)

Exposure	Europe (EU)	North America (NA)
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.00208 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/04/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA 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 05/17/21.

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix F. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112497.

Appendix

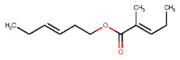
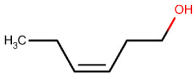
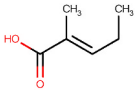
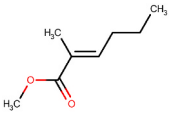
Read-across Justification

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).
- 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	Read-across Material
Principal Name	2-Pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester	*cis*-3-Hexenol	2-Methyl-2-pentenoic acid	2-Hexenoic acid, 2-methyl-, methyl ester, (2E)-
CAS No.	76649-17-7	928-96-1	3142-72-1	16493-96-2
Structure				
Similarity (Tanimoto Score)		0.25	0.46	0.56
Read-across Endpoint		• Genotoxicity	• Genotoxicity	• Skin Sensitization
Molecular Formula	$C_{12}H_{20}O_2$	$C_6H_{12}O$	$C_6H_{10}O_2$	$C_8H_{14}O_2$
Molecular Weight	196.29	100.161	114.144	142.198
Melting Point (°C, EPI Suite)	2.27	−38.47	24.40	−41.94
Boiling Point (°C, EPI Suite)	253.72	156.50	214.00	170.80
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.97	124.92	23.73	199.98
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.42	1.61	1.89	2.67
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.69E+00	1.60E+04	6.33E+03	4.30E+02
J_{max} (μg/cm^2/h, SAM)	1.03	651.83	279.33	29.15
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.10E+02	1.57E+00	9.54E-02	4.05E+01
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	• Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition ≫ α,β-unsaturated esters	• No alert found	• No alert found	
Carcinogenicity (ISS)	• No alert found	• No alert found	• No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	• No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found	• No alert found	
Oncologic Classification	• Acrylate Reactive Functional Groups	• Not classified	• Not classified	
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found			• No alert found
Protein Binding (OECD)	• Michael addition|Michael addition ≫ Polarised Alkenes|Michael addition ≫ Polarised Alkenes ≫ Polarised alkene - esters			• Michael addition|Michael addition ≫ Polarised Alkenes|Michael addition ≫ Polarised Alkenes ≫ Polarised alkene - esters
Protein Binding Potency	• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)|Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Methacrylates (MA)			• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)|Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Methacrylates (MA)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found			• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Alert for Schiff base formation identified			• Alert for Schiff base formation 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	• No metabolites	• See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester (CAS # 76649-17-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, *cis*-3-hexenol (CAS # 928-96-1), 2-methyl-2-pentenoic acid (CAS # 3142-72-1), and 2-hexenoic acid, 2-methyl-, methyl ester, (2E)- (CAS # 16493-96-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Read-across alcohol *cis*-3-hexenol (CAS # 928-96-1) and read-across acid 2-methyl-2-pentenoic acid (CAS # 3142-72-1) are used as read-across analogs for the target ester 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester (CAS # 76649-17-7) for the genotoxicity endpoint.
  - The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - The read-across materials are major metabolites or analogs of the major metabolites of the target material.
  - Structural differences between the target material and the read-across analogs are mitigated by the fact that the target material could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - The target material and the read-across analogs have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to 40% skin absorption, and J_{max} for the read-across analog corresponds to 80% skin absorption. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - The target ester presents alerts for DNA Binding and Oncologic Classification characterization schemes. However, the methyl group on the α-carbon of the vinylene group inhibits reactivity. Additionally. neither the corresponding alcohol nor acid has any alert. Therefore, predictions are superseded by the data.
  - According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Hexenoic acid, 2-methyl-, methyl ester, (2E)- (CAS # 16493-96-2) was used as a read-across analog for the target material 2-pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester (CAS # 76649-17-7) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of unsaturated esters.
  - The target material and the read-across analog share an α,β-unsaturated acid branch with a methyl group in the α position.
  - The key difference between the target material and the read-across analog is that the target material has an unsaturated 3-hexenol group and a 2-methyl-2-pentenoic acid group, whereas the read-across analog has a methanol substituent and a 2-methyl-2-hexenoic acid moiety. These structural differences are toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and read-across analog present several alerts for skin sensitization. The data described in the skin sensitization section shows that both chemicals are skin sensitizers. Therefore, data are consistent with the *in silico* alerts.
  - 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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