Food and Chemical Toxicology 110 (2017) S151–S159

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, 3,7-dimethyl-1-octanyl acetate, CAS Registry Number 20780-49-8

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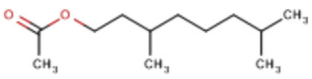
ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form
12 April 2017
Accepted 23 April 2017
Available online 25 April 2017

Version: 011717. This version replaces any previous versions.
Name: 3,7-Dimethyl-1-octanyl acetate
CAS Registry Number: 20780-49-8



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor

(*continued on next page*)

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http://dx.doi.org/10.1016/j.fct.2017.04.032
0278-6915/

(*continued*)

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; Safford et al., 2015) 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
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
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
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence
RIFM's Expert Panel* 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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analogue acetic acid, C7-9 branched alkyl esters, C-8 rich (CAS # 108419-32-5) show that this material is not genotoxic. Data from the suitable read across analogue isoamyl acetate (CAS# 123-92-2) show that this material does not have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The repeated dose and developmental toxicity endpoints were completed using C11-C14 branched alkyl acetate ester, C13 rich (CAS# 108419-35-8) and acetic acid, C7-9 branched alkyl esters, C-8 rich (CAS # 108419-32-5) as suitable read across analogues, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic	(EPA HPVIS, 1994)
Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day	(EPA HPV Test Plan – Alkyl Acetate C6-C13 Category, 2000)
Developmental and Reproductive Toxicity: Developmental toxicity NOAEL = 500 mg/kg/day, No reproductive toxicity data available, exposure is below the TTC	(EPA HPV Test Plan – Alkyl Acetate C6-C13 Category, 2000)
Skin Sensitization: Not a sensitization concern (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)	(EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 540 L/kg	(Episuite ver 4.1)
Ecotoxicity: Screening Level: 96 h Algae EC50: 0.334 mg/L	(Episuite ver 4.1)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; RIFM, 2002)
Critical Ecotoxicity Endpoint: 96 h Algae EC50: 0.334 mg/L	(Episuite ver 4.1)
RIFM PNEC is: 0.0334 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe: <1	

1. Identification

1 **Chemical Name:** 3,7-Dimethyl-1-octanyl acetate
2 **CAS Registry Number:** 20780-49-8
3 **Synonyms:** Dihydrocitronellyl acetate; 3,7-Dimethyloctanyl acetate; 3,7-Dimethyl-1-octanyl acetate; 1-Octanol, 3,7-dimethyl-, acetate; Tetrohydrogeranyl acetate; 酢酸アルキル（C=7~20）ステル; 3,7-Dimethyloctyl acetate
4 **Molecular Formula:** $C_{12}H_{24}O_2$
5 **Molecular Weight:** 200.32
6 **RIFM Number:** 1012

2. Physical data

1 **Boiling Point:** 231 °C [FMA database], 225.84 °C [EPI Suite]
2 **Flash Point:** 91 °C [GHS], 195 °F; CC [FMA]
3 **Log K_{OW}:** 4.65 [EPI Suite]
4 **Melting Point**: −8.81 °C [EPI Suite]
5 **Water Solubility:** 4.696 mg/L [EPI Suite]
6 **Specific Gravity:** 0.865 [FMA database]
7 **Vapor Pressure:** 0.0634 mmHg @ 20 °C [EPI Suite 4.0], 0.03 mm Hg 20C [FMA database], 0.097 mm Hg @ 25 °C [EPI Suite]
8 **UV Spectra:** No absorbance between 290 and 400 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9 **Appearance/Organoleptic:** A colourless liquid with a medium, fresh, waxy, clean, rose, sweet, fruity, honey odor**http://www.thegoodscentscompany.com/data/rw1017891.html#toorgano, retrieved 4/8/2016

3. Exposure

1 **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2 **95**th **Percentile Concentration in Hydroalcoholics:** 0.012% (RIFM, 2016)
3 **Inhalation Exposure*:** 0.00012 mg/kg/day or 0.0097 mg/day (RIFM, 2016)
4 **Total Systemic Exposure**:** 0.00073 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015).

**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).

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 Analogues Selected:
a **Genotoxicity:** Acetic acid, C7-9 branched alkyl esters, C-8 rich (CAS # 108419-32-5)
b **Repeated Dose Toxicity:** C11-C14 branched alkyl acetate ester, C13 rich (CAS# 108419-35-8) and Acetic acid, C7-9 branched alkyl esters, C-8 rich (CAS # 108419-32-5)
c **Developmental and Reproductive Toxicity:** C11-C14 branched alkyl acetate ester, C13 rich (CAS# 108419-35-8) and Acetic acid, C7-9 branched alkyl esters, C-8 rich (CAS # 108419-32-5)
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

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

3,7-Dimethyl-1-octanyl acetate is reported to occur in the following foods*:

Mentha oils.

*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, contains information on published volatile compounds which 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 1/17/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3,7-dimethyl-1-octanyl acetate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 3,7-Dimethyl-1-octanyl acetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM,

2014). There are no studies assessing the mutagenic/clastogenic activity of 3,7-dimethyl-1-octanyl acetate however, read across can be made to acetic acid, C7-9 branched alkyl esters, C-8 rich (CAS # 108419-32-5; see Section 5). The mutagenic activity of acetic acid, C7-9-branched alkyl esters, C8-rich (CAS # 108419-32-5) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with EPA OPP 42 using the standard plate incorporation method. *Salmonella typhimurium strains* TA1535, TA1537, TA1538, TA98, and TA100 were treated with acetic acid, C7-9-branched alkyl esters, C8-rich in DMSO (dimethyl sulfoxide) at concentrations up to 600 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (EPA HPVIS, 1994; Study report, accessed 07/14/2016). Under the conditions of the study, acetic acid, C7-9-branched alkyl esters, C8-rich was not mutagenic in the Ames test.

The clastogenic activity of acetic acid, C7-9-branched alkyl esters, C8-rich was evaluated in an in vivo micronucleus test conducted in compliance with GLP regulations. The test material was administered in corn oil via oral gavage, to groups of male and female CD1 mice. Doses of 625, 1250, or 2500 mg/kg were administered. Mice from each dose level were euthanized at 24, 48 or 72 h, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (EPA HPVIS, 1994; Study report) (accessed 07/14/2016). Under the conditions of the study, acetic acid, C7-9-branched alkyl esters, C8-rich was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, acetic acid, C7-9-branched alkyl esters, C8-rich does not present a concern for genotoxic potential and this can be extended to 3,7-Dimethyl-1-octanyl acetate.

Additional References: Kuroda et al., 1984.

Literature Search and Risk Assessment Completed on: 06/24/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for 3,7-dimethyl-1-octanyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3,7-dimethyl-1-octanyl acetate. Read across analogue C11-C14 branched alkyl acetate ester, C13 rich (CAS# 108419-35-8, see Section 5) has a 13 week GLP, gavage subchronic study. The test material, C11-C14 branched alkyl acetate ester, C13 rich was administered to a group of 20 Sprague-Dawley rats/sex/group at doses of 100, 500, and 1000 mg/kg/day administered by gavage, 5 days a week for 13 weeks. The study was conducted in accordance with the EPA TSCA 798.2650 protocol. There was an increase in terminal liver and kidney weights, however they were not considered to be adverse treatment related alterations. Thus, the NOAEL was determined to be 1000 mg/kg/day, the highest dose tested (EPA HPV Test Plan for Alkyl acetate C6-C13 Category). In another study, read across material, acetic acid, C7-9 branched alkyl esters, C8-rich (CAS # 108419-32-5; see section) has a 90-day gavage study conducted in a group of 20 Sprague-Dawley rats/sex/group. The animals were administered the test material at doses of 0 (water) or 100, 500 or 1000 mg/kg/day. The NOAEL was 1000 mg/kg/day, the highest dose tested. There were no significant adverse findings for clinical signs, hematology and clinical chemistry parameters, organ weights, necropsy at the histopathological examination. A dose dependent increase in liver and kidney weights was considered adaptive and mild tubular nephropathy in male rats consistent with species specific alpha-2-u-globulin effects were observed (EPA HPV Test Plan – Alkyl Acetate C6-C13 Category, 2000). The most conservative NOAEL of 1000 mg/kg/day was selected for the repeated dose toxicity endpoint. **Therefore, the MOE for 3,7-dimethyl-1-octanyl acetate can be calculated by dividing the NOAEL for acetic acid C7-9 branched alkyl esters, C8-rich by the total systemic exposure for 3,7-dimethyl-1-octanyl acetate, 1000/0.00073 or 1369863.**

In addition, the total systemic exposure for 3,7-dimethyl-1-octanyl acetate (0.73 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 7/5/2016.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3,7-dimethyl-1-octanyl acetate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on 3,7-dimethyl-1-octanyl acetate or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 3,7-dimethyl-1-octanyl acetate. Read across material, C11-C14 branched alkyl acetate ester, C13 rich (CAS# 108419-35-8; see Section 5) has limited developmental toxicity data. A GLP developmental toxicity study was conducted in female Sprague-Dawley rats in accordance with EPA Test Guideline 798.4900. In this study, 22 mated female rats received 0 (distilled water), 500, 1300, and 2500 mg/kg C11-C14 branched alkyl acetate ester daily, by oral gavage, on days 6–15 of gestation. Maternal toxicity was observed at 1300 and 2500 mg/kg/day as a decrease in body weight. Despite maternal toxicity, there were no reports of toxicity towards the developing fetus. Thus the NOAEL for maternal toxicity was determined to be 500 mg/kg/day and the developmental toxicity NOAEL was determined to be 2500 mg/kg/day the highest dose tested (EPA HPV Test Plan for Alkyl acetate C6-C13 Category). Since there were limited data available regarding the protocol and details on the results obtained, the data on developmental toxicity was considered limited for determining a NOAEL for the developmental toxicity endpoint. Read across material, acetic acid, C7-9 branched alkyl esters, C8-rich (CAS# 108419-32-5; see section) has an EPA 798.4900 developmental toxicity study that was conducted on 22 mated female Sprague-Dawley rats per dose. The animals were treated with test material, acetic acid, C7-9 branched alkyl esters, C8-rich, at doses of 0 (water) or 100, 500 or 1000 mg/kg/day on days 6–15 of gestation. Maternal toxicity was seen at mid and high doses as evidenced by decreases in body weight. There was a slight but not significant increase in fetal malformations and embryo toxicity in the high dose group only. The NOAEL for maternal and developmental toxicity was 100 and 500 mg/kg, respectively (EPA HPV Test Plan – Alkyl Acetate C6-C13 Category, 2000). The most conservative NOAEL of 500 mg/kg/day was selected for the developmental toxicity endpoint. **Therefore, the MOE for 3,7-dimethyl-1-octanyl acetate can be calculated by dividing the NOAEL for acetic acid C7-9 branched alkyl esters, C8-rich by the total systemic exposure for 3,7-dimethyl-1-octanyl acetate, 500/0.00073 or 684932.**

In addition, the total systemic exposure for 3,7-dimethyl-1-octanyl acetate (0.73 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on 3,7-dimethyl-1-octanyl acetate or any read across materials that can

be used to support the reproductive toxicity endpoint. There is a 13-week gavage study conducted in a group of 20 Sprague-Dawley rats/sex/group with read across material, C11-C14 branched alkyl acetate ester (CAS# 108419-35-8; see Section 5) at doses of 100, 500, and 1000 mg/kg/day administered by gavage, 5 days a week for 13 weeks. The study evaluated the male and female reproductive organs (testes, epididymis, prostate, seminal vesicles, ovaries, uterine horns, cervix, corpus of the uterus, and vagina) and reported no adverse effects in either case up to the highest dose tested. The estrus cycle and sperm count, output, motility and morphology were not evaluated so the study is not considered a complete evaluation of reproductive toxicity. In another study, a 13-week gavage study in rats, with read across material acetic acid, C7-9 branched alkyl esters, C8-rich (CAS# 108419-32-5; see section) showed no adverse findings at the histopathology examination of male and female reproductive organs and reproductive organ weights at 1000 mg/kg/day, the highest dose tested (EPA HPV Test Plan – Alkyl Acetate C6-C13 Category, 2000). The estrus cycle and sperm count, output, motility and morphology were not evaluated, so the study is not considered a complete evaluation of reproductive toxicity. The total systemic exposure for 3,7-dimethyl-1-octanyl acetate (0.73 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the reproductive toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 7/5/2016.

10.1.4. Skin sensitization

Based on the existing data and read across to isoamyl acetate (CAS# 123-92-2), 3,7-dimethyl-1-octanyl acetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data and read across to isoamyl acetate (CAS# 123-92-2; see Section 5), 3,7-dimethyl-1-octanyl acetate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In 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 guinea pig Open Epicutaneous Test (OET) (Klecak, 1979, 1985). In human maximization tests, no skin sensitization reactions were observed with 8% (5520 μg/cm^2) 3,7-dimethyl-1-octanyl acetate or 8% (5520 μg/cm^2) isoamyl acetate (RIFM, 1977; RIFM, 1973). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 20% or 23622 μg/cm^2 isoamyl acetate in 75:25 Ethanol:DEP, no reactions indicative of sensitization was observed in any of the 197 volunteers (RIFM, 1987). Based on the available data and read across to isoamyl acetate, 3,7-dimethyl-1-octanyl acetate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/11/16.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV spectra, 3,7-dimethyl-1-octanyl acetate 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 3,7-dimethyl-1-octanyl acetate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, 3,7-dimethyl-1-octanyl acetate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/30/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3,7-dimethyl-1-octanyl acetate, exposure level 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 3,7-dimethyl-1-octanyl acetate. Based on the Creme RIFM model, the inhalation exposure is 0.0097 mg/day. This exposure is 144.3 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: 07/12/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3,7-dimethyl-1-octanyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range Following the RIFM Environmental Framework, 3,7-dimethyl-1-octanyl acetate 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 EPISUITE ver 4.1 did not identify 3,7-dimethyl-1-octanyl acetate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3,7-dimethyl-1-octanyl

acetate 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. 3,7-Dimethyl-1-octanyl acetate 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	1.337 mg/L			1,000,000	0.001337 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.763 mg/L	1.195 mg/L	0.334 mg/L	10,000	0.0334 μg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.692 mg/L	0.501 mg/L	1.026 mg/L			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.65	4.65
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

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: 6/20/2016.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.04.032.

Transparency document

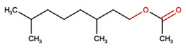
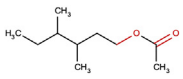
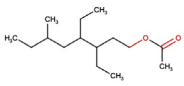
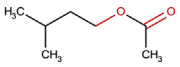
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.04.032.

Appendix

Methods:

- The identified read-across analogues were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).

- The physicochemical properties of target and analogues were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogues were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Strategies used to find read across are highlighted in Schultz et al., 2015.

	Target material	Read across material		
Principal Name	3,7-Dimethyl-1-octanyl acetate	Acetic acid, C7-9-branched alkyl esters, C8-rich	Acetic acid, C11-14-branched alkyl esters, C13-rich	Isoamyl acetate
CAS No.	20780-49-8	108419-32-5	108419-35-8	123-92-2
Structure				
Similarity (Tanimoto score)	1	0.89189	0.81449	0.70909
Read across endpoint		• Genotoxicity, • Repeated dose, • Developmental and reproductive	• Repeated dose, • Developmental and reproductive	• Skin sensitization
Molecular Formula	$C_{12}H_{24}O_2$	$C_{10}H_{20}O_2$	$C_{15}H_{30}O_2$	$C_7H_{14}O_2$
Molecular Weight	200.32	172.27	242.41	130.19
Melting Point (°C, EPISUITE)	−8.81	−31.53	2.47	−56.05
Boiling Point (°C, EPISUITE)	225.84	186.63	257.94	134.87
Vapor Pressure (Pa @ 25 °C, EPISUITE)	12.9	96.1	2.37	756
Log Kow (KOWWIN v1.68 in EPISUITE)	4.65	3.66	5.97	2.25
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	4.696	44.59	0.2068	1100
J_{max} (mg/cm^2/h, SAM)	0.671436	4.88396	0.03195	55.89014
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.28E+002	1.29E+002	5.32E+002	5.52E+001
Genotoxicity				
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	• AN2, SN1, SN2	• AN2, SN1, SN2		
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found		
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found		
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found		
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found		
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized	• Not categorized	• Not categorized	
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder, non cyclic structure	• Non binder, non cyclic structure	• Non binder, non cyclic structure	
Developmental Toxicity Model by CAESAR v2.1.6	• NON-Toxicant (low reliability)	• NON-Toxicant (low reliability)	• Toxicant (good reliability)	
Sensitization				
Protein binding by OASIS v1.1	• No alert found			• No alert found
Protein binding by 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 by OASIS v1.1	• No alert found			• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)			• Sensitizer (good reliability)
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1 • 6 metabolites from Rat S9 simulator. • Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.	See Supplemental Data 2 • 6 metabolites from Rat S9 simulator. • Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.	See Supplemental Data 3 • 6 metabolites from Rat S9 simulator. • Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.	See Supplemental Data 4 • 5 metabolites from Rat S9 simulator.Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.

Summary

There are insufficient toxicity data on 3,7-dimethyl-1-octanyl acetate (CAS # 20780-49-8). Hence *in-silico* evaluation was conducted by determining suitable read across analogues for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogues acetic acid, C7-9-branched alkyl esters, C8-rich (CAS # 108419-32-5), acetic acid, C11-14-branched alkyl esters, C13-rich (CAS # 108419-35-8), and isoamyl acetate (CAS # 123-92-2) were identified as read across materials with data for their respective toxicity endpoints.

Conclusion/Rationale

- Acetic acid, C7-9-branched alkyl esters, C8-rich (CAS # 108419-32-5) could be used as structurally similar read across analogue for the target material 3,7-dimethyl-1-octanyl acetate (CAS # 20780-49-8) for the genotoxicity, repeated dose, developmental, and reproductive toxicological endpoints.
  - o The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - o The key difference between the target substance and the read across analogue is that the target has a 3,7-dimethyl-1-octanyl fragment while the read across has a 3,4-dimethylhexyl fragment. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the branched alkane chain. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxic endpoint perspective.
  - o The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for genotoxicity, repeated dose, developmental, and reproductive endpoints.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the genotoxicity, repeated dose, developmental, and reproductive endpoints are consistent between the target substance and the read across analogue as seen in the table above.
  - o The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the genotoxocity, repeated dose, developmental, and reproductive endpoints are consistent between the metabolites of the read across analogue and the target substance.
  - o The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.
- Acetic acid, C11-14-branched alkyl esters, C13-rich (CAS # 108419-35-8) could be used as structurally similar read across analogue for the target material 3,7-dimethyl-1-octanyl acetate (CAS # 20780-49-8) for the repeated dose, developmental, and reproductive toxicological endpoints.
  - o The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - o The key difference between the target substance and the read across analogue is that the target has a 3,7-dimethyl-1-octanyl fragment while the read across has a 3,4-diethyl-6-methyloctyl group. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the branched alkane chain. The differences in the structure which are responsible for a Tanimoto score <1 are not relevent from a toxic endpoint perspective.
  - o The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the repeated dose, developmental, and reproductive endpoints.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the repeated dose, developmental, and reproductive endpoints are consistent between the target substance and the read across analogue as seen in the table above.
  - o The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the repeated dose, developmental, and reproductive endpoints are consistent between the metabolites of the read across analogue and the target substance.
  - o The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.
- Isoamyl acetate (CAS # 123-92-2) could be used as structurally similar read across analogue for the target material 3,7-dimethyl-1-octanyl acetate (CAS # 20780-49-8) for skin sensitization toxicological endpoint.
  - o The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - o The key difference between the target substance and the read across analogue is that the target has a 3,7-dimethyl-1-octanyl fragment while the read across has a 3-methylpentyl fragment. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the branched alkane chain. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxic endpoint perspective.
  - o The target substance and the read across analogue have similar physical chemical properties except skin absorption which is directly related to J_{max} value. The read across shows greater skin absorption compared to the target.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for skin sensitization endpoint are consistent between the target substance and the read across analogue as seen in the table above.
  - o The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.

- o The structural alerts for skin sensitization endpoint are consistent between the metabolites of the read across analogue and the target substance.
- o The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

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