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Short Review

RIFM fragrance ingredient safety assessment, 3-methyl-2-butenyl acetate, CAS Registry Number 1191-16-8

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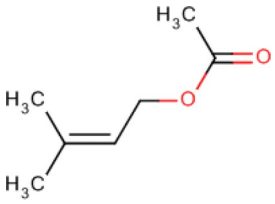
Name: 3-Methyl-2-butenyl acetate CAS Registry Number: 1191-16-8



Abbreviation/Definition List:

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

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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 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.

3-Methyl-2-butenyl acetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and from read-across analog 3-methylbut-2-en-1-ol (CAS # 556-82-1) show that 3-methyl-2-butenyl is not expected to be genotoxic. Data on read-across analogs 3-methylbut-2-en-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7) provide a calculated MOE > 100 for the repeated dose toxicity and developmental toxicity endpoints. The reproductive toxicity and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 3-methyl-2-butenyl is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from 3-methyl-2-butenyl show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 3-methyl-2-butenyl is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-methyl-2-butenyl 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 genotoxic. (RIFM, 2000c; ECHA Dossier: 3-Methyl-2-butenyl acetate; ECHA, 2013)

Repeated Dose Toxicity: NOAEL = 65.4 mg/kg/day. (RIFM, 2002b)

Developmental and Reproductive Toxicity: Developmental Toxicity: NOAEL = 600 mg/kg/day. No reproductive toxicity NOAEL available. Exposure is below the TTC. (RIFM, 2002a)

Skin Sensitization: Not a sensitization concern. (RIFM, 2013c; RIFM, 2014)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 105% (OECD 301B) (RIFM, 1996)

Bioaccumulation: Screening-level: 12.72 L/kg (EPI Suite v4.11, US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 96-h *Danio rerio* LC50: 23.5 mg/L (-RIFM, 2013b)

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 *Danio rerio* LC50: 23.5 mg/L (RIFM, 2013b)

RIFM PNEC is: 23.5 µg/L

Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name:** 3-Methyl-2-butenyl acetate
2. **CAS Registry Number:** 1191-16-8
3. **Synonyms:** 2-Buten-1-ol, 3-methyl-, acetate; Prenyl acetate; 2-Buten-1-ol, 3-methyl-, acetate; 3-Methyl-2-butenyl acetate; アルカン酸(C = 1–6)アルケニル(C = 4–8); 酢酸プレニル; 3-Methylbut-2-en-1-yl acetate; 3-Methyl-2-butenyl acetate
4. **Molecular Formula:** $C_7H_{12}O_2$
5. **Molecular Weight:** 128.17
6. **RIFM Number:** 994
7. **Stereochemistry:** No isomeric center present and no isomers possible.

2. Physical data

1. **Boiling Point:** 151 °C (FMA Database), 149 °C atmospheric pressure (Private communication to FEMA), 149.15 °C (EPI Suite)
2. **Flash Point:** 46 °C (GHS), 122 °F; CC (FMA Database)
3. **Log K_{OW}:** log Pow = 2.0 @ 23 °C, pH = 6.5 (pH of H_20 used) (RIFM, 2012b), log Pow = 2.1 (RIFM, 1997a), 2.18 (EPI Suite)
4. **Melting Point**: No melting temp. found between −100 °C and 20 °C (RIFM, 2012b); −53.9 °C (EPI Suite)
5. **Water Solubility:** 1289 mg/L (EPI Suite)
6. **Specific Gravity:** 0.920 (FMA Database), 0.911–0.920 (Private communication to FEMA)
7. **Vapor Pressure:** 2.6 hPa @ 20 °C; 3.7 hPa @ 25 °C; 17.1 hPa @ 50 °C (RIFM, 2012b), 3.01 mm Hg @ 20 °C (EPI Suite v4.0), 1.9 mm Hg @ 20 °C (FMA Database), 4.17 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance in the region 290–400 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid with a medium sweet, fresh, banana, fruity, jasmin, ripe, heliotrope, balsam odor at 1% or less in dipropylene glycol and a sweet, banana, fruity, ripe, floral, green taste at 30 ppm in water (Luebke, William tgsc, 2006)*

* http://www.thegoodscentscompany.com/data/rw1015091.html, retrieved on 03/11/15.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.026% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00035 mg/kg/day or 0.025 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 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, 2017; Safford et al., 2015, 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
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2. Analogs Selected:
   a. **Genotoxicity:** 3-Methyl-2-buten-1-ol (CAS # 556-82-1)
   b. **Repeated Dose Toxicity:** 3-Methyl-2-buten-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7)
   c. **Developmental and Reproductive Toxicity:** 3-Methyl-2-buten-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

WHO, 2009: 3-Methyl-2-butenyl acetate is an ester that undergoes hydrolysis to form the corresponding alcohol and carboxylic acid. The hydrolyzed products undergo β-oxidation and subsequently metabolize to CO_2 through the tricarboxylic acid pathway.

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

3-Methyl-2-butenyl acetate is reported to occur in the following foods by the VCF* and in some natural complex substances:

Acerola (*Malpighia*)
Apple fresh (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus articus* L.)
Cherimoya (*Annona cherimolia* Mill.)
Citrus fruits
Coffee
Litchi (*Litchi chinensis* Sonn.)
Litchi wine
Melon
Nectarine
Olive (*Olea europaea*)
Passion fruit (*Passiflora* species)
Pepino fruit (*Solanum muricatum*)
Pineapple (*Ananas comosus*)
Raspberry, blackberry, and boysenberry
Strawberry (*Fragaria* species)

*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

Available; accessed on 04/23/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3-methyl-2-butenyl acetate does not present a concern for genetic toxicity.

10.1.2. Risk assessment

The mutagenic activity of 3-methyl-2-butenyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were treated with 3-methyl-2-butenyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2000c). Under the conditions of the study, 3-methyl-2-butenyl acetate was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of 3-methyl-2-butenyl acetate; however, read-across can be made to 3-methylbut-2-en-1-ol (CAS # 556-82-1; see Section 5). The clastogenic activity of 3-methylbut-2-en-1-ol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in olive oil via intraperitoneal injection to groups of male NMRI mice (5/group). Doses of 125, 250, and 500 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2013). Under the conditions of the study, 3-methylbut-2-en-1-ol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-methyl-2-butenyl acetate.

Based on the data available, 3-methyl-2-butenyl acetate does not present a concern for genotoxic potential.

Additional References: RIFM, 2012d.

Literature Search and Risk Assessment Completed On: 05/16/18.

10.1.3. Repeated dose toxicity

The margin of exposure for 3-methyl-2-butenyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are insufficient repeated dose toxicity data on 3-methyl-2-butenyl acetate. 3-Methyl-2-butenyl acetate is expected to be hydrolyzed to 3-methylbut-2-en-1-ol (CAS # 556-82-1; see Section 5) and acetic acid (CAS # 64-19-7; see Section 5). Based on the available data on acetic acid (EFSA, 2012; NICNAS, 2018; US FDA, 2018), acetic acid does not show specific reproductive or developmental toxicity. As such, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

Read-across material 3-methylbut-2-en-1-ol (CAS # 556-82-1; see Section 5) has sufficient repeated dose toxicity data. An enhanced OECD 408 oral (drinking water) 90-day subchronic toxicity study was

conducted in Wistar rats. Groups of 10 rats/sex/dose were administered 3-methyl-2-buten-1-ol in drinking water at concentrations of 0, 200, 1000, or 5000 ppm for 90 days (equivalent to 0, 14.4, 65.4, or 243.8 mg/kg/day for males and 0, 21.0, 82.1, or 307.2 mg/kg/day for females). At 5000 ppm, there was decreased food and water consumption, decreased body weight and bodyweight gain, decreased food efficiency, and decreased urinary volume in both sexes (all alterations reported were significantly different as compared to the controls). At 1000 ppm, decreased food consumption in males and decreased water consumption in males and females were observed. Since there were no effects on body weights, these changes were not considered to be adverse. The NOAEL for repeated dose toxicity was considered to be 1000 ppm (equivalent to 65.4 and 82.1 mg/kg/day for males and females, respectively), based on decreased body weights among high-dose group animals (RIFM, 2002b; ECHA, 2011). The most conservative NOAEL of 65.4 mg/kg/day was selected for this safety assessment.

Therefore, the 3-methyl-2-butenyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-methylbut-2-en-1-ol NOAEL in mg/kg/day by the total systemic exposure for 3-methyl-2-butenyl acetate, 65.4/0.0016, or 40875.

In addition, the total systemic exposure to 3-methyl-2-butenyl acetate (1.6 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: 05/30/18.

10.1.5. Development and reproductive toxicity

The margin of exposure for 3-methyl-2-butenyl acetate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on 3-methyl-2-butenyl acetate or on any read-across materials. The total systemic exposure to 3-methyl-2-butenyl acetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on 3-methyl-2-butenyl acetate. 3-Methyl-2-butenyl acetate is expected to be hydrolyzed to 3-methylbut-2-en-1-ol (CAS # 556-82-1; see Section 5) and acetic acid (CAS # 64-19-7; see Section 5). Based on the available data on acetic acid (EFSA, 2012; NICNAS, 2018; US FDA, 2018), acetic acid does not show specific reproductive or developmental toxicity. As such, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

Read-across material 3-methyl-2-buten-1-ol (CAS # 556-82-1; see Section 5) has sufficient developmental toxicity data. An OECD 414 oral gavage developmental toxicity study was conducted in female Wistar rats. Groups of 25 time-mated female rats/dose were administered via gavage 3-methyl-2-buten-1-ol at doses of 0, 50, 200, or 600 mg/kg/day in 0.5% carboxymethylcellulose on days 6–19 post coitum (pc). At 600 mg/kg/day, observations included unscheduled death of 1 dam on day 19 pc, transient salivation in all dams immediately after treatment between days 6–19 pc, transient occurrence of abdominal position, and lacrimation and/or piloerection shortly after treatment. A statistically significant decrease in food consumption on days 6–8 pc (decrease of 9%) and a statistically significant lowered mean body weight on day 8 pc were observed at 600 mg/kg/day. There were no treatment-related effects on the gestational parameters or fetuses. Under the conditions of this study, there were clear signs of maternal toxicity at 600 mg/kg/day with no corresponding treatment-related effects on the gestational parameters, conception rate, mean number of corpora lutea, total implantations, resorptions, live fetuses, sex ratio, pre- and post-implantation losses, placental and fetal body weights, or external and skeletal examinations up to the highest dose of 600 mg/kg/day. The NOAEL for developmental toxicity was considered to be 600 mg/kg/day, the highest dose tested (RIFM, 2002a; ECHA, 2011).

Therefore, the 3-methyl-2-butenyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the 3-methylbut-2-en-1-ol NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-2-butenyl acetate, 600/0.0016 or 375000.

In addition, the total systemic exposure to 3-methyl-2-butenyl acetate (1.6 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no reproductive toxicity data on 3-methyl-2-butenyl acetate. Read-across material, 3-methyl-2-buten-1-ol (CAS # 556-82-1; see Section 5) has an enhanced OECD 408 oral (drinking water) 90-day subchronic toxicity study conducted in Wistar rats. Groups of 10 rats/sex/dose were administered 3-methyl-2-buten-1-ol in drinking water at concentrations of 0, 200, 1000, or 5000 ppm for 90 days (equivalent to 0, 14.4, 65.4, or 243.8 mg/kg/day for males and 0, 21.0, 82.1, or 307.2 mg/kg/day for females). In addition to systemic toxicity parameters, all males were subjected to sperm analyses (motility, morphology, cauda epididymis-sperm headcount, testis-sperm headcount) at necropsy. There were no effects on sperm parameters up to the highest dose of 5000 ppm or 243.8 mg/kg/day for males (RIFM, 2002b; ECHA, 2011). However, the female estrous cycling was not monitored. Hence, a NOAEL could not be derived for the female reproductive toxicity endpoint. The total systemic exposure to 3-methyl-2-butenyl acetate (1.6 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.

10.1.7. Skin sensitization

Based on the existing data, 3-methyl-2-butenyl acetate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the existing data, 3-methyl-2-butenyl acetate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.4). 3-Methyl-2-butenyl acetate was found to be negative in an *in chemico* direct peptide reactivity assay (DPRA) and *in vitro* KeratinoSens assay and positive in the LuSens and U937-CD86 tests (RIFM, 2012c). However, in a murine local lymph node assay (LLNA), 3-methyl-2-butenyl acetate was found to be non-sensitizing up to 100% (RIFM, 2013c). In a Buehler test, 3-methyl-2-butenyl acetate did not present reactions indicative of sensitization (RIFM, 2014). In a confirmatory human maximization test, no skin sensitization reactions were observed with 20% 3-methyl-2-butenyl acetate (RIFM, 1977). Additionally, in confirmatory human repeat insult patch tests (HRIPTs) with 2326 μg/cm^2 of 3-methyl-2-butenyl acetate in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 9 or 35 volunteers (RIFM, 1971; RIFM, 1972).

Based on weight of evidence from structural analysis as well as *in vitro,* animal, and human studies, 3-methyl-2-butenyl acetate does not present a concern for skin sensitization.

Additional References: RIFM, 2012f.

Literature Search and Risk Assessment Completed On: 07/13/

17.

10.1.9. Phototoxicity/photoallergenicity

Based on available UV spectra, 3-methyl-2-butenyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for 3-methyl-2-butenyl acetate in experimental models. UV absorption spectra indicate no significant absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, 3-methyl-2-butenyl acetate does not present a concern for phototoxicity or photoallergenicity.

10.1.11. UV spectra analysis

The available spectra indicate no significant absorbance in the range of 290–400 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: 04/11/18.

10.1.12. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 3-methyl-2-butenyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.13. Risk assessment

There are no inhalation data available on 3-methyl-2-butenyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.025 mg/day. This exposure is 56 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: 02/06/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3-methyl-2-butenyl acetate 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, 3-methyl-2-butenyl 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 EPI Suite v4.11 (US EPA, 2012a) did not identify 3-methyl-2-butenyl acetate as either 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). 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 (2015), 3-methyl-2-butenyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1997b: A manometric respirometry test was conducted according to the OECD 301F method to determine the biodegradability of the test material. A sample of test material (100 mg/L) was stirred in a closed flask containing inoculum and incubated 28 days. Biodegradation of the test material reached 82% by the end of day 28.

RIFM, 1996: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test following the OECD 301B method. Biodegradation of 105% was observed after 28 days.

RIFM, 2000a: Ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. After 28 days, biodegradation of 23% was observed.

RIFM, 2010: A study was conducted to determine the ready biodegradability of the test material by measurement of the formed carbon dioxide following the OECD 301B guidelines. Biodegradation of 100% was observed after 28 days.

10.2.3.2. Ecotoxicity. RIFM, 2000b: The effect of the test material on the mobility of *Daphnia magna* under static conditions was evaluated according to the OECD 202 method. Under the conditions of this study, the 48-h EC50 was 26 mg/L.

RIFM, 2012a: A study was conducted to evaluate the effect of the test material on the immobilization of *Daphnia magna* according to the OECD 202 method. The 48-h EC50 was reported to be 69.6 mg/L

(64.3 mg/L [mean measured concentration]).

RIFM, 2013a: An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EyC50 (yield) and ErC50 (growth rate) were reported to be greater than 84.4 mg/L.

RIFM, 2013b: A study was conducted to assess the acute toxic effects of the test material to zebra fish (*Danio rerio*) over a 96-h period under semi-static conditions following the OECD 203 guidelines. The 72-h LC50 of the test material in zebra fish was reported to be 23.5 mg/L (mean measured concentration).

10.2.3.3. Other available data. 3-Methyl-2-butenyl acetate has been registered under REACH but no additional data is available.

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)**	141.5			1,000,000	0.1451	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	13.47	27.48	11.36			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.879	7.199	1.909	10,000	0.0879	Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	72.76	42.02	33.49			Neutral Organic SAR (Baseline toxicity)
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	23.5			1,000	23.5	
Daphnia		26				
Algae		84.4				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.1	2.1
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	100–1000
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 23.5 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/02/18.

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. The links listed above were active as of 10/09/2018.

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.2019.110705.

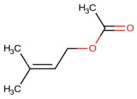
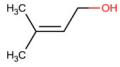
Appendix

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 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 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 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	
Principal Name	3-Methyl-2-butenyl acetate	3-Methyl-2-buten-1-ol	Acetic acid
CAS No.	1191-16-8	556-82-1	64-19-7
Structure			
Similarity (Tanimoto Score)		0.77	
Read-across Endpoint		• Repeated Dose Toxicity • Developmental Toxicity • Genotoxicity	• Repeated Dose Toxicity • Developmental Toxicity
Molecular Formula	$C_7H_{12}O_2$	$C_5H_{10}O$	$C_2H_4O_2$
Molecular Weight	128.17	86.13	60.05
Melting Point (°C, EPI Suite)	−53-.90	−59.25	16
Boiling Point (°C, EPI Suite)	149.15	137.75	118
Vapor Pressure (Pa @ 25 °C, EPI Suite)	556	314	12.9
Log Kow (KOWWIN v1.68 in EPI Suite)	2.18	1.17	0.09
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1289	4.094E+004	475900
Jmax (μg/cm^2/h, SAM)	302.414	1096.249	6283.04
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	5.73E+001	1.39E+000	5.477E-007
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2	• AN2	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• No alert found	• No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated dose (HESS)	• Not categorized	• Not categorized	• Acetamide (Renal Toxicity) Alert|Carboxylic acids (Hepatotoxicity) No rank
Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)			• Non-binder, non-cyclic structure

	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)	• Toxicant (good reliability)	• Toxicant (low reliability)
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 metabolism

Summary

There are insufficient toxicity data on 3-methyl-2-butenyl acetate (CAS # 1191-16-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 3-methyl-2-buten-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7) were identified as read-across materials with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target substance 3-methyl-2-butenyl acetate (CAS # 1191-16-8) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to 3-methyl-2-buten-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7) in the first step with 0.95 probability. Hence, 3-methyl-2-buten-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7) can be used as read-across for the target material. Read-across materials 3-methyl-2-buten-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7) were in domain for the *in vivo* rat and in domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19).

Conclusions

- 3-Methyl-2-buten-1-ol (CAS # 556-82-1) and acetic acid (CAS # 64-19-7) were used as read-across analogs for the target material 3-methyl-2-butenyl acetate (CAS # 1191-16-8) for the repeated dose toxicity, developmental toxicity, and genotoxicity endpoints.
  - o 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.
  - o The read-across materials are major metabolites of the target.
  - o Structural differences between the target substance and the read-across analog are mitigated by the fact that the target 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.
  - o The target substance and the read-across analogs have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analogs are toxicologically insignificant.
  - o The read-across material acetic acid (CAS # 64-19-7) has an Acetamide Precursor Renal Toxicity alert and a Carboxylic Acids Hepatotoxicity alert with no rank under HESS categorization. The wealth of data in the literature suggest fast rates of clearance for acetic acid. In addition, acetic acid is one of the natural constituents of the human metabolome according to the Human Metabolome Database. Therefore, the alerts for acetic acid are superseded by data.
  - o Alerts for genotoxicity are identical between the target and the read-across.
  - o According to the QSAR OECD Toolbox v3.4, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.

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