Food and Chemical Toxicology 110 (2017) S619–S628

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, menthyl acetate (isomer unspecified), CAS Registry Number 16409-45-3

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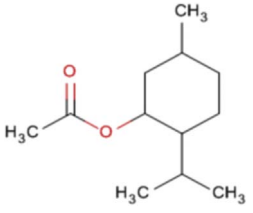
Version: 072517. This version replaces any previous versions.
Name: Menthyl acetate (isomer unspecified)
CAS Registry Number: 16409-45-3
Additional CAS Numbers*:
2623-23-6 *l*-Menthyl acetate (1α,2β,5α)
89-48-5 Menthyl acetate (1α,2β,5α)
29066-34-0 *dl*-Menthyl acetate
*These materials are included in this assessment because they are a mixture of isomers.



Abbreviation/Definition List:

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http://dx.doi.org/10.1016/j.fct.2017.10.014
Received 21 August 2017; Received in revised form 27 September 2017; Accepted 9 October 2017
Available online 10 October 2017

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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 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
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

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 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 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

The material (menthyl acetate (isomer unspecified)) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that menthyl acetate (isomer unspecified) is not genotoxic nor does it 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 toxicity endpoint was completed using *l*-menthol (CAS # 2216-51-5) and *d*,*l*-menthol (isomer unspecified; CAS # 1490-04-6) as read across analogs, which provided a MOE > 100. The developmental toxicity endpoint was completed using menthol (CAS # 89-78-1) and *d*,*l*-menthol (isomer unspecified; CAS # 1490-04-6) as read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, menthyl acetate (isomer unspecified) 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, 2013e; RIFM, 2013a)

Repeated Dose Toxicity: NOAEL = 300 mg/kg/day. (RIFM, 1979)

Developmental Toxicity: NOAEL = 425 mg/kg/day and **Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC. (RIFM, 1973b)

Skin Sensitization: Not sensitizing. (ECHA REACH dossier: menthyl acetate)

Phototoxicity/Photoallergenicity: Not 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: 48% (OECD 301D) for CAS # 29066-34-0 (RIFM, 1999)

Bioaccumulation: Screening Level: 202.4 l/kg (US EPA, 2012a)

Ecotoxicity: Critical Measured Value: 72-hr Algae ErC50: 2.7 mg/l for CAS # 89-48-5 (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: 72-hr Algae ErC50: 2.7 mg/l for CAS # 89-48-5 (RIFM, 2013b)

RIFM PNEC is: 2.7 μg/l

- Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe: < 1

1. Identification

Chemical Name: Menthyl acetate (isomer unspecified)	Chemical Name: *l*-Menthyl acetate (1α,2β,5α)	Chemical Name: Menthyl acetate (1α,2β,5α)	Chemical Name: *dl*-Menthyl acetate
CAS Registry Number: 16409-45-3	**CAS Registry Number:** 2623-23-6	**CAS Registry Number:** 89-48-5	**CAS Registry Number:** 29066-34-0
Synonyms: Cyclohexanol, 5-methyl-2-(1-methylethyl), acetate; 1-Isopropyl-4-methylcyclohex-2-yl acetate; Menthol acetate (isomer unspecified); Menthyl acetate (isomer unspecified); *p*-Menth-3-yl acetate; l-Menthyl acetate (isomer unspecified); 5-Methyl-2-(1-methylethyl)cyclohexanol acetate; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate; Menthyl acetate; アルカン酸 (C = 1～18)メンチル; 2-Isopropyl-5-methylcyclohexyl acetate	**Synonyms:** 1R-(1α,2β,5α])-5-Methyl-2-(1-methylethyl) cyclohexanol; l-(−)-Menthyl acetate; l-Menthyl acetate (1α,2β,5α); 2-Isopropyl-5-methylcyclohexyl acetate; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate, [1R-(1α,2β,5α)]-; ｱﾙｶﾝ酸(C = 1～18)ﾒﾝﾁﾙ	**Synonyms:** 2-Isopropyl-5-methylcyclohexyl acetate; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate, (1α,2β,5α)-; Menthol, acetate, *cis*-1,3,*trans*-1,4-; Menthyl acetate; Menthyl acetate (1α,2β,5α); Menthyl acetate racemic; アルカン酸(C = 1～18)メンチル	**Synonyms:** (.+-.)-Menthyl acetate; dl-Menthyl acetate; 2-Isopropyl-5-methylcyclohexyl acetate; 5-Methyl-2-(1-methylethyl)cyclohexanol acetate; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate, (1.α.,2.β.,5.α.)-(.+-.)-; Menthyl acetate
Molecular Formula: $C_{12}H_{22}O_2$	**Molecular Formula:** $C_{12}H_{22}O_2$	**Molecular Formula:** $C_{12}H_{22}O_2$	**Molecular Formula:** $C_{12}H_{22}O_2$
Molecular Weight: 198.31	**Molecular Weight:** 198.06	**Molecular Weight:** 198.06	**Molecular Weight:** 198.06
RIFM Number: 338	**RIFM Number:** 5285	**RIFM Number:**6070	**RIFM Number:** 5647

2. Physical data*

1. **Boiling Point:** 227 °C [FMA database], 234.5 °C [US EPA, 2012a]
2. **Flash Point:** 198 °F; CC [FMA database]
3. **Log K_{OW}:** 4.39 [US EPA, 2012a]
4. **Melting Point:** 0.67 °C [US EPA, 2012a]
5. **Water Solubility:** 17.13 mg/l [US EPA, 2012a]
6. **Specific Gravity:** 0.918 [FMA database]
7. **Vapor Pressure:** 0.0596 mm Hg @ 20 °C [US EPA, 2012a], 0.0913 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** Minor absorbance in the region 290–700 nm; molar absorption below benchmark (1000 l mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid, mild and sweet, slightly fruity-herbaceous, minty odor, delicately floral. Cool mouth feel, sweet taste with only a trace of mint flavor.

*Physical data for all materials included in this assessment are identical.

3. Exposure***

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0036% (RIFM, 2016b)
3. **Inhalation Exposure*:** 0.00065 mg/kg/day or 0.047 mg/day (RIFM, 2016b)
4. **Total Systemic Exposure**:** 0.0021 mg/kg/day (RIFM, 2016b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics, inhalation exposure and total exposure.

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 toxicity (Expert judgment)

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for explanation.

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** *l*-menthol (CAS # 2216-51-5); *d,l*-menthol (isomer unspecified; CAS # 1490-04-6)
   c. **Developmental and Reproductive Toxicity:** menthol (CAS # 89-78-1); *d,l*-menthol (isomer unspecified; CAS # 1490-04-6)
   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

ECHA REACH dossier: menthyl acetate, (accessed on 2/3/2017): The aim of the study was to determine the metabolic activity of human hepatocytes towards the test material, a racemic mixture of menthyl acetates (CAS # 89-48-5). The test material, menthyl acetate racemate, was incubated with cryopreserved hepatocytes from humans. Samples were taken after defined time points (0, 15, 60, 120 and 240 min) and the content of the test item and potential metabolite, menthol, was determined. The stock solutions of the test material were prepared in methyl *tert*-butyl ether (TBME). The stock solutions were further diluted in Krebs-Henseleit (KH) buffer and applied to reaction vials. The cryopreserved hepatocytes were thawed using Krebs-Henseleit buffer. After centrifugation, the cells were re-suspended in KH buffer to the final concentration of 1.0×10^6 cells/ml. The test material (at 20 μM and 100 μM) was incubated with the hepatocytes and 3 replicates were prepared for each concentration and the corresponding time points. The solutions within the vials were agitated at low speed. The vials were then incubated at 37°C/5% CO^2 for a total incubation time of 4 h. After the indicated time points (0, 15, 60, 120 and 240 min (T1 – T5)) the respective reactions were stopped with 1.3 ml TBME. Samples were stored at −80 °C immediately. The percentage of menthyl acetate racemate remaining after 240 min was between 28.5% and 35.5%. The measured amount of menthol was between 7 and 12 μg/ml when 20 μM of test material was applied. The range was 4–17 μg/ml when 100 μM of test material was applied. The amount of menthol detected was similar throughout the incubation time from 0 to 240 min. Therefore, there was no correlation between metabolized menthyl acetate racemate and the production of menthol. The amount of menthol detected without hepatocytes was between 3 and 6 μg/ml. Thus, this indicates that there is abiotic hydrolysis of the test material in the test solution in absence of hepatocytes.

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

Menthyl acetate (isomer unspecified), *l*-menthyl acetate (1α,2β,5α) and *dl*-menthyl acetate are not reported to occur in food by the VCF*; menthyl acetate (isomer unspecified) and *l*-menthyl acetate (1α,2β,5α) are found in some natural complex substances (NCS).

Menthyl acetate (1α,2β,5α) is reported to occur in the following foods:

Acerola (*Malpighia*)
Buchu oil
Calamus (sweet flag) (*Acorus calamus* L.)
Camomile
Citrus fruits
Coriander leaf (*Coriandrum sativum* L.)
Ginger (*Zingiber* species)
Lemon balm (*Melissa officinalis* L.)
Mangifera species
Mentha oils
Raspberry, blackberry and boysenberry

*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

Menthyl acetate (isomer unspecified), *l*-menthyl acetate (1α,2β,5α) and *dl*-menthyl acetate are pre-registered for 11/30/2010; no dossier available as of 7/25/2017. Menthyl acetate (1α,2β,5α) has a dossier available, accessed 7/25/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, menthyl acetate (isomer unspecified) does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Menthyl acetate (isomer unspecified) was tested in the BlueScreen assay and was found negative for genotoxicity in the presence and absence of metabolic activation indicating a lack for genotoxic concern (RIFM, 2013d). There are no studies assessing the mutagenic activity of menthyl acetate (isomer unspecified), however, the additional material, menthyl acetate (1α,2β,5α) (CAS # 89-48-5; see section 5), was evaluated in an *in vitro* mammalian cell gene mutation assay (HPRT/mouse lymphoma assay) conducted in compliance with GLP regulations and in accordance with OECD TG 486. Chinese hamster lung fibroblasts (V79) were treated with menthyl acetate (1α,2β,5α) in solvent DMSO (dimethyl sulfoxide) at concentrations up to 120 μg/ml in the presence and absence of metabolic activation (S9) at the 4-h and 24-h timepoints. No statistically significant increases in the frequency of mutant colonies were observed with any dose of the test item, either with or without metabolic activation (RIFM, 2013e). Under the conditions of the study, menthyl acetate (1α,2β,5α) was considered to be non-mutagenic in the *in vitro* mammalian cell mutagenicity study and this can be extended to menthyl acetate (isomer unspecified).

There are no studies assessing the clastogenic activity of menthyl acetate (isomer unspecified). Again, we can use data from menthyl acetate (1α,2β,5α) which was assessed for clastogenicity in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD 487. Human peripheral blood lymphocytes (HPBL) were treated with menthyl acetate (1α,2β,5α) in ethanol at concentrations up to 1983 μg/ml in the presence and absence of metabolic activation (S9) at the 4-h and 20-h timepoints. Menthyl acetate (1α,2β,5α) did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2013a). Under the conditions of the study, menthyl acetate (1α,2β,5α) was considered to be non-clastogenic in the *in vitro* micronucleus test and this can be extended to menthyl acetate (isomer unspecified).

Based on the available data, menthyl acetate (1α,2β,5α) does not present a concern for genotoxic potential and this can be extended to menthyl acetate.

Additional References: RIFM, 2013c.

Literature Search and Risk Assessment Completed on: 01/16/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for menthyl acetate (isomer unspecified) 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 menthyl acetate or any of the materials listed under section 1 of the safety assessment. The *in vitro* metabolism study conducted on menthyl acetate with human hepatocytes suggests that menthyl acetate is hydrolyzed to menthol (see section 6). The metabolite, menthol (CAS # 89-78-1), has sufficient repeated dose toxicity data. In an OECD/GLP

407 repeated dose toxicity study, groups of 10 rats/sex/dose were administered *l*-menthol (CAS # 2216-51-5) at doses of 0 (soybean oil), 200, 400 and 800 mg/kg/day. There was an increase in absolute and relative liver weight among all of the treated males and females at ≥400 mg/kg/day as compared to the controls. Histopathological examination revealed vacuolation of the hepatocytes among the treated animals, however, there was no dose-response. The report did not mention the magnitude of liver weight increases among treated the animals, hence, the significance of liver weight alterations could not be determined. OECD SIDS (2003) cites an unpublished report submitted to JECFA that states "no adverse effects on weight gain, excretion of glucuronides, water, or electrolytes, or interference with central nervous system reactions to stimulants were observed when groups of 40 rats of each sex were fed (−)-or (±)-menthol in the diet for 5.5 weeks at doses of 0, 100, or 200 mg/kg bw per day." Based on these observations, the OECD SIDS dossier authors concluded that a NOAEL of 200 mg/kg/day could be determined since no effects on liver were observed during a longer duration dietary study on *l*-menthol (Thorup et al., 1983). In another study, test material, *d*,*l*-menthol (CAS # 1490-04-6), was administered via diet to groups of 10 B6C3F1 mice/sex/dose at concentrations of 0, 930, 1870, 7500 and 15000 ppm. The study was conducted to determine the dietary concentrations for a following 2-year carcinogenicity study. Mortality was reported among the treated animals, however this was not due to test material administration. There was a decrease in body weight gain among the high dose females as compared to the controls. There were reports of increases in the incidences of perivascular lymphoid hyperplasia and interstitial nephritis among the female mice in the 2 high dose groups. Thus, the two concentrations selected for the chronic 2-year study were 2000 and 4000 ppm. A subsequent 2-year carcinogenicity study was conducted on *d*, *l*-menthol in 2% corn oil administered via diet to B6C3F1 mice (50/sex/dose) at concentrations of 0, 2000 or 4000 ppm for 103 weeks followed by a 1-week treatment-free period. There was a significant decrease in the survival among the high dose females, however, there were no reports of test material-related tumors observed among the treated animals. Thus, under the conditions of this study, *d*, *l*-menthol was concluded to be non-carcinogenic for B6C3F1 mice. The NOAEL in mice was considered to be 2000 ppm (equivalent to 300 mg/kg/day, as per the conversion factors for mice, available in the JECFA guidelines for the preparation of toxicological working papers on food additives), based on decreased survival among the high dose females (RIFM, 1979). In another study, groups of 10 Fischer 344 rats/sex/dose were administered test material, *d*,*l*-menthol (CAS # 1490-04-6), via diet in 2% corn oil for 13 weeks at concentrations of 0, 930, 1870, 7500 and 15000 ppm. The study was conducted to determine the dietary concentrations for a subsequent 2-year carcinogenicity study. There were incidences of interstitial nephritis reported among the high dose males. There were no other treatment-related alterations reported during the 13-week treatment. Based on these results, the concentrations for the chronic 2-year study were determined to be 3700 and 7500 ppm *d*,*l*-Menthol in 2% corn oil was administered via diet to Fischer 344 (50/sex/dose) at concentrations of 3700 and 7500 ppm. There were no significant differences in survival rates among the treated animals. Based on the histopathologic examination, *d*,*l*-menthol was neither toxic nor carcinogenic to Fischer 344 rats under the conditions of this study. Thus, the NOAEL was considered to be 7500 ppm or 750 mg/kg/day (using conversion factors for rats, available in the JECFA guidelines for the preparation of toxicological working papers on food additives), the highest dose tested (RIFM, 1979). The most conservative NOAEL of 300 mg/kg/day from the long term 2-year carcinogenicity study in mice was considered for the repeated dose toxicity endpoint. **Therefore, the menthyl acetate (isomer unspecified) MOE is equal to the *d*,*l*-menthol NOAEL in mg/kg/day divided by the total systemic exposure to menthyl acetate (isomer unspecified), 300/0.0021 or 142857.**

In addition, the total systemic exposure to menthyl acetate (isomer unspecified) (2.1 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/3/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for menthyl acetate (isomer unspecified) is adequate for the developmental toxicity endpoint at the current level of use.

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on menthyl acetate or any of the materials listed under section 1 of the safety assessment. The *in vitro* metabolism study conducted on menthyl acetate with human hepatocytes suggests that menthyl acetate is hydrolyzed to menthol (see section 6). The metabolite, menthol has sufficient developmental toxicity data. Menthol (CAS # 89-78-1) has gavage developmental toxicity studies conducted in mice, rats, hamsters and rabbits. Groups of 22–23 pregnant albino CD-1 mice/dose group were administered menthol in corn oil via gavage at doses of 0, 1.85, 8.59, 39.9 and 185 mg/kg/day from day 6 through day 15 of gestation. There were no effects on implantation, maternal or fetal survival among treated animals as compared to the control group up to the highest dose tested (RIFM, 1973b). The NOEL for maternal and developmental toxicity was considered to be 185 mg/kg/day. In another study, groups of 22–25 pregnant Wistar rats/dose group were administered menthol in corn oil via gavage at doses of 0, 2.18, 10.15, 47.05 and 218 mg/kg/day from day 6 through day 15 of gestation. Menthol produced no effects among the treated animals when compared to the control group up to the highest dose tested. The NOEL for maternal and developmental toxicity was considered to be 218 mg/kg/day (RIFM, 1973b). In another study, groups of 21–23 pregnant Syrian hamsters/dose group were administered menthol in corn oil via gavage at doses of 0, 4.05, 21.15, 98.2 and 405 mg/kg/day from day 6 through day 10 of gestation. Menthol produced no effects among the treated animals when compared to the control group up to the highest dose tested. The NOEL for maternal and developmental toxicity was considered to be 405 mg/kg/day (RIFM, 1973b). In another study, groups of 11–14 pregnant rabbits/dose group were administered menthol in corn oil via gavage at doses of 0, 4.25, 19.75, 91.7 and 425 mg/kg/day from day 6 through day 18 of gestation. Mortality was reported among the treated and control animals, however, there was no dose responses and no alterations in clinical signs reported, hence, this finding was not considered to be treatment-related. In addition, no effect on maternal and fetal survival and no dose-related increases in the number of abnormalities in soft or skeletal tissues were observed up to the highest dose tested. Thus, the NOAEL for maternal and developmental toxicity was considered to be 425 mg/kg/day, the highest dosage tested (RIFM, 1973b). The NOAEL for developmental toxicity was determined to be 425 mg/kg/day, the highest dosage tested among the treated rabbits (RIFM, 1973b). **Therefore, the menthyl acetate MOE for the developmental toxicity endpoint is equal to the menthol NOAEL in mg/kg/day divided by the total systemic exposure to menthyl acetate, 425/0.0021 or 202381.**

In addition, the total systemic exposure to menthyl acetate (isomer unspecified) (2.1 μg/kg bw/day) is below the TTC (30 μg/kg bw/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 menthyl acetate or any of the materials listed under section 1 of the safety assessment. The *in vitro*

metabolism study conducted on menthyl acetate with human hepatocytes suggests that menthyl acetate is hydrolyzed to menthol (see Section 6). A dietary 13-weeks study was conducted where test material, *d*, *l*-menthol (isomer unspecified) (CAS # 1490-04-6) was administered to groups of 10 B6C3F1 mice/sex/dose at dietary concentrations of 0, 930, 1870, 7500 and 15000 ppm. There were no changes observed in the histopathological examination of testes, prostate, uterus, ovaries, mammary glands and adrenals in the treated mice at any of the doses administered. In a following 2-year carcinogenicity study, no changes in reproductive organs (testes, prostate, uterus, ovaries, mammary gland and adrenals) were observed in histopathological examinations at concentrations of 2000 or 4000 ppm (RIFM, 1979). Another dietary 13-weeks study was conducted, where the test material *d*, *l*-menthol (isomer unspecified) (CAS # 1490-04-6) was administered to groups of 10 Fischer 344 rats/sex/dose at dietary concentrations of 0, 930, 1870, 7500 and 15000 ppm. There were no changes observed in the histopathological examination of testes, prostate, uterus, ovaries, mammary glands and adrenals in the treated mice at any of the doses administered. In a following 2-year carcinogenicity study, no changes in reproductive organs (testes, prostate, uterus, ovaries, mammary gland and adrenals) were observed in histopathological examinations at concentrations of 3700 and 7500 ppm (RIFM, 1979). However, since there were no sperm analysis or estrous cycling parameters reported in any of the studies conducted, a NOAEL for the reproductive toxicity endpoint could not be determined. The total systemic exposure to menthyl acetate (isomer unspecified) (2.1 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/3/2017.

10.1.4. Skin sensitization

Based on existing data, menthyl acetate (isomer unspecified) does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on existing material-specific data, menthyl acetate (isomer unspecified) does not present a concern for skin sensitization. The chemical structure of this material indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.13; OECD Toolbox v3.4). In the Local Lymph Node Assay (LLNA), menthyl acetate (1α,2β,5α) was considered to be non-sensitizing up to the maximum tested concentration of 100% (ECHA REACH Dossier: menthyl acetate, accessed 1/24/17; RIFM, 2012). Additionally, no reactions indicative of skin sensitization were observed in the human maximization test to menthyl acetate (isomer unspecified) (RIFM, 1972; RIFM, 1973a).

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/24/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, menthyl acetate (isomer unspecified) does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity or photoallergenicity studies available for menthyl acetate (isomer unspecified) in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of significant absorbance in the critical range, menthyl acetate (isomer unspecified) does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/06/14.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, menthyl acetate (isomer unspecified), 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 menthyl acetate (isomer unspecified). Based on the Creme RIFM model, the inhalation exposure is 0.047 mg/day. This exposure is 29.8 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/8/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of menthyl acetate (isomer unspecified) 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 (US EPA, 2012b; 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, menthyl acetate (isomer unspecified) was identified as a fragrance material with 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 menthyl acetate (isomer unspecified) as possibly persistent or 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 EPI Suite v4.11). 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), menthyl acetate (isomer unspecified) presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. CAS # 29066-34-0.

RIFM, 1999: A biodegradation study was conducted according to the “closed bottle method”. After 28 days, biodegradation of 48% was

observed.

10.2.2.1.2. Ecotoxicity. CAS # 29066-34-0.

RIFM, 1999: A *Daphnia magna* acute toxicity study was conducted according to the Council Directive 92/69 EEC C.2 (1992) method. The 48-hr EC0/EC100 was reported to be 9.1 mg/l.

CAS # 89-48-5.

RIFM, 2013b: An algae growth inhibition study was conducted according to the OECD 201 method. The 72-h eC50 based on the growth rate was reported to be 2.7 mg/l.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.228 mg/L			1,000,000	0.00228 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.071 mg/L	1.724 mg/L	0.503 mg/L	10,000	0.0503 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.171mg/L	0.829 mg/L	1.535 mg/L			Neutral Organic
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	6.72 mg/L					
Daphnia		9.1 mg/L				
Algae		2.7 mg/L		1000	2.7 µg/L	

RIFM, 2016a: A 96-h fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The LC50 was reported to be 6.72 mg/l.

10.2.2.2. Other available data. Menthyl acetate (isomer unspecified) has been registered under 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.39	4.39
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10-100*	10-100*
Risk Characterization: PEC/ PNEC	**< 1**	**< 1**

*Combined regional volumes.

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

The RIFM PNEC is 2.7 µg/l. The revised PEC/PNECs for EU and NA: < 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: 03/20/2017.

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.2017.10.014.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.014.

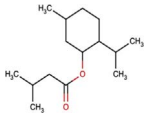
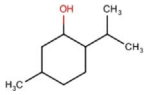
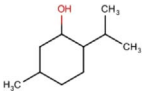
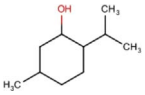
Appendix

Read across justification

Methods

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

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, appropriate read across analogs from the cluster were confirmed by using 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 analog were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- 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 v2.1.7 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 analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material		
Principal Name	Menthyl acetate (isomer unspecified)	Menthol	*l*-Menthol	*d*, *l*-Menthol (isomer unspecified)
CAS No.	16409-45-3	89-78-1	2216-51-5	1490-04-6
Structure				
Similarity (Tanimoto score)		NA[a]	NA[a]	NA[a]
Read across endpoint		• Developmental	• Repeated dose	• Repeated dose • Developmental and reproductive
Molecular Formula	$C_{12}H_{22}O_2$	$C_{10}H_{20}O$	$C_{10}H_{20}O$	$C_{10}H_{20}O$
Molecular Weight	198.31	156.69	156.27	156.27
Melting Point (°C, EPISUITE)	0.67	−5.90	−5.90	−5.90
Boiling Point (°C, EPISUITE)	234.50	218.94	218.94	218.94
Vapor Pressure (Pa @ 25 °C, EPISUITE)	12.2	1.02	1.02	1.02
Log Kow (KOWWIN v1.68 in EPISUITE)	4.00	3.19	3.19	3.19
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	17.13	490	490	490
J_{max} (mg/cm^2/h, SAM)	4.654	45.301	45.301	45.301
Henry's Law (Pa·m^3/mol, Bond Method,	9.90E-004	1.52E-005	1.52E-005	1.52E-005

EPISUITE)				
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 without OH and NH_2 group	• Weak binder without OH group		• Weak binder without OH group
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Toxicant (good reliability)		• Toxicant (good reliability)
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See supplemental data 1 • Moderate binder OH group, Carboxylic acid (hepatotoxicity alert)	See supplemental data 2 • Moderate binder OH group, Valproic acid (hepatotoxicity alert)	See supplemental data 3 • Moderate binder OH group, Valproic acid (hepatotoxicity alert)	See supplemental data 4 • Moderate binder OH group, Valproic acid (hepatotoxicity alert)

NA[a] Metabolites of the target substance.

Summary

There are insufficient toxicity data on menthyl acetate (isomer unspecified) (CAS # 16409-45-3). Hence, *in silico* evaluation was conducted by determining read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, menthol (CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5) and *d*, *l*-menthol (isomer unspecified) (CAS # 1490-04-6) were identified as read across materials with data for their respective toxicological endpoints.

- **Metabolism**

Metabolism of the target substance was not considered for the risk assessment and therefore metabolism data was not reviewed except where it pertains as described in specific endpoint sections above. Metabolism of the target material menthyl acetate (isomer unspecified) (CAS # 16409-45-3) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (see table above). The target substance is predicted to metabolize to menthol (CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5), *d*, *l*-menthol (isomer unspecified) (CAS # 1490-04-6) and acetic acid (CAS # 64-19-7) in the first step with 0.95 probability. Hence, menthol (CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5) and *d*, *l*-menthol (isomer unspecified) (CAS # 1490-04-6) can be used as read across analogs for the target substance. Menthol (CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5) and *d*, *l*-menthol (isomer unspecified) (CAS # 1490-04-6) were out of domain for *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.

Conclusion/Rationale

- Menthol (CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5) and *d*, *l*-menthol (isomer unspecified) (CAS # 1490-04-6) are used as read across analogs for the target menthyl acetate (isomer unspecified) (CAS # 16409-45-3) for the repeated dose, reproductive and developmental toxicity endpoints.
  - The read across analogs are major metabolites of the target substance.
  - Menthyl acetate is an ester of menthol and acetic acid.
  - The structural difference between the target substance and the read across analogs can be mitigated by the fact that the target substance could be rapidly hydrolyzed to the metabolites. Therefore, the toxicity profile of the read across analogs as well as the target substance is expected to be the similar.
  - 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 deemed to be toxicologically insignificant for the repeated dose, and reproductive and developmental toxicity endpoints.
  - Structural alerts for the repeated dose, reproductive and developmental toxicity endpoints are consistent between the target substance and the read across analogs. The read across analogs are predicted to be toxicants for the developmental endpoint with moderate reliability only by the CAESAR model v.2.1.6. The data described in developmental and reproductive endpoint section support that the read across materials are safe at the current level of use for the developmental toxicity endpoint, so this *in silico* prediction will be overridden.
  - The structural alerts for the repeated dose, and reproductive and developmental toxicity endpoints are consistent between the metabolites of the read across analogs and the target substance.

Explanation of Cramer class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? No

Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? No
Q17. Readily hydrolyzed to a common terpene? Yes
Q18. One of the list (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)? No, Class Low (Class I)

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