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Short review

RIFM fragrance ingredient safety assessment, *l*-menthyl lactate, CAS Registry Number 59259-38-0

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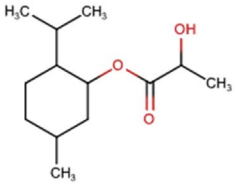
Version: 092617. This version replaces any previous versions.
Name: *l*-Menthyl lactate
CAS Registry Number: 59259-38-0
Additonal CAS Numbers*:
61597-98-6 *l*-Menthyl L-Lactate (no reported use)
17162-29-7 5-Methyl-2-(1-methylethyl)cyclohexyl lactate
*These materials were included because they are a mixture of isomers



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; 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

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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
Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test.
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultraviolet/Visible Spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WOE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 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 (*l*-menthyl lactate) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read-across analog menthyl acetate (1α,2β,5α) (CAS # 89-48-5) show that *l*-menthyl lactate is not genotoxic nor does it have skin sensitization potential. The fertility 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 (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) as a read-across analog, which provided a MOE $>$ 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, *l*-menthyl lactate was found not to be a 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, 2013b; RIFM, 2013a)

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

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

Skin Sensitization: Not sensitizing. (ECHA REACH Dossier: menthyl acetate; RIFM, 2012)

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: 100% (OECD 301) (RIFM, 1991)

Bioaccumulation: Screening Level: 74.19 L/kg (US EPA, 2012a)

Ecotoxicity: Screening Level: 96-hour Algae EC50: 3.125 mg/L (US EPA, 2012a)

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-hour Algae EC50: 3.125 mg/L (US EPA, 2012a)
RIFM PNEC is: 0.3125 µg/L
- Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe: < 1

1. Identification

Chemical Name: *l*-Menthyl lactate	Chemical Name: *l*-Menthyl L-Lactate	Chemical Name: 5-Methyl-2-(1-methylethyl) cyclohexyl lactate
CAS Registry Number: 59259-38-0 **Synonyms:** α-Hydroxypropanoic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester; (−)-p-Menthan-3-yl lactate; (1R-(1a(R),2b,5a))-5-Methyl-2-(1-methylethyl) cyclohexyl lactate; Propanoic acid, 2-hydroxy-, 5-methyl-2-(1-methylethyl) cyclohexyl ester; Covafresh LM; Frescolat Type ML; Frigydil; 2-Hydroxypropanoic acid, 5-methyl-2-(1-methylethyl) cyclohexyl ester; Lactic acid, p-menth-3-yl ester; Menthyl lactate; 乳酸メンチル; 2-Isopropyl-5-methylcyclohexyl 2-hydroxypropanoate; *l*-Menthyl lactate **Molecular Formula:** $C_{13}H_{24}O_3$ **Molecular Weight:** 228.33 **RIFM Number:** 5095	**CAS Registry Number:** 61597-98-6 **Synonyms:** *l*-Menthyl (S)-lactate; *l*-Menthyl L-Lactate; Frescolat ML; Propanoic acid, 2-hydroxy-, (1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl ester, (2S)-; Propanoic acid, 2-hydroxy-, 5-methyl-2-(1-methylethyl) cyclohexyl ester, [1R-[1a(S*),2b,5a]]- **Molecular Formula:** $C_{13}H_{24}O_3$ **Molecular Weight:** 228.33 **RIFM Number:** N/A	**CAS Registry Number:** 17162-29-7 **Synonyms:** 1-Methyl-4-isopropyl-3-(2-hydroxypropionate)cyclohexanol; 5-Methyl-2-(1-methylethyl)cyclohexyl lactate; Frescolat® ML.; Menthyl lactate; Propanoic acid, 2-hydroxy-, 5-methyl-2-(1-methylethyl) cyclohexyl ester; Propanoic acid, 2-hydroxy, menthyl ester **Molecular Formula:** $C_{13}H_{24}O_3$ **Molecular Weight:** 228.33 **RIFM Number:** N/A

2. Physical data*

1. **Boiling Point:** 297.71 °C [US EPA, 2012a]
2. **Flash Point:** 123 °C [GHS Database]
3. **Log K_{OW}:** 3.34 [US EPA, 2012a]
4. **Melting Point**: 47.66 °C [US EPA, 2012a]
5. **Water Solubility:** 141.4 mg/L [US EPA, 2012a]
6. Specific Gravity: Not Available
7. **Vapor Pressure:** 0.0000472 mmHg @ 20 °C [US EPA, 2012a], 9.69e-005 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless liquid to white crystalline solid with weak odor, reminiscent of tobacco and chamomile. Almost tasteless with lasting gentle cooling effect.

*Physical data for both 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: 0.21% (RIFM, 2017b)
3. **Inhalation Exposure*:** 0.000059 mg/kg/day or 0.0044 mg/day (RIFM, 2017a)
4. **Total Systemic Exposure**:** 0.0093 mg/kg/day (RIFM, 2017b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate 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 (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:** Menthyl acetate (1α,2β,5α) (CAS # 89-48-5)
   b. **Repeated Dose Toxicity:** *l*-Menthol (CAS # 2216-51-5); *d,l*-menthol (isomer unspecified; CAS # 1490-04-6)
   c. Reproductive Toxicity: Developmental: Menthol (CAS # 89-78-1)
   d. **Skin Sensitization:** Menthyl acetate (1α,2β,5α) (CAS # 89-48-5)

e. Phototoxicity/Photoallergenicity: None
f. Local Respiratory Toxicity: None
g. Environmental Toxicity: None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

l-Menthyl lactate, *l*-menthyl L-lactate and 5-methyl-2-(1-methylethyl)cyclohexyl lactate are not reported to occur in food by the VCF*.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, 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

l-Menthyl lactate and 5-methyl-2-(1-methylethyl)cyclohexyl lactate are pre-registered for 2010, no dossier available as of 9/21/2017. *l*-Menthyl L-lactate has a dossier available, accessed 4/3/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, *l*-menthyl lactate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. *l*-Menthyl lactate was assessed in the BlueScreen assay and found to be negative for genotoxicity, with and without metabolic activation (RIFM, 2014). There are no studies assessing the mutagenic activity of *l*-menthyl lactate; however, the material menthyl acetate (1α,2β,5α) (CAS # 89-48-5; see Section 5) was identified as a sufficient read-across analog. The mutagenic activity of menthyl acetate (1α,2β,5α) 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 incubated with *l*-menthyl lactate in DMSO (dimethyl sulfoxide) at concentrations up to 120 μg/mL in the presence and absence of metabolic activation (S9) at the 4-hour and 24-hour timepoints. No toxicologically significant increases in the frequency of mutant colonies were observed with any dose of the test item, either with or without metabolic activation (RIFM, 2013b). 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 *l*-menthyl lactate.

There are no studies assessing the clastogenic activity of *l*-menthyl lactate. Again, we can use the read-across material menthyl acetate (1α,2β,5α) which was assessed for clastogenicity in an *in vitro* micronucleus assay conducted in compliance with GLP regulations in accordance with OECD 487. Human peripheral blood lymphocytes (HPBL) were treated incubated 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-hour and 20-hour 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 *l*-menthyl lactate.

Additional References: None.

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

10.1.2. Repeated dose toxicity

The margin of exposure for *l*-menthyl lactate 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 *l*-menthyl lactate. Metabolites, *l*-menthol (CAS # 2216-51-5; see Section 5) and *d,l*-menthol (CAS # 1490-04-6; see Section 5) have sufficient repeated dose toxicity data and can be used as read-across materials. 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 the treated 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 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 *l*-menthyl lactate MOE is equal to the *d,l*-menthol NOAEL in mg/kg/day divided by the total systemic exposure to *l*-menthyl lactate, 300/0.0093 or 32258.

In addition, the total systemic exposure to *l*-menthyl lactate (9.3 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. Reproductive Toxicity

The margin of exposure for *l*-menthyl lactate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on *l*-menthyl lactate or any of the read-across materials. The total systemic exposure to *l*-menthyl lactate is below the TTC for the fertility 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 *l*-menthyl lactate. The metabolite, menthol (CAS # 89-78-1; see Section 5) has sufficient developmental toxicity data and can be used as a read-across material. Menthol 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 the 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 response and no alterations in clinical signs reported, hence this finding was not considered to be treatment-related. In addition, no effects 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 in among the treated rabbits (RIFM, 1973b).

Therefore, the *l*-menthyl lactate MOE is equal to the d,l-menthol NOAEL in mg/kg/day divided by the total systemic exposure to *l*-menthyl lactate, 425/0.0093 or 45699.

In addition, the total systemic exposure to *l*-menthyl lactate (9.3 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 fertility data on *l*-menthyl lactate. A dietary 13-week 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 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-week 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 treated mice at any of the doses administered. In another 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 fertility endpoint could not be determined.

The total systemic exposure to *l*-menthyl lactate (9.3 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility 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 the read-across to menthyl acetate (1α,2β,5α) (CAS # 89-48-5), *l*-menthyl lactate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. No skin sensitization studies are available on *l*-menthyl lactate. Based on read-across to menthyl acetate (1α,2β,5α) (CAS # 89-48-5; see Section 5), *l*-menthyl lactate does not present a concern for skin sensitization. The chemical structures of these materials indicate 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). Based on weight of evidence from menthyl acetate, *l*-menthyl lactate does not present a concern for skin sensitization.

Additional References: None.

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

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *l*-menthyl lactate 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 *l*-menthyl lactate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on lack of absorbance, *l*-menthyl lactate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/10/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, *l*-menthyl lactate, 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 *l*-menthyl lactate. Based on the Creme RIFM model, the inhalation exposure is 0.0044 mg/day. This exposure is 318 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: 4/26/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *l*-menthyl lactate 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, which is considered proprietary information, 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, *l*-menthyl lactate 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 *l*-menthyl lactate 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).

10.2.2. Risk assessment

Based on current Volume of Use (2011), *l*-menthyl lactate presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. For CAS # 17162-29-7.

RIFM, 1991: Ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D guidelines. Biodegradation of 100% was observed after 28 days.

10.2.2.2. Ecotoxicity. For CAS # 17162-29-7.

RIFM, 1991: A *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method under static conditions. The 48-hour EC50 was reported to be greater than 125 mg/L but less than 287 mg/L.

RIFM, 1991: Fish (Zebra Fish) acute toxicity study was conducted according to the OECD 203 method under static conditions. The geometric mean of LC0/LC100 after 96 h was 22 mg/L.

10.2.3. Other available data

l-Menthyl lactate (CAS # 61597-98-6) has been registered under REACH with no additional data.

11. Risk assessment refinement

Since *l*-menthyl lactate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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; #40315).

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	21.02 mg/L			1,000,000		
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	5.040 mg/L	9.078 mg/L	3.125 mg/L	10,000	0.3125 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	11.75 mg/L	7.554 mg/L	9.383 mg/L			Neutral Organic SAR (Baseline Toxicity)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.34	3.34
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1-10*	< 1*
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Combined Regional Volumes for all CAS#.

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

The RIFM PNEC is 0.3125 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: 1/27/2017.

12. 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.2017.11.041.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.11.041.

Appendix

Read-across justification

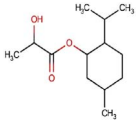
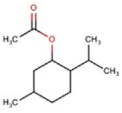
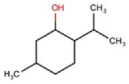
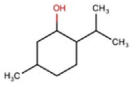
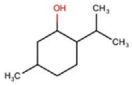
Methods:

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was

examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.

- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read-across analogs were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

Principal Name	Target material	Read-across material			
	l-Menthyl lactate	Menthyl acetate (1α,2β,5α)	Menthol	*l*-Menthol	*d,l*-Menthol (isomer unspecified)
CAS No.	59259-38-0	89-48-5	89-78-1	2216-51-5	1490-04-6
Structure					
Similarity (Tanimoto score)		0.74	NA[a]	NA[a]	NA[a]
Read-across endpoint		• Genotoxicity • Skin sensitization	• Developmental	• Repeated dose	• Repeated dose
Molecular Formula	$C_{13}H_{24}O_3$	$C_{12}H_{22}O_2$	$C_{10}H_{20}O$	$C_{10}H_{20}O$	$C_{10}H_{20}O$
Molecular Weight	228.33	198.31	156.69	156.27	156.27
Melting Point (°C, EPISUITE)	47.66	0.67	−5.90	−5.90	−5.90
Boiling Point (°C, EPISUITE)	297.71	234.50	218.94	218.94	218.94
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.0129	12.2	1.02	1.02	1.02
Log K_{ow} (KOWWIN v1.68 in EPISUITE)	3.34	4.00	3.19	3.19	3.19
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	141.4	17.13	490	490	490
J_{max} (mg/cm^2/h, SAM)	8.908	4.654	45.301	45.301	45.301
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.05E-004	9.90E-004	1.52E-005	1.52E-005	1.52E-005
Genotoxicity					
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• AN2, Schiff base formation • SN1, Nucleophilic attack • SN2, Acylation			
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found			
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-Carcinogen (low reliability)	• Non-Carcinogen (low reliability)			
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	• H-acceptor-path 3-H-acceptor	• No alert found			
Oncologic Classification	• Not classified	• Not classified			
Repeated dose toxicity					
Repeated Dose (HESS)	• Not categorized			• Not categorized	• Not categorized
Reproductive toxicity					
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder without OH and NH_2 group		• Weak binder without OH group		

Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (moderate reliability)		• Toxicant (good reliability)		
Skin Sensitization					
Protein binding by OASIS v1.1	• No alert found	• No alert found			
Protein binding by OECD	• Acylation	• Acylation			
Protein binding potency	• Not possible to classify	• Not possible to classify			
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	See supplemental data 2	See supplemental data 3	See supplemental data 4	See supplemental data 5

NA[a] Metabolites of the target substance.

Summary:

There are insufficient toxicity data on *l*-menthyl lactate (CAS # 59259-38-0). 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, menthyl acetate (1α,2β,5α) (CAS # 89-48-5), 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. Metabolism of the target material *l*-menthyl lactate (CAS # 59259-38-0) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (see table above). The target substance is predicted to be metabolized to menthol (CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5), *d*,*l*-menthol (isomer unspecified) (CAS # 1490-04-6) and lactic acid (CAS # 50-21-5) in the first step with 0.95 pre-calculated 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 use 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:

- Menthyl acetate (1α,2β,5α) (CAS # 89-48-5) could be used as a read-across analog for *l*-menthyl lactate (CAS # 59259-38-0) for the skin senzitization and genotoxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of esters.
  - o The target substance and the read-across analogs all share the menthol core structure.
  - o The key difference between the target substance and the read-across analog is that the target material is a lactic acid whereas the read-across analog is of the group of esters or unesterified menthols.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto scores in the table above. The Tanimoto score is mainly driven by the aliphatic ester fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read-across analog have similar physical-chemical properties. Any differences in the physical-chemical properties of the target substance and the read-across analog are deemed to be toxicologically insignificant for the genotoxicity and skin sensitization endpoints.
  - o Structural alerts for skin sensitization and genotoxicity endpoints are consistent between the target substance and the read-across analog, as seen in the table above. The target substance as well as the read-across analog are predicted to be sensitizers with good reliability by QSAR OECD Toolbox (v3.4). The predictions will be superseded by the available data.
  - o According to OASIS model, the read-across analog has an alert for DNA binding-Schiff base formation and according to ISS model for *in vivo* mutagenicity (micronucleus) the target is predicted to be path-3-H-bond acceptor. No other model shows similar alerts for the target or the read-across analog. The data described in the genotoxicity section show that the read-across analog does not pose a concern for the genotoxicity endpoint. Therefore, these alerts are superseded by the available data.
  - o The target substance and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the skin senzitization and genotoxicity endpoints are consistent between the metabolites of the read-across analog and the target substance.
- 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 *l*-menthyl lactate (CAS # 59259-38-0) for the repeated dose and developmental toxicity endpoints.
  - o The read-across analogs are the major metabolites of the target substance.
  - o *l*-Menthyl lactate is an ester formed by menthol and lactic acid.
  - o The structural difference in 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 analog as well as the target substance is expected to be 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 developmental toxicity endpoints.
- The target substance and the read-across analogs have similar physical-chemical properties, except for the J_{max} values which are higher compared to the target substance, this difference predicts that the read-across analogs will have higher skin absorption than the target substance. Differences in the physical-chemical properties of the target substance and the read-across analogs are estimated to be toxicologically insignificant for the repeated dose and developmental toxicity endpoints.
- Structural alerts for the repeated dose and developmental toxicity endpoints are consistent between the target substance and the read-across analogs, as seen in the table above. The read-across analogs are predicted to be toxicants for the developmental toxicity endpoint with moderate and good reliability by the CAESAR model v.2.1.6. The data described in the developmental toxicity endpoint section demonstrate that the read-across materials are safe at the current level of use for the developmental toxicity endpoint, so these *in silico* predictions are superseded.
- The structural alerts for the repeated dose 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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