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Short review

RIFM fragrance ingredient safety assessment, menthyl isovalerate CAS Registry Number 16409-46-4

A.M. Api [a, *], D. Belsito [b], D. Botelho [a], D. Browne [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], M. Francis [a], A.D. Fryer [h], K. Joshi [a], S. La Cava [a], A. Lapczynski [a], D.C. Liebler [i], D. O'Brien [a], R. Parakhia [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], D. Salvito [a], T.W. Schultz [k], I.G. Sipes [l], Y. Thakkar [a], E.H. Theophilus [a], A.K. Tiethof [a], Y. Tokura [m], S. Tsang [a], J. Wahler [a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo CEP 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996- 4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA*
[m] *Member RIFM Expert Panel, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan*

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* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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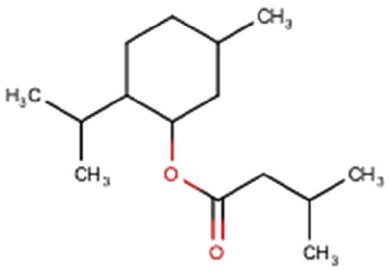


Abbreviation/Definition List:
2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions 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
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.
This material (menthyl isovalerate) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data on the read across analog menthyl acetate (1α,2β,5α) (CAS # 89-48-5) show that this material 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 developmental toxicity endpoint was completed using menthol (CAS # 89-78-1) as a read across analog, which provided a MOE > 100. 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 phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, menthyl isovalerate 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, 2013c; 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)

(*continued on next page*)

(*continued*)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening Level: 2.8 (Biowin 3)	(US EPA, 2012a)
Bioaccumulation: Screening Level: 3054 l/kg	(US EPA, 2012a)
Ecotoxicity: Screening Level: 48-hour *Daphnia magna* LC50: 0.063 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: 48-hour *Daphnia magna* LC50: 0.063 mg/l	(US EPA, 2012a)
RIFM PNEC is: 0.0063 μg/l	
• Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe: <1	

1. Identification

1. **Chemical Name:** Menthyl isovalerate
2. **CAS Registry Number:** 16409-46-4
3. **Synonyms:** Butanoic acid, 3-methyl-, 5-methyl-2-(1-methylethyl)-cyclohexyl ester; 1-Isopropyl-4-methylcyclohex-2-yl 3-methylbutanoate; Menthyl isovalerate; *p*-Menth-3-yl isovalerate; Menthyl isovalerianate; Menthyl isopentanoate; Menthyl 3-methybutanoate; Validol; 2-Isopropyl-5-methylcyclohexyl 3-methylbutanoate
4. **Molecular Formula:** $C_{15}H_{28}O_2$
5. **Molecular Weight:** 240.39
6. **RIFM Number:** 814

2. Physical data

1. **Boiling Point:** 275.72 °C [US EPA, 2012a]
2. **Flash Point:** >93 °C [GHS]
3. **Log K_{OW}:** 5.79 [US EPA, 2012a]
4. **Melting Point**: 22.1 °C [US EPA, 2012a]
5. **Water Solubility:** 0.3057 mg/l [US EPA, 2012a]
6. **Specific Gravity:** 0.90900 @ 25 °C*
7. **Vapor Pressure:** 0.00411 mmHg @ 20 °C [US EPA, 2012a], 0.00674 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 oily liquid with sweet, herbaceous, somewhat balsamic-minty, rose-like odor

*http://www.thegoodscentscompany.com/data/rw1020381.html#tophyp, retrieved 2/9/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Toothpaste:** (no reported use in hydroalcoholics): 0.79% (RIFM, 2016)
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.013 mg/kg/day (RIFM, 2016)

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

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:** Menthol (CAS # 89-78-1); *d,l*-menthol (isomer unspecified; CAS # 1490-04-6)
   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)

Menthyl isovalerate is reported to occur in the following foods*:

Mentha oils
Nutmeg (Myristica fragrans Houtt.)

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. –Version 15.1–Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 8/1/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, menthyl isovalerate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Menthyl isovalerate was assessed in the BlueScreen assay and found negative for both genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013b). There are no data assessing the mutagenic activity of menthyl isovalerate, however, read across can be made to menthyl acetate (1α,2β,5α) (CAS # 89-48-5; see section 5). 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 with menthyl acetate (1α,2β,5α) 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, 2013c). 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 isovalerate.

There are no studies assessing the clastogenic activity of menthyl isovalerate. Again we can use the read across structural analog 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 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 isovalerate.

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 isovalerate.

Additional References: None.

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

10.1.2. Repeated dose toxicity

The margin of exposure for menthyl isovalerate 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 isovalerate. Hydrolysis product, *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. 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 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 cites an unpublished report submitted to JECFA (World Health Organisation (WHO), 1999) 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 15,000 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 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 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 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 15,000 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 menthyl isovalerate MOE is equal to the *d,l*-menthol NOAEL in mg/kg/day divided by the total systemic exposure to menthyl isovalerate, 300/0.013 or 23076.**

In addition, the total systemic exposure to menthyl isovalerate (13 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 menthyl isovalerate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on menthyl isovalerate or any of the read across materials. The total systemic exposure to menthyl isovalerate 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 menthyl isovalerate. The hydrolysis product, menthol (CAS # 89-78-1; see section 5) has sufficient developmental toxicity data. 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 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 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 in among treated rabbits (RIFM, 1973b). **Therefore, the menthyl isovalerate MOE for the developmental toxicity endpoint is equal to the menthol NOAEL in mg/kg/day divided by the total systemic exposure to menthyl isovalerate, 425/0.013 or 32692.**

In addition, the total systemic exposure to menthyl isovalerate (13 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and 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 menthyl isovalerate. 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 15,000 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 the 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 15,000 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 the 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 menthyl isovalerate (13 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and 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 existing data and read across to menthyl acetate (1α,2β,5α) (CAS # 89-48-5), menthyl isovalerate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available on menthyl isovalerate. Based on read across to menthyl acetate (1α,2β,5α) (CAS # 89-48-5), menthyl isovalerate 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 isovalerate or menthyl acetate (isomer unspecified) (RIFM, 1976; RIFM, 1972; RIFM, 1973a). Based on weight of evidence and read across to l-menthyl acetate, menthyl isovalerate 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, menthyl isovalerate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity or photoallergenicity studies available for menthyl isovalerate 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 · cm-1 (Henry et al., 2009). Based on lack of absorbance, menthyl isovalerate 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, menthyl isovalerate, 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 isovalerate. Based on the Creme RIFM model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14,000 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: 2/9/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of menthyl isovalerate 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, menthyl isovalerate 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) identified menthyl isovalerate as possibly persistent but not 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), menthyl isovalerate presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Menthyl isovalerate has been preregistered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.196 mg/L			1,000,000	0.000196 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.198 mg/L	0.274 mg/L	0.064 mg/L			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.079 mg/L	0.063 mg/L	0.2 mg/L	10,000	0.0063 µg/L	Neutral Organic SAR (Baseline Toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.79	5.79
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0063 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.

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 https://doi.org/10.1016/j.fct.2017.09.035.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2017.09.035.

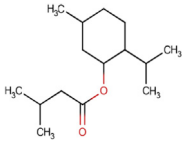
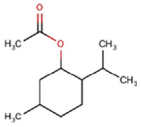
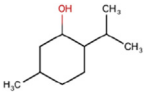
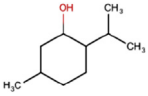
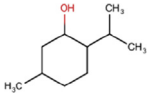
Appendix

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 isovalerate	Menthyl acetate (1α,2β,5α)	Menthol	*l*-Menthol	*d,l*-Menthol (isomer unspecified)
CAS No.	16409-46-4	89-48-5	89-78-1	2216-51-5	1490-04-6
Structure					
Similarity (Tanimoto score)		0.69	NA[a]	NA[a]	NA[a]
Read across endpoint		• Genotoxicity		• Repeated dose	• Repeated dose

(*continued*)

	Target material	Read across material			
		• Skin sensitization	• Developmental and reproductive		• Developmental and reproductive
Molecular Formula	$C_{15}H_{28}O_2$	$C_{12}H_{22}O_2$	$C_{10}H_{20}O$	$C_{10}H_{20}O$	$C_{10}H_{20}O$
Molecular Weight	240.39	198.31	156.69	156.27	156.27
Melting Point (°C, EPISUITE)	22.10	0.67	−5.90	−5.90	−5.90
Boiling Point (°C, EPISUITE)	275.72	234.50	218.94	218.94	218.94
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.899	12.2	1.02	1.02	1.02
Log Kow (KOWWIN v1.68 in EPISUITE)	5.79	4.00	3.19	3.19	3.19
Water Solubility (mg/l, @ 25 °C, WSKOW v1.42 in EPISUITE)	0.3057	17.13	490	490	490
J_{max} (mg/cm^2/h, SAM)	24.892	4.654	45.301	45.301	45.301
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.32E-003	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 (genotox and non-genotox) 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	• No alert found	• No alert found			
Oncologic Classification	• Not classified	• Not classified			
Repeated dose toxicity					
Repeated Dose (HESS)	• Not categorized			• Not categorized	• Not categorized
Reproductive and developmental toxicity					
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder 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 (moderate reliability)		• Toxicant (good reliability)		• Toxicant (good reliability)
Skin Sensitization					
Protein binding by OASIS v1.4	• 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 v1.4	• 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 menthyl isovalerate (CAS # 16409-46-4). 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, analogs 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 menthyl isovalerate (CAS # 16409-46-4) 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 isovaleric acid (CAS # 503-74-2) 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 materials 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* rat 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) is used as a structurally similar read across analog for menthyl isovalerate (CAS # 16409-46-4) for the skin senzitization and genotoxicity endpoints.
  - The target substance and the read across analog are structurally similar and belong to the structural class of esters.
  - The target substance and the read across analog have a substituted cyclohexyl fragment on the alcohol portion in common.
  - The key difference between the target substance and the read across analog is that the target breaks down to isovaleric acid while the read across breaks down to acetic acid. The differences in structure between the target substance and the read across analog do not raise additional structural alerts, so the structural differences are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analog have a Tanimoto score as mentioned in the above table. 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.
  - The target substance and the read across analog have similar physical-chemical properties. Any differences in some of the physical-chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the skin senzitization and genotoxicity endpoints.
  - Structural alerts for the skin senzitization and genotoxicity endpoints are consistent between the target substance and the read across analog as seen in the table above. The target substance and the read across analog are predicted to be sensitizers with good reliability by QSAR OECD Toolbox (v3.4). The predictions will be overridden in the case of availability of data. In addition, according to QSAR OECD Toolbox (v3.4), the read across analog is predicted to have DNA binding alerts, so according to these predictions, the read across analog is expected to be more reactive compared to the target substance. This prediction could be overridden based on the available data for the read across analog.
  - The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - The structural alerts for the skin senzitization and genotoxicity endpoints are consistent between the metabolites of the read across analog and the target substance.
  - The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant.
- Menthol (CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5) and *d, l*-menthol (isomer unspecified) (CAS # 1490-04-6) are used as structurally similar read across analogs for the target, menthyl isovalerate (CAS # 16409-46-4), for the repeated dose, reproductive and developmental toxicity endpoints.
  - The read across analogs are major metabolites of the target substance.
  - Menthyl isovalerate is an ester formed by menthol and isovaleric acid.
  - 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 metabolite. Therefore, the toxicity profile of the read across analogs 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, 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 as seen in the table above. The read across analogs are predicted to be toxicants for the developmental endpoint with moderate and good reliability by only 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 these *in silico* predictions will be overridden.
  - The structural alerts for the repeated dose, reproductive and developmental toxicity endpoints are consistent between the metabolites and the target substance.
  - The structural differences between the target substance and the read across analogs are deemed to be toxicologically insignificant.

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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