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RIFM fragrance ingredient safety assessment, menthol, CAS Registry Number 89-78-1

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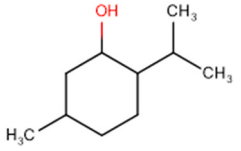
Version: 011722. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: Menthol
CAS Registry Number: 89-78-1
Additional CAS Numbers*:
15356-60-2 *d*-Menthol
3623-51-6 dl-Neomenthol
1490-04-6 *d,l*-Menthol (isomer unspecified)
2216-51-5 *l*-Menthol
15356-70-4 Menthol racemic
2216-52-6 (+)-Neomenthol

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*Included because the materials are 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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding

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DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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Summary: The existing information supports the use of this material as described in this safety assessment.

Menthol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that menthol is not genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints, and show that there are no safety concerns for menthol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; menthol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to menthol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; menthol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2018e; ECHA REACH Dossier: Menthol; ECHA, 2011b)
Repeated Dose Toxicity: 300 mg/kg/day.	(National Cancer Institute, 1979)
Reproductive Toxicity: Developmental toxicity NOAEL: 419 mg/kg/day. Fertility NOAEL: 419 mg/kg/day.	(ECHA REACH Dossier: Menthol; ECHA, 2011b)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 1995; RIFM, 2018g; RIFM, 2018c; RIFM, 1990a; RIFM, 1974b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 100% (Method C.4-B) for CAS # 2216-51-5	RIFM (1992b)
Bioaccumulation:	
Critical Measured Value: BCF: ≥ 0.5 - ≤ 15 (OECD 305) for CAS # 89-78-1	(ECHA REACH Dossier: Menthol; ECHA, 2011b)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 72-h Algae EbC50: 9.8 mg/L for CAS # 89-78-1	RIFM (2000)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 72-h Algae EbC50: 9.8 mg/L for CAS # 89-78-1	RIFM (2000)

RIFM PNEC is: 9.8 μg/L

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

1. Identification

Chemical Name: Menthol

CAS Registry Number: 89-78-1
Synonyms: Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1α,2β,5α)-; 5-Methyl-2-(1-methylethyl)cyclohexanol; 3-Hydroxy-p-menthane; p-Methan-3-ol; p-メンタン-1 (3,4,又は8) オール; p-isdメンタン-1-(3, 4-又は 8-)オール; 2-Isopropyl-5-methylcyclohexanol; Menthol Rac; Menthol Iso Rac; Reaction mass of (1S, 2R, 5R)-rel-5-methyl-2-(1-methylethyl)- cyclohexan-1-oland DL-Menth; Menthol

Chemical Name: Menthol racemic

CAS Registry Number: 15356-70-4
Synonyms: p-Methan-3-ol; 1-Methyl-4-isopropylcyclohexan-3-ol; 2-Isopropyl-5-methylcyclohexanol; 3-p-Menthanol; 3-Hydroxy-p-menthane; 5-Methyl-2-(1-methylethyl)cyclohexanol; 5-Methyl-2-isopropylcyclohexanol; 5-Methyl-2-isopropylhexahydrophenol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1α,2β,5α)-(±); *dl*-Menthol; Menthol racemic

Chemical Name: *l*-Menthol

CAS Registry Number: 2216-51-5
Synonyms: *l*-3-p-Menthanol; *l*-4-Isopropyl-1-methylcyclohexan-3-ol; *l*-Menthol; p-Methan-3-ol; 2-Isopropyl-5-methylcyclohexanol; 3-Hydroxy-p-menthane; 5-Methyl-2-(1-methylethyl) cyclohexanol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1.α.,2β,5.α.)]-; Menthol L Dest; Menthol L Komp.; Menthol Laevo Std; Menthol Nat; p-メンタン-1-(3, 4-又は 8-)オール

Chemical Name: *d,l*-Menthol (isomer unspecified)
CAS Registry Number: 1490-04-6
Synonyms: p-Menthan-3-ol; p-Methan-3-ol; 2-Isopropyl-5-methylcyclohexanol; 3-Hydroxy-p-menthane; 5-Methyl-2-(1-methylethyl)cyclohexanol; AEC Menthol Crystals BP; AEC Menthol Crystals *dl*-Racemic; Cyclohexanol, 5-methyl-2-(1-methylethyl)-; *d,l*-Menthol (isomer unspecified); Fancol Menthol; Jeen Menthol Racemic USP; Menthol Crystals; Menthol Fluessig; Menthyl

(*continued on next page*)

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Molecular Formula: $C_{10}H_{20}O$ **Molecular Weight:** 156.69 g/mol **RIFM Number:** 5425 **Stereochemistry:** 1α,2β,5 α)-(±) Isomer specified. Three stereocenters present, and a total of 8 stereoisomers possible.	**Molecular Formula:** $C_{10}H_{20}O$ **Molecular Weight:** 156.69 g/mol **RIFM Number:** 368 **Stereochemistry:** 1α,2β,5α isomer specified. Three stereocenters present, and a total of 8 stereoisomers possible.	**Molecular Formula:** $C_{10}H_{20}O$ **Molecular Weight:** 156.69 g/mol **RIFM Number:** 599 **Stereochemistry:** 1α,2β,5α isomer specified. Three stereocenters present, and a total of 8 stereoisomers possible.	alcohol; p-メンタン-1-(3,4-又は 8-)オール; Unichem MENT **Molecular Formula:** $C_{10}H_{20}O$ **Molecular Weight:** 156.69 g mol **RIFM Number:** 5247 **Stereochemistry:** Isomer not specified. Three stereocenters present, and a total of 8 stereoisomers possible.
Chemical Name: *dl*-Neomenthol **CAS Registry Number:** 3623-51-6 **Synonyms:** (+/−)-Neomenthol (racemic); *dl*-Neomenthol; 2-Isopropyl-5-methylcyclohexanol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1α,2α,5β)-(+/−)-; Menthol neo rac.	**Chemical Name:** *d*-Menthol **CAS Registry Number:** 15356-60-2 **Synonyms:** (+)-Menthol; *d*-Menthol; p-Methan-3-ol; 2-Isopropyl-5-methylcyclohexanol; 3-Hydroxy-p-menthane; 5-Methyl-2-(1-methylethyl)cyclohexanol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1.α.,2β,5.α.)]-; Menthol D (NG)	**Chemical Name**: Neomenthol **CAS Registry Number:** 491-01-0 **Synonyms:** 2-Isopropyl-5-methylcyclohexanol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1α,2α,5β)-; Menthol, *trans*-1,3,*trans*-1,4-; neomenthol; Neomenthol	**Chemical Name:** (+)-Neomenthol **CAS Registry Number:** 2216-52-6 **Synonyms:** (+)-neomenthol; (+)-Neomenthol; (1S,2S,5R)-Neomenthol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1S,2S,5R); *D*-NeoMenthol
Molecular Formula: $C_{10}H_{20}O$ **Molecular Weight:** 156.69 g/mol **RIFM Number:** 5301 **Stereochemistry:** 1α,2α,5β)-(±) Isomer specified. Three stereocenters present, and a total of 8 stereoisomers possible.	**Molecular Formula:** $C_{10}H_{20}O$ **Molecular Weight:** 156.69 g/mol **RIFM Number:** 5424 **Stereochemistry:** 1.α.,2β,5.α. isomer specified. Three stereocenters present, and a total of 8 stereoisomers possible.	**Molecular Formula:** $C_{10}H_{20}O$ **Molecular Weight:** 156.27 g/mol **RIFM Number:** None **Stereochemistry:** 1α,2α,5β isomer specified. Three stereocenters present, and a total of 8 stereoisomers possible.	**Molecular Formula:** $C_{10}H_{20}O$ **Molecular Weight:** 156.26 g/mol **RIFM Number:** 7372 **Stereochemistry:** 1S,2S,5R isomer specified. Three stereocenters present, and a total of 8 stereoisomers possible.

2. Physical data*

1. **Boiling Point:** 218.94 °C (EPI Suite), 214.5 °C corrected to 1013 hPa (RIFM, 2018a)
2. **Flash Point:** 92 °C (RIFM, 2010b), 92 °C (Globally Harmonized System), 95.5 °C (corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2018b)
3. **Log K_{OW}:** 3.16 at 25 °C (RIFM, 2010a), 3.31 (Abraham and Rafols, 1995), 3.38 (EPI Suite), 3.02 and 3.32 (2 peaks) (RIFM, 2018d)
4. **Melting Point**: 43 °C (Mentha and Allied Products Ltd.), −5.9 °C (EPI Suite), 37.3 °C at 985 hPa (RIFM, 2018a)
5. **Water Solubility:** 434.5 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0041 mm Hg at 20 °C (EPI Suite v4.0), 0.00767 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L • mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Crystalline solid

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

3. Volume of use (Worldwide band)

1. >1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.05% (RIFM, 2020)
2. **Inhalation Exposure**:** 0.00031 mg/kg/day or 0.023 mg/day (RIFM, 2020)
3. **Total Systemic Exposure***:** 0.035 mg/kg/day (RIFM, 2020)

*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 fine fragrance, inhalation exposure, and total exposure.

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

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** 100%

Hotchkiss (1998): An *in vitro* skin penetration study was conducted with radiolabeled stereoisomer *l*-menthol using rat skin. The skin was either occluded with a Teflon cap or left open to the atmosphere. The absorption through the skin at 48 h was 1% (unoccluded) and 3% (occluded).

2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
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2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification:** None

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurence

Menthol is reported to occur in the following foods by the VCF*:
Acerola (*Malpighia*)
Avocado (*Persea americana* Mill.)
Buchu oil.
Cabbage (*Brassica oleracea*)
Calamus (sweet flag) (*Acorus calamus* L.)
Camomile.
Cherimoya (*Annona cherimolia* Mill.)
Citrus fruits.
Cocoa category.
Coriander leaf (*Coriandrum sativum* L.)
Dill (*Anethum* species)
Egg.
Elderberry (*Sambucus nigra* L.)
Fennel (*Foeniculum vulg.,* ssp. *capillaceum*; var.)
Guava and feyoa
Honey.
Juniperus communis.
Lemon balm (*Melissa officinalis* L.)
Lemon grass oil.
Litchi (*Litchi chinensis* Sonn.)
Mangifera species.
Melon.
Mentha oils.
Ocimum species.
Olive (*Olea europaea*)
Pineapple (*Ananas comosus*)
Raspberry, blackberry, and boysenberry.
Rice (*Oryza sativa* L.)
Rum.
Sweetgrass oil (*Hierochloe odorata*)
Tea.
Thyme (*Thymus* species)
Vaccinium species

l-Menthol is reported to occur in the following foods* and in some natural complex substances by the VCF:
Clam.
Mangifera species.
Mentha oils

dl-Neomenthol is reported to occur in the following foods by the VCF*:
Buchu oil.
Cabbage (*Brassica oleracea*)
Mentha oils.

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

9. REACH dossier

Menthol, *l*-menthol, *d,l*-menthol (isomer unspecified), *d*-menthol, and *dl*-neomenthol have dossiers available; accessed on 06/18/21. Menthol racemic, neomenthol, and (+)-neomenthol are pre-registered for 2010; no dossiers available as of 06/18/21.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, menthol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of menthol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with menthol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2018e). Under the conditions of the study, menthol was not mutagenic in the Ames test.

The clastogenicity of menthol was assessed in an *in vitro* chromosome aberration study. Chinese hamster ovary cells were treated with menthol at concentrations up to 5 mg/mL (5000 μg/mL) in the presence and absence of metabolic activation (solvent not specified). No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2011b). Under the conditions of the study, menthol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, menthol does not present a concern for genotoxic potential.

Additional References: Shelby et al., 1993; Ivett et al., 1989; Murthy et al., 1991; Tennant et al., 1987; ECHA, 2011b.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for menthol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on menthol. In an OECD 407/GLP repeated dose toxicity study, groups of 10 rats/sex/dose were administered *l*-menthol (CAS # 2216-51-5) via gavage 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 concentrations ≥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 pattern. The report did not mention the magnitude of liver weight increases among treated animals; hence, the significance of liver weight alterations could not be determined. The OECD (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 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 the 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 bodyweight 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 2 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 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 (National Cancer Institute, 1979).

In another study, groups of 10 Fischer 344 rats/sex/dose were administered test material, *d,l*-menthol (CAS # 1490-04-6), via diet in 2% corn oil for 13 weeks at concentrations of 0, 930, 1870, 7500, and 15000 ppm. The study was conducted to determine the dietary concentrations for a subsequent 2-year carcinogenicity study. There were incidences of interstitial nephritis reported among the high-dose males. There were no other treatment-related alterations reported during the 13-week treatment. Based on these results, the concentrations for the chronic 2-year study were determined to be 3700 and 7500 ppm. *d,l*-Menthol in 2% corn oil was administered via diet to Fischer 344 (50/sex/dose) at concentrations of 3700 and 7500 ppm. There were no significant differences in survival rates among the treated animals. Based on the histopathologic examination, *d,l*-menthol was neither toxic nor carcinogenic to Fischer 344 rats under the conditions of this study. Thus, the NOAEL was considered to be 7500 ppm or 750 mg/kg/day (using conversion factors for rats, available in the JECFA guidelines for the preparation of toxicological working papers on food additives), the highest dose tested (National Cancer Institute, 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 menthol MOE for the repeated dose toxicity endpoint can be calculated by dividing the *d,l*-menthol NOAEL in mg/kg/day by the total systemic exposure to menthol, 300/0.035 or 8571.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.3. Reproductive toxicity

The MOE for menthol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on menthol. Menthol (CAS # 89-78-1) has gavage developmental toxicity studies conducted in mice, rats, hamsters, and rabbits. Groups of 22–23 pregnant albino CD-1 mice/dose group were administered menthol in corn oil via gavage at doses of 0, 1.85, 8.59, 39.9, and 185 mg/kg/day from day 6 through day 15 of gestation. There were no effects on implantation, maternal or fetal survival among treated animals as compared to the control group up to the highest dose tested (FDA, 1973). 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 (FDA, 1973). 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 (FDA, 1973). 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 were no dose responses and no alterations in clinical signs reported; hence, this finding was not considered to be treatment-related. In addition, no effect on maternal and fetal survival and no dose-related increases in the number of abnormalities in soft or skeletal tissues were observed up to the highest dose tested. Thus, the NOAEL for maternal and developmental toxicity was considered to be 425 mg/kg/day, the highest dosage tested (FDA, 1973k). The NOAEL for developmental toxicity was determined to be 425 mg/kg/day, the highest dosage tested among the treated rabbits (FDA, 1973).

Further, an OECD 443/GLP Extended One-Generation Reproductive Toxicity (EOGRT) study with F2 generation extension was conducted in Sprague Dawley rats, groups of 25 rats/sex/dose were administered *d,l*-menthol (CAS # 1490-04-6), in diet at concentrations 0, 4000, 8000 or 16000 ppm (equivalent to 203–247, 419–499, and 837–1016 mg/kg/day in males and 229–300, 455–594 and 892–1205 mg/kg/day). Male rats received *d,l*-menthol orally via the diet for 10 weeks before pairing and until termination. Female rats received *d,l*-menthol orally via the diet for 10 weeks before pairing, throughout pairing and gestation, and during lactation. In the F1 generation, 40 males and 40 females were treated from weaning to their scheduled termination (relevant to each cohort). There was no treatment-related mortality observed in F0 and F1 generations. In F1 and F2 generations, offspring growth was reduced from day 4 of age to weaning in the high-dose litters (absolute body weight on day 21 of age being 17–18% lower than control). The extent of the reduction in offspring growth in the high-dose group in both generations was considered to be adverse. There was no adverse effect on F1 or F2 offspring birth weight, ano-genital distance, sex ratio, survival from day 1 of age to weaning. Thus, the NOAEL for developmental toxicity was considered to be 8000 ppm (equivalent to 419 mg/kg/day) based on reduced offspring weight in F1 and F2 generation at the highest dose (ECHA, 2011b).

The NOAEL for OECD 443 (419 mg/kg/day) was considered for the safety assessment. **Therefore, the menthol MOE for the developmental toxicity endpoint can be calculated by dividing the menthol NOAEL in mg/kg/day by the total systemic exposure to menthol, 419/0.035, or 11971.**

There are sufficient fertility data on menthol. A dietary 13-week study was conducted where test material, *d,l*-menthol (CAS # 1490-04-6; isomer unspecified), was administered to groups of 10 B6C3F1 mice/sex/dose at dietary concentrations of 0, 930, 1870, 7500, and 15000 ppm. There were no changes observed in the histopathological examination of testes, prostate, uterus, ovaries, mammary glands, and adrenals in the treated mice at any of the doses administered. In a following 2-year carcinogenicity study, no changes in reproductive organs (testes, prostate, uterus, ovaries, mammary gland, and adrenals) were observed in histopathological examinations at concentrations of 2000 or 4000 ppm (National Cancer Institute, 1979). Another dietary 13-week study was conducted, where the test material *d,l*-menthol (CAS # 1490-04-6; isomer unspecified) was administered to groups of 10

Fischer 344 rats/sex/dose at dietary concentrations of 0, 930, 1870, 7500, and 15000 ppm. There were no changes observed in the histopathological examination of testes, prostate, uterus, ovaries, mammary glands, and adrenals in the treated mice at any of the doses administered. In a following 2-year carcinogenicity study, no changes in reproductive organs (testes, prostate, uterus, ovaries, mammary gland, and adrenals) were observed in histopathological examinations at concentrations of 3700 and 7500 ppm (National Cancer Institute, 1979). However, since there were no sperm analysis or estrous cycling parameters reported in any of the studies conducted, a NOAEL for the reproductive toxicity endpoint could not be determined.

Further, an OECD 443/GLP EOGRT study with F2 generation extension was conducted in Sprague Dawley rats, groups of 25 rats/sex/dose were administered *d,l*-menthol (CAS # 1490-04-6), in diet at concentrations 0, 4000, 8000, or 16000 ppm (equivalent to 203–247, 419–499, and 837–1016 mg/kg/day in males and 229–300, 455–594 and 892–1205 mg/kg/day). No test material-related changes in general clinical condition, and estrous cycle regularity pre-coital interval, mating performance, conception rate, and fertility index were observed. Similarly, there was no treatment-related effect on the hematological parameters in F0 and F1 animals or sperm motility/counts/morphology of the F0 and F1 males. The macroscopic examination did not reveal any treatment-related abnormalities. There was no adverse effect on F1 or F2 offspring birth weight, ano-genital distance, sex ratio, survival from day 1 of age to weaning. When compared to controls, for F1 litters in the high-dose group, the mean number of uterine implantation sites was statistically significantly low, resulting in a lower total number of offspring born and subsequently live offspring on Day 1 and Day 4 of age. In addition, mean values of litter size in the high-dose F1 and F2 litters were lower than all other study groups in both generations. The lower number of uterine implantation sites and subsequently small litter size in the high-dose group in both F0 and F1 generations were considered treatment-related and adverse (ECHA, 2011b).

The NOAEL for fertility was considered to be 8000 ppm (419 mg/kg/day), based on the lower number of uterine implantation sites and subsequently small litter size in the high-dose group in both F0 and F1 generations.

Therefore, the menthol MOE for the fertility endpoint can be calculated by dividing the menthol NOAEL in mg/kg/day by the total systemic exposure to menthol, 419/0.035, or 11971.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.4. Skin sensitization

Based on the existing data on menthol and menthol isomers (*l*-menthol CAS # 2216-51-5; *d*-menthol CAS # 15356-60-2; menthol racemic CAS # 15356-70-4), menthol does not present a concern for skin sensitization under the current declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data on menthol and menthol isomers (*l*-menthol (CAS # 2216-51-5); *d*-menthol (CAS # 15356-60-2); menthol racemic (CAS # 15356-70-4); and *dl*-isomenthol (CAS # 3623-52-7)), menthol does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2; Toxtree v3.1.0). *dl*-Isomenthol was found to be negative in an *in vitro* KeratinoSens and human cell line activation test (h-CLAT) (RIFM, 2018g; RIFM, 2018c). In a murine local lymph node assay (LLNA), *l*-menthol was not sensitizing up to the highest tested concentration of 30% (7500 μg/cm^2) (RIFM, 1995). In guinea pig sensitization tests, including a Buehler test and an open epicutaneous test, no reactions indicative of sensitization were observed with *l*-menthol and menthol isomers (Brazilian, racemic, *l*-menthol, *d*-menthol) (RIFM, 1990a; RIFM, 1974b). In another guinea pig study conducted according to the modified Draize procedure, a positive response was reported for *l*-menthol only after the same animals were re-tested utilizing the full induction and challenge procedure (Sharp, 1978). This result is not considered to be of significance as the test was not conducted on naïve animals (Sharp, 1978; ECHA, 2011a). Furthermore, in 2 separate human maximization tests, no skin sensitization reactions were observed when conducted using 8% (5520 μg/cm^2) concentration of *l*-menthol and menthol racemic, respectively (RIFM, 1974a; RIFM, 1973).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, menthol does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: Valosen et al., 1999; Ishihara et al., 1986; Xu et al., 2006; Friedrich et al., 2007.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, menthol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for menthol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, menthol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV Spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L • mol-^{1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for menthol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on menthol. Based on the Creme RIFM Model, the inhalation exposure is 0.023 mg/day. This exposure is 60.9 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: Perrucci (1995a); Perrucci et al., 1995b; Robin et al., 1998; Pinching and Doving, 1974; Nishino et al., 1997; Ishizuka et al., 1997; DeCort et al., 1993; Shimizu et al., 2008; Freund et al., 2011; Wise et al., 2012; Boyd and Sheppard, 1969; Luke (1962); Price (1977); O'Mullane et al., 1982; Rakieten et al., 1954; Highstein and Zeligman, 1951; Kowalski et al., 1962; Melis et al., 1989; Burrow et al., 1983; Cohen and Dressler, 1982; Duchamp (1982); Revial et al., 1982; Miyazaki et al., 1992; Laude et al., 1994; Tamaoki et al., 1995; Tamaoki et al., 1996; Rice, 1994a; Willis et al., 2011; Perrucci (1995); Clark et al., 1996; Wright et al., 1997; Friedman et al., 1998; Silver (1992); Ellis and Baxendale, 1997; Rice, 1994b; Ilmberger et al., 2001; Bensafi et al., 2002; Pickworth et al., 2000; Benowitz et al., 2004; Morice et al., 1994; Eccles, 1983; Gonzalez-Mangado et al., 1995.

Literature Search and Risk Assessment Completed On: 06/21/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of menthol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, menthol 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 menthol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), menthol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. **For CAS # 89–78–1.**

RIFM, 2018f: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 79% was observed after 18 days.

For CAS # 2216–51–5.

RIFM, 1992b: Biodegradation of the test material was evaluated in the ready test according to the Directive 79/831 EEC, Annex V, Part C, Method C.4-B: modified OECD screening test guidelines. After 28 days, biodegradation of 100% was observed.

RIFM, 2003a: A 28-day biodegradation study was conducted using activated sludge in a closed bottle test according to the OECD 301D method. At the end of the incubation period, biodegradation of 93% and 79% was observed with 0.84 mg/L and 2.0 mg/L of menthol, respectively.

RIFM, 1997: A biodegradation study was conducted using activated sludge in a sealed vessel test CO_2 production test using an acclimatized inoculum from a modified semi-continuous activated sludge test. The average extent of mineralization of the test material in the sealed vessel test was 93.1%.

For CAS # 15356–60–2.

RIFM, 2003b: A biodegradation study was conducted using activated sludge in a closed bottle test according to the OECD 301D guidelines. Maximum biodegradation of 92% and 76% was reached with 0.84 mg/L and 2.01 mg/L of *d*-menthol, respectively.

11.2.3.2. Ecotoxicity. **For CAS # 89–78–1.**

RIFM, 1990c: A 48-h *Daphnia magna* acute toxicity test with menthol was conducted according to the OECD 202 guidelines. The EC50 was reported to be 44.3 mg/L.

RIFM, 1990b: A 96-h acute fish (*Brachydanio rerio*) acute toxicity test was conducted according to the OECD 203 guidelines under static conditions. The calculated LC50 was reported to be 22.3 mg/L based on nominal test concentration.

RIFM, 2000: A 72-h algae inhibition test was conducted according to the "Algal growth inhibition test" Council Directive EEC 92/69/EEC C.3 method under static conditions. Under the test conditions, the EbC50 and ErC50 were both >9.8 and < 18.2 mg/L, and the NOEC was 4.6 mg/L, based on the nominal concentration.

For CAS # 2216–51–5.

RIFM, 1992a: A 96-h acute fish (*Brachydanio rerio*) acute toxicity test was conducted according to the "Acute Toxicity for Fish" (C.1) Directive 67/548/EEC method, under static conditions. The calculated LC50 (geometric mean of LC0/LC100) was reported to be 15.5 mg/L.

RIFM, 2002b: A 48-h *Daphnia magna* acute toxicity test with *l*-menthol was conducted according to the OECD 202 guidelines, under static conditions. The EC50 was reported to be 26.6 mg/L.

RIFM, 2002a: A 72-h algae inhibition test was conducted according to the OECD 201 method under static conditions. Under the test conditions, the 72-h NOEC was 9.65 mg/L, and the EbC50 and ErC50 were 20 and 21.4 mg/L, respectively, based on mean measured concentration.

11.2.4. Other available data

Menthol (CAS # 89-78-1) has been registered under REACH, and the following additional data are available at this time (ECHA, 2011b):

In a flow-through bioaccumulation study, corresponding to OECD Guideline 305C, a BCF of <0.5–15 at 0.2 mg/L test concentration and <4.6–11 at 0.02 mg/L test concentration for *dl*-menthol was determined with *Cyprinus carpio* as test organism (15–20 animals/concentration) within 6 weeks.

11.2.5. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	20.6			1000000	0.0206	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	7.379	4.760	6.008	10000	0.476	Neutral organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	15.5					
Daphnia		26.6				
Algae		9.8		1000	9.8	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.16	3.16
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	>1000	>1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Regional Volume of Use combined for all CAS #

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

The RIFM PNEC is 9.8 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/18/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/17/22.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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