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RIFM fragrance ingredient safety assessment, 1-menthyl methylether, CAS Registry Number 1565-76-0

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, 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*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, 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*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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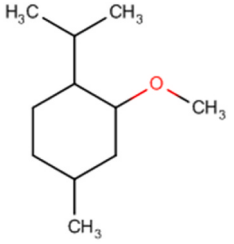

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Abbreviation/Definition List:

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

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
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.

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

1-Menthyl methylether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 1-menthyl methylether is not genotoxic. Data on 1-menthyl methylether 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 1-menthyl methylether for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet (UV/Vis) spectra; 1-menthyl methylether is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 1-menthyl methylether is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 1-menthyl methylether 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2001; RIFM; 2015g; RIFM; 2015h; RIFM, 2021; RIFM, 2016c)

Repeated Dose Toxicity: NOAEL = 267 mg/kg/day. RIFM (2016a)

Reproductive Toxicity: Developmental toxicity: 800 mg/kg/day. Fertility: 800 mg/kg/day. RIFM (2016a)

Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. (RIFM, 2015e)

Photoirritation/Photoallergenicity: Not expected to be photoirritating/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: 14% (OECD 301F) RIFM (2015d)

Bioaccumulation:
Screening-level: 228.7 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Critical Ecotoxicity Endpoint: 72-h Algae EC50: 3.25 mg/L RIFM (2016b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)

Critical Ecotoxicity Endpoint: 72-h Algae EC50: 3.25 mg/L RIFM (2016b)

RIFM PNEC is: 3.25 μg/L

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

1. Identification

1. **Chemical Name:** 1-Menthyl methylether
2. **CAS Registry Number:** 1565-76-0
3. **Synonyms:** Cyclohexane, 2-methoxy-4-methyl-1-(1-methylethyl)-, (1S,2R,4R)-; 1-Isopropyl-2-methoxy-4-methylcyclohexane; 2-Isopropyl-5-methylcyclohexyl methyl ether; Menthyl methyl ether; 1-Menthyl methylether
4. **Molecular Formula:** $C_{11}H_{22}O$
5. **Molecular Weight:** 170.29 g/mol
6. **RIFM Number:** 1228
7. **Stereochemistry:** Three stereocenters and 8 possible stereoisomers

2. Physical data

1. **Boiling Point:** 201.9 °C at 1013 hPa (RIFM, 2015b), 191.76 °C (EPI Suite)
2. **Flash Point:** 65.5 °C (corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015a), 61 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.369 ± 0.012 (25 ± 1 °C, pH 5.532) (Symrise, 2015m; #69349), 4.08 (EPI Suite)
4. **Melting Point**: below −100 °C at 1013 hPa (RIFM, 2015b), −27.5 °C (EPI Suite)
5. **Water Solubility:** 20.08 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.764 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2019).

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Toothpaste:** 0.092% (RIFM, 2017b)

(No Reported Use in Fine Fragrance).

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.0052 mg/kg/day (RIFM, 2017b)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class III, High* (Expert Judgment).

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
III	III	I

*See the Appendix below for further details.

6.2. Analogs selected

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

6.3. Read-across justification

None.

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

1-Menthyl methylether is not reported to occur in foods by the VCF*.

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

Available (ECHA, 2017); accessed on 09/24/20.

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, 1-menthyl methylether does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1-menthyl methylether 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 1-menthyl methylether in ethanol 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, 2001). Under the conditions of the study, 1-menthyl methylether was not mutagenic in the Ames test.

A mammalian cell gene mutation assay (hypoxanthine phosphoribosyl transferase assay) was conducted according to OECD TG 476 and GLP guidelines. Chinese hamster lung cells were treated with 1-menthyl methylether in ethanol at concentrations up to 425.0 μg/mL (as determined in a preliminary toxicity assay) for 4 and 24 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2015h). Under the conditions of the study, 1-menthyl methylether was not mutagenic to mammalian cells *in vitro*.

The clastogenicity of 1-menthyl methylether was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with 1-menthyl methylether in ethanol at concentrations up to 1700.0 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed at 317.2 and 555.1 μg/mL with S9 metabolic activation (RIFM, 2015g). Under the conditions of the study, 1-menthyl methylether was considered to be clastogenic in the *in vitro* chromosome aberration assay.

To confirm the positive results observed in the *in vitro* chromosome aberration study, the clastogenic activity of 1-menthyl methylether was evaluated in an *in vitro* micronucleus test conducted in compliance with

GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 1-menthyl methylether in ethanol at concentrations up to 1703 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 170 μg/mL in the presence and absence of metabolic activation. 1-Menthyl methylether did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2021). Under the conditions of the study, 1-menthyl methylether was considered to be non-clastogenic in the *in vitro* micronucleus test.

To further confirm the positive results observed in the *in vitro* chromosome aberration study, a GLP-compliant 3D reconstructed skin micronucleus (RSMN) assay was conducted to evaluate the genotoxic potential of 1-menthyl methylether (CAS # 1565-76-0) in EpiDerm. Acetone was used as the vehicle. EpiDerm tissues were treated with 1-menthyl methylether at 24-h intervals for 48 and 72 h, at concentrations up to 100 mg/mL 1-Menthyl methylether did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration (RIFM, 2016c). Under the conditions of the study, 1-menthyl methylether was concluded to be negative for the induction of micronuclei in the RSMN in EpiDerm.

Based on the data available, 1-menthyl methylether does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/06/20.

11.1.2. Repeated dose toxicity

The MOE for 1-menthyl methylether 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 1-menthyl methylether. In a GLP- and OECD 422-compliant toxicity study, 12 SD rats were administered 1-menthyl methylether via gavage at doses of 0, 50, 200, and 800 mg/kg/day. Males were treated for a total of 6 weeks (2 weeks pre-mating, 2 weeks mating, and 2 weeks post-mating), and females were treated for 2 weeks pre-mating, throughout gestation, and for 5 days after delivery. An additional 6 SD rats/sex/dose were administered 1-methyl methylether at 0 and 800 mg/kg/day and maintained as recovery groups for 2 weeks after the treatment period. Both sexes of the recovery groups were dosed for 6 weeks. No treatment-related mortality occurred throughout the study period. No effects were seen in clinical signs, body weights, food consumption, sensory function, motor activity, urinalysis, hematology, or blood biochemistry. Absolute and relative liver weights, as well as hepatocellular hypertrophy, were seen in both sexes at the high dose; however, in the absence of adverse histopathological effects, these were considered to be adaptive responses. Thus, based on no adverse effects seen up to the highest dose, the NOAEL for this study was considered 800 mg/kg/day (RIFM, 2016a).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 800/3 or 267 mg/kg/day.

Therefore, the 1-menthyl methylether MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1-menthyl methylether NOAEL in mg/kg/day by the total systemic exposure to 1-menthyl methylether, 267/0.0052, or 51346.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/20.

11.1.3. Reproductive toxicity

The MOE for 1-menthyl methylether is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 1-menthyl methylether. In a GLP- and OECD 422-compliant toxicity study, 12 SD rats were administered 1-menthyl methylether via gavage at doses of 0, 50, 200, and 800 mg/kg/day. Males were treated for a total of 6 weeks (2 weeks pre-mating, 2 weeks mating, 2 weeks post-mating), and females were treated for 2 weeks pre-mating, throughout gestation, and for 5 days after delivery. An additional 6 SD rats/sex/dose were administered 1-methyl methylether at 0 and 800 mg/kg/day and maintained as recovery groups for 2 weeks after the treatment period. Both sexes of the recovery groups were dosed for 6 weeks. No treatment-related mortality occurred throughout the study period. There were no treatment-related effects on the mating period, mating index, gestation period, male and female fertility indices, gestation index, pre-, and post-implantation loss rates, live birth index, mean litter size, external examination of pups, body weights of pups, sex ratio of pups, and viability index of postnatal days 0 and 4. Thus, the NOAEL for developmental toxicity and fertility was considered to be 800 mg/kg/day, the highest dose tested (RIFM, 2016a).

Therefore, the 1-menthyl methylether MOE for the reproductive toxicity endpoint can be calculated by dividing the 1-menthyl methylether NOAEL in mg/kg/day by the total systemic exposure to 1-menthyl methylether, 800/0.0052, or 153846.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.1.4. Skin sensitization

Based on the existing data, 1-menthyl methylether presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, 1-menthyl methylether is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 1-Menthyl methylether was found to be inconclusive in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens tests, but positive in the human cell line activation test (h-CLAT) (ECHA, 2017). In a murine local lymph node assay (LLNA), 1-menthyl methylether was not found to be sensitizing up to 100% (ECHA, 2017; RIFM, 2015e). In another LLNA, 1-menthyl methylether was found to be sensitizing at 25%, but the results were inconclusive, as the reliability check study was older than 6 months and the recorded lymph node cell counts varied markedly within the groups because radioactive labeling was not used for the assessment (ECHA, 2017; RIFM, 2004). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 4959 μg/cm^2 of 1-menthyl methylether in 1:3 ethanol:diethylphthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2006).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, 1-menthyl methylether does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis spectra, 1-menthyl methylether would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.0			1000000	0.002	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.043	0.737	1.356	10000	0.0737	Neutral organics
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	5.17					
Daphnia		6.44				
Algae		3.25		1000	3.25	

for 1-menthyl methylether in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 1-menthyl methylether does not present a concern for photoirritation or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/23/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-menthyl methylether is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are limited inhalation data available on 1-menthyl methylether. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 4700 times lower than the Cramer Class III TTC value of 0.47 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: RIFM, 2017a.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1-menthyl methylether was performed following the RIFM Environmental Framework (Salvito, 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, 1-menthyl methylether 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 1-menthyl methylether as possibly persistent but not 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 (2019), 1-menthyl methylether presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation:

RIFM, 2015d: The ready biodegradability of the test material was evaluated using the manometric respirometry test with non-adapted activated sludge according to OECD 301F guidelines. Biodegradation of 14% was observed after 28 days.

Ecotoxicity:

RIFM, 2016b: An acute fish (*Gobiocypris rarus*) toxicity test was conducted according to the OECD 203 guideline, under semi-static (closed system) conditions. The 96-h LC50 value based on geometric mean measured concentration was reported to be 5.17 mg/L (95% CI: 4.65–5.75 mg/L).

RIFM, 2015f: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under semi-static conditions (closed system). The 48-h EC50 value based on geometric mean measured concentration was reported to be 6.44 mg/L (95% CI: 6.29–6.58 mg/L).

RIFM, 2015c: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 values based on mean measured concentration for growth rate and biomass were reported to be 9.62 mg/L (95% CI: 9.10–10.03 mg/L) and 3.25 mg/L (95% CI: 2.79–3.65 mg/L), respectively.

Other available data:

1-Menthyl methylether has been registered for REACH with no additional information available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	4.37	4.37
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	<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 3.25 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: 10/29/20.

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 04/11/22.

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.

Appendix

1N,2N,3N,43N,5N,6N,42N,7N,16N,17N,19N,23N,24N,25N,26N, 22N,33N

Explanation of Cramer Classification

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 A normal constituent of the body? No.
Q2 Contains functional groups associated with enhanced toxicity? No.
Q3 Contains elements other than C, H, O, N, and divalent S? No.
Q43 Possibly harmful divalent sulfur? No
Q5 Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6 Benzene derivative with certain substituents? No.
Q42 Possibly harmful analog of benzene? No.
Q7 Heterocyclic? No.
Q16 Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17 Readily hydrolyzed to a common terpene? No.
Q18 One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories). No.
Q19 Open chain? No.
Q23 Aromatic? No.

Q24 Monocarbocyclic with simple substituents? No.
Q25 Cyclopropane (see explanation in Cramer et al., 1978)? No.
Q26 Monocycloalkanone or a bicyclo compound? No.
Q22 A common component of food? No.
Q33 Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No.

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