Food and Chemical Toxicology 153 (2021) 112168

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-, CAS Registry Number 198404-98-7

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

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member 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 Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member 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 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 Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996- 4500, USA*
[l] *Member 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 Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling editor: Aristides Tsatsakis

Keywords:
Genotoxicity
Repeated Dose, Developmental, and Reproductive Toxicity
Skin Sensitization
Phototoxicity/Photoallergenicity
Local Respiratory Toxicity
Environmental safety

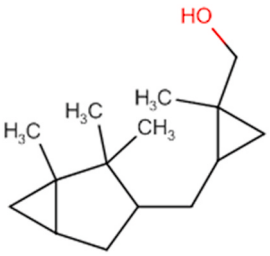
(*continued on next column*)

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

https://doi.org/10.1016/j.fct.2021.112168
Received 30 October 2020; Received in revised form 3 March 2021; Accepted 30 March 2021
Available online 6 April 2021

(*continued*)

Version: 102720. This version replaces any previous versions.
Name: Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl) methyl]
CAS Registry Number: 198404-98-7



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, 2017; Safford et al., 2015a, 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 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
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, 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).

(*continued on next column*)

(*continued*)

*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.

Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- is not genotoxic. Data on cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl) methyl]- provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the threshold of toxicological concern (TTC) for a Cramer Class III material, and the exposure to cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- is below the TTC (0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl) methyl]- 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, 2012; RIFM, 2000)
Repeated Dose Toxicity: NOAEL = 6.6 mg/kg/day. RIFM (1999b)
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization; the current, declared use level is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 0% (OECD 301C) RIFM (2015)
Bioaccumulation:
Critical Measured Value: BCF: 52–64 (Japanese Pharmaceutical and Food Safety Bureau Testing Methods for New Chemical Substances) RIFM (2016)
Ecotoxicity:
Critical Ecotoxicity Endpoint: 28-Day Zebrafish NOEC (OECD 210): 0.055 mg/L RIFM (1999a)
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: 28-Day Zebrafish NOEC (OECD 210): 0.055 mg/L RIFM (1999a)
RIFM PNEC is: 1.1 μg/L
•Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-
2. **CAS Registry Number:** 198404-98-7
3. **Synonyms:** 1-Methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)cyclopropanemethanol; Javanol; (1-Methyl-2-(1,2,2-trimethylbicyclo[3.1.0]hex-3-ylmethyl)cyclopropyl)methanol; Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-
4. **Molecular Formula:** $C_{15}H_{26}O$
5. **Molecular Weight:** 222.37

6. **RIFM Number:** 6678
7. **Stereochemistry:** Stereoisomer not specified. A total of 5 chiral centers and 32 isomers are possible.

2. Physical data

1. **Boiling Point:** Not Available
2. **Flash Point:** 136 °C (Globally Harmonized System)
3. **Log K_{OW}:** Not Available
4. **Melting Point**: Not Available
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000365 mm Hg at 20 °C (EPI Suite v4.0)
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, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.10% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000092 mg/kg/day or 0.0067 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2017)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

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

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.
Additional References: None.

8. Natural occurrence

Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- 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; accessed 01/16/20 (ECHA, 2019).

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, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- 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 *Escherichia coli* strain WP2uvrA were treated with cyclopropanemethanol 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 dose in the presence or absence of S9 (RIFM, 2012). Under the conditions of the study, cyclopropanemethanol was not mutagenic in the Ames test.

The clastogenicity of cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster V79 cells were treated with cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl] in DMSO at concentrations of up to 2250 μg/mL in the presence and absence of metabolic activation. 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 (RIFM, 2000). Under the conditions of the study, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Under the conditions of the study, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/30/20.

11.1.2. Repeated dose toxicity

The MOE for cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- 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 cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo [3.1.0]hex-3-yl)methyl]-. In an OECD 407 and GLP-compliant study, 5 Wistar rats/sex/group we11.1.2.1re administered cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl) methyl]- (purity: 89.1%) via gavage at doses of 0 (vehicle control: PEG 300), 20, 100, and 500 mg/kg/day for 28 days. No treatment-related effects on mortality, clinical signs, functional observation battery (FOB), body weight, bodyweight gain, or hematology changes were reported in any of the dose levels tested. Significantly increased levels of triglycerides (>2 fold) and increased activity of gamma-glutamyl transferase (approximately 2-fold) were reported in both sexes at 500 mg/kg/day. Significantly increased absolute and relative liver weights were reported in both sexes at 500 mg/kg/day. Liver weight changes were accompanied by clinical chemistry changes and thus were considered to be treatment-related adverse effects. Significantly increased absolute and relative kidney weights were reported in males at 500 mg/kg/day. Significantly decreased relative thymus weight was reported in males at concentrations ≥100 mg/kg/day. Thymus focus/foci were seen in 1 male during macroscopic examination at 500 mg/kg/day. Macroscopic examination revealed enlarged liver in 1 male at 500 mg/kg/day. Microscopic examination revealed an increased incidence of tubular basophilia and tubular mineralization (corticomedullary junction) of the kidneys in both sexes at 500 mg/kg/day. These kidney findings were accompanied by a hyaline tubular cast in 1 male at 500 mg/kg/day, and these findings were non-specific and considered treatment-related. Tubular basophilia was reported in 2 males, and tubular mineralization was reported in 1 male at 100 mg/kg/day. Based on clinical chemistry changes (increased gamma-glutamyl transferase and triglycerides), increased liver weights, increased kidney weights, decreased thymus weight with accompanied thymus focus/foci in males at 500 mg/kg/day, and evidence of tubular basophilia and tubular mineralization at concentrations ≥100 mg/kg/day, the NOAEL for repeated dose toxicity was considered to be 20 mg/kg/day (RIFM, 1999b).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day or OECD 407 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 20/3 or 6.6 mg/kg/day.

Therefore, the cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo [3.1.0]hex-3-yl)methyl]- MOE for the repeated dose toxicity endpoint can be calculated by dividing the cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo [3.1.0]hex-3-yl)methyl]- NOAEL in mg/kg/day by the total systemic exposure to cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo [3.1.0]hex-3-yl)methyl]-, 6.6/0.0012 or 5500.

In addition, the total systemic exposure to cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo [3.1.0]hex-3-yl)methyl]- (1.2 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

*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: 02/20/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl) methyl]- or any read-across materials. The total systemic exposure to cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (1.2 μg/kg/day) is below the TTC for cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/20.

11.1.4. Skin sensitization

Based on existing data and the application of DST, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl) methyl]- does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- did not lead to skin sensitization reactions in 10 animals at 100% (ECHA, 2019; RIFM, 1997b). Additionally, in a confirmatory human repeat insult patch test with 4% or 2000 μg/cm^2 of cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- in dimethyl phthalate, no reactions indicative of sensitization were observed in any of the 54 volunteers (RIFM, 1998e). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: NICNAS, 2014.

Literature Search and Risk Assessment Completed On: 01/17/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1
Maximum acceptable concentrations for cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	0.0020%
2	Products applied to the axillae	0.021%	0.0055%
3	Products applied to the face using fingertips	0.41%	4.8×10^{-4}%
4	Fine fragrance products	0.39%	0.10%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0060%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	0.0011%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.059%
10	Household care products with mostly hand contact	2.7%	0.012%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.33%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- 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 significant 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/18/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-. Based on the Creme RIFM Model, the inhalation exposure is 0.0067 mg/day. This exposure is 70.15 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/26/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- 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, cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- 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 cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- 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, 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.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 2015: The ready biodegradability of the test material was evaluated using the modified MITI test (I) according to the OECD 301C guideline. Biodegradation of 0% was observed after 28 days.

RIFM, 1998d: The inherent biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 302C guideline. Biodegradation of 0% was observed after 48 days.

RIFM, 1997a: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 0% was observed after 38 days.

RIFM, 2016: The bioconcentration potential of the test material in the common carp was evaluated using the Japanese Pharmaceutical and Food Safety Bureau guidelines under flow-through conditions with the uptake of 28 days. The BCF values for the nominal test concentrations of 4.74 μg/L and 0.474 μg/L were reported to be between 52 and 64.

11.2.1.2.2. Ecotoxicity. RIFM, 1998a: The acute fish (carp) toxicity test was conducted according to the OECD 203 guidelines under static conditions. The 96-h LC50 value based on the mean measured concentration was reported to be 1 mg/L.

RIFM, 1998b: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on average exposure concentration was reported to be 0.38 mg/L (95% CI: 0.30–0.52 mg/L).

RIFM, 1998c: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 values based on nominal concentrations for cell growth inhibition and growth rate reduction were reported to be 0.53 mg/L (0.26–1.1 mg/L) and 1.0 mg/L (95% CI: 0.58–1.8 mg/L), respectively. The 72-h EC10 values based on nominal concentrations for cell growth inhibition and growth rate reduction were reported to be 0.26 mg/L (0.13–0.56 mg/L) and 0.31 mg/L (95% CI: 0.18–0.53 mg/L), respectively. The NOEC values based on nominal and mean measured concentrations were reported to be 0.24 mg/L and 0.14 mg/L, respectively.

RIFM, 1999a: The 28-day fish (zebrafish) early-life stages toxicity test was conducted according to the OECD 210 guideline under flow-through conditions. The LC50 value based on the nominal concentration for mortality for 30 days was reported to be 0.14 mg/L, and the overall NOEC value based on nominal concentrations for other effects for 28 days was reported to be 0.055 mg/L.

11.2.1.2.3. Other available data. Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]- has been registered for REACH with no additional information available at this time.

11.2.1.3. 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.1			1000000	0.0011	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.178	<u>0.138</u>	0.370	10000	0.0138	Neutral Organic
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.14		<u>0.055</u>	50	1.1	
Daphnia		0.38				
Algae		1.0	0.14			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.8	4.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
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 1.1 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 volumes of use.

Literature Search and Risk Assessment Completed On: 02/19/20.

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 05/31/20.

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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment, November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2019. (1-Methyl-2-(1,2,2-trimethylbicyclo(3.1.0)-hex-3-ylmethyl)cyclopropyl) methanol Registration Dossier. Retrieved from. https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/29448/1.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

NICNAS, 2014. National Industrial Chemicals Notification and Assessment Scheme, Public Report: Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0] hex-3-Yl)methyl]-. File No: LTD/1713. Retrieved from. https://www.nicnas.gov.au/search?sort=&num_ranks=10&collection=nicnas-meta&query=javanol&f.Content+Type|3=Assessments&showonly=assessments.

RIFM (Research Institute for Fragrance Materials, Inc), 1997a. Ready Biodegradability Test with Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl)methyl]- (Javanol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57883.

RIFM (Research Institute for Fragrance Materials, Inc), 1997b. Contact Hypersensitivity to Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl) methyl]- (Javanol) in Albino guinea Pigs Maximization-Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57890.

RIFM (Research Institute for Fragrance Materials, Inc), 1998a. Hour Acute Toxicity Study in Carp with Cyclopropanemethanol, 1-methyl-2-[(1,2,2- trimethylbicyclo[3.1.0] hex-3-Yl)methyl]- (Javanol). RIFM, Woodcliff Lake, NJ, USA, p. 96. Unpublished report from Givaudan. RIFM report number 57878.

RIFM (Research Institute for Fragrance Materials, Inc), 1998b. Acute Toxicity Study in Daphnia Magna with Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo [3.1.0]hex-3-Yl)methyl]- (Javanol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57879.

RIFM (Research Institute for Fragrance Materials, Inc), 1998c. Fresh Water Algal Growth Inhibition Test with Cyclopropanemethanol, 1-methyl-2-[(1,2,2- trimethylbicyclo [3.1.0]hex-3-Yl)methyl]-. [Amendment Attached]. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57880.

RIFM (Research Institute for Fragrance Materials, Inc), 1998d. Inherent Biodegradability of Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl) methyl]- (Javanol). [Amendment Attached]. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57882.

RIFM (Research Institute for Fragrance Materials, Inc), 1998e. Repeated Insult Patch Test with Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl) methyl]- (Javanol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57891.

RIFM (Research Institute for Fragrance Materials, Inc), 1999a. Zebra Fish (Danio rerio) Early Life Stage Toxicity Test with Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl)methyl]- (Javanol)(flow-through). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57884.

RIFM (Research Institute for Fragrance Materials, Inc), 1999b. Day Oral Toxicity (Gavage) Study in the Wistar Rat and 5-day Oral Toxicity (Range-finding) Study in the Rat with Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl)methyl]- (Javanol). RIFM, Woodcliff Lake, NJ, USA, p. 28. Unpublished report from Givaudan. RIFM report number 57892.

RIFM (Research Institute for Fragrance Materials, Inc), 2000. In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells with Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl)methyl]- (Javanol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57888.

RIFM (Research Institute for Fragrance Materials, Inc), 2012. Salmonella typhimurium and Escherichia coli Reverse Mutation Assay with Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl)methyl]- (Javanol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 63436.

RIFM (Research Institute for Fragrance Materials, Inc), 2015. Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl)methyl]- (Sandal Cyclopropane): Biodegradataion Study. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71040.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-Yl)methyl]- (Sandal Cyclopropane):

Bioconcentration Study in Common Carp. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71039.
RIFM (Research Institute for Fragrance Materials, Inc), 2017. Expos. Surv. 16. May 2017.
Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015b. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.