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Short Review

RIFM fragrance ingredient safety assessment, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone, CAS Registry Number 36306-87-3

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*

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Name: 3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone
CAS Registry Number: 36306-87-3

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

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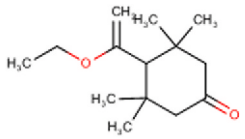
(*continued*)

Additional CAS Numbers*: 36306-86-2 1-Ethoxy-4-(1-ethoxyvinyl)-3,3,5,5-tetramethylcyclohexene

*Included because they are a chemical mixture



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; 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
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 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.

3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone is not genotoxic. Data on 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 III material, and the exposure to 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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, 2003; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 32.3 mg/kg/day.	RIFM (2016a)
Reproductive Toxicity: Developmental toxicity: 324 mg/kg/day. Fertility: 925 mg/kg/day.	RIFM (2016a)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(RIFM, 2016b; ECHA, 2017; RIFM, 2016c)
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: 4% (OECD 302C) for CAS # 36306-87-3	RIFM (1999)
Bioaccumulation	
Screening-level: 84.13 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity	
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50 (OECD 202): 8.4 mg/L for CAS # 36306-87-3	RIFM (2015a)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50 (OECD 202): 8.4 mg/L for CAS # 36306-87-3	RIFM (2015a)

RIFM PNEC is: 8.4 μg/L

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

1. Identification

Chemical Name: 3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone	Chemical Name: 1-Ethoxy-4-(1-ethoxyvinyl)-3,3,5,5-tetramethylcyclohexene
CAS Registry Number: 36306-87-3	**CAS Registry Number:** 36306-86-2
Synonyms: Cyclohexanone, 4-(1-ethoxyethenyl)-3,3,5,5-tetramethyl-; 4-(1-Ethoxyethenyl)-3,3,5,5-tetramethylcyclohexanone; 4-(1-Ethoxyvinyl)-3,3,5,5-tetramethylcyclohexanone; Kephalis; LRG 1182; Tetramethyl ethoxy vinyl cyclohexanone; 3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone	**Synonyms:** 1-Ethoxy-4-(1-ethoxy-vinyl)-3,3,5,5-tetramethylcyclohexene; 3,3,5,5-Tetramethyl-1-ethoxy-4-(1-ethoxyvinyl)-1-cyclohexene; Cyclohexene, 1-ethoxy-4-(1-ethoxyethenyl)-3,3,5,5-tetramethyl-
Molecular Formula: $C_{14}H_{24}O_2$	**Molecular Formula:** $C_{16}H_{28}O_2$
Molecular Weight: 224.34	**Molecular Weight:** 252.39
RIFM Number: 934	**RIFM Number:** 5680

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Stereochemistry: Isomer not specified. One chiral center present and a total of 2 enantiomers possible.	**Stereochemistry:** Isomer not specified. One chiral center present and a total of 2 enantiomers possible.

2. Physical data

CAS # 36306-87-3	CAS # 36306-86-2
Boiling Point: 282.2 °C (EPI Suite), 272 °C (546 K) at 1017 ± 3 hPa (decomposition observed >272 °C) (RIFM, 2015e)	**Boiling Point:** 286.31 °C (EPI Suite)
Flash Point: >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA]), 120 °C (RIFM, 2015e)	**Flash Point:** Not available
Half-life at pH 4 and 20, 25, 40 and 50 °C = 1.5, 1.1, 0.49 and 0.26 h, respectively; half-life at pH 7 and 20, 25, 50 and 60 °C = 64, 44, 8.2 and 4.9 days, respectively; half-life at pH 9 and 25 °C was >1 yr (RIFM, 2015e)	
Log K_{OW}: Log Pow = 4.3 at 25 °C (RIFM, 1996a), 3.42 (EPI Suite)	**Log K_{OW}:** 5.04 (EPI Suite)
Melting Point: 66.01 °C (EPI Suite), less than −80 °C (193 K) at 1017 ± 3 hPa (RIFM, 2015e)	**Melting Point**: 69.58 °C (EPI Suite)
Water Solubility: 39 mg/L (EPI Suite)	**Water Solubility:** 1.142 mg/L (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:**
Vapor Pressure: 0.00201 mm Hg at 20 °C (EPI Suite v4.0), 0.004 mm Hg at 20 °C (FMA), 0.00362 mm Hg @ 25 °C (EPI Suite)	**Vapor Pressure:** 0.0015 mm Hg at 20 °C (EPI Suite v4.0); 0.00272 mm Hg at 25 °C (EPI Suite);
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
Appearance/Organoleptic: A light green-yellow, almost colorless, clear liquid	**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:** 0.45% (RIFM, 2016d)
2. **Inhalation Exposure*:** 0.00087 mg/kg/day or 0.065 mg/day (RIFM, 2016d)
3. **Total Systemic Exposure**:** 0.0077 mg/kg/day (RIFM, 2016d)

*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).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

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)

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
III	III	I

*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). See the Appendix below for further details.

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 (discrete chemical) or composition (NCS)

3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone and 36306-86-2 1-ethoxy-4-(1-ethoxyvinyl)-3,3,5,5-tetramethylcyclohexenenot are 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 for 3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone; accessed 02/12/20 (ECHA, 2017); 1-ethoxy-4-(1-ethoxyvinyl)-3,3,5,5-tetramethylcyclohexene (CAS # 36306-86-2) has been pre-registered for 2010 (no dossier available as of 04/22/20).

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, 3,3,5,5-tetramethyl-4-

ethoxyvinylcyclohexanone does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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, 2003). Under the conditions of the study, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone was not mutagenic in the Ames test.

The clastogenic activity of 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone in dimethyl sulfoxide (DMSO) at concentrations up to 512 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 175 μg/mL in the presence and absence of metabolic activation. 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone does not present a concern for genotoxic potential.

Additional References: RIFM, 2015d.

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

11.1.2. Repeated dose toxicity

The MOE for 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone. In an OECD 422 and GLP-compliant study, 10 SPF-bred Wistar rats/sex/dose were administered 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone through diet at concentrations of 1500, 5000, and 15000 ppm. Treatment duration was 29 days in males and 41–47 days in females. No treatment-related mortality occurred throughout the study. No treatment-related changes were noted in clinical appearance or functional observations. Body weights, bodyweight gain, and food consumption were decreased in animals of both sexes receiving the highest dose. Liver effects included hepatocellular hypertrophy in low-dose group females and in both sexes of mid- and high-dose groups. In addition, absolute and relative liver weights were significantly increased in males at the mid dose and both sexes at the high dose. Spleen effects included dose-dependent changes in extramedullary hematopoiesis (increased for males and decreased for females) along with significantly increased absolute and relative spleen weight in high-dose males. Kidney effects included increased hyaline droplet accumulation in males at all doses, increased tubular basophilia in high-dose males, increased relative kidney weight in both sexes at the highest dose, and granular casts in males in the mid- and high-dose groups. Kidney discoloration and enlargement was reported in 1 high-dose male, and an accentuated lobular pattern of the liver was seen in 1 high-dose female. These were considered toxicologically relevant because they were associated with relevant histological findings (hyaline droplet accumulation and granular casts in the kidney and hepatocellular hypertrophy). Effects on hematology and clinical biochemistry that would suggest altered organ function were of lower frequency and severity at the low dose and thus were not considered adverse at this dose. Based on the kidney, liver, and spleen effects, as well as decreased food consumption and body weight, the NOAEL was considered to be 1500 ppm (reported to be equivalent to 97 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*.

Thus, the derived NOAEL for the repeated dose toxicity data is 97/3 or 32.3 mg/kg/day.

Therefore, the 3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone NOAEL in mg/kg/day by the total systemic exposure for 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone, 32.3/0.0077, or 4195.

*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: 02/28/20.

11.1.3. Reproductive toxicity

The MOE for 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone. In an OECD 422 and GLP-compliant study, 10 SPF-bred Wistar rats/sex/dose were administered 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone through the diet at concentrations of 1500, 5000, and 15000 ppm. Males were exposed for 2 weeks prior to mating, during mating, and up to termination (total 29 days). Females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation (total 41–47 days). No fertility toxicity was observed up to the highest dose level tested. No treatment-related changes were noted in the gestation index and duration, parturition, maternal care, and early postnatal pup development consisting of mortality, clinical signs, and macroscopic examination. At the high dose (15000 ppm), pups had statistically significant lower body weights on day 4 compared to controls. However, this was considered to reflect a slight developmental delay that was secondary to the statistically significant lower body weight of the dams at this dose level. Based on no toxic effects seen up to the highest dose, the NOAEL for the fertility endpoint was considered to be 15000 ppm (reported to be equivalent to 925 mg/kg/day). Based on statistically significant lower body weights of pups on day 4 and by taking a conservative approach, the developmental toxicity NOAEL was considered to be 5000 ppm (reported to be equivalent to 324 mg/kg/day) (RIFM, 2016a).

Therefore, the 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone MOE for the fertility endpoint can be calculated by dividing the 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone NOAEL in mg/kg/day by the total systemic exposure for 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone, 925/0.0077, or 120130.

Therefore, the 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone MOE for the developmental toxicity endpoint can be calculated by dividing the 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone NOAEL in mg/kg/day by the total systemic exposure for 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone, 324/0.0077, or 42078.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/30/20.

11.1.4. Skin sensitization

Based on the existing data, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone is not considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.2). However, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens test (RIFM, 2016b; ECHA, 2017; RIFM, 2016c). In a guinea pig open epicutaneous test (OET), 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 10% did not lead to skin sensitization reactions (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone at 10% (6900 μg/cm^2) (RIFM, 1976).

Based on the weight of evidence (WoE) from *in vitro* studies, animal studies, and human studies, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: ECHA, 2017 (Skin sensitization; 003 wt of evidence); ECHA, 2017 (Skin sensitization; 004 wt of evidence).

Literature Search and Risk Assessment Completed On: 03/06/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 et al., 2009). Based on the lack of absorbance, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 et al., 2009).

Additional References: None.

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

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone. Based on the Creme RIFM Model, the inhalation exposure is 0.065 mg/day. This exposure is 7.2 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: None.

Literature Search and Risk Assessment Completed On: 04/01/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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, 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone 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 (2015), 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. ***For CAS # 36306-87-3.***

RIFM, 1999: The inherent biodegradability of the test material was determined using the manometric respirometry test according to the OECD 302C guideline. Biodegradation of 4% was observed after 28 days.

RIFM, 1996b: The ready biodegradability of the test material was determined using the manometric respirometry test according to the OECD 301F guideline. No biodegradation was observed after 28 days.

11.2.3.2. Ecotoxicity. ***For CAS # 36306-87-3.***

RIFM, 2015a: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on measured concentrations was reported to be 8.4 mg/L (95% CI: 5.9–12 mg/L).

RIFM, 2015c: The acute fish (Carp) toxicity test was conducted according to the OCED 203 guidelines under semi-static conditions. The 96-h LC50 values based on mean measured concentration was reported to be 9.1 mg/L.

RIFM, 2015b: 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 concentrations for growth rate and yield were reported to be 25 mg/L (95% CI: 24–27 mg/L) and 10 mg/L (95% CI: 9.3–12 mg/L), respectively.

11.2.4. Other available data

3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone has been registered for REACH with no additional information available at this time.

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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.3	4.3
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**

*Combined Regional VoU for both CAS #s.

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

The RIFM PNEC is 8.4 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: 04/01/20.

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 09/30/20.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.771			1000000	0.000771	
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	1.014	2.952	3.386	10000	0.1014	Vinyl/Allyl Ethers
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	9.733	6.302	8.079			Neutral Organics SAR
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	9.1					
Daphnia		8.4		1000	8.4	
Algae		10				

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,5N,6N,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
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? 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 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. Class High (Class III)

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