



Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, methyl cyclohexadiene (mixture of isomers), CAS Registry Number 30640-46-1



A.M. Api^a, F. Belmonte^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, A. Lapczynski^a, M. Lavelle^a, D.C. Lieblerⁱ, M. Na^a, D. O'Brien^a, A. Patel^a, T.M. Penning^j, G. Ritacco^a, F. Rodriguez-Ropero^a, J. Romine^a, N. Sadekar^a, D. Salvito^a, T.W. Schultz^k, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m, S. Tsang^a

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

^b Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Malmö University Hospital, Department of Occupational & Environmental Dermatology, Södra Förstadsgatan 101, Entrance 47, Malmö, SE-20502, Sweden

^d School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA

^e Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

^f University of São Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, São Paulo, CEP 05508-900, Brazil

^g University of Würzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

^h Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

ⁱ 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 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 The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^l Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

^m 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

Keywords:

Genotoxicity

Repeated dose

Developmental

And reproductive toxicity

Skin sensitization

Phototoxicity/photoallergenicity

Local respiratory toxicity

Environmental safety

* Corresponding author.

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

Version: 121018. This version replaces any previous versions.

Name: Methyl cyclohexadiene (mixture of isomers)

CAS Registry Number: 30640-46-1

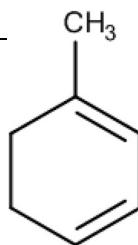
Additional CAS Numbers*:

1489-56-1 1-Methyl-1,3-cyclohexadiene (no reported use)

1888-90-0 Cyclohexene, 3-methylene- (no reported use)

1489-57-2 2-Methyl-1,3-cyclohexadiene (no reported use)

*Included because the materials are isomers



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

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

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LOEL - Lowest Observable Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

QRA - Quantitative Risk Assessment

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

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.

Methyl cyclohexadiene (mixture of isomers) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/ photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog (–)(R)- α -phellandrene (CAS # 4221-98-1) show that methyl cyclohexadiene (mixture of isomers) is not expected to be genotoxic. Data on read-across analog (–)(R)- α -phellandrene (CAS # 4221-98-1) provide a calculated MOE > 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure is below the TTC (1.4 mg/day). Data show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; methyl cyclohexadiene (mixture of isomers) is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl cyclohexadiene (mixture of isomers) was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.

(RIFM, 2000; RIFM, 2015)

Repeated Dose Toxicity: NOAEL = 8.33 mg/kg/day.

RIFM (2018)

Developmental and Reproductive Toxicity: NOAEL = 75 mg/kg/day and 200 mg/kg/day, respectively.

RIFM (2018)

Skin Sensitization: Not a sensitization concern under current, declared levels of use.

RIFM (2005)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 69% (OED 301F) (RIFM, 2010)

Bioaccumulation: Screening-level: 69.13 L/kg

Ecotoxicity: Screening-level: Fish LC50: 9.583 mg/L

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

(UV Spectra, RIFM Database)

RIFM (2010)

(EPI Suite v4.11; US EPA, 2012a)

(RIFM Framework; Salvito et al., 2002)

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1

Critical Ecotoxicity Endpoint: Fish LC50: 9.583 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00958 µg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at screening-level

1. Identification

Chemical Name: Methyl cyclohexadiene (mixture of isomers)

CAS Registry Number: 30640-46-1

Synonyms: Methylcyclohexadiene; Limadiene; Methyl cyclohexadiene; 1-Methylcyclohexa-1,3-diene; Cyclohexadiene, methyl- (Mixture of isomers); Methyl cyclohexadiene (mixture of isomers)

Molecular Formula: C₇H₁₀

Molecular Weight: 94.15

RIFM Number: 6506

Stereochemistry: Isomer not specified. No stereocenter and no stereoisomers possible.

Chemical Name: Cyclohexene, 3-methylene-

CAS Registry Number: 1888-90-0

Synonyms: 1-Methylene-2-cyclohexene; 3-Methylene-1-cyclohexene; Cyclohexene, 3-methylene-; Methylene cyclohexene

Molecular Formula: C₇H₁₀

Molecular Weight: 94.15

RIFM Number: 6506

Stereochemistry: Isomer not specified. No stereocenter and no stereoisomers possible.

Chemical Name: 1-Methyl-1,3-cyclohexadiene

CAS Registry Number: 1489-56-1

Synonyms: 1-Methyl-1,3-cyclohexadiene; 1-Methylcyclohexa-1,3-diene; 2,3-Dihydrotoluene; 5,6-Dihydrotoluene

Molecular Formula: C₇H₁₀

Molecular Weight: 94.15

RIFM Number: None

Stereochemistry: Isomer not specified. No stereocenter and no stereoisomers possible.

Chemical Name: 2-Methyl-1,3-cyclohexadiene

CAS Registry Number: 1489-57-2

Synonyms: 2-Methyl-1,3-cyclohexadiene; 2-Methylcyclohexa-1,3-diene; 3,4-Dihydrotoluene

Molecular Formula: C₇H₁₀

Molecular Weight: 94.15

RIFM Number: 6506

Stereochemistry: Isomer not specified. No stereocenter and no stereoisomers possible.

Appearance/Organoleptic: Not available

Appearance/Organoleptic: Not available

3. Exposure***

1. Volume of Use (worldwide band): 0.1–1 metric ton per year (IFRA, 2015)

2. 95th Percentile Concentration in Hydroalcoholics: 0.000012% (RIFM, 2017b)

3. Inhalation Exposure*: 0.0000032 mg/kg/day or 0.00023 mg/day (RIFM, 2017b)

4. Total Systemic Exposure:** 0.0000074 mg/kg/day (RIFM, 2017b)

*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 IV. 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 or 97.5th percentile, inhalation exposure, and total exposure.

4. Derivation of systemic absorption

1. Dermal: Assumed 100%

2. Oral: Assumed 100%

3. Inhalation: Assumed 100%

5. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v	OECD
	2.6	QSAR Toolbox v 3.2
Class I, Low	Class I, Low	Class I, Low

2. Analogs Selected:

- Genotoxicity:** (−)-(R)- α -Phellandrene (CAS # 4221-98-1)
- Repeated Dose Toxicity:** (−)-(R)- α -Phellandrene (CAS # 4221-98-1)
- Developmental and Reproductive Toxicity:** (−)-(R)- α -Phellandrene (CAS # 4221-98-1)
- Skin Sensitization:** None
- Phototoxicity/Photoallergenicity:** None

CAS #: 30640-46-1

Boiling Point: 117.82 °C (EPI Suite)

Flash Point: 16 °C (GHS)

Log K_{ow}: log Pow = 2.9, 3.5, and 3.5 (Givaudan, 2009u), 3.29 (EPI Suite)

Melting Point: −61.86 °C (EPI Suite)

Water Solubility: 54.36 mg/L (EPI Suite)

Specific Gravity: 0.834 (Bedoukian)

Vapor Pressure: 15.6 mm Hg @ 20 °C (EPI Suite v4.0), 20.6 mm Hg @ 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)

Appearance/Organoleptic: Not available

CAS #: 1888-90-0

Boiling Point: Not available

Flash Point: Not available

Log K_{ow}: Not available

Melting Point: Not available

Water Solubility: Not available

Specific Gravity: Not available

Vapor Pressure: 15.6 mm Hg @ 20 °C (EPI Suite v4.0), 24.3 mm Hg @ 20 °C (EPI Suite v4.0), 31.7 mm Hg @ 25 °C (EPI Suite)

UV Spectra: Not available

CAS #: 1489-56-1

Boiling Point: 117.82 °C (EPI Suite)

Flash Point: Not available

Log K_{ow}: 3.29 (EPI Suite)

Melting Point: −61.86 °C (EPI Suite)

Water Solubility: 54.36 mg/L (EPI Suite)

Specific Gravity: Not available

Vapor Pressure: 20.6 mm Hg @ 25 °C (EPI Suite)

UV Spectra: Not available

Appearance/Organoleptic: Not available

CAS #: 1489-57-2

Boiling Point: 117.82 °C (EPI Suite)

Flash Point: Not available

Log K_{ow}: 3.29 (EPI Suite)

Melting Point: −61.86 °C (EPI Suite)

Water Solubility: 54.36 mg/L (EPI Suite)

Specific Gravity: 0.834 (Bedoukian)

Vapor Pressure: 24.3 mm Hg @ 20 °C (EPI Suite v4.0), 31.7 mm Hg @ 25 °C (EPI Suite)

UV Spectra: Not available

f. Local Respiratory Toxicity: None

g. Environmental Toxicity: None

3. Read-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. Natural occurrence (discrete chemical) or composition (NCS)

None of the materials in this safety assessment are 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.

8. IFRA standard

None

9. Reach Dossier

Pre-registered in 2010; not available as of 12/10/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, methyl cyclohexadiene (mixture of isomers) does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Methyl cyclohexadiene (mixture of isomers) was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of methyl cyclohexadiene (mixture of isomers); however, read-across can be made to (–)-(R)-α-phellandrene (CAS # 4221-98-1; see Section V). The mutagenic activity of (–)-(R)-α-phellandrene 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 (–)-(R)-α-phellandrene 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, 2000). Under the conditions of the study, (–)-(R)-α-phellandrene was not mutagenic in the Ames test, and this can be extended to methyl cyclohexadiene (mixture of isomers).

The clastogenic activity of methyl cyclohexadiene (mixture of isomers) 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 methyl cyclohexadiene (mixture of isomers) in minimal essential medium at concentrations up to 941.6 µg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation

for 24 h. Methyl cyclohexadiene (mixture of isomers) did not induce binucleated cells with micronuclei when tested up to the maximum recommended concentration in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, methyl cyclohexadiene (mixture of isomers) was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, methyl cyclohexadiene (mixture of isomers) does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/11/18.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for methyl cyclohexadiene (mixture of isomers) is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data available for methyl cyclohexadiene (mixture of isomers). Read-across material (–)-(R)-α-phellandrene (CAS # 4221-98-1; see Section V) has sufficient repeated dose toxicity data. In an OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 12 Sprague Dawley rats/sex/dose were administered (–)-(R)-α-phellandrene via oral gavage at doses of 0, 25, 75, or 200 mg/kg/day in corn oil. Males were treated for 49 days (2 weeks prior to mating, during 2 weeks of mating, and for 21 days post-mating), while females were treated for 51–52 days (2 weeks prior to mating, throughout gestation, and for 13 days post-delivery). Additional groups of 6 rats/sex/dose were administered 0 or 200 mg/kg/day (–)-(R)-α-phellandrene for 49 days and were assigned to serve as the recovery groups. No treatment-related adverse effects were observed for sensory function, motor activity, urinalysis, hematology, clinical chemistry, or thyroid hormone quantification for either sex at all tested doses. Females in the 200 mg/kg/day high-dose group had statistically significant decreases in body weight and food consumption. Similarly, body weights from females in the recovery group were decreased (not statistically significant) at the end of the recovery time. In males, absolute and relative liver weights were statistically significantly increased in animals receiving 75 and 200 mg/kg/day doses. In females, absolute liver weights were statistically significantly increased at 200 mg/kg/day, while relative liver weights were statistically significantly increased at 75 and 200 mg/kg/day compared to control animals. Recovery groups also demonstrated an increase (not statistically significant) in relative liver weights in both males and females. Centrilobular hepatocellular hypertrophy was observed at 75 mg/kg/day (males) and 200 mg/kg/day (both sexes). However, hypertrophy was not observed in any of the males and females from the recovery groups at the end of the recovery period. Therefore, the NOAEL for repeated dose toxicity was considered to be 25 mg/kg bw/day based on the adverse events observed in the liver (RIFM, 2018).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 25/3 or 8.33 mg/kg/day.

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

Therefore, the methyl cyclohexadiene (mixture of isomers) MOE for the repeated dose toxicity endpoint can be calculated by dividing the (–)-(R)-α-phellandrene NOAEL in mg/kg/day by the total systemic exposure to methyl cyclohexadiene (mixture of isomers), 8.33/0.0000074 or 1125676.

In addition, the total systemic exposure to methyl cyclohexadiene (mixture of isomers) (0.0074 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a

Cramer Class I material at the current level of use.

Additional References: RIFM, 2017a.

Literature Search and Risk Assessment Completed On: 11/08/18.

10.1.3. Developmental and reproductive toxicity

The MOE for methyl cyclohexadiene (mixture of isomers) is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental and reproductive toxicity data on methyl cyclohexadiene (mixture of isomers). Read-across material (−)-(R)- α -phellandrene (CAS # 4221-98-1; see Section V) has sufficient developmental and reproductive toxicity data that can be used to support the developmental and reproductive toxicity endpoints. In an OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 12 Sprague Dawley rats/sex/dose were administered (−)-(R)- α -phellandrene via oral gavage at doses 0, 25, 75, or 200 mg/kg/day in corn oil. Males were treated for 49 days (2 weeks prior to mating, during 2 weeks of mating, and 21 days post-mating), while females were treated for 51–52 days (2 weeks prior to mating, throughout gestation, and for 13 days post-delivery). Additional groups of 6 rats/sex/dose were administered 0 or 200 mg/kg/day (−)-(R)- α -phellandrene for 49 days and were assigned to serve as the 14-day treatment-free recovery groups. In addition to systemic toxicity parameters, developmental and reproductive toxicity parameters were also assessed. At postnatal day (PND) 4, an increase (not statistically significant) in post-implantation loss and decreases in live birth and viability indices of pups were observed in 2 dams whose pups were all found dead at 200 mg/kg/day. Additionally, in 1 low-dose group dam, all pups were deceased. The litter losses could not be attributed to a dose-response relationship. Furthermore, it could not be concluded with certainty whether the deaths in the 2 high-dose dams with litter losses were test material-related or incidental in nature. Among the 3 dams whose pups were all dead, only 1 dam at necropsy exhibited dilatation with gas in the stomach, enlarged adrenal glands, and small thymus and spleen. The others showed no gross findings. A statistically significant decrease in pup body weights was observed at 200 mg/kg/day (PND 13: 26% and 25% for male and female pups, respectively, as compared to controls); these effects were jointly observed with overt signs of systemic toxicity in dams that presented a statistically significant reduction in body weight and food consumption (GD 7 to PPD 13) as well as liver effects. No gross abnormalities were reported in pups. The authors of the study report determine the NOAEL for reproductive toxicity to be 200 mg/kg/day for males, the highest dose tested, and 75 mg/kg/day for females, based on statistically significant decreases in body weight and food consumption during gestation and postpartum periods in the 200 mg/kg/day dose group. Since no substantial fertility effect was reported, the NOAEL for reproductive toxicity for both males and females was considered to be 200 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was considered to be 75 mg/kg/day, based on a decrease in body weight among high-dose group pups (RIFM, 2018).

The methyl cyclohexadiene MOE for the developmental toxicity endpoint can be calculated by dividing the (−)-(R)- α -phellandrene NOAEL in mg/kg/day by the total systemic exposure to methyl cyclohexadiene, 75/0.0000074 or 10135135.

The methyl cyclohexadiene MOE for the reproductive toxicity endpoint can be calculated by dividing the (−)-(R)- α -phellandrene NOAEL in mg/kg/day by the total systemic exposure to methyl cyclohexadiene, 200/0.0000074 or 27027027.

In addition, the total systemic exposure to methyl cyclohexadiene (0.0074 μ g/kg/day; mixture of isomers) is below the TTC (30 μ g/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the

developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/09/18.

10.1.4. Skin sensitization

Methyl cyclohexadiene (mixture of isomers) was predicted to be non-reactive to skin proteins, and no skin sensitization reactions were observed in the Buehler test. Based on weight of evidence (WoE) from structural analysis and animal studies, methyl cyclohexadiene (mixture of isomers) does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, methyl cyclohexadiene (mixture of isomers) is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD toolbox v4.2). In a guinea pig Buehler test, methyl cyclohexadiene (mixture of isomers) did not present reactions indicative of sensitization up to 100% (RIFM, 2005).

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

Additional References: RIFM, 2009.

Literature Search and Risk Assessment Completed On: 11/08/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, methyl cyclohexadiene (mixture of isomers) would not be expected to present a concern for phototoxicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for methyl cyclohexadiene (mixture of isomers) 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, methyl cyclohexadiene (mixture of isomers) does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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: 10/18/18.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on methyl cyclohexadiene (mixture of isomers). Based on the Creme RIFM Model, the inhalation exposure is 0.00023 mg/day. This exposure is 6087 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Cartwheel 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: 11/13/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methyl cyclohexadiene (mixture of isomers) 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 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

(mixture of isomers) presents no risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2010: The ready biodegradability of the test material was evaluated according to the OCED 301F method. Under the conditions of this study, biodegradation of 69% was observed after 28 days.

10.2.3.2. Ecotoxicity. No data available.

10.2.4. Other available data

Methyl cyclohexadiene (mixture of isomers) has been registered under REACH with no additional data available at this time.

10.2.5. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μ g/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>9.583</u>			1,000,000	0.00958	

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, methyl cyclohexadiene (mixture of isomers) was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify methyl cyclohexadiene (mixture of isomers) as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF \geq 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), methyl cyclohexadiene

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} used	3.29	3.29
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	< 1	< 1
Risk Characterization: PEC/PNEC	< 1	< 1

*Combined Regional Volume of Use for all CAS #s.

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

The RIFM PNEC is 0.00958 μ g/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/14/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>
- **NTP:** <https://ntp.niehs.nih.gov/>
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <http://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <http://toxnet.nlm.nih.gov/>
- **IARC:** <http://monographs.iarc.fr>
- **OECD SIDS:** <http://webnet.oecd.org/hpv/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:** <http://www.safe.nite.go.jp/english/db.html>
- **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 05/20/19.

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 A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2019.111112>.

Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in [Schultz et al. \(2015\)](#). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment ([OECD, 2015](#)) and the European Chemicals Agency read-across assessment framework ([ECHA, 2016](#)).

- First, the materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints ([Rogers and Hahn, 2010](#)).
- The physical-chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 ([US EPA, 2012a](#)).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model ([Shen et al., 2014](#)).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 ([OECD, 2018](#)).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 ([OECD, 2018](#)).
- Developmental toxicity was predicted using CAESAR v2.1.7 ([Cassano et al., 2010](#)).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 ([OECD, 2018](#)), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 ([OECD, 2018](#)).

	Target Material	Read-across Material
Principal Name	Methyl cyclohexadiene (mixture of isomers)	(-)-(R)- α -Phellandrene
CAS No.	30640-46-1	4221-98-1
Structure		
Similarity (Tanimoto Score)	0.49	<ul style="list-style-type: none"> • Genotoxicity • Repeated dose toxicity • Reproductive toxicity • Developmental toxicity
Read-across Endpoint		
Molecular Formula	C_7H_{10}	$C_{10}H_{16}$
Molecular Weight	94.15	136.23
Melting Point (°C, EPI Suite)	-61.86	-40.80
Boiling Point (°C, EPI Suite)	117.82	172.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.75E + 003	1.87E + 002
Log Kow(KOWWIN v1.68 in EPI Suite)	3.29	4.62
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	54.36	2.862
J_{max} (μ g/cm ² /h, SAM)	325.64	67.12

Henry's Law (Pa·m ³ /mol, Bond Method, EPI Suite)	1.34E+004	5.56E+003
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	● No alert found	● No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	● No alert found	● No alert found
Carcinogenicity (ISS)	● Non-carcinogen (low reliability)	● Non-carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	● No alert found	● No alert found
<i>In Vitro</i> Mutagenicity (Ames, ISS)	● No alert found	● No alert found
<i>In Vivo</i> Mutagenicity (Micronucleus, ISS)	● No alert found	● No alert found
Oncologic Classification	● Not classified	● Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	● Not categorized	● Aliphatic/Alicyclic hydrocarbons (α -2u-globulin nephropathy) Rank C
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	● Non-binder, without OH or NH ₂ group	● Non-binder, without OH or NH ₂ group
Developmental Toxicity (CAESAR v2.1.6)	● Non-toxicant (low reliability)	● Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on methyl cyclohexadiene (mixture of isomers) (CAS # 30640-46-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical-chemical properties, and expert judgment, (–)-(R)- α -phellandrene (CAS # 4221-98-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- (–)-(R)- α -Phellandrene (CAS # 4221-98-1) was used as a read-across analog for the target material methyl cyclohexadiene (mixture of isomers) (CAS # 30640-46-1) for the genotoxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints.
 - o The target substance and the read-across analog are structurally similar and belong to a class of unsaturated monocyclic hydrocarbons.
 - o The target substance and the read-across analog share alkyl substituted cyclohexadiene ring structures.
 - o The key difference between the target substance and the read-across analog is that the read-across analog has a methyl group at C-2 and an isopropyl group at C-5, whereas the target substance has a methyl group at C-1. These structural differences are toxicologically insignificant.
 - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
 - o The physical-chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
 - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
 - o The read-across analog has an alert of aliphatic/alicyclic hydrocarbons (α -2u-globulin nephropathy) with Rank C. The alert is given due to the fulfillment of the following 3 criteria: an isopropyl substitution on the hydrocarbon structure; a log K_{ow} of greater than or equal to 3.5; and a molecular weight less than 200. Rank C is given because the toxicological mechanism is not well known. The training set used for this alert shares the 3 criteria mentioned above with the read-across analog, but the read-across analog does not show any reactive sub-structural features that match with the substance used in the training set. The data described in the repeated dose toxicity section confirm that the margin of exposure is adequate at the current level of use. Therefore, the predictions are superseded by data.
 - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., et al., 2010, July. CAESAR models for developmental toxicity. In: Chemistry Central Journal. vol. 4. Springer International Publishing, pp. 1–11 Suppl 1:S4.

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 Chapter R.11: PBT Assessment, November 2012 v1.1. <http://echa.europa.eu/>, Accessed date: 10 December 2018.

ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. [www.echa.europa.eu/documents/10162/13628/raaf_en.pdf](http://echa.europa.eu/documents/10162/13628/raaf_en.pdf), Accessed date: 10 December 2018.

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., Lhuaguenot, 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.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. <http://www.oecd.org/>, Accessed date: 10 December 2018.

OECD, 2018. The OECD QSAR Toolbox, v3.2-4.2. <http://www.qsartoolbox.org/>, Accessed date: 10 December 2018.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000. Mutagenicity Study of (−)(R)-alpha-Phellandrene (Phellandren Alpha L) in the *Salmonella typhimurium*/mammalian Microsome Reverse Mutation Assay (Ames-Test). Unpublished report from Symrise. RIFM report number 62846 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Buehler Sensitization Test with Cyclohexadiene, Methyl- (Mixture of Isomers). Unpublished report from Bedoukian Research Inc. RIFM report number 31719 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Partition Coefficient N-Octanol/water of Cyclohexadiene, Methyl- (Mixture of Isomers) (Lime Dienes). Unpublished report from Givaudan. RIFM report number 57578 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Ready Biodegradability of Cyclohexadiene, Methyl- (Mixture of Isomers) (Lime Dienes). Unpublished report from Givaudan. RIFM report number 59901 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Methyl Cyclohexadiene (Mixture of Isomers) in the BlueScreen HC Assay (−/+ S9 Metabolic Activation). RIFM report number 66188 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Methyl Cyclohexadiene (Mixture of Isomers): Micronucleus Test in Human Lymphocytes in Vitro. RIFM report number 68505 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. (R)-alpha-Phellandrene (Phellandren): Two-Week Repeated Oral Dose Range Finding Study in Sprague-Dawley Rats [Non-GLP]. Unpublished report from RIFM report number 72697 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Exposure Survey. 16 May 2017.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. (R)-alpha-Phellandrene (Phellandren Fraction Ex eucalyptus Oil): Combined Repeated Oral Dose Toxicity Study with the Reproduction/developmental Toxicity Screening Test in SD Rats. Unpublished report from Symrise. RIFM report number 73744 (RIFM, Woodcliff Lake, NJ, USA.).

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Baskett, 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.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. *J. Chem. Inf. Model.* 50 (5), 742–754.

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., 2015. 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.

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.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., et al., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. *Regul. Toxicol. Pharmacol.* 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. *Food Chem. Toxicol.* 74 (12), 164–176.

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.