Food and Chemical Toxicology 163 (2022) 113021

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, 3,5-dimethylcyclohexene-1--methanol, CAS Registry Number 67634-16-6

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

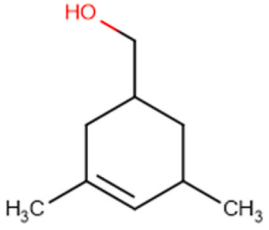
[a] *Research Institute for Fragrance Materials Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), 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: Dr. Jose Luis Domingo

Version: 120921. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: 3,5-Dimethylcyclohexene-1-methanol



(*continued on next column*)

(*continued*)

CAS Registry Number: 67634-16-6
Additional CAS Numbers*:
67634-17-7 2,4-Dimethylcyclohex-3-ene-1-methanol
*Included because the materials are a mixture of isomers.

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

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.113021
Received 9 December 2021; Accepted 11 April 2022
Available online 14 April 2022

(*continued*)

AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

3,5-Dimethylcyclohexene-1-methanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3,5-dimethylcyclohexene-1-methanol is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 3,5-dimethylcyclohexene-1-methanol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from 3,5-dimethylcyclohexene-1-methanol and read-across analog 2,4,6-trimethyl-3-cyclohexene-1-methanol (CAS # 68527-77-5) provided a No Expected Sensitization Induction Level (NESIL) of 3800 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3,5-dimethylcyclohexene-1-methanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3,5-dimethylcyclohexene-1-methanol 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.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2017b; RIFM, 2017)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 3800 μg/cm^2. RIFM (2005a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.05 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 36.8 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 32.45 mg/L (RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 32.45 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.03245 μg/L

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

1. Identification

Chemical Name: 3,5-dimethylcyclohexene-1-methanol	**Chemical Name:** 2,4-dimethylcyclohex-3-ene-1-methanol
CAS Registry Number: 67634-16-6	**CAS Registry Number:** 67634-17-7
Synonyms: 3-cyclohexene-1-methanol, 3,5-dimethyl-; 3,5-dimethylcyclohexene-1-methanol; (3,5-dimethylcyclohex-1-en-1-yl) methanol	**Synonyms:** (2,4-dimethylcyclohex-3-en-1-yl) methanol; 2,4-dimethylcyclohex-3-ene-1-methanol; 3-cyclohexene-1-methanol, 2,4-dimethyl-; floralol
Molecular Formula: $C_9H_{16}O$	**Molecular Formula:** $C_9H_{16}O$
Molecular Weight: 140.22	**Molecular Weight:** 140.22
RIFM Number: 5826	**RIFM Number:** 5827
Stereochemistry: Isomer not specified. One chiral center present, and 2 total enantiomers possible.	**Stereochemistry:** Isomer not specified. One chiral center present, and 2 total enantiomers possible.

2. Physical data*

1. **Boiling Point:** 223.88 °C (EPI Suite)
2. **Flash Point:** 76 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.88 (EPI Suite)
4. **Melting Point**: 6.17 °C (EPI Suite)
5. **Water Solubility:** 941.7 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0102 mm Hg at 20 °C (EPI Suite v4.0), 0.0171 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})

9. **Appearance/Organoleptic:** Not Available

*All physical data for both materials included in this assessment are identical.

3. Volume of use (Worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.014% (RIFM, 2021)
2. **Inhalation Exposure******:** 0.00024 mg/kg/day or 0.017 mg/day (RIFM, 2021)
3. **Total Systemic Exposure*******:** 0.00089 mg/kg/day (RIFM, 2021)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

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

6.2. Analogs Selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2,4,6-Trimethyl-3-cyclohexene-1-methanol (CAS # 68527-77-5)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

8. Natural occurrence

3,5-Dimethylcyclohexene-1-methanol and 2,4-Dimethylcyclohex-3-ene-1-methanol 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

3,5-Dimethylcyclohexene-1-methanol and 2,4-dimethylcyclohex-3-ene-1-methanol have been pre-registered for 2010; no dossiers available as of 12/09/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3,5-dimethylcyclohexene-1-methanol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.29
2	Products applied to the axillae	0.087
3	Products applied to the face/body using fingertips	1.8
4	Products related to fine fragrances	1.6
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.41
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.41
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.41
5D	Baby cream, oil, talc	0.41
6	Products with oral and lip exposure	0.96
7	Products applied to the hair with some hand contact	3.3
8	Products with significant ano-genital exposure (tampon)	0.17
9	Products with body and hand exposure, primarily rinse-off (bar soap)	3.2
10A	Household care products with mostly hand contact (hand dishwashing detergent)	11
10B	Aerosol air freshener	11
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	6.3
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3,5-dimethylcyclohexene-1-methanol, the basis was a skin sensitization NESIL of 3800 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 3,5-dimethylcyclohexene-1-methanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3,5-Dimethylcyclohexene-1-methanol 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, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 3,5-dimethylcyclohexene-1-methanol 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. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3,5-dimethylcyclohexene-1-methanol 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, 2017b). Under the conditions of the study, 3,5-dimethylcyclohexene-1-methanol was not mutagenic in the Ames test.

The clastogenic activity of 3,5-dimethylcyclohexene-1-methanol 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 3,5-dimethylcyclohexene-1-methanol in DMSO at concentrations up to 1400 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h 3,5-Dimethylcyclohexene-1-methanol did not induce binucleated cells with micronuclei when tested up to the maximum dose either with or without S9 (RIFM, 2017). Under the conditions of the study, 3,5-dimethylcyclohexene-1-methanol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 3,5-dimethylcyclohexene-1-methanol does not present a concern for genotoxic potential.

Additional References: RIFM, 2013b.

Literature Search and Risk Assessment Completed On: 04/23/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3,5-dimethylcyclohexene-1-methanol or any read-across materials. The total systemic exposure to 3,5-dimethylcyclohexene-1-methanol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3,5-dimethylcyclohexene-1-methanol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.89 μg/kg/day) is below the TTC for 3,5-dimethylcyclohexene-1-methanol (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: None.

Literature Search and Risk Assessment Completed On: 04/02/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 3,5-dimethylcyclohexene-1-methanol or any read-across materials. The total systemic exposure to 3,5-dimethylcyclohexene-1-methanol is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 3,5-dimethylcyclohexene-1-methanol or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.89 μg/kg/day) is below the TTC for 3,5-dimethylcyclohexene-1-methanol (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to 2,4,6-trimethyl-3-cyclohexene-1-methanol (CAS # 68527-77-5), 3,5-dimethylcyclohexene-1-methanol and its structural isomer 2,4-dimethylcyclohex-3-ene-1-methanol are considered skin sensitizers.

11.1.4.1. Risk assessment. Limited skin sensitization studies exist for 3,5-dimethylcyclohexene-1-methanol and the isomer 2,4-dimethylcyclohex-3-ene-1-methanol (CAS # 67634-17-7). Based on the existing data and the read-across 2,4,6-trimethyl-3-cyclohexene-1-methanol (CAS # 68527-77-5), 3,5-dimethylcyclohexene-1-methanol and its isomer 2,4-dimethylcyclohex-3-ene-1-methanol are considered a weak skin sensitizer. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material 2,4,6-trimethyl-3-cyclohexene-1-methanol was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and U937-CD86 test, but positive in the h-CLAT (RIFM, 2014; RIFM, 2015; RIFM, 2018). The predictions in the *in chemico* and *in vitro* tests were not supported by *in vivo* data on the read-across material. The read-across material 2,4,6-trimethyl-3-cyclohexene-1-methanol was found to be non-sensitizing in a murine local lymph node assay (LLNA) up to 25% (6250 μg/cm^2) (RIFM, 2005a), whereas sensitization reactions were observed in a Buehler study at 60% with 7/10 (RIFM, 1981). The target material was predicted to be a sensitizer in a guinea pig maximization test with 100% 3,5-dimethylcyclohexene-1-methanol, as sensitization reactions were observed in 6/20 test group animals (RIFM, 1986). In 2 separate Confirmation of No Induction in Humans tests (CNIHs) with less than 100 subjects each, the target material 2,4-dimethylcyclohex-3--ene-1-methanol did not induce sensitization reactions at 10% (5000 μg/cm^2 and 7752 μg/cm^2) (RIFM, 1983b; RIFM, 1983c). The No Observed Effect Level (NOEL) was derived from a 103-subject CNIH with 3.3% (3897 μg/cm^2) of read-across material 2,4,6-trimethyl-3-cyclohexene-1-methanol in 1:3 ethanol:diethyl phthalate (RIFM, 2005b). In additional CNIHs with less than 100 subjects, the read-across material 2,4,6-trimethyl-3-cyclohexene-1-methanol did induce sensitization reactions at 10% or (5000 μg/cm^2) (RIFM, 1982) or 5% (2500 μg/cm^2) (RIFM, 1983a).

Based on the available data on read-across 2,4,6-trimethyl-3-cyclohexene-1-methanol, summarized in Table 1, 3,5-dimethylcyclohexene-1-methanol is considered to be a skin sensitizer with a defined NESIL of 3800 μg/cm^2(see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/05/21.

Table 1
Data summary for 2,4,6-trimethyl-3-cyclohexene-1-methanol.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
>6250 [1]	Weak sensitizer	3897	NA	5000	3800

NOEL = No observed effect level; LOEL = lowest observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.5. Phototoxicity/Photoallergenicity

Based on the available UV/Vis spectra, 3,5-dimethylcyclohexene-1-methanol 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 3,5-dimethylcyclohexene-1-methanol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 3,5-dimethylcyclohexene-1-methanol does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/13/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 3,5-dimethylcyclohexene-1-methanol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 3,5-dimethylcyclohexene-1-methanol. Based on the Creme RIFM Model, the inhalation exposure is 0.017 mg/day. This exposure is 82 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/16/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3,5-dimethylcyclohexene-1-methanol 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, 3,5-dimethylcyclohexene-1-methanol 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 3,5-dimethylcyclohexene-1-methanol 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 etal., 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 3,5-dimethylcyclohexene-1-methanol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 3,5-Dimethylcyclohexene-1-methanol has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	32.45			1000000	0.03245	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	2.88	2.88
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 Volumes for all CAS #

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

The RIFM PNEC is 0.03245 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/29/21.

12. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 12/09/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113021.

Appendix

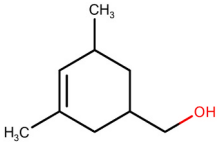
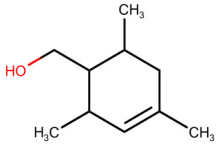
Read-across Justification

Methods

The read-across analog(s) was/were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, 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 material and the read-across analogs were calculated using EPI Suite (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	3,5-Dimethylcyclohexene-1-methanol	2,4,6-Trimethyl-3-cyclohexene-1-methanol
CAS No.	67634-16-6	68527-77-5
Structure		
Similarity (Tanimoto Score)		0.87
	CC1CC(CO)CC(C)=C1	CC1CC(C)=CC(C)C1CO
Endpoint		Skin sensitization
Molecular Formula	$C_9H_{16}O$	$C_{10}H_{18}O$
Molecular Weight	140.226	154.253
Melting Point (°C, EPI Suite)	6.17	13.51
Boiling Point (°C, EPI Suite)	223.88	237.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.28E+00	9.96E-01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	9.42E+02	3.60E+02
Log K_{OW}	2.88	3.3
J_{max} (μg/cm^2/h, SAM)	83.83	38.03
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.21E+00	1.60E+00
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.
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 the target material, 3,5-dimethylcyclohexene-1-methanol (CAS # 67634-16-6). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 2,4,6-trimethyl-3-cyclohexene-1-methanol (CAS # 68527-77-5) was identified as a read-across material with data for the skin sensitization endpoint.

Conclusion

- 2,4,6-Trimethyl-3-cyclohexene-1-methanol (CAS # 68527-77-5) was used as a read-across analog for the target material 3,5-dimethylcyclohexene-1-methanol (CAS # 67634-16-6) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of alkyl cyclic alcohols.
  - o The target material and the read-across analog share a cyclohexene-1-methanol fragment.
  - o The key difference between the target material and the read-across analog is that the target has 2 methyl substitutions on the cyclohexene ring, whereas the read-across material has 3 methyl substitutions. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material 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 material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no *in silico* alerts for the target material and the read-across analog. The *in silico* profile is consistent with the data.

- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the skin sensitization endpoint 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., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 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, November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

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.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

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/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Delayed Contact Hypersensitivity Study on 2,4,6-Trimethyl-3-Cyclohexene-1-Methanol (Isocyclogeraniol) in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 21789.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Evaluation of Potential Irritation and Sensitization Hazards by Dermal Contact of 2,4,6-Trimethyl-3-Cyclohexene-1-Methanol (Isocyclogeraniol) in Humans. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 21790.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983a. Evaluation of Potential Hazards by Dermal Contact of 2,4,6-Trimethyl-3-Cyclohexene-1-Methanol (Isocyclogeraniol) in Humans. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 21792.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983b. Repeated Insult Patch Test with 2,4-Dimethylcyclohex-3-Ene-1-Methanol. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 51024.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983c. Repeated Insult Patch Test with 2,4-Dimethylcyclohex-3-Ene-1-Methanol. Unpublished Report from International Flavors and Fragrances. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 51025.

RIFM (Research Institute for Fragrance Materials, Inc.), 1986. 2,4-Dimethylcyclohex-3-ene-1-methanol (Vert): Magnusson & Kligman Maximisation Study in the guinea Pig. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 59908.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. 2,4,6-Trimethyl-3-cyclohexene-1-methanol (Isocyclogeraniol) Diluted with Vehicle 1:3 EtOH:DEP: Local Lymph Node Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 48755.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005b. Repeated Insult Patch Test with 2,4,6-Trimethyl-3-Cyclohexene-1-Methanol. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 49110.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. Report on the Testing of 3,5-Dimethylcyclohexene-1-Methanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 66075.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Report on the Testing of 2,4-Dimethylcyclohex-3-Ene-1-Methanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 66757.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Fragrance Material in Vitro Sensitization: Direct Peptide Reactivity Assay (DPRA). RIFM Report Number 68623. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Induction of Antioxidant-Response Element Dependent Gene Activity Cytotoxicity (Using MTT) in the Keratinocyte ARE- Reporter Cell Line Keratinosens. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69647.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. 3,5-Dimethylcyclohexene-1-methanol: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 71523.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017b. 3,5-Dimethylcyclohexene-1-methanol: Bacterial Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 71809.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Non-animal Methods to Predict Skin Sensitization (I): the Cosmetics Europe Database. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 73469.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76272.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76775.

RIFM (Research Institute for Fragrance Materials, Inc.), 2021. Exposure Survey, 31, March 2021.

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.

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., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 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, 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, v2.0. United States Environmental Protection Agency, Washington, DC, USA.