Food and Chemical Toxicology 163 (2022) 113028

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, tetrahydromuguol, CAS Registry Number 41678-36-8

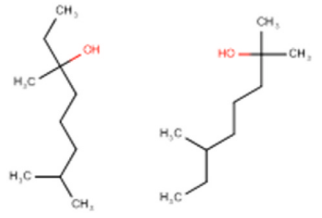
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. 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: 121521. 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.



(*continued on next column*)

(*continued*)

Name: Tetrahydromuguol
CAS Registry Number: 41678-36-8

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

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.113028
Received 15 December 2021; Accepted 12 April 2022
Available online 15 April 2022

(*continued*)

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.

Tetrahydromuguol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydromuguol is not genotoxic. Data on read-across analog 2,6-dimethyl-2-heptanol (CAS # 13254-34-7) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog tetrahydrolinalool (CAS # 78-69-3) provided tetrahydromuguol a No Expected Sensitization Induction Level (NESIL) of 11000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; tetrahydromuguol is not phototoxic and not expected to be photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to tetrahydromuguol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; tetrahydromuguol 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, 2016; RIFM, 2017a)
Repeated Dose Toxicity: NOAEL = 238 mg/kg/day.	RIFM (2015)
Reproductive Toxicity: Developmental toxicity and Fertility: NOAEL = 714 mg/kg/day.	RIFM (2015)
Skin Sensitization: NESIL = 11000 μg/cm^2.	RIFM (2021)
Phototoxicity/Photoallergenicity: Not phototoxic/not expected to be photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 1981)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 37% (OECD 301C)	RIFM (2000)
Bioaccumulation: Screening-level: 103 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia* LC50: 0.281 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia* LC50: 0.281 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0281 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Tetrahydromuguol
2. **CAS Registry Number:** 41678-36-8
3. **Synonyms:** 3,7 & 2,6-Dimethyl-2-octenol; 3,7-Dimethylocten-2-ol; Tetrahydro allo-ocimenol; 3,7-Dimethyloct-1-en-2-ol; Tetrahydro muguol
4. **Molecular Formula:** $C_{10}H_{20}O$
5. **Molecular Weight:** 154.25 g/mol
6. **RIFM Number:** 560
7. **Stereochemistry:** Stereoisomer not specified. One chiral center present and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 198 °C (Fragrance Materials Association [FMA]), 228.21 °C (EPI Suite)
2. **Flash Point:** 80 °C (Globally Harmonized System), 176 °F; CC (FMA)
3. **Log K_{OW}:** 3.56 (EPI Suite)
4. **Melting Point**: -12.16 °C (EPI Suite)
5. **Water Solubility:** 211.8 mg/L (EPI Suite)
6. **Specific Gravity:** 0.834 (FMA)
7. **Vapor Pressure:** 0.00776 mm Hg at 20 °C (EPI Suite v4.0), 0.013 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:** A colorless liquid

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015).

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 1.8% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0033 mg/kg/day or 0.20 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.018 mg/kg/day (RIFM, 2019)

*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

1. **Cramer Classification:** Class I, Low* (Expert Judgment)

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

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** 2,6-Dimethyl-2-heptanol (CAS # 13254-34-7)
   c. **Reproductive Toxicity:** 2,6-Dimethyl-2-heptanol (CAS # 13254-34-7)
   d. **Skin Sensitization:** Tetrahydrolinalool (CAS # 78-69-3)
   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

Tetrahydromuguol is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Tetrahydromuguol has been pre-registered for 2010; no dossier available as of 12/15/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for tetrahydromuguol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.18
2	Products applied to the axillae	0.25
3	Products applied to the face/body using fingertips	0.18
4	Products related to fine fragrances	4.7
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.2
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.18
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.18
5D	Baby cream, oil, talc	0.061
6	Products with oral and lip exposure	0.18
7	Products applied to the hair with some hand contact	0.18
8	Products with significant ano-genital exposure (tampon)	0.061
9	Products with body and hand exposure, primarily rinse-off (bar soap)	9.2
10A	Household care products with mostly hand contact (hand dishwashing detergent)	24
10B	Aerosol air freshener	9.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.061
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 tetrahydromuguol, the basis was the subchronic reference dose of 2.38 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 11000 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).
cCalculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, tetrahydromuguol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Tetrahydromuguol 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, 2014). 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 and clastogenic effects of the target material.

The mutagenic activity of tetrahydromuguol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with tetrahydromuguol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. A small increase in the mean number of revertant colonies was observed at 15 μg/plate in absence of S9 (RIFM, 2016). However, there was no indication of dose-response, no reproducibility, and it was within the historical control range. Therefore, the increase was not considered biologically relevant. Under the conditions of the study, tetrahydromuguol was not mutagenic in the Ames test.

The clastogenic activity of tetrahydromuguol 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 tetrahydromuguol in DMSO at concentrations of/up to 1563 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 360 μg/mL in the presence and absence of metabolic activation. Tetrahydromuguol did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, tetrahydromuguol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, tetrahydromuguol does not present a concern for genotoxic potential.

Additional References: RIFM, 2014.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for tetrahydromuguol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on tetrahydromuguol. Read-across material 2,6-dimethyl-2-heptanol (CAS # 13254-34-7; see Section VI) has sufficient data for the repeated dose toxicity endpoint. In a GLP and OECD 422-compliant study, 10 SPF-bred Wistar Han rats/sex/dose were administered 2,6-dimethyl-2-heptanol via the diet at doses of 0, 1000, 3000, and 10000 ppm (corresponding to 0, 70, 228, and 714 mg/kg/day for males and 0, 80, 251, and 830 mg/kg/day for females, according to the study report). Males were treated for 29 days (2 weeks prior to mating, during mating, and up to termination); females were treated for 39–57 days (during 2 weeks prior to mating, during mating, during postcoitum, and during at least 4 days of lactation). No mortality occurred throughout the treatment period. No treatment-related effects were seen in clinical appearance, functional observations, clinical laboratory investigations, or gross necropsy. Bodyweight gains were decreased in males at the high dose, but this was attributed to palatability issues. Cortical hyaline droplets were detected with increased incidence and severity in the kidneys of males at the high dose, but this was attributed to α-2u-globulin nephropathy (immunohistochemistry not mentioned). α-2u-Globulin nephropathy is specific to male rats and thus not considered relevant to human health. Absolute liver weights were increased in both sexes at the high dose, but this effect was only statistically significant in females. Relative liver weights were increased in both sexes at the high dose, and this effect was statistically significant in both sexes. However, there were no accompanying histopathological liver effects. In the absence of treatment-related adverse effects up to the highest dose, the NOAEL for this study was considered to be 714 mg/kg/day (RIFM, 2015).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 714/3 or 238 mg/kg/day.

Therefore, the tetrahydromuguol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,6-dimethyl-2-heptanol NOAEL in mg/kg/day by the total systemic exposure to tetrahydromuguol, 238/0.018, or 13222.

In addition, the total systemic to tetrahydromuguol (18 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.

11.1.2.1.1. Derivation of subchronic RfD. 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) and a subchronic reference dose (RfD) of 2.38 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for tetrahydromuguol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 238 mg/kg/day by the uncertainty factor, 100 = 2.38 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/21.

11.1.3. Reproductive toxicity

The MOE for tetrahydromuguol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on tetrahydromuguol. Read-across material 2,6-dimethyl-2-heptanol (CAS # 13254-34-7; see Section VI) has sufficient data for the reproductive toxicity endpoint. In a GLP and OECD 422-compliant study, 10 SPF-bred Wistar Han rats/sex/dose were administered 2,6-dimethyl-2-heptanol via the diet at doses of 0, 1000, 3000, and 10000 ppm (corresponding to 0, 70, 228, and 714 mg/kg/day for males and 0, 80, 251, and 830 mg/kg/day for females, according to the study report). Males were treated for 29 days (2 weeks prior to mating, during mating, and up to termination); females were treated for 39–57 days (during 2 weeks prior to mating, during mating, during postcoitum, and during at least 4 days of lactation). No mortality occurred throughout the treatment period. No treatment-related adverse effects were observed on mating, fertility and conception indices, precoital time, number of corpora lutea and implantation sites, gestation index and duration, parturition, maternal care, sex ratio, or early postnatal pup development (mortality, clinical signs, body weights, and macroscopic examination). In the absence of treatment-related adverse effects up to the highest dose, the developmental toxicity and fertility NOAEL for this study was considered to be 714 mg/kg/day (RIFM, 2015).

Therefore, the tetrahydromuguol MOE for the developmental toxicity and fertility endpoints can be calculated by dividing the 2,6-dimethyl-2-heptanol NOAEL in mg/kg/day by the total systemic exposure to tetrahydromuguol, 714/0.018, or 39666.

In addition, the total systemic to tetrahydromuguol (18 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity and fertility endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

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

21.

11.1.4. Skin sensitization

Based on the existing data and read-across material tetrahydrolinalool (CAS # 78-69-3), tetrahydromuguol is considered a skin sensitizer with a defined NESIL of 11000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for tetrahydromuguol. Based on the existing data and read-across material tetrahydrolinalool (CAS # 78-69-3; see Section VI), tetrahydromuguol is considered a 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). In a murine local lymph node assay (LLNA), read-across material tetrahydrolinalool was found to be sensitizing with an EC3 value of 7.6% (1900 μg/cm^2) (ECHA, 2011; RIFM, 2017b). In a human maximization test, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 tetrahydromuguol (RIFM, 1974). In another human maximization test, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 read-across material tetrahydrolinalool (RIFM, 1976). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 12.5% or 9690 μg/cm^2 of tetrahydromuguol in 95% ethanol, no reactions indicative of sensitization were observed in any of the 40 volunteers (RIFM, 1964). In 2 more CNIH tests with 27% or 11250 μg/cm^2 and 10% or 4132 μg/cm^2 of read-across material tetrahydrolinalool in 1:3 alcohol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 109 and 110 volunteers, respectively (RIFM, 2021; RIFM, 2020c).

Based on weight of evidence (WoE) from structural analysis, human studies, and data on the read-across material tetrahydrolinalool, tetrahydromuguol is a sensitizer with a WoE NESIL of 11000 μg/cm^2 (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) and a subchronic reference dose of 2.38 mg/kg/day.

Additional References: ECHA, 2011; RIFM, 1982.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the existing data and UV/Vis absorption spectra, tetrahydromuguol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. 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. Additionally, in a human phototoxicity study, no reactions indicative of a phototoxic response were observed after application of 5.5% tetrahydromuguol and UV exposure (RIFM, 1981). Based on the human study data and the lack of absorbance, tetrahydromuguol 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, 1000 L mol^{-1} • cm^{-1}, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for tetrahydromuguol 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 tetrahydromuguol. Based on the Creme RIFM Model, the inhalation exposure is 0.20 mg/day. This exposure is 7.0 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: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydromuguol 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, tetrahydromuguol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified tetrahydromuguol as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value

Table 1
Data Summary for tetrahydrolinalool as read-across material for tetrahydromugoul

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
1900 [1]	Moderate	11250	2760	NA	11000

NOEL = No observed effect level; CNIH= Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; 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.

< 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

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

11.2.3. Key studies

11.2.3.1. Biodegradation. **RIFM, 2000**: The ready biodegradability of the test material was evaluated using the modified MITI test according to the OECD 301C guideline. Biodegradation of 5.1% by BOD and 37% by GC was observed after 28 days.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

Tetrahydromuguol has been pre-registered for REACH with no additional data at this time.

11.2.5. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.56	3.56
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0281 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/03/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	9.14			1000000	0.00914	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.771	0.281	2.885	10000	0.0281	Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** v1.11	5.148	3.375	4.552			Neutral Organic SAR (Baseline Toxicity)

- **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 12/15/21.

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.2022.113028.

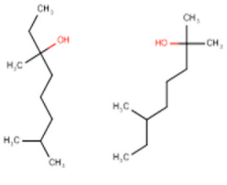
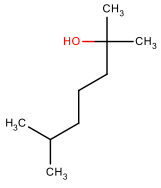
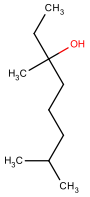
Appendix

Read-across Justification

Methods

The read-across analogs 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	Read-across Material
Principal Name	Tetrahydromuguol	2,6-Dimethyl-2-heptanol	Tetrahydrolinalool
CAS No.	41678-36-8	13254-34-7	78-69-3
Structure			
Similarity (Tanimoto Score)		0.61	1.0
Endpoint		• Repeated dose toxicity • Reproductive toxicity	• Skin sensitization
Molecular Formula	$C_{10}H_{22}O$, $C_{10}H_{22}O$	$C_9H_{20}O$	$C_{10}H_{22}O$
Molecular Weight (g/mol)	158.28, 158.28	144.26	158.28
Melting Point (°C, EPI Suite)	31.5, −11.77	−23.45	31.50
Boiling Point (°C, EPI Suite)	196.5, 192.8	173.00	196.50
Vapor Pressure (Pa @ 25 °C, EPI Suite)	9.50, 15.2 188.9, 188.9	48.53 572.00	9.51 188.90

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)			
Log K_{OW}	3.6, 3.6	3.11	3.60
J_{max} (μg/cm^2/h, SAM)	23.79, 23.799	59.55	23.79
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.54, 5.54	4.17	5.54
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	
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 domain alerts identified.		No skin sensitization reactivity domain 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	See Supplemental Data 3

Summary

There are insufficient toxicity data on tetrahydromuguol (CAS # 41678-36-8). 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, 2,6-dimethyl-2-heptanol (CAS # 13254-34-7) and tetrahydrolinalool (CAS # 78-69-3) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 2,6-Dimethyl-2-heptanol (CAS # 13254-34-7) was used as a read-across analog for the target material, tetrahydromuguol (CAS # 41678-36-8), for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog belong to a class of tertiary alcohols.
  - o The key difference between the target material and the read-across analog is that the target material has a C8 long branched alkyl chain whereas the read-across analog has a C7 long branched alkyl chain. Moreover, the hydroxy group in the target is at the third position whereas it is at the second position in the read-across analog. These structural differences are toxicologically insignificant.
  - o 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 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 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Tetrahydrolinalool (CAS # 78-69-3) was used as a read-across analog for the target material, tetrahydromuguol (CAS # 41678-36-8), for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a class of tertiary alcohols.
  - o The key difference between the target material and the read-across analog is that the target material is an isomer of the read-across analog. This structural difference is toxicologically insignificant.
  - o 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 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 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

Q1. Normal constituent of the body? No.

Q2. Contains functional groups associated with enhanced toxicity? No.

Q3. Contains elements other than C, H, O, N, and divalent S? No.

Q43. Possibly harmful divalent sulfur (not detected via Q3) No.

Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q42. Possibly harmful analog of benzene No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No.
Q17. Readily hydrolyzed to a common terpene? Yes.
Q18. One of the list? (see Cramer et al., 1978 for detailed explanation on list of categories) No, Low (Class I).

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.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of Cramer classification between Toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

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.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2011. 3,7-Dimethyloctan-3-ol registration dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/14146/1/2.

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.), 1964. Repeated Insult Patch Test with Tetrahydromuguol. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 50549.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1801. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1976. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1796.

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Phototoxicity Testing of Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 47075.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Toxicology Studies of Tetrahydrolinalool in the guinea Pig. Unpublished Report from Takasago International Corporation. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 35061.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000. Hydroxycitronellal, 6-octenal, 3,7-dimethyl-, (3R)- ((+)-citronellal), 6-octenal, 3,7-dimethyl-, (3S)- ((-)-citronellal) and Tetrahydromuguol (Linacsol): Test on Biodegradability by Microorganisms. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Takasago International Corporation. RIFM report number 74036.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Report on the Testing of Tetrahydromuguol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 67084.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. 2,6-Dimethyl-2-heptanol (Dimetol): Combined 28-day Repeated Dose Toxicity Study with the Reproductive/developmental Toxicity Screening Test in Rats by Dietary Administration. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71895.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Tetrahydromuguol (3,7-Dimethylocten-2-Ol): Reverse Mutation Assay 'Ames Test' Using Salmonella typhimurium and Escherichia coli. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 70262.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017a. Tetrahydromuguol (3,7-Dimethylocten-2-Ol): Micronucleus Test in Human Lymphocytes in Vitro. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 71557.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017b. Tetrahydrolinalool: Murine Local Lymph Node Assay (LLNA). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from BASF. RIFM report number 72569.

RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey, 24, March 2019.

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.), 2020c. Tetrahydrolinalool: Repeated Insult Patch Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 76636.

RIFM (Research Institute for Fragrance Materials, Inc.), 2021. Tetrahydrolinalool: Repeated Insult Patch Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 77095.

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.