Food and Chemical Toxicology 163 (2022) 113026

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, dihydromyrcenyl acetate, CAS Registry Number 53767-93-4

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: 111721. 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*)

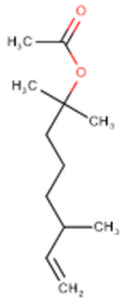
Name: Dihydromyrcenyl acetate
CAS Registry Number: 53767-93-4

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.113026
Received 19 November 2021; Accepted 12 April 2022
Available online 15 April 2022

(*continued*)



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
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., 2020)
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 (Safford et al., 2017; Comiskey 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, 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

(*continued on next column*)

(*continued*)

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.

Dihydromyrcenyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that dihydromyrcenyl acetate is not genotoxic. Data on read-across analogs dihydromyrcenol (CAS # 18479-58-8) and acetic acid (CAS # 64-19-7) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog ocimenyl acetate (CAS # 72214-23-4) provided dihydromyrcenyl acetate a No Expected Sensitization Induction Level (NESIL) of 2200 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; dihydromyrcenyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; dihydromyrcenyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1979a; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day.	RIFM (2007)
Reproductive Toxicity: Developmental toxicity: NOAEL = 500 mg/kg/day. Fertility: NOAEL = 500 mg/kg/day.	(RIFM, 2009; RIFM, 2007)
Skin Sensitization: NESIL = 2200 μg/cm^2.	RIFM (2013b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra; RIFM Database; RIFM, 1980b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 87.7% (OECD 301B)	RIFM (1996)
Bioaccumulation:	
Screening-level: 414 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 0.937 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, 2002)
Critical Ecotoxicity Endpoint 96-h Algae EC50: 0.937 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0937 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** Dihydromyrcenyl acetate
2. **CAS Registry Number:** 53767-93-4
3. **Synonyms:** 2,6-Dimethyloct-7-en-2-yl acetate; 7-Octen-2-ol, 2,6-dimethyl-, acetate; 1,1,5-Trimethylhept-6-en-1-yl acetate; Dihydromyrcenyl acetate
4. **Molecular Formula:** $C_{12}H_{22}O_2$
5. **Molecular Weight:** 198.3
6. **RIFM Number:** 1124
7. **Stereochemistry:** No stereoisomer specified. One stereocenter and a total of 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 216.93 °C (EPI Suite), 210 °C (483 K) (RIFM, 2016a)
2. **Flash Point:** 80 °C (Globally Harmonized System), 176 °F; CC (Fragrance Materials Association [FMA]), 81.5 °C (mean rounded off to the nearest 0.5 °C) (RIFM, 2016c)
3. **Log K_{OW}:** 4.47 (EPI Suite), v4.0 (RIFM, 2016b)
4. **Melting Point**: -3.58 °C (EPI Suite)
5. **Water Solubility:** 6.77 mg/L (EPI Suite)
6. **Specific Gravity:** 0.873 (FMA)
7. **Vapor Pressure:** 0.102 mm Hg at 20 °C (EPI Suite v4.0), 0.08 mm Hg at 20 °C (FMA), 0.153 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \bullet cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless mobile liquid that has a sweet, spicy-herbaceous, fresh, and somewhat fruity odor with Bergamot-Lime character and moderate to poor tenacity

3. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.53% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0014 mg/kg/day or 0.094 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.019 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (RIFM, 2015; Safford, 2015; Safford, 2017; Comiskey, 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 (RIFM, 2015; Safford, 2015; Safford, 2017; Comiskey, 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	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Dihydromyrcenol (CAS # 18479-58-8) and acetic acid (CAS # 64-19-7)
   c. **Reproductive Toxicity:** Dihydromyrcenol (CAS # 18479-58-8) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** Ocimenyl acetate (CAS # 72214-23-4)
   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

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

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

9. REACH Dossier

Available; accessed 03/24/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for dihydromyrcenyl acetate 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)	0.0025
2	Products applied to the axillae	0.050
3	Products applied to the face/body using fingertips	0.20
4	Products related to fine fragrances	0.94
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.24
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.24
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.24
5D	Baby cream, oil, talc	0.080
6	Products with oral and lip exposure	0.0025
7	Products applied to the hair with some hand contact	0.23
8	Products with significant ano-genital exposure (tampon)	0.080
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.29
10B	Aerosol air freshener	2.5
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.080
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 dihydromyrcenyl acetate, the basis was the reference dose of 0.50 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2200 $\mu g/cm^2$.
[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).
[c]Calculations 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, dihydromyrcenyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Dihydromyrcenyl acetate was assessed in the BlueScreen assay and found negative for toxicity (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 dihydromyrcenyl acetate has been evaluated in a bacterial reverse mutation assay conducted similarly to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with dihydromyrcenyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5.0 μL/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1979a). Under the conditions of the study, dihydromyrcenyl acetate was not mutagenic in the Ames test.

The clastogenic activity of dihydromyrcenyl acetate 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 dihydromyrcenyl acetate in DMSO at concentrations up to 1983 μg/mL in the presence and absence of S9 for 3 h and in the absence of metabolic activation for 24 h. Dihydromyrcenyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, dihydromyrcenyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on dihydromyrcenyl acetate. Dihydromyrcenyl acetate is expected to be hydrolyzed to dihydromyrcenol (CAS # 18479-58-8) and acetic acid (CAS # 64-19-7).

Based on the available data (EFSA, 2012; WHO, 2006), acetic acid does not show specific reproductive toxicity. Thus, acetic acid does not pose any systemic (repeated dose) or reproductive toxicity to human health when used in fragrances.

Hydrolysis product dihydromyrcenol has sufficient repeated dose toxicity data. An OECD 408 gavage 90-day subchronic study was conducted to investigate the systemic toxicity of the test material, dihydromyrcenol, which is a mixture of 44.2% 2,6-dimethyl-7-octen-2-ol and 54.8% 2,6-dimethyl-7-octen-2-yl formate. The test material was administered via gavage to 4 groups of 10 Sprague Dawley Crl:CD(SD) IGS BR strain rats/sex/dose for 90 consecutive days at dose levels of 0, 10, 50, 500, or 1000 mg/kg/day. Bodyweight gains were reduced among the animals treated with 50, 500, and 1000 mg/kg/day. Hematological alterations were reported among the animals of the 500 and 1000 mg/kg/day dose groups. However, hematological alterations were not considered to be related to treatment with dihydromyrcenol (RIFM, 2010). The absolute and relative liver weights were increased for the males treated at 50 mg/kg/day and higher, while this was only seen in the females treated at 500 and 1000 mg/kg/day. The absolute and relative kidney weights were increased for both the males and females of the 500 and 1000 mg/kg/day dose groups. There were no macroscopic abnormalities reported. Histopathological examination revealed adaptive alterations in the liver among the animals of the 500 and 1000 mg/kg/day dose groups. α-2u-Globulin-related nephropathy was reported among the treated males. Adipose infiltration of the bone marrow was reported among the males of the high-dose group, indicative of marrow hypoplasia. There was no dose response. No changes were observed at 50 mg/kg/day for the females; thus, the NOEL for the females was considered to be 50 mg/kg/day. The kidney changes were identified histopathologically and confirmed with Mallory's Heidenhain staining and were found to be consistent with hydrocarbon nephropathy, which is not relevant to humans (RIFM, 2007). Thus, the NOAEL for the repeated dose toxicity was considered to be 50 mg/kg/day based on a decrease in bodyweight gains among the 500 and 1000 mg/kg/day dose groups.

Therefore, the dihydromyrcenyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the dihydromyrcenol NOAEL in mg/kg/day by the total systemic exposure to dihydromyrcenyl acetate, 50/0.019, or 2632.

In addition, the total systemic exposure to dihydromyrcenyl acetate (19 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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 reference dose (RfD) of 0.50 mg/kg/day.

11.1.2.1.1. Derivation of RfD. The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for dihydromyrcenyl acetate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.50 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on dihydromyrcenyl acetate. Dihydromyrcenyl acetate is expected to be hydrolyzed to dihydromyrcenol (CAS # 18479-58-8) and acetic acid (CAS # 64-19-7).

Acetic acid has been reviewed by EFSA (EFSA, 2012), NICNAS (NICNAS, 2013), and JECFA (WHO, 2006) for its use as a food additive and by CIR (CIR, 2010) for its use in cosmetics. It was concluded that acetic acid does not show specific reproductive or developmental toxicity. Acetic acid is recognized as Generally Recognized as Safe by the US FDA and is estimated to be consumed by humans at about 1 g/day for centuries without any adverse effects. Furthermore, estimations of the daily intake of acetic acid have also been reported to vary from about 1 to 2.1 g per day for subjects older than 2 years (NICNAS, 2013).

The hydrolysis product dihydromyrcenol has sufficient reproductive toxicity data.

A GLP developmental toxicity study was conducted with test

material dihydromyrcenol, which is a mixture of 44.2% 2,6-dimethyl-7-octen-2-ol and 54.8% 2,6-dimethyl-7-octen-2-yl formate. Groups of 25 pregnant Sprague Dawley rats/dose were administered via gavage the test material, dihydromyrcenol, at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil on gestation days (GD) 7–17. The high-dose females were reported to have a reduction in bodyweight gain and food consumption. Secondary to the maternal reduction in body weights, there was a reduction in fetal body weight among the high-dose group. The high-dose group fetuses were reported to have reversible variations in ossification, which include retarded ossification of the metatarsal bones in the hind paws and an increase in supernumerary thoracic ribs with associated increases or decreases in thoracic and lumbar vertebrae, respectively. The reported fetal effects were considered to be reversible minor variations and often occurred at maternally toxic doses. Thus, the maternal and developmental toxicity NOELs of 500 mg/kg/day were considered for dihydromyrcenol. It was concluded that dihydromyrcenol was not a selective developmental toxicant in rats under the conditions of this study (RIFM, 2009). An *in vitro* dermal absorption study was conducted with dihydromyrcenol on human skin. Under the most severe conditions, occluded in a 70:30 ethanol:water vehicle, only 5.67% of dihydromyrcenol was absorbed (RIFM, 2008).

Therefore, the dihydromyrcenyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the dihydromyrcenol NOAEL in mg/kg/day by the total systemic exposure to dihydromyrcenyl acetate, 500/0.019 or 26316.

An OECD 408 gavage 90-day subchronic study was conducted to investigate the systemic toxicity of the test material, dihydromyrcenol, a mixture of 44.2% 2,6-dimethyl-7-octen-2-ol and 54.8% 2,6-dimethyl-7-octen-2-yl formate. The test material was administered via gavage to 4 groups of 10 Sprague Dawley Crl:CD(SD)IGS BR strain rats/sex/dose for 90 consecutive days at dose levels of 0, 10, 50, 500, or 1000 mg/kg/day. Estrous cycle measurements and sperm analysis were performed on all the high-dose females and males at necropsy. There were no alterations in the female reproductive parameters observed. There was a significant decrease in spermatid count among the high-dose group animals. However, the study report concluded that these effects were not considered to be adverse due to the absence of any histopathological correlations. A conservative NOAEL of 500 mg/kg/day was considered for this safety assessment, based on alterations in the male reproductive system at the highest dose group (RIFM, 2007). An *in vitro* dermal absorption study was conducted with dihydromyrcenol on human skin. Under the most severe conditions, occluded in a 70:30 ethanol:water vehicle, only 5.7% of dihydromyrcenol was absorbed (RIFM, 2008). **Therefore, the dihydromyrcenyl acetate MOE for the fertility endpoint can be calculated by dividing the dihydromyrcenol NOAEL in mg/kg/day by the total systemic exposure to dihydromyrcenyl acetate, 500/0.019, or 26316.**

In addition, the total systemic exposure to dihydromyrcenyl acetate (19 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 03/09/21.

11.1.4. Skin sensitization

Based on the existing data and read-across ocimenyl acetate (CAS # 72214-23-4), dihydromyrcenyl acetate is considered a sensitizer with a defined NESIL of 2200 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for dihydromyrcenyl acetate. Based on the existing data and read-across analog ocimenyl acetate (CAS # 72214-23-4; see Section VI), dihydromyrcenyl acetate is considered a sensitizer with a NESIL of 2200 μg/cm^2. The chemical structure of these materials indicates that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In guinea pigs, a maximization test and a Buehler test did not present reactions indicative of sensitization to dihydromyrcenyl acetate (RIFM, 1979b; RIFM, 1979c). In a human maximization test, skin sensitization reactions were observed with 4% or 2760 μg/cm^2 of read-across ocimenyl acetate; however, in another human maximization test, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 of read-across ocimenyl acetate when tested 2 months later (RIFM, 1974). In a modified Shelanski-Shelanski repeat insult patch test with 5000 μg/cm^2 dihydromyrcenyl acetate in alcohol SDA 39C, a questionable reaction was observed in 1 of the 53 volunteers (RIFM, 1980a). However, in a Confirmation of No Induction in Humans test (CNIH) with 2204 μg/cm^2 of read-across analog ocimenyl acetate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2013b).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across analog ocimenyl acetate, dihydromyrcenyl acetate is a sensitizer with a WoE NESIL of 2200 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) and an RfD of 0.50 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/28/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV absorption spectra and *in vivo* study data, dihydromyrcenyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In a guinea pig phototoxicity/photoallergenicity study, 10% dihydromyrcenyl acetate in ethanol did not result in any reactions (RIFM, 1980b). Based on the *in vivo* study data and the lack of absorbance, dihydromyrcenyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/02/21.

Table 1
Data summary for ocimenyl acetate as read-across for dihydromyrcenyl acetate.

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
NA	NA	2204	2760	2760	2200

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.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for dihydromyrcenyl acetate 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 dihydromyrcenyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.094 mg/day. This exposure is 14.9 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of dihydromyrcenyl acetate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, dihydromyrcenyl acetate 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) did not identify dihydromyrcenyl acetate 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), dihydromyrcenyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1996**:** Biodegradation of the test material was evaluated by the sealed vessel test according to the OECD 301B method. Dihydromyrcenyl acetate (10 mg/L) was incubated with filtered activated sludge for 28 days. The rate of degradation after 28 days was 87.7%.

RIFM, 2001**:** Ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. Under the conditions of the study, the biodegradation achieved a maximum of 30% after 28 days.

11.2.2.1.2. Ecotoxicity. RIFM, 2000**:** An acute immobilization study (limit test) was conducted with *Daphnia magna* according to the OECD 202I method under static conditions. There was no biologically significant effect (≤10%) determined in the saturated solution (5.8 mg/L) and control.

RIFM, 2016d**:** A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions and in a closed system. Under the conditions of this study, the 48-h EC50 based on the mean measured concentration was reported to be 1.3 mg/L.

RIFM, 2016e**:** An algae growth inhibition test was conducted according to the OECD 201 method. Under the conditions of the study, based on the mean measured concentration the EC50 for growth rate inhibition (72-h ERC50) was 5.4 mg/L, and the EC50 for yield inhibition (72-h EYC50) was 2.5 mg/L. The EC10 values based on the mean measured concentration for growth rate and yield were reported to be 2.9 mg/L and 1.2 mg/L, respectively.

11.2.2.1.3. Other available data. Dihydromyrcenyl acetate has been registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement. Since dihydromyrcenyl acetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.0	4.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	<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 0.0937 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: 03/12/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	4.87			1000000	4.87	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.801	3.022	0.937	10000	0.0937	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	2.605	1.779	2.843			Neutral Organic SAR

- **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 11/17/21.

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.2022.113026.

Appendix

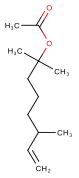
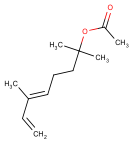
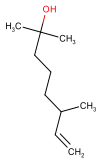
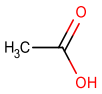
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).

- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target 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 Materials		
Principal Name	Dihydromyrcenyl acetate	Ocimenyl acetate	Dihydromyrcenol	Acetic acid
CAS No.	53767-93-4	72214-23-4	18479-58-8	64-19-7
Structure				
Similarity (Tanimoto Score)		1.0	NA	NA
Read-across Endpoint		Skin sensitization	Repeated dose toxicity Reproductive toxicity	Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{12}H_{22}O_2$	$C_{12}H_{20}O_2$	$C_{10}H_{20}O$	$C_2H_4O_2$
Molecular Weight	198.31	196.29	156.21	60.05
Melting Point (°C, EPI Suite)	−3.58	−2.09	−13.10	−21.26
Boiling Point (°C, EPI Suite)	216.93	228.95	191.28	122.30
Vapor Pressure (Pa @ 25°C, EPI Suite)	20.4	11	16.6	2.29E+003
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.47	4.39	3.47	0.09
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6.77	8.196	252.2	475900
J_{max} (μg/cm^2/h, SAM)	23.820	15.220	100.489	6283.044
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.69E+002	1.43E+002	4.12E+000	1.45E-002
Repeated Dose Toxicity				
Repeated Dose (HESS)			• Not categorized	• Carboxylic acids (Hepatoxicity) No rank
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)	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 domains alert identified.	• No skin sensitization reactivity domains alert 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	• N/A	• N/A

Summary

There are insufficient toxicity data on dihydromyrcenol acetate (CAS # 53767-93-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, ocimenyl acetate (CAS # 72214-23-4), dihydromyrcenol (CAS # 18479-58-8), and acetic acid (CAS # 64-19-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target material dihydromyrcenol acetate (CAS # 53767-93-4) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to dihydromyrcenol (CAS # 18479-58-8) and acetic acid (CAS # 64-19-7) in the first step with a 0.95 probability. Hence, dihydromyrcenol and acetic acid can be used as read-across analogs for the target material. These read-across analogs were in domain for the *in vivo* rat and the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification was provided.

Conclusions

- Ocimenyl acetate (CAS # 72214-23-4) was used as a read-across analog for the target material dihydromyrcenol acetate (CAS # 53767-93-4) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to aliphatic esters.
  - o The target material and the read-across analog share a myrcenyl fragment.
  - o The key difference between the target material and the read-across analog is that the target material has 1 vinyl group while the read-across analog has a vinyl group in conjugation with either a vinyl or vinylene group The read-across analog is expected to be more reactive compared to the target with this structural difference.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the myrcenyl fragment. 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.
- Dihydromyrcenol (CAS # 18479-58-8) and acid acetic acid (CAS # 64-19-7) are used as read-across analogs for the target ester dihydromyrcenol acetate (CAS # 53767-93-4) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target material and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o The read-across acid is given an alert of HESS categorization for repeated dose and developmental toxicity by CAESAR. According to the human metabolome database, acetic acid is one of the common constituents of the human body. These small acids are excreted via different routes very easily. The data show that acetic acid at current levels of exposure does not pose a concern for human health or environmental endpoints. Therefore, the alert will be superseded by the data.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

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

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

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

CIR, 2010. Methyl acetate. Retrieved from. https://www.cir-safety.org/sites/default/files/116_final_methyl.pdf.

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.

EFSA, 2012. Scientific Opinion on the safety and efficacy of acetic acid, sodium diacetate and calcium acetate as preservatives for feed for all animal species. EFSA J. 10 (2), 2571, 2011, Retrieved from. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2571.

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., 2020. Fragrance Skin Sensitization Evaluation and Human Testing, Dermatitis: November 16, 2020. Volume Publish Ahead of Print Issue. https://doi.org/10.1097/DER.0000000000000684. Retrieved from.

NICNAS, 2013. Acetic Acid: Human Health Tier II Assessment. Retrieved from. https://www.industrialchemicals.gov.au/sites/default/files/Acetic%20acid_Human%20health%20tier%20II%20assessment.pdf.

OECD, 2015. *Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment (IATA)*. ENV/JM/HA, p. 7, 2015, 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), 1974. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1779. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1979a. Evaluation of Dihydromyrcenyl Acetate in the Salmonella/microsome Mutagenicity Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Naarden Inc. RIFM report number 15004.

RIFM (Research Institute for Fragrance Materials, Inc), 1979b. Maximization Test with Diydromyrcenyl Acetate in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Naarden Inc. RIFM report number 15005.

RIFM (Research Institute for Fragrance Materials, Inc), 1979c. Delayed Contact Hypersensitivity with Fragrance Materials: Guinea Pig Sensitization (Buehler and Griffith). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 50425.

RIFM (Research Institute for Fragrance Materials, Inc), 1980a. Evaluation of Potential Hazards by Dermal Contact of Fragrance Materials in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 1982.

RIFM (Research Institute for Fragrance Materials, Inc), 1980b. Photosensitization Test with Dihydromyrcenyl Acetate in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 45927.

RIFM (Research Institute for Fragrance Materials, Inc), 1996. The Ultimate Biodegradability of Base Perfumes in the Sealed Vessel Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 49461.

RIFM (Research Institute for Fragrance Materials, Inc), 2000. Dihydromyrcenyl Acetate: Acute Immobilisation Test to Daphnia Magna STRAUS Limit Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 53746.

RIFM (Research Institute for Fragrance Materials, Inc), 2001. Dihydromyrcenyl Acetate: Ready Biodegradability Closed Bottle Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 53747.

RIFM (Research Institute for Fragrance Materials, Inc), 2007. Dihydromyrcenol: Ninety Day Repeated Dose Oral (Gavage) Toxicity Study in the Rat. RIFM Report Number 52794. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. In Vitro Human Skin Penetration of Fragrance Material Dihydromyrcenol and 2,6-Dimethyloct-7-En-2-Yl Formate under Occluded Conditions from a 70% Ethanol Vehicle. RIFM Report Number 55341. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2009. Evaluation of the Developmental Toxicity of Dyhydromyrcenol and 2,6-Dimethyloct-7-En-2-Yl Formate in Rats. RIFM Report Number 48473. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Expert Review of Hematological Data in a Ninety Day Repeated Dose Oral (Gavage) Toxicity Study of Dimyrcetol in the Rat. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from LyondellBasell Industries. RIFM report number 71830.
RIFM (Research Institute for Fragrance Materials, Inc), 2013a. Report on the Testing of Dihydromyrcenyl Acetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65229. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013b. Ocimenyl Acetate: Repeated Insult Patch Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 66417.
RIFM (Research Institute for Fragrance Materials, Inc), 2014. Dihydromyrcenyl Acetate: Micronucleus Test in Human Lymphocytes in Vitro. RIFM Report Number 67619. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015. Novel Database for Exposure to Fragrance Ingredients in Cosmetics and Personal Care Products. RIFM Report Number 68681. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc)., 2016a. Boiling Point of Dihydromyrcenyl Acetate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71671.
RIFM (Research Institute for Fragrance Materials, Inc), 2016b. Partition Coefficient N-Octanol/water of Dihydromyrcenyl Acetate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71674.
RIFM (Research Institute for Fragrance Materials, Inc), 2016c. Flash Point of Dihydromyrcenyl Acetate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71677.
RIFM (Research Institute for Fragrance Materials, Inc), 2016d. Dihydromyrcenyl Acetate: Acute Toxicity to Daphnia Magna in a 48-hour Immobilization Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71680.
RIFM (Research Institute for Fragrance Materials, Inc), 2016e. Dihydromyrcenyl Acetate: Toxicity to Pseudokirchneriella Subcapitata in a 72-hour Algal Growth Inhibition Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71681.
RIFM (Research Institute for Fragrance Materials, Inc), 2017. Exposure Survey 15. March 2017.
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 Report Number 76272. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2020b. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. RIFM, Woodcliff Lake, NJ, USA.
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.
WHO, 2006. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA): Safety Evaluation of Certain Food Additives. Retrieved from. https://apps.who.int/iris/bitstream/handle/10665/43265/9241660546_eng.pdf?sequence=1&isAllowed=y.