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Short Review

RIFM fragrance ingredient safety assessment, ocimenol, CAS Registry Number 5986-38-9

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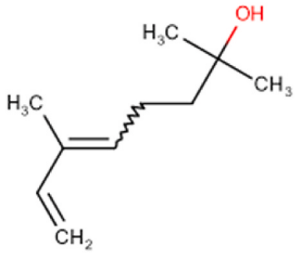
Name: Ocimenol
CAS Registry Number: 5986-38-9



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., 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., 2015, 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

(*continued on next column*)

(*continued*)

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.

Ocimenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog myrcenyl acetate (CAS # 1118-39-4) show that ocimenol is not expected to be genotoxic. Data on read-across analog myrcene (CAS # 123-35-3) provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across analog dihydromyrcenol (CAS # 18479-58-8) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from read-across material dihydromyrcenol (CAS # 18479-58-8) and its isomer 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (CAS # 53219-21-9) show that there are no safety concerns for ocimenol for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on UV/Vis spectra; ocimenol is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to ocimenol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; ocimenol was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current VoU in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2015a; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day.	NTP (2010)
Reproductive Toxicity: NOAEL = 500 mg/kg/day	(RIFM, 2009; RIFM, 2007)
Skin Sensitization: Not a concern for skin sensitization.	(RIFM, 2019a; RIFM, 2019b)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant/photoallergen.	(UV/Vis spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 2.6 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 79.1 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 12.59 mg/L (RIFM Framework; Salvito, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 12.59 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.01259 µg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Ocimenol
2. **CAS Registry Number:** 5986-38-9
3. **Synonyms:** 2,6-Dimethyl-5,7-octadien-2-ol; 5,7-Octadien-2-ol, 2,6-dimethyl-; 2,6-Dimethylocta-5,7-dien-2-ol; Ocimenol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25 g/mol
6. **RIFM Number:** 556

7. **Stereochemistry:** One geometric center is present and two isomers are possible.

2. Physical data

1. **Boiling Point:** 204.05 °C (EPI Suite)
2. **Flash Point:** 89 °C (Globally Harmonized System), 193 °F; closed cup (FMA)
3. **Log K_{OW}:** 3.38 (EPI Suite)
4. **Melting Point**: −11.39 °C (EPI Suite)
5. **Water Solubility:** 304.5 mg/L (EPI Suite)
6. **Specific Gravity:** 0.876 (FMA)
7. **Vapor Pressure:** 0.0358 mm Hg at 20 °C (EPI Suite v4.0), 0.0577 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (99 L mol^{-1} • cm^{-1} under basic conditions) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless oily liquid

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.15% (RIFM, 2020a)
2. **Inhalation Exposure*:** 0.0000023 mg/kg/day or 0.00016 mg/day (RIFM, 2020a)
3. **Total Systemic Exposure**:** 0.00050 mg/kg/day (RIFM, 2020a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 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 (Comiskey, 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 II, Intermediate (Expert Judgment)

Expert Judgment*	Toxtree v3.1	OECD QSAR Toolbox v4.5
II	III	I

*See Appendix below for details.

2. Analogs Selected:

a. **Genotoxicity:** Myrcenyl acetate (CAS # 1118-39-4)
b. **Repeated Dose Toxicity:** Myrcene (CAS # 123-35-3); Weight of Evidence (WoE): dihydromyrcenol (CAS # 18479-58-8)
c. **Reproductive Toxicity:** Dihydromyrcenol (CAS # 18479-58-8); WoE: myrcene (CAS # 123-35-3)
d. **Skin Sensitization:** Dihydromyrcenol (CAS # 18479-58-8); 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (CAS # 53219-21-9)
e. **Photoirritation/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

Ocimenol is reported to occur in the following foods by the VCF*:
Apricot (*Prunus armeniaca* L.)
Citrus fruits.
Fennel (*Foeniculum vulg.,* ssp. *Capillaceum*; var.)
*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

Ocimenol has been pre-registered for 2010; no dossier available as of 10/24/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Ocimenol was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with metabolic activation, negative for cytotoxicity without metabolic activation, and negative for 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 (Thakkar et al., 2022). Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of ocimenol; however, read-across can be made to myrcenyl acetate (CAS # 1118-39-4; see Section VI).

The mutagenic activity of myrcenyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with myrcenyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, myrcenyl acetate was not mutagenic in the Ames test, and this can be extended to ocimenol.

The clastogenic activity of myrcenyl 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 myrcenyl acetate in DMSO at concentrations up to 1000 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of metabolic activation. Myrcenyl acetate did induce binucleated cells with micronuclei when tested at 119 and 139 μg/mL in the 3-h treatment without S9 (RIFM, 2015b). However, the micronucleated binucleated cell frequencies at these concentrations were within the 95% confidence vehicle historical control ranges (0.20%–1.50%). Therefore, the statistically significant increases at these concentrations were considered biologically non-relevant and not indicative of clastogenic effects. Under the conditions of the study, myrcenyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to ocimenol.

Based on the data available, myrcenyl acetate does not present a concern for genotoxic potential, and this can be extended to ocimenol.

Additional References: RIFM, 2016; DiSotto et al., 2008; Mitic--Culafic et al., 2009; Lutz et al., 1980; Eder et al., 1982; Ishidate et al., 1984; Oda et al., 1978; Kuroda et al., 1984; Yoo (1986); Mademtzoglou et al., 2011; Yoo, 1985; DiSotto et al., 2011.

Literature Search and Risk Assessment Completed On: 10/14/22.

11.1.2. Repeated dose toxicity

The MOE for ocimenol 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 ocimenol. Read-across analog myrcene (CAS # 123-35-3; see Section VI) has sufficient repeated dose toxicity data. Several studies have been performed to assess the toxicity of the target material in rats and mice, including subchronic and chronic NTP studies. In a 2-year rat study using concentrations of 0 mg/kg/day, 250 mg/kg/day, 500 mg/kg/day, and 1000 mg/kg/day (NTP, 2010), there was clear evidence of β-myrcene carcinogenicity in male rats based on the increased incidences of renal tubule adenoma and/or carcinoma at the 250 and 500 mg/kg/day doses. In females, although the incidence of renal tubule adenoma was not significant compared to their respective controls, it was slightly above the historical control range in the highest-dose group. The marginal increase in renal tubule adenoma incidence was considered to be equivocal evidence of carcinogenicity in females. Moreover, β-myrcene administration also resulted in increased incidence and/or severity of a number of non-neoplastic renal lesions, including nephrosis and exacerbation of chronic progressive nephropathy in both sexes and papillary mineralization in the males. Specifically, significantly increased papillary mineralization in males that received the 250 and 500 mg/kg/day doses and were found within the loop of Henle as linear accumulations of angular to stippled basophilic material and was considered to be a chronic manifestation of α2u-globulin nephropathy, an effect also seen during chronic studies of the structurally related compound *d*-limonene (NTP, 1990). Nephrosis observed during chronic administration of β-myrcene in rats was more severe in males than in females. The co-localization of nephrosis with the renal tubule necrosis in the outer medulla (in the 90-day study) combined with the proliferative nature of the lesion (karyomegaly and tubule hyperplasia) suggests that it is an adverse event in response to repeated renal tubule injury, primarily in the proximal tubules. However, it is unknown if this unusual regenerative response could ultimately lead to neoplasia, either directly or through exacerbation of chronic progressive nephropathy (CPN). The presence of renal neoplasms in female rats also suggests a mechanism of carcinogenesis that may be related to nephrosis and distinct from the α2u-globulin mechanism. However, the underlying mechanism of β-myrcene-induced renal carcinogenesis in male and female rats continues to be unknown (NTP, 2010). Additional treatment-related toxicity included olfactory epithelium degeneration in rats of both sexes at a dose of 2000 mg/kg/day for 90 days and a dose-dependent increase in nasal inflammation in male rats during the 2-year study. Moreover, liver weights were significantly increased in animals at all doses during the 90-day study. In B6C3F1 mice, the incidences of liver neoplasms were significantly increased in animals receiving the 250 (both sexes) and 500 mg/kg/day (males only) doses for 2 years. Liver neoplasms included hepatocellular adenoma and hepatocellular carcinoma in males and females and hepatoblastoma in males. In addition, significant increases in hepatocellular hypertrophy incidences were observed in the 500 mg/kg/day dose group, along with increased incidences of mixed cell foci in females. Reported observations from these subchronic and chronic studies suggest that the liver and kidney are the most susceptible organs to myrcene treatment in rodents. Based on the available data and the observed effects in kidneys, liver, and nasal epithelium at the lowest dose, a Lowest Observed Adverse Effect Level (LOAEL) of 250 mg/kg/day was determined for the repeated dose toxicity endpoint.

Myrcene is a non-genotoxic carcinogen in rats and mice (NTP, 2010). The carcinogenicity data on β-myrcene have been reviewed by the Expert Panel of the Flavor and Extracts Manufacturing Association (Adams et al., 2011), as well as in the scientific opinion on flavoring group evaluation (EFSA, 2015). In addition, β-myrcene has been listed on California's Proposition 65 list, but a safe harbor level (NSRL/MADL) has not been determined (OEHHA, 2015). Due to the 100% incidence of nephropathy in males at the lowest dose, a benchmark dose level (BMDL) could not be determined from these studies (EFSA, 2015).

tIn addition, WoE material dihydromyrcenol (CAS # 18479-58-8; see Section VI) also 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, 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 animals treated with 500 and 1000 mg/kg/day. Hematological alterations were reported among animals of the 50 (males only), 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 males treated at 50 mg/kg/day and higher, while this was only seen in females treated at 500 and 1000 mg/kg/day. The absolute and relative kidney weights were increased for both 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, which included centrilobular hepatocyte enlargement with associated centrilobular lipid vacuolation of the hepatocytes observed among animals of the high-dose group. Similar effects were reported among 2 animals of the 500 mg/kg/day. α2μ-globulin related nephropathy was reported among treated males. Adipose infiltration of the bone marrow was reported among 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 females, and, thus, the NOEL for females was considered to be 50 mg/kg/day. The kidney changes were identified histopathologically, confirmed with Mallory-Heidenhain staining, and were found to be consistent with hydrocarbon nephropathy, which is not relevant to humans. Thus, the NOAEL for males was considered to be 10 mg/kg/day (RIFM, 2007). Since the hematological alterations were not considered to be related to treatment with dihydromyrcenol (RIFM, 2010), the NOAEL for the repeated dose toxicity was considered to be 50 mg/kg/day, based on the decrease in bodyweight gains among 500 and 1000 mg/kg/day dose groups.

The NOAEL was derived from the 2-year rat study on the read-across material, myrcene, by dividing the LOAEL by a safety factor of 10 (ECHA, 2012), which is equal to 25 mg/kg/day. Data on

dihydromyrcenol were only included as weight of evidence. **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 25/0.00050, or 50000**.

In addition, the total systemic exposure to ocimenol (0.5 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/13/22.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no developmental toxicity data on ocimenol. Read-across analog dihydromyrcenol (CAS # 18479-58-8; see Section VI) has sufficient developmental toxicity data. A GLP-compliant developmental toxicity study was conducted with the test material, dihydromyrcenol, tested as 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

Table 1
Summary of existing data on dihydromyrcenol as a read-across for ocimenol.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL(induction) μg/cm²	WoE NESIL μg/cm²	LLNA[3] Weighted Mean EC3 Value μg/cm²	GPMT[4]	Buehler[4]
No evidence of sensitization[6]	23620	2760	N/A	N/A	Negative up to 6250 (25%)	Negative	Negative
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative [2]; Borderline	Negative [2]	Positive		No alert found	Michael addition; Radical reactions	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available

[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[2]Data derived from CNIH or HMT

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

[4]Studies conducted according to the OECD TG 406 are included in the table.

[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[6]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

Sprague Dawley rats/dose were administered via gavage test material dihydromyrcenol at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil on gestation days (GD) 7–17. High-dose females were observed to have a reduction in bodyweight gain and food consumption. Secondary to the maternal reduction in body weight, 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, with no dose response. 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 and the maternal and developmental toxicity NOAELs of 1000 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). The conservative NOEL of 500 mg/kg/day was considered for the developmental toxicity endpoint.

Therefore, the ocimenol MOE for the developmental toxicity endpoint can be calculated by dividing the dihydromyrcenol NOEL in mg/kg/day by the total systemic exposure to ocimenol, 500/0.00050, or 1000000.

There are no fertility data on ocimenol. Read-across analog dihydromyrcenol (CAS # 18479-58-8) has sufficient fertility data. 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 high-dose females and males at necropsy. No alterations in the female reproductive parameters were observed. There was a significant decrease in spermatid count among 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 in the highest-dose group (RIFM, 2007). **Therefore, the ocimenol MOE for the fertility endpoint can be calculated by dividing the dihydromyrcenol NOAEL in mg/kg/day by the total systemic exposure to ocimenol, 500/0.00050 or 1000000**.

In addition, the WoE material myrcene (CAS # 123-35-3) was used. In a developmental toxicity study (similar to OECD 414 and non-GLP-compliant), pregnant Wistar rats (16 females/group in the control, low-dose, and mid-dose groups and 29 females in the high-dose group) were administered myrcene via oral gavage at doses of 0, 250, 500, or 1200 mg/kg/day in corn oil during gestation days (GDs) 6–15. On GD 20, females were euthanized, the gravid uterus was weighed, and the numbers of implantation sites, living and dead fetuses, resorptions, and corpora lutea were recorded. Fetuses were weighed and examined for external malformations and fixed for visceral examinations or cleared and stained with Alizarin Red S for skeletal evaluation. At 1200 mg/kg/day, mortality was reported in 1 dam on GD 11 after progressive and severe bodyweight loss, which started on the first day of treatment (GD 6). Furthermore, a statistically significant decrease in maternal weight gain was reported in high-dose dams, which resulted in a significant reduction in the gravid uterus weight. Statistically significant reductions in the number of implantation sites, live fetuses, and individual fetal weights were reported at 1200 mg/kg/day. Additionally, high-dose group fetuses exhibited a higher rate of irregularly positioned hind paws and significantly higher incidences of delayed ossification; the most pronounced effects were reported in the skull bones (9.6%), caudal vertebrae (37.8%), metacarpus (9.1%), and metatarsus (29.2%). The NOAEL for maternal toxicity was considered to be 500 mg/kg/day, based on mortality and decreased maternal bodyweight gain among high-dose group dams. The NOAEL for developmental toxicity was considered to be 500 mg/kg/day, based on increased incidences of skeletal malformations reported in high-dose group fetuses (Delgado et al., 1993a).

In a peri- and postnatal developmental toxicity study, pregnant Wistar rats (12–20 females/group) were administered myrcene via oral gavage at doses of 0, 250, 500, 1000, or 1500 mg/kg/day in corn oil from GD 15 through parturition and lactation up to weaning (postnatal day [PND] 21). All F1 generation pups were examined at birth and up to weaning for mortality, weight gain, and physical signs of postnatal development (e.g., ear unfolding, incisor eruption, fur development, and eye opening). On PND 21, all dams (parental generation) were euthanized. The reproductive capacity of pups (F1 generation) was evaluated after reaching maturity (120 days) by mating 1:3 (male:female) progeny from the same treatment group of different litters for 15 days. On PND 4, the number of male and female live pups per litter was counted (F2 generation), and the number of implantation sites for each F1 pregnant female was evaluated. Male reproductive organs (testes, cauda epididymis, and prostate) were excised and weighed with the concomitant evaluation of spermatozoa in the testes and cauda epididymis from F1 males. Mortality was reported in 5 pregnant females (parental generation) at 1500 mg/kg/day. A statistically significant decrease in body weight was reported in pregnant females on GD 20 (parental generation) at ≥1000 mg/kg/day, and decreased body weight persisted up to delivery (PND 1) at 1500 mg/kg/day. A higher rate of stillbirths was reported at the 1000 mg/kg/day dose. Increased labor duration was reported at 500 mg/kg/day (for 1 dam) and 1000 mg/kg/day (for 3 dams), which could be attributed to β-myrcene. The increased stillbirths and labor duration at ≥500 mg/kg/day reflect how β-myrcene could induce parturition disturbance. A statistically significant increase in pup mortality (F1 generation) was reported at ≥500 mg/kg/day during the first week of lactation. A statistically significant decrease in pup weight (F1 generation) was reported at >500 mg/kg/day, which recovered for all treatment groups at PND 21. Delayed appearance of developmental landmarks such as the primary coat was reported at ≥500 mg/kg/day, and ear unfolding and eye opening were reported at ≥1000 mg/kg/day. A statistically significant decrease in fertility (after 120 days maturation) was reported in F1 generation females when treated with doses ≥1000 mg/kg/day. The NOAEL for maternal toxicity was considered to be 1000 mg/kg/day due to mortality in pregnant rats (parental generation) and persisted decreased body weight up to PND 1 (F1 generation) at 1500 mg/kg/day. The NOAEL for developmental toxicity was considered to be 250 mg/kg/day, based on decreased pup body weight, increased pup mortality, parturition disturbance, and delayed appearance of developmental landmarks at ≥500 mg/kg/day. The NOAEL for fertility was considered to be 500 mg/kg/day, based on impaired fertility in F1 females, which resulted from dams treated at ≥1000 mg/kg/day (Delgado et al., 1993b).

In a 1-generation reproduction toxicity study (similar to OECD 415/non-GLP-compliant), Wistar rats (15 males/group and 45 females/group) were administered myrcene via oral gavage at doses of 0, 100, 300, or 500 mg/kg/day in peanut oil. Male rats were treated for 91 days prior to mating and during the mating period, and females were treated continuously for 21 days before mating, during mating and pregnancy, and throughout lactation up to PND 21. On GD 21, 1/3 of the females of each group were euthanized and subjected to cesarean section. The remaining dams gave birth to their offspring. The progeny were examined at birth and subsequently up to PND 21. Males were euthanized at the end of the mating period, and no treatment-related effects were reported on the number of spermatids in the testis or on the number of spermatozoa in the cauda epididymis at any dose level. Fertility indices (such as mating index and pregnancy index) were not affected at any dose levels. No signs of maternal toxicity and no increase in externally visible malformations were observed at any dose. At 500 mg/kg/day, a statistically significant increase in the resorption rate and a parallel

statistically significant decrease in the ratio of live fetuses per implantation site were reported. Furthermore, the frequency of skeletal malformations such as fused or zygomatic, dislocated sternum (non-aligned sternebrae), and extra lumbar ribs were increased in the high-dose group pups. No treatment-related effects were reported on postnatal weight gain, but the day of primary coat appearance, incisor eruption, and eye opening was slightly delayed in the exposed offspring. The NOAEL for fertility was considered to be 300 mg/kg/day, based on increased resorption rate and a parallel decrease in the ratio of live fetuses per implantation site in the high-dose group. The NOAEL for developmental toxicity was considered to be 300 mg/kg/day, based on the increased frequency of skeletal malformations among high-dose group pups (Paumgartten et al., 1998).

In addition, the total systemic exposure to ocimenol (0.5 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/13/22.

11.1.4. Skin sensitization

Based on the existing data and data on read-across material dihydromyrcenol (CAS # 18479-58-8) and its isomer 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (CAS # 53219-21-9), ocimenol presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for ocimenol. Therefore, read-across material dihydromyrcenol (CAS # 18479-58-8; see Section VI) and its isomer 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (CAS # 53219-21-9; see Section VI) were used for the risk assessment of ocimenol. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, ocimenol is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material dihydromyrcenol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens assay; however, it was positive in a human cell line activation test (h-CLAT) (RIFM, 2019a; RIFM, 2020b; RIFM, 2019b; RIFM, 2020c; RIFM, 2018). Based on the 2 out of 3 Defined Approach, following OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021), dihydromyrcenol is predicted *in vitro* to be a non-sensitizer. In murine local lymph node assays (LLNA), read-across analog dihydromyrcenol and its isomer, 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv., were found to be non-sensitizing when tested up to 25% and 30% (6250 μg/cm^2 and 7500 μg/cm^2), respectively (RIFM, 2007b; RIFM, 1996). In guinea pig maximization tests and a Buehler test, 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (isomer to the read-across analog) did not present reactions indicative of sensitization (RIFM, 1994a; RIFM, 1994b). In human maximization tests, no skin sensitization reactions were observed with ocimenol or read-across analog dihydromyrcenol (RIFM, 1974; RIFM, 1977). In CNIHs with 5000 μg/cm^2 and 2500 μg/cm^2 read-across material dihydromyrcenol in ethanol:diethyl phthalate (3:1), no reactions indicative of sensitization were observed in any of the 107 and 104 volunteers, respectively (RIFM, 2001; RIFM, 2002). Additionally, in 2 CNIHs with 23620 μg/cm^2 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (isomer to the read-across material) in diethyl phthalate and 1:3 alcohol SD39C:DEP, no reactions indicative of sensitization were observed in any of the 109 and 99 volunteers, respectively (RIFM, 1995; RIFM, 2006).

Based on WoE from structural analysis, *in vitro* studies, animal studies, and human studies on the read-across material as well as the target material, ocimenol does not present a concern for skin sensitization.

Additional References: RIFM, 1975; RIFM, 1972; RIFM, 1964; RIFM, 1973.

Literature Search and Risk Assessment Completed On: 02/08/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, ocimenol would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for ocimenol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, ocimenol does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient (99 L mol^{-1} • cm^{-1} under basic conditions) is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/03/22.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for ocimenol is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on ocimenol. Based on the Creme RIFM Model, the inhalation exposure is 0.00016 mg/day. This exposure is 2937.5 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	12.59			1000000	0.01259	

use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ocimenol 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 of 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, ocimenol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified ocimenol as possibly being 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, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current VoU (2019), ocimenol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Ocimenol has been pre-registered for REACH with no additional data at this time.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.4	3.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.01259 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 10/06/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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 03/27/23.

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.2023.114207.

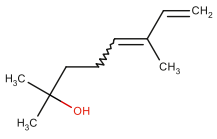
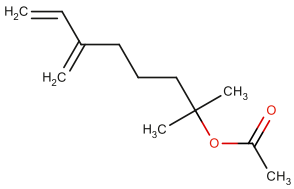
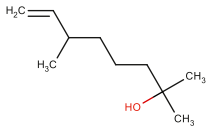
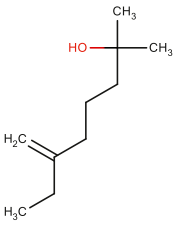
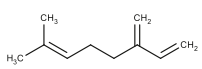
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). 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 Chemicals Agency read-across assessment framework (ECHA, 2017b).

- 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 v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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 v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

Principal Name	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
	Ocimenol	Myrcenyl acetate	Dihydromyrcenol	7-Octen-2-ol, 2-methyl-6-methylene-, dihydro deriv.	Myrcene
CAS No.	5986-38-9	1118-39-4	18479-58-8	53219-21-9	123-35-3
Structure					
Similarity (Tanimoto Score)		0.28	0.38	0.35	0.42
SMILES	CC(C=C) = CCCC(C)(C)O	CC(=O)OC(C)(C)CCCC(=C)C=C	CC(CCCC(C)(C)O)C=C	CCC(=C)CCCC(C)(C)O	CC(C)=CCCC(=C)C=C
Endpoint		Genotoxicity	Skin sensitization Repeated dose toxicity (WoE) Reproductive toxicity	Skin sensitization	Repeated dose toxicity Reproductive toxicity (WoE)
Molecular Formula	$C_{10}H_{18}O$	$C_{12}H_{20}O_2$	$C_{10}H_{20}O$	$C_{10}H_{20}O$	$C_{10}H_{16}$
Molecular Weight (g/mol)	154.253	196.29	156.269	156.269	136.238
Melting Point (°C, EPI Suite)	−11.39	−2.53	−13.10	−10.63	−64.83
Boiling Point (°C, EPI Suite)	204.05	221.78	191.28	197.93	167.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.69E+00	1.60E+01	1.65E+01	1.11E+01	2.79E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.05E+02	7.02E+00	2.52E+02	1.95E+02	4.00E+00
Log K_{OW}	3.38	4.47	3.47	3.6	4.33
J_{max} (μg/cm²/h, SAM)	34.38	0.96	29.70	25.24	0.81
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	3.49E+00	1.22E+02	4.12E+00	4.87E+00	9.28E+03
Genotoxicity					
DNA Binding (OASIS v1.4,	No alert found	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫			

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
	Ocimenol	Myrcenyl acetate	Dihydromyrcenol	7-Octen-2-ol, 2-methyl-6-methylene-, dihydro deriv.	Myrcene
QSAR Toolbox v4.2)		Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters			
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found			
Carcinogenicity (ISS)	No alert found	No alert found			
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found			
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found			
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found			
Oncologic Classification	Not classified	Not classified			
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not categorized		Not categorized		Not categorized
Reproductive Toxicity					
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure		Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	NON-toxicant (low reliability)		NON-toxicant (low reliability)		NON-toxicant (low reliability)
Skin Sensitization					
Protein Binding (OASIS v1.1)	No alert found		No alert found	No alert found	
Protein Binding (OECD)	No alert found		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)	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.	
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on ocimenol (CAS # 5986-38-9). 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, myrcenyl acetate (CAS # 1118-39-4), dihydromyrcenol (CAS # 18479-58-8), 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (CAS # 53219-21-9), and myrcene (CAS # 123-35-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Myrcenyl acetate (CAS # 1118-39-4) was used as a read-across analog for the target material, ocimenol (CAS # 5986-38-9), for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the conjugated unsaturated aliphatic group.
  - o The key difference between the target material and the read-across analog is the target material has a conjugated vinyl vinylene group and tertiary alcohol, whereas the read-across analog has 2 conjugated vinyl groups and an ester group. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$80%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog has alerts for the nucleophilic attack, nucleophilic substitution, and acylation due to the ester that is not present in the target material. These alerts are of no concern since the ester will undergo ester hydrolysis, which will form acetic acid and a similar tertiary alcohol to the target material. Furthermore, the read-across analog has an alert for Schiff base formation after aldehyde release. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Dihydromyrcenol (CAS # 18479-58-8) was used as a read-across analog for the target material, ocimenol (CAS # 5986-38-9), for the repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the unsaturated tertiary alcohol group.
  - o The key difference between the target material and the read-across analog is the target material has a conjugated vinyl and vinylene, whereas the read-across analog only has an isolated vinyl group. The metabolism predicted through OASIS TIMES has predicted that there is no notable difference in metabolism when comparing the conjugated unsaturations to the isolated unsaturations. Therefore, this structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Neither the target material nor the read-across analog has alerts for skin sensitization, repeated dose toxicity, or reproductive toxicity. The data on the read-across analog confirms that the material does not pose a concern for skin sensitization, repeated dose toxicity, or reproductive toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of *in silico* alerts is consistent with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 7-Octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. (CAS # 53219-21-9) was used as a read-across analog for the target material, ocimenol (CAS # 5986-38-9), for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the unsaturated tertiary alcohol group.
  - o The key difference between the target material and the read-across analog is the target material has a conjugated vinyl and vinylene, whereas the read-across analog only has an isolated vinyl group. The metabolism predicted through OASIS TIMES has predicted that there is no notable difference in metabolism when comparing the conjugated unsaturations to the isolated unsaturations. Therefore, this structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Neither the target material nor the read-across analog has alerts for skin sensitization. The data on the read-across analog confirms that the material does not pose a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of *in silico* alerts is consistent with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Myrcene (CAS # 123-35-3) was used as a read-across analog for the target material, ocimenol (CAS # 5986-38-9), for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the conjugated unsaturated group.
  - o The key difference between the target material and the read-across analog is the target material has a conjugated vinyl vinylene group and tertiary alcohol, whereas the read-across analog has 2 conjugated vinyl groups and an isolated vinylene group. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$80%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o Neither the target material nor the read-across analog has alerts for repeated dose toxicity or reproductive toxicity. The data on the read-across analog confirms that the material does not pose a concern for repeated dose toxicity or reproductive toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of *in silico* alerts is consistent with the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for a detailed explanation). No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? Yes.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes.
Q21. Three or more different functional groups? No.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories). No. Class Low (Class I).

References

Adams, T.B., Gavin, C.L., McGowen, M.M., Waddell, W.J., Cohen, S.M., 2011. The FEMA GRAS assessment of aliphatic and aromatic terpene hydrocarbons used as flavor ingredients. Food Chem. Toxicol. 49 (10), 2471–2494.

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.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718, 2020.

Delgado, I.F., Carvalho, R.R., deAlmeida-Nogueira, A.C.M., Mattos, A.P., Figueiredo, L. H., Oliveira, S.H.P., Chahoud, I., Paumgartten, F.J.R., 1993a. Study on embryo-foetotoxicity of beta-myrcene in the rat. Food Chem. Toxicol. 31 (1), 31–35.

Delgado, I.F., deAlmeida-Nogueira, A.C.M., Souza, C.A.M., Costa, A.M.N., Figueiredo, L. H., Mattos, A.P., Chahoud, I., Paumgartten, F.J.R., 1993b. Peri- and postnatal developmental toxicity of beta-myrcene in the rat. Food Chem. Toxicol. 31 (9), 623–628.

DiSotto, A., Evandrib, M.G., Mazzanti, G., 2008. Antimutagenic and mutagenic activities of some terpenes in the bacterial reverse mutation assay. Mutat. Res. Genet. Toxicol. Environ. Mutagen 653 (1–2), 130–133.

DiSotto, A., Mazzanti, G., Carbone, F., Hrelia, P., Maffei, F., 2011. Genotoxicity of lavender oil, linalyl acetate, and linalool on human lymphocytes in vitro. Environ. Mol. Mutagen. 52 (1), 69–71.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.8: Characterisation of Dose [concentration]-Response for Human Health. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017a. Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

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

Eder, E., Henschler, D., Neudecker, T., 1982. Mutagenic properties of allylic and alpha, beta-unsaturated compounds: consideration of alkylating mechanisms. Xenobiotica 12 (12), 831–848.

EFSA, 2015. Scientific Opinion on Flavouring Group Evaluation 78, Revision 2 (FGE.78Rev2): consideration of aliphatic and alicyclic and aromatichydrocarbons evaluated by JECFA (63rd meeting) structurally related toaliphatic hydrocarbons evaluated by EFSA in FGE.25Rev3, 2015 EFSA J. 13 (4), 4067. Retrieved from. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4067.

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), 2019. Volume of Use Survey, January-December 2019.

Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22 (8), 623–636.

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.

Kuroda, K., Tanaka, S., Yu, Y.S., Ishibashi, T., 1984. Rec-assay of food additives. Nippon Kosnu Eisei Zasshi 31 (6), 277–281.

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.

Lutz, D., Neudecker, T., Eder, E., 1980. Mutagenic effects of allylic alcohols and their corresponding aldehydes. Arch. Pharmacol. 311 (Suppl. l), R25.

Mademtzoglou, D., Akmoutsou, P., Kounatidis, I., Franzios, G., Drosopoulou, E., Vokou, D., Mavragani-Tsipidou, P., 2011. Applying the Drosophila wing spot test to assess the genotoxic impact of 10 essential oil constituents used as flavouring agents or cosmetic ingredients. Flavour Fragrance J. 26 (6), 447–451.

Mitic-Culafic, D., Zegura, B., Nikolic, B., Vukovic-Gacic, B., Knezevic-Vukcevic, J., Filipic, M., 2009. Protective effect of linalool, myrcene and eucalyptol against t-butyl hydroperoxide induced genotoxicity in bacteria and cultured human cells. Food Chem. Toxicol. 47 (1), 260–266.

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.

National Toxicology Program, 1990. Toxicology and Carcinogenesis Studies of D-Limonene in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP-TR-347. PB-90-2802.

National Toxicology Program, 2010. Toxicology and Carcinogenesis Studies of Beta-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 557. Unpublished.

Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen. 9, 177–181.
OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf.
OECD, 2021. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from. http://www.qsartoolbox.org/.
OEHHA, 2015. Beta-Myrcene. Retrieved from. https://oehha.ca.gov/proposition-65/chemicals/beta-myrcene.
Paumgartten, F.J.R., DeCarvalho, R.R., Souza, C.A.M., Madi, K., Chahoud, I., 1998. Study of the effects of beta-myrcene on rat fertility and general reproductive performance. Braz. J. Med. Biol. Res. 31 (7), 955–965.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964. Repeated Insult Patch Test with 7-Octen-2-Ol, 2-Methyl-6-Methylene-, Dihydro Deriv. (Dihydromyrcenol). RIFM report number 47074 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF Incorporated.
RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Repeated Insult Patch Test with Dihydromyrcenol. Unpublished Report from International Flavors and Fragrances. RIFM report number 50437 (RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1802 (RIFM, Woodcliff Lake, NJ, USA.
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.), 1975. Primary Skin Irritation Study with Dihydromycenol in guinea Pigs. RIFM report number 54838 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise GmbH & Co. KG.
RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1702 (RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1994a. Test for Delayed Contact Hypersensitivity of 7-Octen-2-Ol, 2-Methyl-6-Methylene-, Dihydro Deriv. (Dihydromyrcenol) Using the guinea Pig Maximization Test. RIFM report number 24241 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Haarmann & Reimer GmbH.
RIFM (Research Institute for Fragrance Materials, Inc.), 1994b. The Buehler Test on 7-Octen-2-Ol, 2-Methyl-6-Methylene-, Dihydro Deriv. (Dihydromyrcenol). RIFM report number 24242 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Haarmann & Reimer GmbH.
RIFM (Research Institute for Fragrance Materials, Inc.), 1995. Repeated Insult Patch Test on Dihydromyrcenol on Human Subjects. RIFM report number 25722 (RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1996. Local Lymph Node Assay of 7-Octen-2-Ol, 2-Methyl-6-Methylene-, Dihydro Deriv. (Dihydromyrcenol). RIFM report number 35547 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Haarmann & Reimer GmbH.
RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Repeated Insult Patch Test with Dihydromyrcenol. RIFM report number 54405 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances.
RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Repeated Insult Patch Test with Dihydromyrcenol. RIFM report number 54404 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances.
RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Repeated Insult Patch Test (Modified Draize Procedure) with Dihydromyrcenol and D-Limonene. RIFM report number 45702 (RIFM, Woodcliff Lake, NJ, USA.
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.), 2007b. Dihydromyrcenol: Local Lymph Node Assay. RIFM report number 52911 (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 report number 71830 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from LyondellBasell Industries.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Report on the Testing of Ocimenol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 66933 (RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Myrcenyl Acetate: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM report number 69291 (RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015b. Myrcenyl Acetate: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 69578 (RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Myrcenyl Acetate: Reverse Mutation Assay 'Ames Test' Using Salmonella typhimurium and Escherichia coli. RIFM report number 76125 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF.
RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Dihydromyrcenol: in Vitro Sensitization: Dendritic Cell Line Activation Assay Human Cell Line Activation Test (H-CLAT). RIFM report number 73752 (RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2019a. Dihydromyrcenol and 2,6-Dimethyloct-7-En-2-Yl Formate (Dimyrcetol): Direct Peptide Reactivity Assay. RIFM report number 77342 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF.
RIFM (Research Institute for Fragrance Materials, Inc.), 2019b. Dihydromyrcenol and 2,6-Dimethyloct-7-En-2-Yl Formate (Dimyrcetol): ARE-Nrf2 Luciferase Test (KeratinoSens™). RIFM report number 77344 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. Exposure Survey 27. May 2020.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. Dihydromyrcenol: KeratinoSens Assay. RIFM report number 76373 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020c. Direct Peptide Reactivity Assay (DPRA): Test Report on Dihydromyrcenol. RIFM report number 76532 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan.
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.
Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. Mutagenesis 37 (1), 13–23, 2022.
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.
Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. J. Osaka City Med. Cent. 34 (3–4), 267–288 [Osaka-shi Igakkai Zasshi].