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Short Review

RIFM fragrance ingredient safety assessment, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-, CAS Registry Number 53834-70-1

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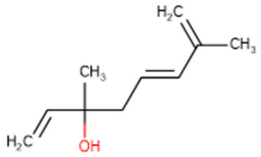


Name: 1,5,7-Octatrien-3-ol, 3,7-dimethyl-, (5E)-CAS Registry Number: 53834-70-1
Additional CAS Numbers*: 20053-88-7 (E,R)-3,7-Dimethyl-1,5,7-octatrien-3-ol (No Reported Use)
*Included because these materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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 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.
1,5,7-Octatrien-3-ol, 3,7-dimethyl-, (5E)- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- is not genotoxic. Data on read-across analog myrcene (CAS # 123-35-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across materials 3,7-dimethyloct-1-en-3-ol (CAS # 18479-49-7) and myrcene (CAS # 123-35-3) show that there are no safety concerns for 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) 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, 2021; RIFM, 2020)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day. NTP (2010)

(*continued on next page*)

(*continued*)

Reproductive Toxicity: Developmental Toxicity NOAEL = 250 mg/kg/day. Fertility NOAEL = 300 mg/kg/day.	(Delgado et al., 1993a; Paumgartten et al., 1998)
Skin Sensitization: Not a concern for skin sensitization.	(ECHA, 2018; RIFM, 2010b)
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:	
Critical Measured Value: 93.8 % (OECD 301F)	RIFM (2018)
Bioaccumulation:	
Screening-level: 64.27 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 17.13 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: 17.13 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.01713 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America (not reported) and Europe: Not applicable; cleared at screening-level	

1. Identification

Chemical Name: 1,5,7-Octatrien-3-ol, 3,7-dimethyl-, (5E)-	**Chemical Name:** (E,R)-3,7-Dimethyl-1,5,7-octatrien-3-ol
CAS Registry Number: 53834-70-1	**CAS Registry Number:** 20053-88-7
Synonyms: 1,5,7-Octatrien-3-ol, 3,7-dimethyl-, (5E)-	**Synonyms:** Dehydrolinalool; Hotrienol; (E,R)-3,7-Dimethyl-1,5,7-octatrien-3-ol
Molecular Formula: $C_{10}H_{16}O$	**Molecular Formula:** $C_{10}H_{16}O$
Molecular Weight: 152.23 g/mol	**Molecular Weight:** 152.23 g/mol
RIFM Number: 1305	**RIFM Number:** Not available
Stereochemistry: E-isomer specified. Two stereocenters and 4 total stereoisomers are possible.	**Stereochemistry:** E,R-isomer specified. Two stereocenters and 4 total stereoisomers are possible.

2. Physical data

CAS # 53834-70-1	CAS # 20053-88-7
Boiling Point: 202.57 °C (EPI Suite v4.11)	**Boiling Point:** 202.57 °C (EPI Suite v4.11)
Flash Point: Not Available	**Flash Point:** Not Available
Log K_{OW}: 3.24 (EPI Suite)	**Log K_{OW}:** 3.24 (EPI Suite v4.11)
Melting Point: −12.70 °C	**Melting Point**: −12.7 °C (EPI Suite v4.11)
Water Solubility: 4.07E+02 mg/L at 25 °C (WSKOW v1.42 in EPI Suite)	**Water Solubility:** 406.5 mg/L (EPI Suite v4.11)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 8.41E+00 Pa at 25 °C (EPI Suite v4.11)	**Vapor Pressure:** 0.0631 mm Hg at 25 °C (EPI Suite v4.11)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** Not Available
Appearance/Organoleptic: Not Available	**Appearance/Organoleptic:** A colorless or pale straw-colored 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 v3.2.7)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0. 0000028% (RIFM, 2022)
2. **Inhalation Exposure**:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2022)
3. **Total Systemic Exposure***:** 0.000047 mg/kg/day (RIFM, 2022)

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

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

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford, 2015; Safford, 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1 Cramer Classification:

Class I, Low (Expert Judgment)

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

*See the Appendix below for details.

2 Analogs Selected:
- a. Genotoxicity: None
- b. Repeated Dose Toxicity: Myrcene (CAS # 123-35-3); Weight of Evidence (WoE) - dihydromyrcenol (CAS # 18479-58-8)
- c. Reproductive Toxicity: Myrcene (CAS # 123-35-3); WoE - dihydromyrcenol (CAS # 18479-58-8)
- d. Skin Sensitization: 3,7-Dimethyloct-1-en-3-ol (CAS # 18479-49-7) and myrcene (CAS # 123-35-3)
- 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.

7.1. Additional References

None.

8. Natural occurrence

1,5,7-Octatrien-3-ol, 3,7-dimethyl-, (5E)- is reported to occur in the following foods by the VCF*:

Grape (*Vitis* species)

Kiwifruit (*Actinidia chinensis,* syn. *A. deliciosa*)

Syzygium species.

Wine.

(E,R)-3,7-Dimethyl-1,5,7-octatrien-3-ol 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

1,5,7-Octatrien-3-ol, 3,7-dimethyl-, (5E)- and (E,R)-3,7-dimethyl-1,5,7-octatrien-3-ol have been pre-registered for 2010; no dossiers available as of 09/15/23.

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, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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, 2021). Under the conditions of the study, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- was not mutagenic in the Ames test.

The clastogenic activity of 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- in DMSO at concentrations up to 1550 μg/mL in the DRF study, and micronuclei analysis was conducted up to 1000 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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, 2020). Under the conditions of the study, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/27/23.

11.1.2. Repeated dose toxicity

The MOE for 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-. Read-across material myrcene (CAS # 123-35-3; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. 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 doses 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 α-2u-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 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 α-2u-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 does 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, the lowest observable 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).

Although β-myrcene is carcinogenic at high doses, it is not genotoxic. Therefore, the positive cancer endpoint at high doses is a result of cytotoxicity, which does not occur at or below the NOAEL.

The NOAEL was derived by dividing the LOAEL (250 mg/kg/day) by a safety factor of 10, which is equal to 25 mg/kg/day.

Therefore, the 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- MOE is equal to the myrcene NOAEL in mg/kg/day divided by the total systemic exposure to 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-, 25/0.000047, or 531914.

In addition, the total systemic exposure to 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- (0.047 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

In addition, data on material dihydromyrcenol (CAS # 18479-58-8; see Section VI) can be used as WoE. 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 the animals treated with 500 and 1000 mg/kg/day. Hematological alterations were reported among the animals of the 50, 500, and 1000 mg/kg/day dose groups. However, hematological alterations were not considered to be related to treatment with dihydromyrcenol (RIFM, 2010a). 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, and thus, the NOEL for the females was considered to be 50 mg/kg/day. The kidney changes were identified histopathologically and confirmed with Mallory-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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/07/22.

11.1.3. Reproductive toxicity

The MOE for 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-. Read-across material myrcene (CAS # 123-35-3) has sufficient data to support the reproductive toxicity endpoints.

In a developmental toxicity study (similar to OECD 414/non-GLP-compliant), pregnant Wistar rats (16 females/group in the control, low-, 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 weight 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., 1993b).

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 also 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 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 bodyweight, 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., 1993a).

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, one-third 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 were 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).

The most conservative NOAEL of 250 mg/kg/day from the peri- and postnatal developmental toxicity study was selected for the developmental toxicity endpoint. A NOAEL of 300 mg/kg/day from the 1-generation reproduction toxicity study was selected for the fertility endpoint.

Therefore, the 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- MOE for the developmental toxicity endpoint can be calculated by dividing the myrcene NOAEL in mg/kg/day by the total systemic exposure to 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-, 250/0.000047 or 5319148.

Therefore, the 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- MOE for the fertility endpoint can be calculated by dividing the myrcene NOAEL in mg/kg/day by the total systemic exposure to 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-, 300/0.000047, or 6382978.

In addition, the total systemic exposure to 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- (0.047 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

In addition, data on material dihydromyrcenol (CAS # 18479-58-8; see Section VI) can be used as WoE. A GLP-compliant developmental toxicity study was conducted with dihydromyrcenol 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 Sprague Dawley rats/dose were dihydromyrcenol via gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil on gestational 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 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. The reported fetal effects were considered to be reversible minor variations and often occurred at maternally toxic doses. Thus, the maternal and developmental toxicity NOEL of 500 mg/kg/day was 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 OECD 408 gavage 90-day subchronic study was conducted to investigate the systemic toxicity of 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).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/07/22.

11.1.4. Skin sensitization

Based on the existing data on read-across materials 3,7-dimethyloct-1-en-3-ol (CAS # 18479-49-7) and myrcene (CAS # 123-35-3), 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- presents no concern for skin sensitization.

11.1.4.1. Risk assessment. No skin sensitization studies are available for 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-. Therefore, the structurally related materials 3,7-dimethyloct-1-en-3-ol (CAS # 18479-49-7; see Section VI) and myrcene (CAS # 123-35-3; see Section VI) were used for the risk assessment of 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-. The data on the read-across materials are summarized in Table 1 (3,7-dimethyloct-1-en-3-ol) and Table 2 (myrcene). Based on the existing data on the read-across materials, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- is not considered a skin sensitizer. 1,5,7-Octatrien-3-ol, 3,7-

Table 1
Summary of existing data on 3,7-dimethyloct-1-en-3-ol as a read-across for 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL (induction) μg/cm^2	WoE NESIL μg/cm^2	LLNA[2] Weighted Mean EC3 Value μg/cm^2	GPMT	Buehler
No evidence of sensitization[4]	N/A	N/A	N/A	N/A	Negative at 12500 (50%)	N/A	N/A
	***In vitro* Data[3]**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	Negative	Negative	N/A		No alert found	No alert found	No alert found

Table 2
Summary of existing data on myrcene as a read-across for 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL (induction) μg/cm^2	WoE NESIL μg/cm^2	LLNA[b] Weighted Mean EC3 Value μg/cm^2	GPMT	Buehler
No evidence of sensitization[c]	N/A	2760	N/A	N/A	Negative at 12500 (50%)	N/A	N/A
	***In vitro* Data**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	N/A	N/A	N/A		No alert found	Radical reactions; SN2	Michael addition; Nucleophilic addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.
[3]Studies conducted according to the OECD TG 442, Cottrez et al., (2016); Forreryd et al., (2016) are included in the table.
[a] 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).
[b] Based on animal data using classification defined in ECETOC (ECETOC, 2003).
[c] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

dimethyl-, (5E)- and read-across materials 3,7-dimethyloct-1-en-3-ol and myrcene are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material 3,7-dimethyloct-1-en-3-ol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (ECHA, 2018). In a murine local lymph node assay (LLNA), read-across material 3,7-dimethyloct-1-en-3-ol was found to be non-sensitizing when tested up to 50% (12500 μg/cm^2) (ECHA, 2018). In a murine LLNA, read-across material myrcene was found to be non-sensitizing when tested up to 50% (12500 μg/cm2) (RIFM, 2010b). In human maximization tests, no skin sensitization reactions were observed when read-across material myrcene was tested at 2760 μg/cm^2 (RIFM, 1974; RIFM, 1977).

Based on the WoE from structural analysis and *in vitro*, animal, and human studies on the read-across materials 3,7-dimethyloct-1-en-3-ol and myrcene, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/17/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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 no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/21/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)-. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/23/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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, 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5E)- presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 2018:** The ready biodegradability of the test material was evaluated according to the manometric respirometry test following the OECD 301F method. Based on the test conditions, biodegradation of 93.8% was observed after 28 days.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. 1,5,7-Octatrien-3-ol, 3,7-dimethyl-, (5E)- has been pre-registered for REACH, with no additional information available 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	17.13			1000000	0.01713	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.24	3.24
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band*	<1	Not reported
Risk Characterization: PEC/PNEC	**<1**	**NA**

*Combined Regional VoU for both CAS #s.

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

The RIFM PNEC is 0.01713 μg/L. The revised PEC/PNECs for EU and NA (not reported) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/18/23.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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://pubchem.ncbi.nlm.nih.gov/source/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 09/15/23.

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.2023.114122.

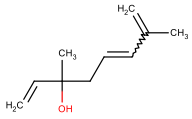
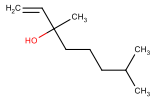
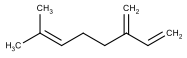
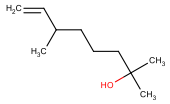
Appendix

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 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 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	WoE Material
	(e)-3,7-dimethylocta-1,5,7-trien-3-ol; (5e)-3,7-dimethylocta-1,5,7-trien-3-ol; 1305; 1,?5,?7-?octatrien-?3-?ol, 3,?7-?dimethyl-?, (5e)?-	3,7-Dimethyloct-1-en-3-ol	Myrcene	Dihydromyrcenol
CAS No.	53834-70-1	18479-49-7	123-35-3	18479-58-8
Structure				
Similarity (Tanimoto Score)		0.29	0.33	0.26
SMILES	CC(=C)C=CCC(C)(O)C=C	CC(C)CCCC(C)(O)C=C	CC(C)=CCCC(=C)C=C	CC(CCCC(C)(C)O)C=C
Endpoint		Skin sensitization	Skin sensitization Repeated dose toxicity Reproductive toxicity	Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{10}H_{16}O$	$C_{10}H_{20}O$	$C_{10}H_{16}$	$C_{10}H_{20}O$
Molecular Weight	152.237	156.269	136.238	156.269
Melting Point (°C, EPI Suite)	−12.70	−13.10	−64.83	−13.10
Boiling Point (°C, EPI Suite)	202.57	191.28	167.00	191.28
Vapor Pressure (Pa @ 25°C, EPI Suite)	8.41E+00	1.65E+01	2.79E+02	1.65E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.07E+02	2.52E+02	4.00E+00	2.52E+02
Log KOW	3.24	3.47	4.33	3.47
J_{max} (μg/cm^2/h, SAM)	41.99	29.70	0.81	29.70
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.60E+00	4.12E+00	9.28E+03	4.12E+00
Repeated Dose Toxicity				
Repeated Dose (HESS)	Not categorized		Not categorized	Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.5)	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	

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across Material	Read-across Material	WoE Material
	(e)-3,7-dimethylocta-1,5,7-trien-3-ol; (5e)-3,7-dimethylocta-1,5,7-trien-3-ol; 1305; 1,?5,?7-?octatrien-?3-?ol, 3,?7-?dimethyl-?, (5e)?-	3,7-Dimethyloct-1-en-3-ol	Myrcene	Dihydromyrcenol
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 domain alerts identified.	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 1,5,7-octatrien-3-ol (CAS # 53834-70-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, chemical properties, and expert judgment, 3,7-dimethyloct-1-en-3-ol (CAS # 18479-49-7) and myrcene (CAS # 123-35-3) were identified as read-across analogs, and dihydromyrcenol (CAS # 18479-58-8) was identified as a WoE analog with sufficient data for toxicological evaluation.

Conclusions

- 3,7-Dimethyloct-1-en-3-ol (CAS # 18479-49-7) was used as a read-across analog for the target material 1,5,7-octatrien-3-ol (CAS # 53834-70-1) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar in that they are both branch tertiary alcohol with terminal alkene groups.
  - o The key difference between the target material and the read-across analog is that the target material has 2 terminal and 1 internal alkene, whereas the read-across analog contains one terminal alkene. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog do not display *in silico* alerts for the skin sensitization endpoint. Data for the read-across analog indicates that it is not 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 *in silico* alerts are 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 1,5,7-octatrien-3-ol (CAS # 53834-70-1) for the repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar in that they are branched alkyl chains containing 3 alkenes.
  - o The key difference between the target material and the read-across analog is the target material contains a tertiary alcohol while the read-across analog contains no alcohol. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o 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 For both the target material and the read-across analog, there are no *in silico* alerts for the repeated dose, skin sensitization, and reproductive toxicity endpoints. The data sections from those endpoints indicate that the read-across analog is not a concern. 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 are consistent with the data.

- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- 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 WoE analog for the target material 1,5,7-octatrien-3-ol (CAS # 53834-70-1) for the repeated dose toxicity and reproductive toxicity endpoints.
  - The target material and the WoE analog are structurally similar in that they are both branch tertiary alcohol with terminal alkene groups.
  - The key difference between the target material and the WoE analog is that the target material has 2 terminal and 1 internal alkene, whereas the WoE analog contains one terminal alkene. Additionally, the terminal alkene and the tertiary alcohol in the target material are on the same side of the molecule, while in the WoE analog, they are isolated from each other. The WoE analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - The similarity between the target material and the WoE analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the WoE analog.
  - Both the target material and WoE analog do not display *in silico* alerts for the repeated dose toxicity and reproductive toxicity endpoints. Data for the WoE analog indicates that it is not a concern for repeated dose toxicity and reproductive toxicity. Therefore, based on the structural similarity between the target material and the WoE analog and the data on the WoE analog, the *in silico* alerts are consistent with the data.
  - The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE 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 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.
Q44. Free α,β-unsaturated heteroatom? 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).

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