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RIFM fragrance ingredient safety assessment, 3,7-dimethyloct-6-en-3-ol, CAS registry number 18479-51-1

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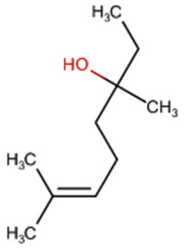
Name: 3,7-Dimethyloct-6-en-3-ol CAS Registry Number: 18,479-51-1
Additional CAS*:
2270-57-7 Dihydrolinalool (no reported use)
*Included because the materials are isomers



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)

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(*continued*)

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

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

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

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

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

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

3,7-Dimethyloct-6-en-3-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog linalool (CAS # 78-70-6) show that this material is not expected to be genotoxic. Data on read-across analog dihydromyrcenol (CAS # 18,479-58-8) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for 3,7-dimethyloct-6-en-3-ol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3,7-dimethyloct-6-en-3-ol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 3,7-dimethyloct-6-en-3-ol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 3,7-dimethyloct-6-en-3-ol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 1999; RIFM, 1983; RIFM, 2001)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day.	RIFM (2007)
Reproductive Toxicity: Developmental toxicity: NOAEL = 500 mg/kg/day. Fertility: NOAEL = 500 mg/kg/day.	(RIFM, 2007; RIFM, 2009)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: 3,7-Dimethyloct-6-en-3-ol; ECHA, 2017a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra, RIFM Database)	
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 65% (OECD 301 D)	(ECHA REACH Dossier: 3,7-Dimethyloct-6-en-3-ol; ECHA, 2017a)
Bioaccumulation: Screening-level: 97.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 3.635 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Fradmework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 3.635 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.3635 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1	

1. Identification

Chemical Name: 3,7-Dimethyloct-6-en-3-ol	Chemical Name: Dihydrolinalool
CAS Registry Number: 18,479-51-1	**CAS Registry Number:** 2270-57-7
Synonyms: 1,2-Dihydrolinalool; 6-Octen-3-ol, 3,7-dimethyl-; 脂肪族不飽和アルコール(C = 9–24); 3,7-Dimethyloct-6-en-3-ol	**Synonyms:** 3,7-Dimethyl-6-octen-3-ol; 6-Octen-3-ol, 3,7-dimethyl, (.+-.)-; Dihydro Linalol
Molecular Formula: $C_{10}H_{20}O$	**Molecular Formula:** $C_{10}H_{20}O$
Molecular Weight: 156.26	**Molecular Weight:** 156.26
RIFM Number: 5440	**RIFM Number:** None

2. Physical data*

1. **Boiling Point:** 205.52 °C (EPI Suite)
2. **Flash Point:** 68 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.52 (EPI Suite)
4. **Melting Point**: −10.08 °C (EPI Suite)
5. **Water Solubility:** 228.1 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0327 mm Hg at 20 °C (EPI Suite v4.0), 0.0528 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})

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

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

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)***

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.16% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.00086 mg/kg/day or 0.060 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0079 mg/kg/day (RIFM, 2016)

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

***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 hydroalcoholics, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low* (Expert Judgment)

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
I	III	I

*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). See Appendix below for further details.

6.2. Analogs Selected

a. **Genotoxicity:** Linalool (CAS # 78-70-6)
b. **Repeated Dose Toxicity:** Dihydromyrcenol (CAS # 18,479-58-8)
c. **Developmental and Reproductive Toxicity:** Dihydromyrcenol (CAS # 18,479-58-8)
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification**: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional references
None.

8. Natural occurrence

3,7-Dimethyloct-6-en-3-ol is reported to occur in the following foods by the VCF*:

Honey
Raspberry, blackberry, and boysenberry

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

9. REACH dossier

Available; accessed 08/18/20 (ECHA, 2017a).

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, 3,7-dimethyloct-6-en-3-ol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3,7-Dimethyloct-6-en-3-ol was assessed in the BlueScreen assay and found negative for cytotoxicity (positive: <80% relative cell density) and genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 3,7-dimethyloct-6-en-3-ol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA102, and TA97 were treated with 3,7-dimethyloct-6-en-3-ol 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, 1999). Under the conditions of the study, 3,7-dimethyloct-6-en-3-ol was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 3,7-dimethyloct-6-en-3-ol; however, read-across can be made to linalool (CAS # 78-70-6; see Section VI).

The clastogenicity of linalool was assessed in an in vitro chromosome aberration study conducted in compliance with GLP regulations and in an equivalent manner with OECD TG 473. Chinese hamster ovary cells

were treated with linalool in DMSO at concentrations up to 500.0 nL/mL (435.0 μg/mL) in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 1983). Under the conditions of the study, linalool was considered to be non-clastogenic in the in vitro chromosome aberration assay, and this can be extended to 3,7-dimethyloct-6-en-3-ol.

The clastogenic activity of linalool was evaluated in an in vivo micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral intubation to groups of male and female CD-1 mice. Doses of 500, 1000, or 1500 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2001). Under the conditions of the study, linalool was considered to be not clastogenic in the in vivo micronucleus test, and this can be extended to 3,7-dimethyloct-6-en-3-ol.

Based on the data available, linalool does not present a concern for genotoxic potential, and this can be extended to 3,7-dimethyloct-6-en-3-ol.

Additional references

None.

Literature search and risk assessment completed on 10/02/20.

11.1.2. Repeated dose toxicity

The MOE for 3,7-dimethyloct-6-en-3-ol 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 3,7-dimethyloct-6-en-3-ol. Read-across material dihydromyrcenol (CAS # 18,479-58-8; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 408-compliant subchronic study, groups of 10 Sprague Dawley Crl:CD(SD)IGS BR strain rats/sex/dose were administered a mixture of 44.2% 2,6-dimethyl-7-octen-2-ol and 54.8% 2,6-dimethyl-7-octen-2-yl formate via gavage at doses of 0, 10, 50, 500, or 1000 mg/kg/day for 90 days. 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. Hematological alterations were not considered to be related to treatment with dihydromyrcenol due to a lack of dose dependence in any of the parameters (RIFM, 2010). The absolute and relative liver weights were increased for the males treated at 50 mg/kg/day and higher, while this was only seen in the females treated at 500 and 1000 mg/kg/day. The absolute and relative kidney weights were increased for both the males and females of the 500 and 1000 mg/kg/day dose groups. There were no macroscopic abnormalities reported. Histopathological examination revealed adaptive alterations in the liver among the animals of the 500 and 1000 mg/kg/day dose groups. α-2u-Globulin related nephropathy was reported among the treated males. Adipose infiltration of the bone marrow was reported among the males of the high-dose group, indicative of marrow hypoplasia. There was no dose response. No changes were observed at 50 mg/kg/day for the females, 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, based on a decrease in bodyweight gains among the 500 and 1000 mg/kg/day dose groups, the NOAEL for the repeated dose toxicity was considered to be 50 mg/kg/day.

Therefore, the 3,7-dimethyloct-6-en-3-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the dihydromyrcenol NOAEL in mg/kg/day by the total systemic exposure to 3,7-dimethyloct-6-en-3-ol, 50/0.0079, or 6329.

In addition, the total systemic exposure to 3,7-dimethyloct-6-en-3-ol (7.9 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.

Additional references

None.

Literature search and risk assessment completed on 08/13/20.

11.1.3. Reproductive toxicity

The MOE for 3,7-dimethyloct-6-en-3-ol 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 3,7-dimethyloct-6-en-3-ol. Read-across material dihydromyrcenol (CAS # 18,479-58-8; see Section VI) has sufficient data to support the developmental toxicity endpoint. A GLP-compliant developmental toxicity study was conducted with test material 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 administered 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 maternal reduction in body weights, there was a reduction in fetal body weight among the high-dose group. The high-dose group fetuses were reported to have reversible variations in ossification, which included 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). Therefore, the 3,7-dimethyloct-6-en-3-ol MOE for the developmental toxicity endpoint can be calculated by dividing the dihydromyrcenol NOEL in mg/kg/day by the total systemic exposure to 3,7-dimethyloct-6-en-3-ol, 500/0.0079, or 63,291.

There are no fertility data on 3,7-dimethyloct-6-en-3-ol. Read-across material dihydromyrcenol (CAS # 18,479-58-8; see Section VI) has sufficient data to support the fertility endpoint. 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 analyses 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 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). Therefore, the dihydromyrcenol MOE for the fertility endpoint can be calculated by dividing the dihydromyrcenol NOAEL in mg/kg/day by the total systemic exposure to dihydromyrcenol, 500/0.0079 or 63,291.

In addition, the total systemic exposure to 3,7-dimethyloct-6-en-3-ol (7.9 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a

Cramer Class I material at the current level of use.

Additional references

None.

Literature search and risk assessment completed on 10/01/20.

11.1.4. Skin sensitization

Based on the existing data, 3,7-dimethyloct-6-en-3-ol presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, 3,7-dimethyloct-6-en-3-ol is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), the additional material, dihydrolinalool, was not found to be sensitizing up to 100% (w/v) (ECHA, 2017a).

Based on weight of evidence (WoE) from structural analysis and an animal study, 3,7-dimethyloct-6-en-3-ol does not present a concern for skin sensitization under the current, declared levels of use.

Additional references

None.

Literature search and risk assessment completed on 09/15/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3,7-dimethyloct-6-en-3-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 3,7-dimethyloct-6-en-3-ol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 3,7-dimethyloct-6-en-3-ol does not present a concern for phototoxicity or photoallergenicity.

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

Additional references

None.

Literature search and risk assessment completed on 09/01/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3,7-dimethyloct-6-en-3-ol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 3,7-dimethyloct-6-en-3-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.060 mg/day. This exposure is 23.4 times lower than the Cramer Class I TTC level 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 09/30/20.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3,7-dimethyloct-6-en-3-ol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow}, and its molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class-specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 3,7-dimethyloct-6-en-3-ol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 3,7-dimethyloct-6-en-3-ol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on current VoU (2015), 3,7-dimethyloct-6-en-3-ol does present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. Not available.

11.2.2.1.2. Ecotoxicity. Not available.

11.2.2.1.3. Other available data. 3,7-Dimethyloct-6-en-3-ol has been registered for REACH with the following additional data available at this time (ECHA, 2017a):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guideline. Biodegradation of 65% was observed after 28 days.

The acute fish (*Cyprinus carpio*) toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 42 mg/L (95% CI: 32–56 mg/L).

The toxicity of the test material towards *Daphnia magna* was investigated according to ISO Guideline 6341 under semi-static conditions. The 48-h EC50 value based on nominal test concentration was reported

to be 32 mg/L (95% CI: 29–37 mg/L).

The algae (*Scenedesmus subspicatus* and *Selenastrum capricornutum*) growth inhibition test was conducted according to the ISO 8692 guideline under static conditions. The 96-h EC50 value based on nominal test concentration for growth rate was reported to be 78 mg/L (95% CI: 38–160 mg/L).

11.2.3. Risk assessment refinement

Since 3,7-dimethyloct-6-en-3-ol has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>10.03</u>			1000000	0.01003	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	5.565	<u>3.635</u>	4.833	10000	0.364	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.52	3.52
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.3635 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature search and risk assessment completed on 10/01/20.

12. Literature search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/15/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112703.

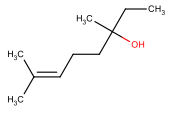
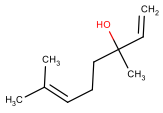
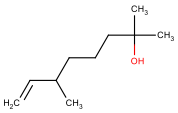
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	3,7-Dimethyloct-6-en-3-ol	Linalool	Dihydromyrcenol
CAS No.	18,479-51-1	78-70-6	18,479-58-8
Structure			
Similarity (Tanimoto Score)		0.86	0.45
Endpoint		Genotoxicity	Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{10}H_{20}O$	$C_{10}H_{18}O$	$C_{10}H_{20}O$
Molecular Weight	156.269	154.253	156.269
Melting Point (°C, EPI Suite)	−10.08	−11.39	−13.10
Boiling Point (°C, EPI Suite)	205.52	198.00	191.28
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.04E+00	2.13E+01	1.65E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.28E+02	1.59E+03	2.52E+02
Log K_{OW}	3.52	2.97	3.47
J_{max} (μg/cm^2/h, SAM)	27.87	121.08	29.70
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.76E+00	2.18E+00	4.12E+00
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
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
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Non-toxicant (low reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There is insufficient toxicity data on 3,7-dimethyloct-6-en-3-ol (CAS # 18,479-51-1). Hence *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, linalool (CAS # 78-70-6) and dihydromyrcenol (CAS # 18,479-58-8) were identified as read-across materials with sufficient toxicological data.

Conclusions

- Linalool (CAS # 78-70-6) was selected as the read-across analog for the target material 3,7-dimethyloct-6-en-3-ol (CAS # 18,479-51-1) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of tertiary alcohols.
  - The target material and the read-across analog have the 1,3-dimethylocta,1-6-dien-3-ol fragment in common.
  - The key difference between the target material and the read-across analog is that the read-across is an α,β-unsaturated tertiary alcohol while the target is a tertiary alcohol that does not have α,β-unsaturation. These structure differences between the target material and the read-across analog do not raise additional structural alerts, so the structure differences are not relevant from a toxicological perspective.
  - The target material and the read-across analog have Tanimoto scores as mentioned in the above table. The Tanimoto score is mainly driven by the 1,3-dimethylocta,1-6-dien-3-ol fragment. The differences in the structure responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the genotoxicity endpoint.
  - According to the QSAR OECD Toolbox (v4.2), structural alerts for genotoxicity are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.
- Dihydromyrcenol (CAS # 18,479-58-8) was selected as a read-across analog for the target material 3,7-dimethyloct-6-en-3-ol (CAS # 18,479-51-1) for the repeated dose and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to the structural class of tertiary alcohols.
  - The target material and the read-across analog have the 1,3-dimethylocta,1-6-dien-3-ol fragment in common.
  - The key difference between the target material and the read-across analog is that the read-across has a carbon-carbon triple bond at the α,β position while the target does not have an α,β-unsaturation. This structure difference between the target material and the read-across analog does not raise additional structural alerts, so the structure differences are not relevant from a toxicological perspective.
  - The target material and the read-across analog have Tanimoto scores, as mentioned in the above table. The Tanimoto score is mainly driven by the 1,3-dimethylocta,1-6-dien-3-ol fragment. The differences in the structure responsible for a Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the repeated dose and reproductive toxicity endpoints.
  - According to the QSAR OECD Toolbox (v4.2), structural alerts are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

Explanation of Cramer Class

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. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C,H,O,N,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? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? Yes
Q20. Aliphatic with some functional groups? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)? No, Class Low (Class I)

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