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RIFM fragrance ingredient safety assessment, 3,7-dimethyloct-1-en-3-ol, CAS Registry Number 18479-49-7

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Name: 3,7-Dimethyloct-1-en-3-ol
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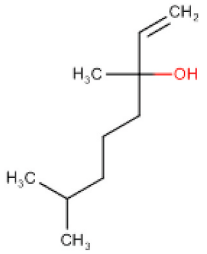

Abbreviation/Definition List:

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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., 2015a, 2017) compared to a deterministic aggregate approach

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

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable 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-1-en-3-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that the material is not genotoxic. Data on read-across analog linalool (CAS # 78-70-6) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and developmental toxicity endpoints. The fertility and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 3,7-dimethyloct-1-en-3-ol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for 3,7-dimethyloct-1-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-1-en-3-ol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3,7-dimethyloct-1-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 genotoxic.	(ECHA REACH Dossier: 3,7-Dimethyloct-1-en-3-ol; ECHA, 2018; RIFM, 2003; RIFM, 2013b)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM (1980)
Reproductive Toxicity: Developmental toxicity: NOAEL = 1000 mg/kg/day. Fertility: No NOAEL available. Exposure is below TTC.	Politano (2008)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: 3,7-Dimethyloct-1-en-3-ol; ECHA, 2018)
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: 61% (OECD 301F)	(ECHA REACH Dossier: 3,7-Dimethyloct-1-en-3-ol; ECHA, 2018)
Bioaccumulation:	
Screening-level: 90 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC_{50}: 0.287 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)

Critical Ecotoxicity Endpoint:: 48-h *Daphnia magna* LC_{50}: 0.287 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0287 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1

1. Identification

1. **Chemical Name:** 3,7-Dimethyloct-1-en-3-ol
2. **CAS Registry Number:** 18479-49-7
3. **Synonyms:** 6,7-Dihydrolinalool; 1-Octen-3-ol, 3,7-dimethyl-; 3,7-Dimethyloct-1-en-3-ol
4. **Molecular Formula:** $C_{10}H_{20}O$
5. **Molecular Weight:** 156.26 g/mol
6. **RIFM Number:** 5439
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 191.28 °C (EPI Suite)
2. **Flash Point:** 68 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.47 (EPI Suite)
4. **Melting Point**: -13.1 °C (EPI Suite)
5. **Water Solubility:** 252.2 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0788 mm Hg at 20 °C (EPI Suite v4.0), 0.124 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

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.34% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0013 mg/kg/day or 0.12 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0086 mg/kg/day (RIFM, 2018)

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

5. Derivation of systemic absorption

1. **Dermal:** 80%

Name	3,7-Dimethyloct-1-en-3-ol
J_{max} (μg/cm^2/h)	29.70[1]
Skin Absorption Class	80%

J_{max} was calculated based on measured log K_{ow} = 3.47 (EPI Suite) and water solubility = 252.2 mg/L (EPI Suite).

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

6. Computational toxicology evaluation

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

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

*See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Linalool (CAS # 78-70-6)
   c. **Reproductive Toxicity:** Linalool (CAS # 78-70-6)
   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-1-en-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

Available; accessed 09/14/21 (ECHA, 2018).

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-1-en-3-ol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3,7-Dimethyloct-1-en-3-ol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

A mammalian cell gene mutation assay (mouse lymphoma assay) was conducted according to OECD TG 490 and GLP guidelines. Mouse lymphoma L5178Y cells were treated with 3,7-dimethyloct-1-en-3-ol in dimethyl sulfoxide (DMSO) at concentrations up to 195 μg/mL (as determined in a preliminary toxicity assay) for 4 and 24 h (no serum was added). Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test item, either with or without metabolic activation (ECHA, 2018). Under the conditions of the study, 3,7-dimethyloct-1-en-3-ol was not mutagenic to mammalian cells in vitro.

The clastogenic activity of 3,7-dimethyloct-1-en-3-ol 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 3,7-dimethyloct-1-en-3-ol in DMSO at concentrations up to 1563.0 μg/mL in a dose range finding (DRF) study (no serum was added); micronuclei analysis was conducted at concentrations up to 291.6 μg/mL in the presence and absence of metabolic activation. 3,7-Dimethyloct-1-en-3-ol did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (ECHA, 2018). Under the conditions of the study, 3,7-dimethyloct-1-en-3-ol was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data available, 3,7-dimethyloct-1-en-3-ol does not present a concern for genotoxic potential.

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-1-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-1-en-3-ol. Read-across material linalool (CAS # 78-70-

6; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. A dermal 90-day (13-week) subchronic toxicity study was conducted in rats. Applications with linalool at doses of 250, 1000, and 4000 mg/kg/day were made daily to the clipped and shaved backs of the animals. The NOAEL was determined to be 250 mg/kg/day, based on reduced body weights among animals of the higher dose groups and mortality among the high-dose group animals (RIFM, 1980). The SAM model prediction (RIFM, 2014; see Section V) suggests a dermal absorption value of 80% for 3,7-dimethyloct-1-en-3-ol. Thus, to account for bioavailability following dermal application, data from RIFM's *in silico* skin absorption model (SAM) were used to revise the NOAEL of 250 mg/kg/day to reflect the systemic dose. At a predicted dermal penetration of 80% of the applied dose, the revised NOAEL from the dermal study on read-across analog linalool is 200 mg/kg/day.

Therefore, the 3,7-dimethyloct-1-en-3-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure to 3,7-dimethyloct-1-en-3-ol, 200/0.0086, or 23256.

In addition, the total systemic exposure to 3,7-dimethyloct-1-en-3-ol (8.6 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 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-1-en-3-ol is adequate for the developmental toxicity endpoint at the current level of use. There are no fertility data on 3,7-dimethyloct-1-en-3-ol or on any read-across materials. The total systemic exposure to 3,7-dimethyloct-1-en-3-ol is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on 3,7-dimethyloct-1-en-3-ol. Read-across material linalool (CAS # 78-70-6; see Section VI) has a gavage developmental toxicity study on groups of 25 presumed pregnant Sprague Dawley rats/dose administered 0, 250, 500, or 1000 mg/kg/day linalool in a corn oil vehicle on gestation days 7–17. The NOAEL was determined to be 1000 mg/kg/day, the highest dosage tested (Politano, 2008). Therefore, the 3,7-dimethyloct-1-en-3-ol MOE for the developmental toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure to 3,7-dimethyloct-1-en-3-ol, 1000/0.0086, or 113636.

There are no fertility data on 3,7-dimethyloct-1-en-3-ol or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to 3,7-dimethyloct-1-en-3-ol (8.6 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

In addition, the total systemic exposure to 3,7-dimethyloct-1-en-3-ol (8.6 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 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-1-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-1-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, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 3,7-Dimethyloct-1-en-3-ol was found to be negative in an in vitro direct peptide reactivity assay (DPRA) (ECHA, 2018). In a murine local lymph node assay (LLNA), 3,7-dimethyloct-1-en-3-ol was not found to be sensitizing up to 50% in 4:1 acetone:olive oil (AOO) (ECHA, 2018).

Based on weight of evidence (WoE) from structural analysis and an animal study, 3,7-dimethyloct-1-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-1-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-1-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, 2009). Based on lack of absorbance, 3,7-dimethyloct-1-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, 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-1-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-1-en-3-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.12 mg/day. This exposure is 11.7 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/30/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3,7-dimethyloct-1-en-3-ol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for

lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3,7-dimethyloct-1-en-3-ol was identified as a fragrance material with the potential to present 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-1-en-3-ol as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 3,7-dimethyloct-1-en-3-ol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 3,7-Dimethyloct-1-en-3-ol has been registered for REACH with the following additional data available at this time (ECHA, 2018):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301 F guideline. Biodegradation of 61% was observed after 28 days.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC_{50} value based on nominal test concentration was reported to be 39 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC_{50} values based on nominal test concentration for growth rate and yield were reported to be 64 mg/L (95% CI: 61–66 mg/L) and 28 mg/L (95% CI: 23–33 mg/L), respectively.

11.2.3. Risk assessment refinement

Since 3,7-dimethyloct-1-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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.47	3.47
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0287 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic

	LC_{50} (Fish) (mg/L)	EC_{50} (*Daphnia*) (mg/L)	EC_{50} (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	11.09			1,000,000	0.01109	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.826	0.287	3.25	10,000	0.0287	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** v1.11	6.185	4.021	5.243			Neutral Organic SAR (Baseline toxicity)

environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 10/02/20.

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%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/14/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113047.

Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 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 Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's 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
Principal Name	3,7-Dimethyloct-1-en-3-ol	Linalool
CAS No.	18479-49-7	78-70-6
Structure	CC(C)CCCC(C)(O)C=C	CC(C)=CCCC(C)(O)C=C
Similarity (Tanimoto Score)		0.47
Endpoint		• Repeated dose toxicity • Developmental toxicity
Molecular Formula	$C_{10}H_{20}O$	$C_{10}H_{18}O$
Molecular Weight (g/mol)	156.27	154.25
Melting Point (°C, EPI Suite)	−13.10	−11.39
Boiling Point (°C, EPI Suite)	191.28	204.05
Vapor Pressure (Pa @ 25°C, EPI Suite)	16.53	11.1
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	252.20	683.7

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Log K_{OW}	3.47	2.97
J_{max} (μg/cm^2/h, SAM)	29.70	52.07
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.12	4.28
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, noncyclic structure	Non-binder, noncyclic 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

Summary

There is insufficient toxicity data on 3,7-dimethyloct-1-en-3-ol (CAS # 18479-49-7). 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) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusion

- Linalool (CAS # 78-70-6) was selected as a structurally similar read-across analog for the target material 3,7-dimethyloct-1-en-3-ol (CAS # 18479-49-7) for the repeated dose and developmental toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of α,β-unsaturated tertiary alcohols.
  - o The target substance and the read-across analog have the 1,3-dimethylocta,1-6-dien-3-ol fragment common among them.
  - o The key difference between the target substance and the read-across analog is that the read-across has an additional vinylene group, which the target lacks. This structure difference is toxicologically insignificant.
  - o The read-across analog has a Tanimoto score 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 the Tanimoto score <1 are not relevant from a toxicological perspective for this endpoint.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant for this endpoint.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts are consistent between the metabolites of the read-across analog and the target substance.

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).

1N,2N,3N,5N,6N,7N,16N,17N, 19Y, 20N,22N,33N.

Y to 20 so 21N, 18N, I. See i233. Terpene structure, but not natural, so no to Q16.

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
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. 3 or more different functional groups? No
Q18. One of the list? (see Cramer et al., 1978 for detailed explanation on list of categories) No, Class I (Low Class)

References

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

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

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

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

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.
ECHA, 2012. Guidance on information requirements and chemical safety assessment, November 2012 v2.1. http://echa.europa.eu/. (Accessed 14 September 2021).
ECHA, 2017. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a. (Accessed 14 September 2021).
ECHA, 2018. 3,7-Dimethyl-1-en-3-ol registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/23520/1/2. (Accessed 14 September 2021).
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.
Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.
Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.
Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.
OECD, 2015. *Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment (IATA)*. ENV/JM/HA, p. 7, 2015, Retrieved from. http://www.oecd.org/. (Accessed 14 September 2021).
OECD, 2020. The OECD QSAR Toolbox, v3.2–4.4. Retrieved from. http://www.qsartoolbox.org/. (Accessed 14 September 2021).
Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., Api, A.M., 2008. Evaluation of the developmental toxicity of linalool in rats. Int. J. Toxicol. 27 (2), 183–188. https://doi.org/10.1080/10915810801977948.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980. 90 Day Subchronic Dermal Toxicity with Linalool in Rats. Report to RIFM. RIFM Report Number 4001. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Evaluation of the Mutagenic Activity of Nerolidol (Isomer Unspecified) in the Salmonella typhimurium Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57195.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. Report on the Testing of 3,7-Dimethyloct-1-En-3-Ol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65332. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Nerolidol: Micronucleus Test in Bone Marrow Cells of the Mouse. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from BASF. RIFM report number 66407.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014. An in Silico Skin Absorption Model for Fragrance Materials. RIFM Report Number 67839. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Expos.c Surv. 21. September 2018.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76272.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.