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RIFM fragrance ingredient safety assessment, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized, CAS Registry Number 73018-51-6

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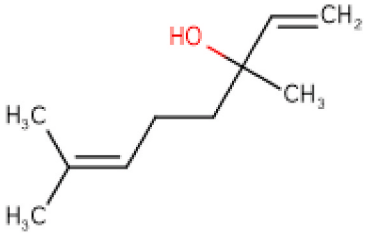
CAS Registry Number: 73018-51-6



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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
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.

1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog linalool (CAS # 78-70-6) show that there are no safety concerns for 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized for skin sensitization under the current declared levels of use. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog linalool (CAS # 78-70-6). The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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.	(RIFM, 2003d; ECHA REACH Dossier: 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized; ECHA, 2017a; RIFM, 1995; RIFM, 2001; RIFM, 1995)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day.	(ECHA REACH Dossier: 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized; ECHA, 2017a)
Reproductive Toxicity: Developmental toxicity NOAEL: 100 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day.	(ECHA REACH Dossier: 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized; ECHA, 2017a)
Skin Sensitization: Not sensitizing.	(RIFM, 2010; Skold, 2002; Skold, 2004; Urbisch, 2015; RIFM, 2005)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 63 mg/m^3.	RIFM (2012)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 65% (OECD 302C)	RIFM (1999b)
Bioaccumulation: Screening-level: 42.33 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.29 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* LC50: 0.29 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.029 μg/L	

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

1. Identification

1. **Chemical Name:** 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized
2. **CAS Registry Number:** 73018-51-6
3. **Synonyms:** Lime Oxide; 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25 g/mol
6. **RIFM Number:** 5981
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** Not Available
2. **Flash Point:** 74 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.4 to 3.7 at 35 °C (RIFM, 1999c), 5.1 to 5.3 at 35 °C (RIFM, 1999c)
4. **Melting Point**: Not Available
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0521 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (32 L mol^{-1} • cm^{-1}, condition not specified) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** The complex combination of hydrocarbons obtained by the acid isomerization of linalool. It consists primarily of monoterpenes, terpene alcohols, and oxygenated cyclic compounds.

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 v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.1% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00041 mg/kg/day or 0.027 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0022 mg/kg/day (RIFM, 2019)

*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%

Data from RIFM's *in silico* skin absorption model (RIFM, 2014) were used to predict the dermal penetration of 80% for 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized as shown below.

	Chemical Name
Name	1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized
J_{max} (μg/cm^2/h)	182.39[1]
Skin Absorption Class	80%

[1] J_{max} was calculated based on measured log K_{ow} = 3.4–3.7 (RIFM, 1999c) and water solubility = 1590 mg/L (EPI Suite v4.11).

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High (Expert Judgment)

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

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Linalool (CAS # 78-70-6)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Linalool (CAS # 78-70-6)
   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

1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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 on 02/12/21 (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, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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, and TA102 were treated with 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized in ethanol 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, 2003d). Under the conditions of the study, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized was not mutagenic in the Ames test.

The clastogenic activity of 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized in dimethyl sulfoxide (DMSO); micronuclei analysis was conducted at concentrations up to 500 μg/mL in the presence and absence of metabolic activation. 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized did not induce binucleated cells with

micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (ECHA, 2017a). Under the conditions of the study, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized does not present a concern for genotoxic potential.

Additional References: RIFM, 1995.

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

11.1.2. Repeated dose toxicity

The MOE for 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized. In a GLP and OECD 422-compliant study, 10 Wistar rats/sex/dose were administered 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized via diet at doses of 0, 100, 300, and 1000 mg/kg/day. Males were treated for 2 weeks prior to pairing, during the pairing period, until the day before necropsy. Females were treated for 2 weeks prior to pairing, during the pairing period, until day 4 post-partum (approximately 55 days). No mortality occurred throughout the study period. No treatment-related effects were observed in clinical signs, water consumption, hematology, organ weights, gross pathology, or histopathology. Food consumption and mean body weight were reduced in both sexes at the mid dose and high dose (dose dependent; statistically significant). Total protein levels were reduced in females at the mid dose and both sexes at the high dose (statistically significant). Albumin levels were reduced in females at the mid dose and high dose (statistically significant). Grip strength was reduced in both sexes at the high dose (only significant in males). Due to the low effect sizes at the mid dose (300 mg/kg/day), effects observed at this dose were not considered adverse. Based on reduced food consumption, body weight, and protein levels in both sexes at the high dose, the NOAEL for this study was considered to be 300 mg/kg/day (ECHA, 2017a).

A default safety factor of 3 was applied as above NOAEL is from the OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity data is 300/3, or 100 mg/kg/day.

Therefore, the 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized NOAEL by the total systemic exposure to 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized, 100/0.0022, or 45454.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized. In a GLP and OECD 422-compliant study, 10 Wistar rats/sex/dose were administered 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized via diet at doses of 0, 100, 300, and 1000 mg/kg/day. Males were treated for 2 weeks prior to pairing, during the pairing period, until the day before necropsy. Females were treated for 2 weeks prior to pairing, during the pairing period, until day 4 post-partum (approximately 55 days). No mortality occurred throughout the study period. Food consumption and mean body weight were reduced in both sexes at the mid dose and high dose (dose dependent; statistically significant). No treatment-related effects were seen on reproductive parameters like mating, fertility and conception indices, precoital time, and numbers of corpora lutea. No histopathological changes were observed in any dose group. With respect to developmental toxicity, pups at the mid and high doses (both sexes) had significantly lower body weights than controls. The high-dose group had a higher incidence of unfed pups (no milk present in the stomach). Based on reduced food consumption, body weight, and reduced pup body weight, the NOAEL for developmental toxicity was considered to be 100 mg/kg/day. The NOAEL for fertility was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2017a). **Therefore, the 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized MOE for the developmental toxicity endpoint can be calculated by dividing the 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized NOAEL in mg/kg/day by the total systemic exposure to 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized, 100/0.0022, or 45455.**

The 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized MOE for the fertility endpoint can be calculated by dividing the 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized NOAEL in mg/kg/day by the total systemic exposure to 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized, 1000/0.0022, or 45455.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/08/21.

11.1.4. Skin sensitization

Based on the existing data for read-across material linalool (CAS # 78-70-6), 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. The target material is a complex combination of hydrocarbons obtained by the acid isomerization of linalool. It consists of monoterpenes, terpene alcohols, and oxygenated cyclic compounds. Based on the target data and the read-across material linalool (CAS # 78-70-6), 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2) but could undergo autoxidation resulting in degradation products that may be protein reactive (Skold, 2004; OECD Toolbox v4.2). Read-across linalool is known to undergo autooxidation resulting in degradation products that are known to be skin sensitizers, protein reactive based on *in vivo* skin sensitization data (Skold, 2004). The target material, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized, was not predicted to be a sensitizer in a Direct Peptide Reactivity Assay (DPRA) and KeratinoSens (RIFM, 2018b; RIFM, 2018a). The read-across material linalool was found to be negative in DPRA and KeratinoSens but positive in the human cell line activation test (h-CLAT) and U937-CD86 test (Urbisch, 2015). In a guinea pig open epicutaneous test (OET) conducted with the target material at 10%, no allergic potential was observed (ECHA, 2017a). In guinea pig test methods and the local lymph node assay (LLNA) on the read-across material, positive and negative results have been reported (Basketter, 2002a, 2002b; Ishihara, 1986; Klecak, 1979, 1985; Sharp, 1978; Skold, 2004). In these LLNAs and guinea pig studies the positive results have been shown to be the result of sensitizing products of autoxidation and irritation (RIFM, 2010; Skold, 2002; Skold, 2004). In a Confirmation of No Induction in Humans test (CNIH), no reactions indicative of sensitization have been observed to linalool at the maximum tested concentration of 12.7% (14,998 μg/cm^2) (RIFM, 2005). Similarly, no reactions were observed in the human maximization test with 20% (13800 μg/cm^2) linalool in

petrolatum (RIFM, 1975). Based on the weight of evidence from linalool, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized does not present a concern for skin sensitization.

Note: Whereas linalool is not considered to be a sensitizer, autoxidation products of this material are known to be contact allergens. Linalool, and natural products rich in linalool, are subject to an IFRA Standard that defines a good manufacturing practice specification limiting peroxide levels to 20 mmol/L with a recommendation to add an antioxidant at the time of production (IFRA, 2004). Similarly, as predicted by OECD Toolbox (v4.2), an analogous autoxidation would be expected to take place for 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized and could result in autoxidation products with a sensitization potential.

Additional References: Greif (1967).

Literature Search and Risk Assessment Completed On: 03/11/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorbance spectra, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized does not present a concern for phototoxicity or photoallergenicity.

11.1.6. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient (32 L mol^{-1} • cm^{-1}) is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/01/21.

11.1.7. Local respiratory toxicity

There are no inhalation data available on 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized; however, in an acute, 2-week inhalation study for the analog linalool (CAS # 78-70-6; see Section VI), a NOAEC of 63 mg/m^3 was reported (RIFM, 2012).

11.1.7.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week acute inhalation study conducted in rats, a NOAEC of 63 mg/m^3 was reported for linalool (RIFM, 2012). The test material-related effects were limited to non-adverse microscopic findings in the nasal cavity. Inflammation and epithelial (squamous and transitional) hyperplasia in nasal level 1 of males and females, as well as subacute inflammation of nasal level 3 in females, were considered exacerbated background lesions as they were also observed in control group males and females and were not considered adverse. Other epithelial findings in nasal level 1 of males and females, inflammation, and/or epithelial changes in nasal levels 2 and 3 in males and nasal level 2 in females had similar incidences in control and test material-exposed groups.

This NOAEC expressed in mg/kg lung weight/day is:

- (63 mg/m^3) × (1 m^3/1000 L) = 0.063 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.063 mg/L) × (61.2 L/d) = 3.86 mg/d
- (3.86 mg/d)/(0.0016 kg lung weight of rat*) = 2412.5 mg/kg lw/day

The 95th percentile calculated exposure was reported to be 0.027 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.042 mg/kg lung weight/day resulting in a MOE of 57440 (i.e., [2412.5 mg/kg lung weight/day]/[0.042 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.027 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: Troy (1977); Jirovetz (1991); Buchbauer (1991); Jirovetz (1990); UGCM, 1997; Buchbauer (1993); Perrucci (1996); Perrucci (1995a); Rice (1994a); Silver (1992); Karr (1992); Regnault-Roger (1995); Rice (1994b); Perrucci (1995b); Sugawara (1998); Coats (1991); Cometto-Muniz (1998); RIFM, 2003b; RIFM, 2003c; Rogers (2003a); RIFM, 2003e; RIFM, 2003a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola (2004a); Barocelli (2004); Rogers (2005); Kuroda (2005); Tanida (2006); Yang (2005); Corsi (2007); Sato (2007); Nakamura (2010); Nakamura (2009); deMouraLinck, 2009; RIFM, 2013; Vethanayagam (2013).

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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, 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and*

bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 1999a: Biodegradability was evaluated by the manometric respirometry test according to OECD Guideline 301F. Mineral medium inoculated with fresh activated sludge and 100 mg/L of 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized were added to 250-mL flasks. The flasks were sealed and incubated for 29 days. Biodegradation of 56% was observed.

RIFM, 1999b: The inherent biodegradability of the test material was determined by the manometric respirometry test according to OECD Guideline 302C. Mineral medium inoculated with fresh activated sludge and 30 mg/L of 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized were added to 250-mL flasks. The flasks were sealed and incubated for 33 days. The degradation rate was 65% after 28 and 33 days.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized 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 OECD 301F guideline. Biodegradation of 61% was observed after 61 days.

The *Daphnia magna* acute immobilization test was conducted according to the 202 guidelines under static conditions. Analysis of the test preparations at 0 h showed measured test concentrations in the range of 0.89 (2.6 mg/L loading rate WAF) to 22 mg/L (100 mg/L loading rate WAF). The dissolved test material may have been 1 or several components of the test material. Given that toxicity cannot be attributed to a single component or mixture of components but the test material as a whole, the results were based on nominal loading rates only. The 48-h EL50 was reported to be 5.3 mg/L Loading Rate WAF.

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. Analysis of the test preparations at 0 h showed measured test concentrations in the range of 0.92 mg/L (10 mg/L loading rate WAF) to 23 mg/L (100 mg/L loading rate WAF). Given that the toxicity cannot be attributed to a single component or a mixture of components but the test material as a whole, the results were based on nominal loading rates only. The 72-h EL50 was reported to be 15 mg/L Loading Rate WAF.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.3	5.3
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 0.029 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

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

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **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 02/09/22.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.2763			1000000	0.0002736	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.856	0.290	3.597	10000	0.0290	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** v1.11	7.283	4.698	5.929			Neutral Organic SAR (Baseline toxicity)

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113096.

Appendix

Read-across Justification

Methods

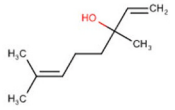
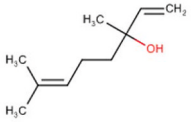
The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent 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, 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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 v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized	Linalool
CAS No.	73018-51-6	78-70-6
Structure		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
		
Similarity (Tanimoto Score)[1]		1.0
Read-across Endpoint		• Skin sensitization • Local respiratory toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$
Molecular Weight (g/mol)	154.25	154.25
Melting Point (°C, EPI Suite)	−11.39	−11.39
Boiling Point (°C, EPI Suite)	204.05	204.05
Vapor Pressure (Pa @ 25°C, EPI Suite)	11.1	11.1
Log K_{ow}	3.4–3.7[1]	2.97
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1590	1590
J_{max} (μg/cm^2/h, SAM)	182.39	121.08
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.23E-005	4.23E-005
Skin Sensitization		
Protein Binding by OASIS V1.1	• No alert found	• No alert found
Protein Binding by OECD	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify	• Not possible to classify
Protein Binding Alerts for Skin Sensitization by OASIS V1.1	• No alert found	• No alert found
Skin Sensitization Model (CAESAR) (Version 2.1.6)	• Sensitizer (Experimental value)	• Sensitizer (Experimental value)
Metabolism		
OECD QSAR Toolbox (4.2)	See Supplemental Data 1	See Supplemental Data 2
Rat Liver S9 Metabolism Simulator		

1. RIFM, 1999b.

Summary

There are insufficient toxicity data on 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized (CAS # 73018-51-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, linalool (CAS # 78-70-6) was identified as a read-across material with sufficient toxicological data.

Conclusion

- Linalool (CAS # 78-70-6) is used as a read-across analog for target material 1,6-octadien-3-ol, 3,7-dimethyl-, acid-isomerized (CAS # 73018-51-6) for the local respiratory toxicity and skin sensitization endpoints.
  - o The target material and the read-across analog belong to the structural class of α,β-unsaturated tertiary alcohols.
  - o The target material and the read-across analog have the 3,7-dimethylocta-1,6-dien-3-ol fragment common among them.
  - o The key difference between the target material and the read-across analog is that the read-across is a calcium oxide mixture of the alcohol while the target material is a pure alcohol. This structural difference between the target material and the read-across analog is not relevant from a toxicological endpoint perspective.
  - o 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 3,7-dimethylocta-1,6-dien-3-ol fragment. The differences in the structure that are responsible for Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - o 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 these endpoints.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts are consistent between the target material and the read-across analog.
  - o The CAESAR model for the skin sensitization endpoint predicts the target material and the read-across analog linalool (CAS # 78-70-6) to be a sensitizer. The target material and the read-across analog do not have other protein binding alerts for skin sensitization. The data described in the skin sensitization section show that the read-across analog does not pose a concern for skin sensitization. Therefore, the alert will be superseded by the availability of 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 endpoints are consistent between the metabolites of the read-across analog and the target material.
  - o 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 between 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.

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? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? Yes, Intermediate (Class II)

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.

Barocelli, E., Calcina, F., Chiavarini, M., Impicciatore, M., Bruni, R., Bianchi, A., Ballabeni, V., 2004. Antinociceptive and gastroprotective effects of inhaled and orally administered Lavandula hybrida Reverchon "Grosso" essential oil. Life Sci. 76 (2), 213–223.

Basketter, D.A., Wright, Z., Gilmour, N.J., Ryan, C.A., Gerberick, G.F., Robinson, M.K., Dearman, R.J., Kimber, I., 2002b. Prediction of human sensitization potency using Local Lymph Node Assay EC3 values. Toxicologist 66 (1-S), 240.

Basketter, D.A., Wright, Z.M., Colson, N.R., Patlewicz, G.Y., Smith-Pease, C.K., 2002a. Investigation of the skin sensitizing activity of linalool. Contact Dermatitis 47 (3), 161–164.

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.

Buchbauer, G., Jirovetz, L., Jager, W., Dietrich, H., Plank, C., Karamat, E., 1991. Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. Zeitschrift fur Naturforschung 46 (11–12), 1067–1072.

Buchbauer, G., Jirovetz, L., Jager, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. J. Pharmaceut. Sci. 82 (6), 660–664.

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.

Coats, J.R., Karr, L.L., Drewes, C.D., 1991. Toxicity and neurotoxic effects of monoterpenoids in insects and earthworms. Am. Cancer Soc. Symposium Ser. 449, 305–316.

Cometto-Muniz, J.E., Cain, W.S., Abraham, M.H., Kumarsingh, R., 1998. Trigeminal and olfactory chemosensory impact of selected terpenes. Pharmacol. Biochem. Behav. 60 (3), 765–770.

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.

Corsi, R.L., Siegel, J., Karamalegos, A., Simon, H., Morrison, G.C., 2007. Personal reactive clouds: introducing the concept of near-head chemistry. Atmos. Environ. 41 (15), 3161–3165.

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.

de Moura Linck, V., da Silva, A.L., Figueiro, M., Piato, A.L., Herrmann, A.P., et al., 2009. Inhaled linalool-induced sedation in mice. Phytomedicine 16 (4), 303–307.

ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017a. 1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized REACH Registration dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/20366/7/6/2.

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

Greif, N., 1967. Cutaneous safety of fragrance material as measured by the maximization test. Am. Perfumer Cosmetics 82, 54–57.

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, 2004. IFRA standard, amendment 38. Linalool. Retrieved from: https://ifrafragrance.org/pdf/web/viewer.html?file=/standards/IFRA_STD_187.pdf.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (suppl 2), 230–240.

Isola, D.A., Rogers, R., Black, M.S., Smith, L.W., 2004. Exposure characterizations of three fragranced products. Int. J. Toxicol. 23 (6), 397.

Jirovetz, L., Buchbauer, G., Jager, W., Raverdino, V., Nikiforov, A., 1990. Determination of lavender oil fragrance compounds in blood samples. Fresen. J. Anal. Chem. 338 (8), 922–923.

Jirovetz, L., Jager, W., Buchbauer, G., Nikiforov, A., Raverdino, V., 1991. Investigations of animal blood samples after fragrance drug inhalation by gas chromatography/mass spectrometry with chemical ionization and selected ion monitoring. Biol. Mass Spectrom. 20 (12), 801–803.

Karr, L.L., Coats, J.R., 1992. Effect of four monoterpenoids on growth and reproduction of the German cockroach (Blattodea: Blattellidae). J. Econ. Entomol. 85 (2), 424–429.

Klecak, G., 1979. The open epicutaneous test (OET), a predictive test procedure in the Guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. Int. Federation Soc. Cosmetic Chem. 9/18/79.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. Curr. Probl. Dermatol. 14, 152–171.

Kuroda, K., Inoue, N., Ito, Y., Kubota, K., Sugimoto, A., Kakuda, T., Fushiki, T., 2005. Sedative effects of the jasmine tea odor and (R)-(-)-linalool, one of its major odor components, on automnomic nerve activity and mood states. Eur. J. Appl. Physiol. 95 (2–3), 107–114.

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.

Nakamura, A., Fujiwara, S., Matsumoto, I., Abe, K., 2009. Stress repression in restrained rats by (R)-(-)-linalool inhalation and gene expression profiling of their whole blood cells. J. Agric. Food Chem. 57, 5480–5485.

Nakamura, A., Fujiwari, S., Ishijima, T., Okada, S., Nakai, Y., Matsumoto, I., Misaka, T., Abe, K., 2010. Neuron differentiation-related genes are upregulated in the hypothalamus of odorant-inhaling rats subjected to acute restraint stress. J. Agric. Food Chem. 58 (13), 7922–7929.

OECD, 2015. *Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment (IATA)*. ENV/JM/HA, p. 7, 2015, Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

Perrucci, S., 1995. Acaricidal activity of some essential oils and their constituents against Tyrophagus longior, a mite of stored food. J. Food Protect. 58 (5), 560–563.

Perrucci, S., Macchioni, G., Cioni, P.C., Flamini, G., Morelli, I., Taccini, F., 1996. The activity of volatile compounds from Lavandula angustifolia against Psoraptes cuniculi. Phytother Res. 10 (1), 5–8.

Perrucci, S., Macchioni, G., Cioni, P.L., Flamini, G., Morelli, I., 1995. Structure/activity relationship of some natural monoterpenes as acaricides against Psoroptes cuniculi. J. Nat. Prod. 58 (8), 1261–1264.

Regnault-Roger, C., Hamraoui, A., 1995. Fumigant toxic activity and reproductive inhibition induced by monoterpenes on Acanthoscelides obtectus (Say) (Coleoptera), a bruchid of kidney bean (Phaseolus vulgaris L.). J. Stored Prod. Res. 31 (4), 291–299.

Rice, P.J., Coats, J.R., 1994a. Insecticidal properties of several monoterpenoids to the house fly (Diptera: Muscidae), red flour beetle (Coleoptera: Tenebrionidae) and southern corn rootworm (Coleoptera: Chrysomelidae). J. Econ. Entomol. 87 (5), 1172–1179.

Rice, P.J., Coats, J.R., 1994b. Insecticidal properties of monoterpenoid derivatives to the house fly (Diptera; Muscidae) and red flour beetle (Coleoptera: Tenebrionidae). Pestic. Sci. 41 (3), 195–202.

RIFM (Research Institute for Fragrance Materials, Inc), 1975. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1799. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995. Mutagenicity Evaluation of 1,6-Octadien-3-Ol, 3,7-dimethyl-, Acid-Isomerized (Hydrogenated) (Lime Oxide)in the Ames Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 41966.

RIFM (Research Institute for Fragrance Materials, Inc), 1999a. Ready Biodegradability of 1,6-Octadien-3-Ol, 3,7-dimethyl-, Acid-Isomerized (Lime Oxide). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51467.

RIFM (Research Institute for Fragrance Materials, Inc), 1999b. Inherent Biodegradability of 1,6-Octadien-3-Ol, 3,7-dimethyl-, Acid-Isomerized (Lime Oxide). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51468.

RIFM (Research Institute for Fragrance Materials, Inc), 1999c. Partition Coefficient N-Octanol/water of 1,6-Octadien-3-Ol, 3,7-dimethyl-, Acid-Isomerized (Lime Oxide). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51469.

RIFM (Research Institute for Fragrance Materials, Inc), 2001. Micronucleus Test in Bone Marrow Cells of the Mouse with Linalool. Private Communication to FEMA. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Hoffmann-LaRoche. RIFM report number 38577.
RIFM (Research Institute for Fragrance Materials, Inc), 2003a. Exposure Characterization of Fragranced Air Fresheners. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 43878.
RIFM (Research Institute for Fragrance Materials, Inc), 2003b. Exposure Characterization from a Fragranced Plug-In Air Freshener. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 41705.
RIFM (Research Institute for Fragrance Materials, Inc), 2003c. Airborne Levels of Selected Fragrance Materials in a Simulated Bathroom. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 41708.
RIFM (Research Institute for Fragrance Materials, Inc), 2003d. Salmonella typhimurium Reverse Mutation Assay with 1,6-Octadien-3-Ol, 3,7-dimethyl-, Acid-Isomerized. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 42043.
RIFM (Research Institute for Fragrance Materials, Inc), 2003e. Indoor Air Quality Evaluation of a Plug-In Air Freshener. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 43292.
RIFM (Research Institute for Fragrance Materials, Inc), 2004a. Exposure Characterization from a Surrogate Fine Fragrance. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 44448.
RIFM (Research Institute for Fragrance Materials, Inc), 2004b. Exposure Characterizations of Three Fragranced Products. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 45348.
RIFM (Research Institute for Fragrance Materials, Inc), 2004c. Airborne Levels of Selected Fragrance Materials Following a Controlled Exposure to a Surrogate Fine Fragrance. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 47425.
RIFM (Research Institute for Fragrance Materials, Inc), 2005. Repeated Insult Patch Test with Linalool. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 49469.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Linalool: B220 Assay Research Report: Comparison of Linalool and Linalool with Anti-oxidant. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 63724.
RIFM (Research Institute for Fragrance Materials, Inc), 2012. A Two-Week Inhalation Toxicity Study of Aerosolized Linalool in the Sprague Dawley Rat. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 63821.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Evaluation of Nose-Only Inhalation Exposure to Aerosolized Linalool in Sprague-Dawley Rats. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 64502.
RIFM (Research Institute for Fragrance Materials, Inc), 2014. An in Silico Skin Absorption Model for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 67839.
RIFM (Research Institute for Fragrance Materials, Inc), 2018a. Induction of Antioxidant-Response-Element Dependent Gene Activity and Cytotyoxicity (Using MTT) in the Keratinocyte ARE- Reporter Cell Line Keratinosens of Multiple Materials. RIFM Report Number 73069. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2018b. 1,6-Octadien-3-ol, 3,7-dimethyl-, Acid-Isomerized (Lime Oxide), Nerolidol (Isomer Unspecified) and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-One (Camphor): Direct Peptide Reactivity Assay (DPRA). RIFM Report Number 73460. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2019. Exposure Survey 24. March 2019.
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.
Rogers, R.E., Isola, D.A., Jeng, C.-J., Smith, L.W., Lefebvre, A., 2005. Simulated inhalation levels of fragrance materials in a surrogate air freshener formulation. Environ. Sci. Technol. 39 (20), 7810–7816.
Rogers, R.E., Isola, D.A., Smith, L.W., Jeng, C.J., Dews, P., Myshaniuk, A., 2003. Characterization of potential human exposure to fragrances during residential consumer product use. J. Allergy Clin. Immunol. 111 (2), S239.
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.
Sato, K., Krist, S., Buchbauer, G., 2007. Antimicrobial effect of vapours of geraniol, (R)-(-)-linalool, terpineol, gamma-terpinene and 1,8-cinole on airborne microbes using an airwasher. Flavour Fragrance J. 22 (5), 435–437.
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.
Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. Ann. N. Y. Acad. Sci. 641, 152–163.
Skold, M., Borje, A., Harambasic, E., Karlberg, A.-T., 2004. Contact allergens formed on air exposure of linalool. Identification and quantification of primary and secondary oxidation products and the effect on skin sensitization. Chem. Res. Toxicol. 17 (12), 1697–1705.
Skold, M., Borje, A., Matura, M., Karlberg, A.-T., 2002. Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hyperperoxide. Contact Dermatitis 46 (5), 267–272.
Sugawara, Y., Hara, C., Tamura, K., Fujii, T., Nakamura, K.I., Masujima, T., Aoki, T., 1998. Sedative effect on humans of inhalation of essential oil of linalool: sensory evaluation and physiological measurements using optically active linalools. Anal. Chim. Acta 365 (1–3), 293–299.
Tanida, M., Niijima, A., Shen, J., Nakamura, T., Nagai, K., 2006. Olfactory stimulation with scent of lavender oil affects autonomic neurotransmission and blood pressure in rats. Neurosci. Lett. 398 (1–2), 155–160.
The Union of German Candle Manufacturers, 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. Unpublished.
Troy, W.R., 1977. Doctoral Dissertation: the Comparative Respiratory Irritation Potential of Fourteen Fragrance Raw Materials. Unpublished.
Urbisch, D., Mehling, A., Guth, K., Ramirez, T., Honarvar, N., et al., 2015. Assessing skin sensitization hazard in mice and men using non-animal test methods. Regul. Toxicol. Pharmacol. 71 (2), 337–351.
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.
Vethanayagam, D., Vilagoftis, H., Mah, D., Beach, J., Smith, L., Moqbel, R., 2013. Fragrance materials in asthma: a pilot study using a surrogate aerosol product. J. Asthma 50 (9), 975–982.
Yang, Y.-C., Lee, H.-S., Lee, S.H., Clark, J.M., Ahn, Y.-J., 2005. Ovicidal and adulticidal activities of Cinnamomum zeylanicum bark essential oil compounds and related compounds against Pediculus humanus capitis (Anoplura: Pediculicidae). Int. J. Parasitol. 35 (14), 1595–1600.