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Short Review

Update to RIFM fragrance ingredient safety assessment, linalyl acetate, CAS registry number 115-95-7

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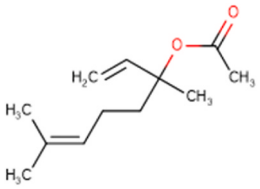

Name: Linalyl acetate
CAS Registry Number: 115-95-7

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is

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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.

Linalyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that linalyl acetate is not genotoxic. Data on read-across analogs linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose, reproductive, and local respiratory toxicity endpoints. Data provided linalyl acetate a No Expected Sensitization Induction Level (NESIL) of 10000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; linalyl acetate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; linalyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 1987; RIFM, 2000)
Repeated Dose Toxicity: NOAEL = 497.9 mg/kg/day.	(ECHA, 2011a)
Reproductive Toxicity: Developmental toxicity NOAEL = 1000 mg/kg/day; Fertility NOAEL = 497.9 mg/kg/day.	(Politano et al., 2008; ECHA, 2011a)
Skin Sensitization: NESIL = 10000 μg/cm^2.	(RIFM, 2022b; RIFM, 2022a)
Photoirritation/Photoallergenicity: Not photoirritating/not expected to be photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1983c; RIFM, 1983a)
Local Respiratory Toxicity: NOAEC = 63 mg/m^3 (linalool) and 12.3 mg/m^3 (acetic acid).	(RIFM, 2012; Ernstgard et al., 2006)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 96.9% (OECD 301B)	RIFM (1994)
Bioaccumulation:	
Screening-level: 182 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 11 mg/L	RIFM (1977)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Fish: LC50: 11 mg/L	RIFM (1977)
RIFM PNEC is: 11 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** Linalyl acetate
2. **CAS Registry Number:** 115-95-7
3. **Synonyms:** Bergamol; 3,7-Dimethyl-1,6-octadien-3-yl acetate; Linalool acetate; 1,6-Octadien-3-ol, 3,7-dimethyl-, acetate; 3,7-Dimethyl-1,6-octadien-3-ol acetate; 酢酸リナリル; 1,5-Dimethyl-1-vinylhex-4-en-1-yl acetate; Linalyl acetate
4. **Molecular Formula:** $C_{12}H_{20}O_2$
5. **Molecular Weight:** 196.29
6. **RIFM Number:** 138
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 220 °C (Fragrance Materials Association [FMA]), 228.95 °C (EPI Suite v4.11)
2. **Flash Point:** 85 °C (Globally Harmonized System), 185 °F (closed cup) (FMA)
3. **Log K_{OW}:** 4.12 ± 0.40 (Cal, 2006), 2.9 (ProcterGamble, 1996), 4.0 (RIFM, 1991c), 4.3 at 35 °C (RIFM, 2004), 4.39 (EPI Suite)
4. **Melting Point**: less than 20 °C (RIFM, 1991c), <20 °C (RIFM, 1991a), −2.09 °C (EPI Suite v4.11)
5. **Water Solubility:** 20.12 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.900 g/mL at 20 °C (RIFM, 1991c), 0.895–0.908 (FMA), 0.902 D20/4–0.898 to 0.903 (RIFM, 1991a), 0.897–0.910 (FMA), 0.91 g/mL (RIFM, 1994)
7. **Vapor Pressure:** 0.07 mm Hg at 20 °C (FMA), 0.131 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless liquid having a sweet, floral-fruity odor (Arctander, 1969)

3. Volume of use (WORLDWIDE BAND)

1. >1000 metric tons per year (IFRA, 2019)

4. exposure to fragrance ingredient (Creme RIFM AGGEGATE exposure model v3.2.12)

1. **95**th **Percentile Concentration in Fine Fragrances:** 1.2% (RIFM, 2023)
2. **Inhalation Exposure*:** 0.0026 mg/kg/day or 0.19 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.023 mg/kg/day (RIFM, 2023)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2024; Safford et al., 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2024; Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** 80%

RIFM, 2007b; RIFM, 2007c; RIFM, 2007d; RIFM, 2008b; RIFM, 2008c; RIFM, 2008d; RIFM, 2007a; RIFM, 2008a**):** A series of *in vitro* human skin penetration studies was conducted with 4% linalool under in-use (unoccluded) and occluded conditions in diethyl phthalate (DEP), dipropylene glycol (DPG), ethanol/water, petrolatum, ethanol/DEP, or ethanol/DPG vehicles. Twelve active dosed diffusion cells were prepared from 7 donors for each application condition (unoccluded, occluded, and an unoccluded control cell). Epidermal membranes were used, and their integrity was assessed by measuring the permeation rate of tritiated water over a period of 1 h. Permeation of linalool from a 5 μL/cm^2 dose was then measured at 12 timepoints over 24 h. Occluded conditions reduced the loss of volatile application vehicles and test compounds but may have also increased skin hydration, factors which caused a significant increase in the permeation of linalool. Under unoccluded experimental conditions, there was a gradual but comprehensive evaporative loss (~97% evaporative loss over 24 h, with less than 7% recovery within the first hour of analysis). Total absorbed dose values from an unoccluded application ranged from 1.8% to 3.57% (DPG < ethanol/DPG < ethanol/DEP < DEP < petrolatum < ethanol/water). Total absorbed dose values from an occluded application ranged from 5.73% to 14.4% (DEP < ethanol/DEP < DPG < petrolatum < ethanol/DPG < ethanol/water). The most conservative dermal penetration of 14.4% was determined. However, the total recovery reported was 8.01% ± 0.69% and 36.3% ± 2.9%, respectively, for the unoccluded and occluded applications. Since the evaporative loss was rapid and recovery of the sample was poor, the study was not used for the safety assessment of linalyl acetate.

Data from RIFM's *in silico* Skin Absorption Model (SAM; RIFM, 2014) were used to predict the dermal penetration of 80% for linalyl acetate, as shown below.

	Parent	Metabolite	Metabolite
Name	Linalyl acetate	Linalool	Acetic acid
J_{max} (μg/cm^2/h)	14.409[1]	101.980[2]	6283.04[3]
Skin Absorption Class	80%	80%	80%

1Jmax was calculated based on measured log Kow = 4 (RIFM, 1991c) and water solubility = 140 mg/L (RIFM, 1991c).
2Jmax was calculated based on measured log Kow = 2.9 (RIFM, 1991b) and water solubility = 1450 mg/L (RIFM, 1991b).
3Jmax was calculated based on measured log Kow = −0.17 (Patel et al., 2002) and Solubility = 106 mg/L (PhysProp Database).

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2 (OECD, 2020)
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7)
   c. **Reproductive Toxicity:** Linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

RIFM, 2003: Esters are readily hydrolyzed by carboxylesterases or esterases (Satoh, 1987). Linalyl acetate has been demonstrated to be hydrolyzed *in vitro* in rat blood and liver preparations. It is expected to be readily hydrolyzed *in vivo*. Acetate is a normal constituent of the body. The metabolism of linalool is known and is primarily through glucuronic acid conjugation and excretion (Parke et al., 1974).

Additional References: None.

8. Natural occurrence (discrete chemical) or composition (NCS)

Linalyl acetate is reported to occur in the following foods by the

VCF*.

Cardamom (Ellettaria cardamomum Maton.)	Myrtle (*Myrtus communis* L.)
Citrus fruits	Pistachio oil (*Pistacia vera*)
Laurel (*Laurus nobilis* L.)	*Salvia* species
Mastic (*Pistacia lentiscus*)	*Satureja* species
Mentha oils	Thyme (*Thymus* species)

*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. This is a partial list.

9. Reach dossier

Available; accessed 08/26/21 (ECHA, 2011b).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for linalyl acetate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.77
2	Products applied to the axillae	0.23
3	Products applied to the face/body using fingertips	4.6
4	Products related to fine fragrances	4.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.1
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	1.1
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	1.1
5D	Baby cream, oil, talc	0.37
6	Products with oral and lip exposure	2.5
7	Products applied to the hair with some hand contact	5.9
8	Products with significant ano-genital exposure (tampon)	0.37
9	Products with body and hand exposure, primarily rinse-off (bar soap)	8.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	12
10B	Aerosol air freshener	30
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.37
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For linalyl acetate, the basis was the subchronic reference dose of 4.98 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 10000 μg/cm^2.

bFor a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

cCalculations by Creme RIFM Aggregate Exposure Model v3.3.

Summary

Human health endpoint Summaries

Genotoxicity

Based on the current existing data and use levels, linalyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of linalyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with linalyl acetate in ethanol at concentrations up to 150 μL/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1987). Under the conditions of the study, linalyl acetate was not mutagenic in the Ames test.

The clastogenicity of linalyl acetate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with linalyl acetate in dimethyl sulfoxide at concentrations up to 333 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (RIFM, 2000). Under the conditions of the study, linalyl acetate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, linalyl acetate does not present a concern for genotoxic potential.

Additional References: RIFM, 1984, Heck et al., 1989, DiSotto et al., 2008, DiSotto et al., 2011; RIFM, 2000.

Literature Search and Risk Assessment Completed On: 03/01/24.

Repeated dose toxicity

The margin of exposure for linalyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are limited repeated dose toxicity data on linalyl acetate. A 90-day dietary study was conducted in rats with 100 mg/kg/day of a mixture containing 24.2 mg/kg/day linalyl acetate (22 ppm), 27.5 mg/kg/day linalyl isobutyrate (25 ppm), and 48.8 mg/kg/day geranyl acetate (44 ppm). The only observed effect was slightly depressed food intake and weight gain in females (RIFM, 1958).

Read-across materials linalool (CAS # 78-70-6; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI) are expected metabolites and have sufficient data to support the repeated dose toxicity endpoint.

Acetic acid has been reviewed by the European Food Safety Authority (EFSA) (2012), the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2013), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO, 2006) for its use as a food additive and by Cosmetic Ingredient Review (CIR) (2010) for its use in cosmetics. Results from repeated oral, inhalation, and dermal exposure of humans to acetic acid under occupational conditions have been reported to have effects on the gastrointestinal tract, digestive disorders including heartburn and constipation, chronic inflammation of the respiratory tract, pharyngitis, catarrhal bronchitis, darkening of the skin, skin dermatitis, and erosion of the exposed front teeth enamel. In addition, skin on the palms of hands was reported to become dry, cracked, and hyperkeratotic. These observed effects were not associated with any systemic findings, suggesting the effects observed could be due to the material's local corrosive activity. The NICNAS review concluded that acetic acid is not considered to cause serious damage to health from

repeated oral exposure, nor is it likely to be a carcinogen (NICNAS, 2013). Based on the available data, the CIR panel concluded that acetic acid is safe under the present practices of use and concentrations (CIR, 2010). Acetic acid is Generally Recognized as Safe (GRAS) by the US FDA and is estimated to be consumed by humans at about 1 g m/day for centuries without any adverse effects. Furthermore, estimations of the daily intake of acetic acid have also been reported to vary from about 1 to 2.1 g per day for subjects older than 2 years (NICNAS, 2013).

In an GLP- and OECD 408-compliant study, groups of 10 Sprague-Dawley rats/sex/dose were administered linalool via diet at target doses of 0, 80, 250, and 750 mg/kg/day (equivalent to actual doses of 0, 53.1, 166.0, and 497.9 mg/kg/day in males and 0, 56.8, 177.4, and 532.1 mg/kg/day in females) for 95−96 days. No treatment-related mortality occurred throughout the study. No treatment-related adverse effects were observed in clinical signs, food consumption, body weights, ophthalmology, hematology, clinical chemistry, endocrine findings, urinalysis, behavior, organ weights, gross pathology, or histopathology. Based on no adverse effects seen up to the highest dose, the repeated dose toxicity no observed adverse effect level (NOAEL) for this study was considered to be 497.9 mg/kg/day (ECHA, 2011a).

In a subchronic study, groups of 20 Sprague Dawley rats/sex/dose were administered linalool via dermal application to the clipped and shaved back at doses of 0, 250, 1000, and 4000 mg/kg/day for 90 days. The measured parameters included body weights, food consumption, hematology, clinical chemistry, urinalysis parameters, gross necropsy, and histopathology. Treatment-related mortality was observed in 9 females and 2 males at high dose. Female body weights were reduced at 1000 mg/kg/day. At 4000 mg/kg/day, lethargy in females, decreased food consumption in males, decreased body weights in females and males, increased liver weights in males and females, increased brain weights in males, increased kidney weights in females, and slight to moderate epithelial hyperplasia of the skin on all treated animals were observed. Based on decreased body weights at 1000 mg/kg/day, the repeated dose toxicity NOAEL for this study was determined to be 250 mg/kg/day (RIFM, 1980). To account for bioavailability following dermal application, data from RIFM's *in silico* SAM model 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 linalool NOAEL from the dermal study is 200 mg/kg/day.

Because the NOAEL of 200 mg/kg/day from the subchronic dermal study was based on adverse effects observed at 1000 mg/kg/day (800 mg/kg/day after SAM refinement), the NOAEL of 497.9 mg/kg/day from the OECD 408-compliant was selected for the repeated dose toxicity endpoint.

Therefore, the linalyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure for linalyl acetate, 497.9/0.023 or 21648.

In addition, the total systemic exposure to linalyl acetate (23 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Derivation of subchronic reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 4.98 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for linalyl acetate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 497.9 mg/kg/day by the uncertainty factor, 100 = 4.98 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/26/23.

Reproductive toxicity

The margin of exposure for linalyl acetate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity or fertility data on linalyl acetate. Read across materials linalool (CAS # 78-70-6; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI) are expected metabolites and have sufficient data to support the developmental toxicity and fertility endpoints.

Acetic acid has been reviewed by the EFSA (2012), NICNAS (2013), and JECFA (WHO, 2006) for its use as a food additive and by CIR (2010) for its use in cosmetics. It was concluded that acetic acid does not show specific reproductive or developmental toxicity. Acetic acid is recognized as GRAS by the US FDA and is estimated to be consumed by humans at about 1 g m/day for centuries without any adverse effects. Furthermore, estimations of the daily intake of acetic acid have also been reported to vary from about 1 to 2.1 g per day for subjects older than 2 years (NICNAS, 2013).

In a developmental toxicity study, 25 pregnant female Sprague Dawley rats/dose were administered linalool via gavage (vehicle: corn oil) at doses of 0, 250, 500, or 1000 mg/kg/day on gestation days 7–17. Animals were observed for viability, clinical signs, body weights, and feed consumption. Cesarean section and necropsy were performed on gestation day 21. Uteri were examined for the number and distribution of implantations, live and dead fetuses, and early and late resorptions. Numbers of corpora lutea were recorded. Fetuses were weighed and examined. Mean relative feed consumption and mean bodyweight gains of the dams were reduced in the highest dose group during the dosage period. After the dosage period, feed consumption and bodyweight gains increased. Based on no adverse effects up to the highest dose, the developmental toxicity NOAEL for this study was considered to be 1000 mg/kg/day (Politano et al., 2008).

In an GLP- and OECD 408-compliant study, groups of 10 Sprague-Dawley rats/sex/dose were administered linalool via diet at doses of 0, 80, 250, and 750 mg/kg/day (equivalent to actual doses of 0, 53.1, 166.0, and 497.9 mg/kg/day in males and 0, 56.8, 177.4, and 532.1 mg/kg/day in females) for 95−96 days. No treatment-related mortality occurred throughout the study. No treatment-related adverse effects were observed in percent motile sperm, epididymal sperm count, homogenization-resistant spermatid count, or percent abnormal sperm. No adverse effects were observed on estrous cycle. Based on no adverse effects seen up to the highest dose, the fertility NOAEL for this study was considered to be 497.9 mg/kg/day (ECHA, 2011a).

Therefore, the linalyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure for linalyl acetate, 1000/0.023 or 43478.

Therefore, the linalyl acetate MOE for the fertility endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure for linalyl acetate, 497.9/0.023, or 21648.

In addition, the total systemic exposure to linalyl acetate (23 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/26/23.

Skin sensitization

Based on the existing data, linalyl acetate is considered a skin sensitizer with a defined No Expected Sensitization Induction Level (NESIL) of 10000 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

Risk assessment. Based on the existing data, linalyl acetate is considered a skin sensitizer. Linalyl acetate is not predicted to be directly reactive to skin proteins (Roberts et al., 2007; OECD Toolbox v4.2). However, linalyl acetate is known to undergo auto-oxidation resulting in degradation products that may be protein reactive (Skold et al., 2008). Linalyl acetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens assay (ECHA, 2011b). The dermal sensitization potential of distilled linalyl acetate was studied in multiple murine local lymph node assays (LLNA). In one study, linalyl acetate (purity = 96.47%) was found to be sensitizing with an EC3 of 4.3% (1075 μg/cm^2) (RIFM, 2002). In another study, the sensitizing potencies of distilled linalyl and air-exposed linalyl acetate were evaluated (Skold et al., 2005; Skold et al., 2008). The distilled linalyl acetate was found to be sensitizing with an EC3 of 25.7% (6425 μg/cm^2), while the 10-week air-exposed linalyl acetate led to an EC3 of 3.6% (900 μg/cm^2) (Skold et al., 2005; Skold et al., 2008). In another LLNA with linalyl acetate containing 0.1 mE/kg peroxides or less, an EC3 of 1.6% (400 μg/cm^2) was observed (RIFM, 2017a). In a human maximization test, positive results were reported at concentrations of 10% (6900 μg/cm^2) linalyl acetate in petrolatum; however, these results were demonstrated to be due to test sample impurities as retesting of purified samples demonstrated no sensitization potential (RIFM, 1974; RIFM, 1982a). In 2 other human maximization tests, no reactions indicative of sensitization were observed at higher concentrations (12% and 20%, corresponding to 8300 μg/cm^2 and 13800 μg/cm^2) to linalyl acetate (Greif, 1967; RIFM, 1975). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2362 μg/cm^2 of linalyl acetate in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 99 volunteers (RIFM, 2017b). In another CNIH conducted with 16.2% (5023 μg/cm^2) using 1:3 EtOH:DEP as the vehicle, no sensitization reactions were observed in any of the 101 volunteers (RIFM, 2021). In 2 more CNIHs conducted with linalyl acetate in 1:3 EtOH:DEP at 8.5% (10,038 μg/cm^2) occlusively and 32.4% (10047 μg/cm^2) semi-occlusively, no reactions indicative of sensitization were observed in any of the 101 and 106 volunteers, respectively (RIFM, 2022b; RIFM, 2022a).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, linalyl acetate is a sensitizer with a WoE NESIL of 10000 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 4.98 mg/kg/day.

Additional References: Greif (1967); RIFM, 1969; Ishihara et al., 1986; RIFM, 1982b; RIFM, 1982c; Procter and Gamble Company (1996); RIFM, 1991c; RIFM, 2004; Organization for Economic Co-Operation and Development (2012); RIFM, 1983b.

Literature Search and Risk Assessment Completed On: 01/02/23.

Photoirritation/photoallergenicity

Based on the available UV spectra along with existing data, linalyl acetate would not be expected to present a concern for photoirritation or photoallergenicity.

Risk assessment. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In guinea pig and rat studies, no reactions indicative of photoirritation were observed following topical application of 30% and up to 10% linalyl acetate, respectively (RIFM, 1983c; RIFM, 1983a). Based on the lack of absorbance and *in vivo* study data, linalyl acetate does not present a concern for photoirritation or photoallergenicity.

UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/05/24.

Local Respiratory Toxicity

There are no inhalation data available on linalyl acetate; however, linalyl acetate is expected to metabolize to linalool (CAS # 78-70-6; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI). In an acute, 2-week inhalation study for linalool, a no observed adverse effect concentration (NOAEC) of 63 mg/m^3 was reported (RIFM, 2012). Additionally, in a 2-h inhalation study to evaluate potential acute irritation during controlled exposure to vapors of acetic acid, a NOEC of 12.3 mg/m^3 was reported (Ernstgard et al., 2006).

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 substance-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 substance-exposed groups.

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

Table 1
Data summary for linalyl acetate.

LLNA EC3 Values μg/cm^2 (vehicles)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
1075 (Purity 96.47 unknown peroxide levels), 5000 (unknown peroxide levels), 6400 (distilled), 900 (air-exposed), 400 (low peroxide) (various quality samples in various vehicles)	Weak -Moderate	10047	N/A	N/A	10000

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

[a] Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

- (63 mg/m^3) × (1 m^3/1000 L) = 0.063 mg/L
- Minute ventilation (MV) 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 0.19 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015 and B. Safford et al., 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 et al., 2009) to give 0.29 mg/kg lung weight/day resulting in a MOE of 8319 (i.e., [2412.5 mg/kg lung weight/-day]/[0.29 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.19 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

In a 2-h inhalation study to evaluate potential acute irritation during controlled exposure to vapors of acetic acid in humans, a NOEC of 12.3 mg/m^3 was reported (Ernstgard et al., 2006). A mild irritative effect was recorded at the highest concentration exposure (NOAEC = 24.6 mg/m^3)—based on subjective ratings by individuals. Measurements before and after all exposure concentrations demonstrated that there were no effects on pulmonary function, nasal swelling, nasal airway resistance, or plasma inflammatory markers (C-reactive protein and interleukin-6).

This NOEC expressed in mg/kg lung weight/day is.

- (12.3 mg/m^3) × (1 m^3/1000 L) = 0.0123 mg/L
- Minute ventilation (MV) of 9.0 L/min for a human (on average)*** × duration of exposure of 120 min per day (min/day) = 1080 L/day
- (0.0123 mg/L) × (1080 L/day) = 13.28 mg/day
- (13.28 mg/day)/(0.65 kg lung weight of human) = 20.43 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.19 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015 and B. Safford et al., 2015). To compare this estimated exposure with the NOEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.29 mg/kg lung weight/day resulting in a MOE of 70.4 (i.e., [20.43 mg/kg lung weight/day]/[0.29 mg/kg lung weight/day]).

The MOE is greater than 10. Since the study was conducted in humans, a safety factor of 10 for interspecies variation is not needed. Therefore, the material exposure by inhalation at 0.19 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

Furthermore, it has been noted that acetic acid is a part of normal cellular metabolism in humans, with an estimated serum concentration of 42 μM (Psychogios et al., 2011). The estimated exposure of acetic acid metabolite from the target material is 3.16 μmole.

The exposure of 0.19 mg/day is expressed in moles as follows.

- Molecular weight of acetic acid = 60.05 g/mol
- (0.19 mg)(mole/60.05 g) × (1 g/1000 mg) = 3.16 × 10^{-6} mol

Considering the average adult blood volume as 5L, the exposure of 3.16 μmoles is equivalent to 0.63 μM. Therefore, the contribution of acetic acid from a completely hydrolyzed target material is less than 2% of the endogenous acetic acid concentration at 42 μM.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey = 9100R7VE.PDF.

**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."

***US EPA. (2011). Exposure Factors Handbook. Chapter 6 Inhalation Rates, pg 6–75. Retrieved from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid = 236252.

Additional References: RIFM, 1969; Troy (1977); Jirovetz et al., 1991; Buchbauer et al., 1991; Jirovetz et al., 1990; The Union of German Candle Manufacturers (1997); Buchbauer et al., 1993; Perrucci (1995a); Rice and Coats (1994); Perrucci et al., 1995b; Barocelli et al., 2004; Shimizu et al., 2008; Heuberger and Ilberger (2010)

Literature Search and Risk Assessment Completed On: 08/22/23.

Environmental endpoint summary

Screening-level assessment

A screening-level risk assessment of linalyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor, as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b) (providing chemical class-specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. Following the RIFM Environmental Framework, linalyl acetate 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 linalyl acetate as possibly persistent and bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), linalyl acetate presents a risk to the aquatic compartment in the

screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 1994:** A study was conducted following OECD Guideline 301B. 10 mg/L of the test substance was incubated for 28 days. At the end of the study, 96.9% biodegradation was observed.

RIFM, 1991a: A study was conducted following OECD Guideline 301C. 100 mg/L of the test substance was incubated for 28 days. At the end of the study, 75% biodegradation was observed.

11.2.1.2.2. Ecotoxicity. **RIFM, 1998:** The 96-h fish (*Cyprinus carpio*) toxicity test was conducted according to the OECD Test Guideline 203, under flow-through conditions. The 96-h LC50 value based on average exposure concentrations was reported to be 11 mg/L.

11.2.1.2.3. Other available data. Linalyl acetate has been registered for REACH, and the following additional information is available (ECHA, 2011b):

An algae growth inhibition study was conducted following OECD Test Guideline 201 under static conditions. The reported 72-h EC50 based on nominal test concentration was 13.1 mg/L.

A *Daphnia magna* immobilization study was conducted according to the OECD Test Guideline 202 under static conditions. The 48-h EC50 value based on mean measured concentration was reported as 59 mg/L (95% CI: 53–65 mg/L).

An additional fish study using Golden Orfe was reported following German standard DIN 38412, part L15, under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 68.12 mg/L.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.64			1000000	0.0026	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.060	1.706	0.497			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.572	1.997	0.437	10000	0.0437	Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.159	0.820	1.520			Neutral Organics
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	11			1,000	11	
Daphnia		59				
Algae		13.1				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.30	4.30
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 11 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the test material does not present a risk to the aquatic

environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 04/12/24.

Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/16/24.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.114805.

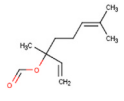
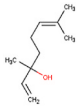
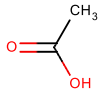
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European 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 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 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 alert system.

Principal Name	Linalyl formate	Linalool	Acetic acid
CAS No.	115-99-1	78-70-6	64-19-7
Structure			
Read-across endpoint		•Repeated dose toxicity •Reproductive toxicity •Local respiratory toxicity	•Repeated dose toxicity •Reproductive toxicity •Local respiratory toxicity
Molecular Formula	$C_{12}H_{20}O_2$	$C_{10}H_{18}O$	CH_2O_2

(*continued on next page*)

(*continued*)

Principal Name	Linalyl formate	Linalool	Acetic acid
Molecular Weight (g/mol)	196.29	154.25	60.05
Melting Point (°C, EPI Suite)	−2.09	−11.39	−21.26
Boiling Point (°C, EPI Suite)	228.95	204.05	122.30
Vapor Pressure (Pa @ 25°C, EPI Suite)	17.47	11.09	2290
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.39	3.38	0.09
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	20.12	683.7	4.759e+005
J_{max} (μg/cm^2/h, SAM)	11.1668059	90.06108298	4659.859
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	176.001525	4.285034	0.0555
Similarity (Tanimoto score)[1]		NA[2]	NA[2]
Repeated Dose Toxicity			
Repeated dose (HESS)	Allyl esters (Hepatotoxicity) Rank A	Not categorized	Not categorized
Reproductive Toxicity			
ER binding (OECD)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental toxicity model (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See Supplemental Data 1	See Supplemental Data 2	No Metabolite possible

Summary

There are insufficient toxicity data on linalyl acetate (CAS # 115-95-7). Hence, *in silico* evaluation was conducted to determine read-across materials. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

There are no metabolism data on linalyl acetate (CAS # 115-95-7). Metabolism of the target material was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized via ester hydrolysis to linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7) in the first step with 0.511 pre-calculated 0.95 intrinsic probability. Hence, linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7) can be used as read-across analogs for the target material. Linalool was out of domain for the *in vivo* and *in vitro* rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided.

Conclusion

- Linalool (CAS # 78-70-6) and acetic acid (CAS # 64-19-7) are used as read-across analogs for the target ester material linalyl acetate (CAS # 115-95-7) for the respiratory, developmental toxicity, fertility, and repeated dose toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target substance and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
    - oThe target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.

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