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Short Review

RIFM fragrance ingredient safety assessment, Linalyl acetate, CAS Registry Number 115-95-7

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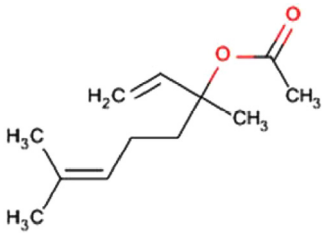

CAS Registry Number: 115-95-7

Abbreviation/Definition list:
Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF – Assessment Factor
DEREK – Derek nexus is an *in silico* tool used to identify structural alerts

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DST – Dermal Sensitization Threshold
ECHA – European Chemicals Agency
EU – Europe/European Union
GLP – Good Laboratory Practice
IFRA – The International Fragrance Association
LOEL – Lowest Observable 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
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
QRA – quantitative risk assessment
REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
TTC – Threshold of Toxicological Concern
UV/Vis Spectra – Ultra Violet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2014) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

* RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for Genetic, Repeated Dose, Developmental, Reproductive, Respiratory, Phototoxicity, Skin Sensitization potential as well as Environmental assessment. Repeated Dose Toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 36 mg/kg/day, based on studies conducted on the major metabolite linalool (CAS # 78-70-6), that resulted in an MOE of 462, considering 14.4% absorption from skin contact and 100% from inhalation. An MOE of >100 is deemed acceptable.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (Bickers et al., 2003; Di Sotto et al., 2011)
Repeated Dose Toxicity: NOAEL = 36 mg/kg/day (RIFM, 1980)
Developmental and Reproductive Toxicity: NOAEL = 200 mg/kg/day (ECHA REACH Dossier: Linalyl acetate)
Skin Sensitization: Not sensitizing (Ishihara et al., 1986; RIFM, 1969; RIFM, 1982a; RIFM, 1983a; RIFM, 2002; Skold et al., 2005; Skold et al., 2008)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (RIFM, 1983b; RIFM, 1983c)
Local Respiratory Toxicity: NOAEC = 10 ppm or 63 mg/m^3 (0.063 mg/L) (RIFM, 2012)

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 75% and 96.9% (RIFM, 1991a; RIFM, 1994)
Bioaccumulation: Screening Level: 182 L/kg (EPISUITE ver 4.1, 2011)
Ecotoxicity: Critical Ecotoxicity Endpoint**:** Fish 96 h LC50: 11 mg/L (RIFM, 1977a)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish 96 h LC50: 11 mg/L (RIFM, 1977a)
RIFM PNEC is: 11 μg/L
- Revised PEC/PNECs (2011 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, Linalyl 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
4 **Molecular Formula:** $C_{12}H_{20}O_2$
5 **Molecular Weight:** 196.29
6 **RIFM Number:** 138

2. Physical data

1 **Boiling Point:** 220 °C (IFRA), 228.95 °C (EPI Suite ver 4.1, 2011)
2 **Flash Point:** 185 °F; CC (IFRA)
3 **Log K_{ow}:** 4.12 ± 0.40 (Cal, 2006), 2.9 (RIFM, 1996), Log P_{ow} = 4.0 (RIFM, 1991b), 4.3 at 35 °C (RIFM, 2004a), 4.39 (EPI Suite ver 4.1, 2011)
4 **Melting Point**: less than 20 °C (RIFM, 1991b), <20 °C (RIFM, 1991a), –2.09 °C (EPI Suite ver 4.1, 2011)
5 **Water Solubility:** 20.12 mg/L (EPI Suite ver 4.1, 2011)

6 **Specific Gravity:** 0.900 g/ml at 20 °C (RIFM, 1991b), 0.895–0.908 (IFRA), 0.902 D20/4 – 0.898 to 0.903 (RIFM, 1991a), 0.897–0.910 (IFRA), 0.91 g/ml (RIFM, 1994)
7 **Vapor Pressure:** 0.0864 mm Hg @ 20 °C (EPI Suite ver 4.1, 2011), 0.07 mm Hg 20 °C (IFRA), 0.131 mm Hg @ 25 °C (EPI Suite ver 4.1, 2011)
8 **UV Spectra:** Absorb in the region of 290–700 nm
9 **Appearance/Organoleptic:** A clear, colorless liquid having a sweet, floral-fruity odor.

3. Exposure

1 **Volume of Use (worldwide band):** >1000 metric tons per year (IFRA, 2011)
2 **Average Maximum Concentration in Hydroalcoholics:** 4.60% (IFRA, 2002)
3 **97.5th Percentile:** 13.00% (IFRA, 2002)
4 **Dermal Exposure*:** 0.3312 mg/kg/day (IFRA, 2002)
5 **Oral Exposure:** Not applicable
6 **Inhalation Exposures**:** 0.03 mg/kg/day (IFRA, 2002)
7 **Total Systemic Exposure (Dermal + Inhalation):** (0.3312 mg/kg/day × 14.4% absorption) + 0.03 mg/kg/day = 0.078 mg/kg/day

* Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

** Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1 **Dermal:** 14.4%

(**RIFM**, 2007a (data also available in **RIFM**, 2007b; and **RIFM**, 2007c; **RIFM**, 2008a; **RIFM**, 2008b, and RIFM, 2001; Lalko et al., 2007; Lalko et al., 2008)) A series of *in vitro* human skin penetration studies were conducted with metabolite linalool (CAS # 78-70-6; see Section 5) 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 seven 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 4% linalool from a 5 µl/cm^2 dose was then measured at 12 time-points 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. 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). Conservatively, 14.4% dermal absorption was selected for this safety assessment.

2 **Oral:** Data not available – not considered.
3 **Inhalation:** Assumed 100%
4 **Total:** Dermal (14.4%) + Inhalation (assume 100%) absorbed = (0.3312 mg/kg/day × 14.4%) + 0.03 mg/kg/day = 0.078 mg/kg/day

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v. 2.6	OECD QSAR Toolbox v. 3.2
I	I	I

2 **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Linalool (CAS # 78-70-6)
   c. **Developmental and Reproductive Toxicity:** Linalool (CAS # 78-70-6); dehydrolinalool (CAS # 29171-20-8)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Linalool (CAS # 78-70-6)
   g. **Environmental Toxicity:** None
3 **Read-across Justification:** See Appendix below

6. Metabolism

Letizia et al., 2003a: 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).

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

Linalyl acetate is reported to occur in food* and as a component in some natural complex substances (NCS):

Bergamot oil
Cardamom (elettaria cardamomum (l.) Maton)
Citrus fruits
Clary (salvia sclarea l.)
Mentha arvensis oil
Mentha oils
Myrtle (myrtus communis l.)
Myrtle leaf
Salvia 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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available; accessed on 05/08/13: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c80e2a4-b39d-6b91-e044-00144f67d249/DISS-9c80e2a4-b39d-6b91-e044-00144f67d249_DISS-9c80e2a4-b39d-6b91-e044-00144f67d249.html.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The genotoxic potential of linalyl acetate was evaluated extensively, as summarized in the Fragrance Material Review (Letizia et al., 2003a). Ames tests using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100, and *Escherichia coli* strain WP2uvrA, both with and without S9 activation, show that linalyl acetate was not mutagenic (RIFM, 1984; RIFM, 1989a). However, in a non GLP compliant study conducted by Di Sotto et al., 2008, linalyl acetate was found positive for mutagenicity in *E. coli* strain WP2uvr both with and without S9 mixture, indicating that it causes base substitutions at concentrations of 9 mg/plate and above. This study was conducted similar to OECD TG 471 with the exception that only three strains of bacteria were utilized and that the maximum dose exceeded the regulatory requirement of 5 mg/plate. The study also indicated that linalyl acetate was cytotoxic at doses >9 mg/plate. As such, mutagenicity was only observed at levels that approached toxicity and at doses that exceeded regulatory requirements. The guideline states the recommended maximum test concentration for soluble non-cytotoxic substances to be 5 mg/plate unless the substance that is being tested contains substantial amounts of potentially mutagenic impurities. Based on the available data, linalyl acetate does have not mutagenic potential.

With regard to clastogenicity, in one *in vitro* chromosome aberration study following OECD TG 473, linalyl acetate was found to be negative (RIFM, 2000). However, in a subsequent micronucleus assay, which was not compliant to GLP regulations, positive effects were observed (DiSotto et al., 2011). The authors of this second study indicate that the positive effect is likely to be aneugenic rather than clastogenic in nature because while there was an increase in micronuclei there was no effect on nucleoplasmic bridges. It is of note that the doses used in the second assay were lower than those used in the first assay. Moreover, the DiSotto publication has several deficiencies as follows: there is no indication that a preliminary toxicity study was conducted to establish the doses used; there is no indication that there were any treatments with metabolic activation; there is no indication that the slides were independently coded and evaluated; the data suggest that Linalyl acetate is a more potent clastogen than the positive control (ethyl methanesulfonate); sufficient detail with regard to cytochalasin-B treatment is not provided; and lastly, May–Grunwald–Giemsa staining was used which may stain non-DNA material, and can be misinterpreted as micronuclei. Furthermore, positive *in vitro* results for linalyl acetate have little implication for *in vivo* genotoxicity since linalyl acetate would readily be converted to linalool and acetate *in vivo*. Linalool has been identified as not having genotoxic potential (RIFM SA Linalool CAS # 78-70-6); therefore; there is little concern that the positive result observed in the second clastogenicity study would be translated systemically *in vivo*. Additionally, the RIFM Expert Panel has reviewed linalyl acetate and other esters related to linalool and concluded that, based on a weight of evidence, this category of materials does not have significant genotoxic potential (Bickers et al., 2003). Taken together, linalyl acetate does not have potential to be genotoxic.

Additional References: Heck et al., 1989; Oda et al., 1978; RIFM, 1987.

Literature Search and Risk Assessment Completed on: 03/25/13.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. The repeated dose toxicity data on linalyl acetate includes a 90-day oral (feed) study conducted with 100 mg/kg/day of a mixture containing 24.2 mg/kg/day linalyl acetate, 27.5 mg/kg/day linalyl isobutyrate and 48.8 mg/kg/day geranyl acetate. The only observed effect was slightly depressed food intake and weight gain in females (RIFM, 1958a). These data are not sufficient to determine a NOAEL for repeated dose toxicity due to insufficient details provided. However, the metabolite linalool (CAS # 78-70-6; see Section 5) has several repeated dose toxicity studies. A dermal 90-day subchronic toxicity study conducted in rats determined the NOAEL to be 250 mg/kg/day, based on reduced body weights (RIFM, 1980). To account for bioavailability following dermal application, the data from an *in vitro* dermal absorption study (RIFM, 2007a; see Section 4) with linalool were used to revise the NOAEL of 250 mg/kg/day to reflect the systemic dose. At a dermal penetration of 14.4% of the applied dose, the revised repeated dose toxicity NOAEL from the dermal study is 36 mg/kg/day. Therefore, the MOE is equal to the linalool NOAEL in mg/kg/day divided by the total systemic exposure, 36/0.078 or 462.

Additional References: Letizia et al., 2003a; Bickers et al., 2003; Stoner et al., 1973; Van Duuren et al., 1971; RIFM, 1998a; Jager et al., 1992; Meyer et al., 1959; Meyer, 1965; Cal et al., 2003; RIFM, 1996; Letizia et al., 2003b; Lapczynski et al., 2008a; Lapczynski et al., 2008b; Lapczynski et al., 2008c; Belsito et al., 2008; Belsito et al., 2010; RIFM, 1958b; RIFM, 1979; RIFM, 2012; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990; Jirovetz et al., 1991; Parke et al., 1974; Green & Tephly, 1996; Meesters et al., 2007; Chadha et al., 1982; Chadha et al., 1984; RIFM, 1998b; Schmitt et al., 2010; Cal, 2006; Cal et al., 2006; Jaaskelainen et al., 2005; Bar et al., 1967; Hagan et al., 1967; Letizia et al., 2003c; RIFM, 1989b; RIFM, 1990; Al-Said et al., 1987; Matsui et al., 1967.

Literature Search and Risk Assessment Completed on: 03/25/13.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on linalyl acetate. Metabolite linalool (CAS # 78-70-6; see Section 5) has a gavage developmental toxicity study conducted in rats, which concluded a NOAEL of 1000 mg/kg/day for developmental toxicity, the highest dosage tested (Politano et al., 2008). Therefore, the MOE for developmental toxicity is equal to the linalool NOAEL in mg/kg/day divided by the total systemic exposure, 1000/0.078 or 12821.

There are no reproductive toxicity data on linalyl acetate. Read-across material dehydrolinalool (CAS # 29171-20-8; see Section 5) has a gavage reproductive toxicity screening study in rats. The NOAELs were determined to be 750 mg/kg/day for males, the highest dosage tested, and 200 mg/kg/day for the offspring and dams, based on maternal clinical signs and decreased live birth index and viability (ECHA REACH Dossier: Linalyl acetate Read across Subs Key Toxicity to reproduction.003 (accessed 02/19/13)). The gavage developmental toxicity study in rats with the metabolite linalool (CAS # 78-70-6) concluded a NOAEL of 500 mg/kg/day for maternal toxicity, based on reduced maternal body weight gain and feed consumption (Politano et al., 2008). The dermal 90-day subchronic toxicity study with linalool in rats (RIFM, 1980), in addition to the systemic endpoints, included organ weights (testes and ovaries) and histopathology (testes, epididymis, ovaries, pituitary, and thyroid) and no effects were observed. Together, these data indicate there

is no concern for reproductive toxicity. The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the dehydrolinalool NOAEL in mg/kg/day divided by the total systemic exposure, 200/0.078 or 2564.

Additional References: Letizia et al., 2003a; Bickers et al., 2003; Stoner et al., 1973; Van Duuren et al., 1971; RIFM, 1998a; Jager et al., 1992; Meyer et al., 1959; Meyer, 1965; Cal et al., 2003; RIFM, 1996; Letizia et al., 2003b; Lapczynski et al., 2008a; Lapczynski et al., 2008b; Lapczynski et al., 2008c; Belsito et al., 2008; Belsito et al., 2010; RIFM, 1958b; RIFM, 1979; RIFM, 2012; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990; Jirovetz et al., 1991; Parke et al., 1974; Green & Tephly, 1996; Meesters et al., 2007; Chadha et al., 1982; Chadha et al., 1984; RIFM, 1998b; Schmitt et al., 2010; Cal, 2006; Cal et al., 2006; Jaaskelainen et al., 2005; Bar & Griepentrog, 1967; Hagan et al., 1967; Letizia et al., 2003c; RIFM, 1989b; RIFM, 1990; Al-Said et al., 1987; Matsui et al., 1967.

Literature Search and Risk Assessment Completed on: 03/25/13.

10.1.4. Skin sensitization

Based on the available data, linalyl acetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Linalyl acetate is not predicted to significantly react, directly, to skin proteins (Roberts et al., 2007; OECD toolbox v3.0). However, linalyl acetate is known to undergo autoxidation resulting in degradation products that may be protein reactive (Skold et al., 2008). In guinea pig test methods and the local lymph node assay (LLNA), positive and negative results have been reported (Ishihara et al., 1986; RIFM, 1969; RIFM, 1977b; RIFM, 1982a); RIFM, 1982b; RIFM, 1983a; RIFM, 2002; Skold et al., 2005; Skold et al., 2008. Various qualities of linalyl acetate have been evaluated in the murine local lymph node assay (LLNA) and guinea pig test methods (RIFM, 1969; Ishihara et al., 1986; RIFM, 1977b; RIFM, 1982a; RIFM, 1982b; RIFM, 1983a; RIFM, 2002; Skold et al., 2005; Skold et al., 2008). The lowest EC3 values have been associated with oxidized samples of linalyl acetate, whereas the higher EC3 values have typically been observed when testing higher purity materials. In the LLNA, positive results have been shown to be the result of irritation and sensitizing products due to autoxidation (RIFM, 2010; Skold et al., 2005; Skold et al., 2008). In the human maximization test positive results were reported at concentrations of 10% in petrolatum. These results were also demonstrated to be the result of test sample impurities as retesting of purified samples demonstrated no sensitization potential (RIFM, 1974; RIFM, 1982c). Finally, no reactions indicative of sensitization were observed at higher concentrations (12.5% and 20.0%) in the human maximization test (Greif, 1967; and RIFM, 1975). Based on the available data, linalyl acetate does not present a concern for skin sensitization.

Note: Whereas linalyl acetate is considered to be a non-sensitizer, autoxidation products of this material are known to be contact allergens.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/25/13.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, Linalyl acetate is not expected to present a concern for phototoxicity.

10.1.5.1. Risk assessment. The UV absorption spectra demonstrate that Linalyl acetate has little to no absorption in the UV range. Though the spectra are not suitable for calculating the molar absorption coefficient for use in benchmark evaluation in the region of 290–700 nm, in Guinea pig and rat studies no reactions indicative of phototoxic responses were observed (RIFM, 1983b; RIFM, 1983c). Based on the existing data, this material does not present a concern for phototoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/25/13.

10.1.6. Local respiratory toxicity

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

10.1.6.1. 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. There are no inhalation data on linalyl acetate. However, in a 2 week acute inhalation study a NOAEC of 10 ppm (63 mg/m^3) for metabolite linalool (CAS # 78-70-6; see Section 5) was reported (RIFM, 2012), which was the highest dose tested. The test substance-related effects were limited to nonadverse microscopic findings in the nasal cavity.

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

- (63 mg/m3) (1m3/1000L) = 0.063 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat × duration of exposure of 360 minutes 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

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 13%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 1.21 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual using RIFM's 2-Box/MPPD in silico models. To compare this estimated exposure with that of Randazzo et al. expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 1.86 mg/kg lung weight/day resulting in an MOE of 1297 (i.e., [2412.5 mg/kg lw/day]/[1.86 mg/kg lung weight/day]).

Since the MOE is greater than 100, the material exposure, by inhalation, at 13% in a combination of the products noted above, is deemed to be safe under the most conservative consumer exposure scenario.

* Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd 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 et al., 1991; Buchbauer et al., 1991; Jirovetz et al., 1990; RIFM, 1997; Buchbauer et al., 1993; Perrucci et al., 1996; Perrucci, 1995; Rice et al., 1994; Silver, 1992; Karr et al., 1992; Regnault-Roger et al., 1995; Rice et al., 1994a; Perrucci et al., 1995; Sugawara et al., 1998; Coats et al., 1991; Cometto-Muñiz et al., 1998; Isola et al., 2003a; RIFM, 2003a; Rogers et al., 2003; RIFM, 2003b; Isola et al., 2003b; Isola et al., 2004a; Larsen et al., 1997; Smith et al., 2004; RIFM, 2004b; Isola et al., 2004b; Barocelli et al., 2004; Rogers et al., 2005; Kuroda et al., 2005; Tanida et al., 2006; Yang et al., 2005; Corsi et al., 2007; Sato et al., 2007; Nakamura et al., 2010; Nakamura et al., 2009; Linck et al., 2009; Matsubara et al., 2011.

Literature Search and Risk Assessment Completed on: 03/25/13.

10.2. Environmental endpoint summary

Analogs Identified/Justification: Not Applicable.

10.2.1. Screening-level assessment

A screening level risk assessment of linalyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 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 (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). 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 EPISUITE ver 4.1 did identify linalyl acetate as being possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current VoU (2011), linalyl acetate presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. 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, 1994).

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 (RIFM, 1991a).

10.2.2.2. Ecotoxicity. A flow through study following OECD Test Guideline 203 using *Cyprinus carpio* was performed. The reported 96 hr LC50 was 11 mg/L (RIFM, 1998c).

10.2.3. Other available data

This material has been registered under REACH. Three additional aquatic toxicity studies are reported. All data are from the ECHA Chemical Information Website accessed 13 March 2013.

An algae growth inhibition study was conducted following OECD Test Guideline 201. The reported 72 hr EC50 was 62 mg/L and the NOEC was 9.6 mg/L.

One *Daphnia* immobilization study is reported following OECD Test Guideline 202. The 48 hr EC50 was reported as 15 mg/L.

An additional fish study using Golden Orfe was also reported following German standard DIN 38412, part L15. The 96 hr LC50 was 68.12 mg/L.

10.2.4. 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 Framework: Salvito et al., 2002).

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

The RIFM PNEC is 11 µg/L. The revised PEC/PNECs for EU and NA are <1 and, therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 03/25/13.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

* Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

	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			1,000,000	0.0026	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.191	1.935	0.572			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.591	2.136	0.471	10,000	0.0471	Vinyl/AllylEsters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.386	0.973	1.745			Neutral Organics
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	11			1,000	11	
Daphnia		15				
Algae		62	9.6			

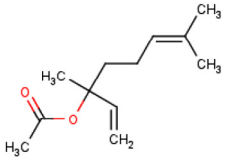
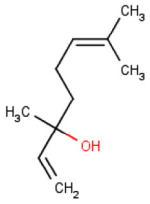
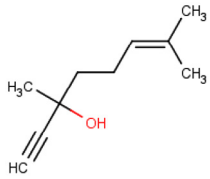
Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix 1

	Target Material	Read across Material	
Principal Name	Linalyl acetate	Linalool	Dehydrolinalool
CAS No.	115-95-7	78-70-6	29171-20-8
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/115-95-7.html	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/29171-20-8.html
Read-across endpoint		• Skin Absorption • Repeated Dose • Devel/Repro • Respiratory	• Devel/Repro
Molecular Formula	C12H20O2	C10H18O	C10H16O
Molecular Weight	196.29	154.25	152.24
Melting Point (°C, EPISUITE)	–2.09	–11.39	15.40
Boiling Point (°C, EPISUITE)	228.95	204.05	212.37
Vapor Pressure (Pa @ 25 °C, EPISUITE)	17.47	11.09	4.64
Log Kow (KOWWIN v1.68 in EPISUITE)	4.39	3.38	2.75
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	20.12	683.7	1084
J_{max} (mg/cm^2/h, SAM)	11.1668059	90.06108298	93.21980338
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	176.001525	4.285034	0.449174
Similarity (Tanimoto score) [a]		NA[a]	NA[a]
Skin Absorption			
Skin Absorption Percentage (SAM)	80%	80%	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized	Not categorized	
Developmental and 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	See supplemental data 3

[a] Metabolites of the target or analog(s) of metabolites.

Summary

There are insufficient toxicity data on Linalyl acetate (CAS # 115-95-7). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Linalool and Dehydrolinalool (analogs) were used as a read-across for Linalyl acetate (target) based on:
  - The read-across materials are the major metabolite of the target and the analog of the metabolite.
  - The target is the acetate form of the linalool. This difference could be mitigated by the fact the target could readily hydrolyzed into the read-across material and acetic acid (Bickers et al., 2003). Besides, the differences between structures do not essentially change the physicochemical properties nor raise any

additional structural alerts and therefore, the toxicity profiles are expected to be similar.
- The target and analog show the same skin absorption range.
- The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
- As per the OECD Toolbox, the target is predicted to metabolize to the analog (metabolite # 2)

Appendix 2: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.01.010.

References

Al-Said, M.S., Al-Khamis, K.I., Islam, M.W., Parmar, N.S., Tariq, M., Ageel, A.M., 1987. Post-coital antifertility activity of the seeds of Coriandrum sativum in rats. J. Ethnopharmacol. 21 (2), 165–173.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., et al., 2014. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. accepted for publication.

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Med. Ernahr. 8, 244–251.

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

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hanifin, J.M., et al., 2008. A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. Food Chem. Toxicol. 46 (2008), S1–S71.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hanifin, J.M., et al., 2010. A safety assessment of non-cyclic alcohols with unsaturated branched chain when used as fragrance ingredients. Food Chem. Toxicol. 48 (Suppl. 3), S1–S42.

Bickers, D., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, H.J., et al., 2003. A toxicological and dermatological assessment of linalool and related esters when used as fragrance ingredients. Food Chem. Toxicol. 41 (7), 919–942.

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. Z. Naturforsch. C Biosci. 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. Pharm. Sci. 82 (6), 660–664.

Cadby, P.A., Troy, W.R., Vey, M.G., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regul. Toxicol. Pharmacol. 36 (3), 246–252.

Cal, K., 2006. How does the type of vehicle influence the in vitro skin absorption and elimination kinetics of terpenes? Arch. Dermatol. Res. 297 (7), 311–315.

Cal, K., Krzyzaniak, M., 2006. Stratum corneum absorption and retention of linalool and terpinen-4-ol applied as gel or oily solution in humans. J. Dermatol. Sci. 42 (3), 265–267.

Cal, K., Sznitowska, M., 2003. Cutaneous absorption and elimination of three acyclic terpenes-in vitro studies. J. Control. Release 93 (3), 369–376.

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., et al., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Chadha, A., Madyastha, K.M., 1982. Omega-hydroxylation of acyclic monoterpene alcohols by rat lung microsomes. Biochem. Biophys. Res. Commun. 108 (3), 1271–1277.

Chadha, A., Madyastha, K.M., 1984. Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. Xenobiotica 14 (5), 365–374.

Coats, J.R., Karr, L.L., Drewes, C.D., 1991. Toxicity and neurotoxic effects of monoterpenoids: in insects and earthworms. ACS Symposium series-American Chemical Society (USA). 449, 305–316.

Cometto-Muñiz, 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.

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.

Di Sotto, A., Evandri, M.G., Mazzanti, G., 2008. Antimutagenic and mutagenic activities of some terpenes in the bacterial reverse mutation assay. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 653 (1), 130–133.

Di Sotto, A., Mazzanti, G., Carbone, F., Hrelia, P., Maffei, F., 2011. Genotoxicity of lavender oil, linalyl acetate, and linalool on human lymphocytes in vitro. Environ. Mol. Mutagen. 52 (1), 69–71.

Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software], (Copyright 2000–2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Research 20 (6), 482–487. Retrieved from: <http://www.epa.gov/opptintr/exposure/pubs/episuite.htmOil>.

Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance ingredients. Regul. Toxicol. Pharmacol. 31 (2), 166–181.

Green, M.D., Tephly, T.R., 1996. Glucuronidation of amines and hydroxylated xenobiotics and endobiotics catalyzed by expressed human UGT1. 4 protein. Drug Metab. Dispos. 24 (3), 356–363.

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

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., et al., 1967. Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet. Toxicol. 5, 141–157.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9 (1), 257.

Hood, R.L., McBailey, W., Svoronos, D., 1978. The effect of dietary monoterpenes on the cholesterol level of eggs. Poult. Sci. 57 (1), 304–306.

Howes, M.J., Houghton, P.J., Barlow, D.J., Pocock, V.J., Milligan, S.R., 2002. Assessment of estrogenic activity in some common essential oil constituents. J. Pharm. Pharmacol. 54 (11), 1521–1528.

IFRA (International Fragrance Association), 2002. Use level survey, 2002.

IFRA (International Fragrance Association), 2011. Volume of use survey, 2011.

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

Isola, D., Smith, L.W., Ansari, R., Black, M.S., 2003a. Exposure characterization from a fragranced plug-in air fresheners. Toxicologist Abstract 1416.

Isola, D., Smith, L.W., Rogers, R.E., Black, M.S., 2003b. Exposure characterization from a fragranced air fresheners. Allergy Clin. Immunol. Int. Abstract P-10–12.

Isola, D., Rogers, R.E., Black, M.S., Smith, L.W., 2004b. Exposure characterizations of three fragranced products. Int. J. Toxicol. Abstract from the 25th annual Meeting of American College of Toxicology.

Isola, D.A., Rogers, R.E., Myshaniuk, A., Jeng, C.-J., Ansari, R., Smith, L.W., 2004a. Exposure characterization from a surrogate fine fragrance. Toxicologist Abstract 518.

Jaaskelainen, H.S., Rantalainen, A.-L., 2005. Synthetic musks and PAHs in sewage treatment process and in sediment of the recipient river. SETAC Europe 15th annual meeting May 22–25. Abstract TUP-03/05.

Jager, W., Buchbauer, G., Jirovetz, L., Fritzer, M., 1992. Percutaneous absorption of lavender oil from a massage oil. J. Soc. Cosmet. Chem. 43 (1), 49–54.

Jirovetz, L., Buchbauer, G., Jager, W., Raverdino, V., Nikiforov, A., 1990. Determination of lavender oil fragrance compounds in blood samples. Fresenius. 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. Effects of four monoterpenoids on growth and reproduction of the German cockroach (Blattodea: Blattellidae). J. Econ. Entomol. 85 (2), 424–429.

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

Lalko, J., Brain, K.R., Green, D.M., Api, A.M., 2007. In vitro human skin penetration of the fragrance material linalool. Toxicologist 102 (1), Abstract 1555.

Lalko, J., Brain, K.R., Green, D.M., Api, A.M., 2008. In vitro human skin penetration of the fragrance material linalool. Int. J. Toxicol. 26 (6), Abstract P32.

Lapczynski, A., Letizia, C.S., Api, A.M., 2008a. Addendum to fragrance material review on linalool. Food Chem. Toxicol. 46 (2008), S190–S192.

Lapczynski, A., Letizia, C.S., Api, A.M., 2008b. Fragrance material review on d-linalool. Food Chem. Toxicol. 46 (2008), S193–S194.

Lapczynski, A., Bhatia, S.P., Letizia, C.S., Api, A.M., 2008c. Fragrance material review on l-linalool. Food Chem. Toxicol. 46 (2008), S195–S196.

Larsen, B., Bomboi-Mingarro, T., Brancaleoni, E., Calogirou, A., Cecinato, A., Coeur, C., et al., 1997. Sampling and analysis of terpenes in air: an interlaboratory comparison. Atmos. Environ. 31, 35–49.

Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003a. Fragrance material review on linalyl acetate. Food Chem. Toxicol. 41 (2003), 965–976.

Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003b. Fragrance material review on linalool. Food Chem. Toxicol. 41 (2003), 943–964.

Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003c. Fragrance material review on linalyl isobutyrate. Food Chem. Toxicol. 41 (7), 1005–1010.

Linck, V.D.M., da Silva, A.L., Figueiró, M., Luis Piato, Â., Paula Herrmann, A., Dupont Birck, F., et al., 2009. Inhaled linalool-induced sedation in mice. Phytomedicine 16 (4), 303–307.

Matsubara, E., Fukagawa, M., Okamoto, T., Ohnuki, K., Shimizu, K., Kondo, R., 2011. The essential oil of Abies sibirica (Pinaceae) reduces arousal levels after visual display terminal work. Flavour Fragr. J. 26 (3), 204–210.

Matsui, A.S., Rogers, J., Woo, Y.K., Cutting, W.C., 1967. Effects of some natural products on fertility in mice. Pharmacology 16 (5), 414–424.
Meesters, R.J.W., Duisken, M., Hollender, J., 2007. Study on the cytochrome P450-mediated oxidative metabolism of the terpene alcohol linalool: indication of biological epoxidation. Xenobiotica 37 (6), 604–617.
Meyer, F., 1965. Penetrating agents. Patent, British, 1,001,949, M49750IVa/30h, 7/20/61.
Meyer, F., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneimittelforschung 9, 516–519.
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 (12), 5480–5485.
Nakamura, A., Fujiwara, S., Ishijima, T., Okada, S., Nakai, Y., Matsumoto, I., et al., 2010. Neuron differentiation-related genes are up-regulated in the hypothalamus of odorant-inhaling rats subjected to acute restraint stress. J. Agric. Food Chem. 58 (13), 7922–7929.
Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). Shokuhin Eisei Hen 9, 177–181.
OECD, 2012. The OECD QSAR Toolbox, v 3.1. <http://www.qsartoolbox.org/>.
Parke, D.V., Rahman, K.H.M.Q., Walker, R., 1974. The absorption, distribution & excretion of linalool in the rat. Biochem. Soc. Trans. 2.4 (1974), 612–615.
Perrucci, S., 1995. Acaricidal activity of some essential oils and their constituents against Tyrophagus longior, a mite of stored food. J. Food Prot. 58 (5), 560–563.
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.
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, 5–8.
Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., Api, A.M., 2008. Evaluation of the developmental toxicity of linalool in rats. Int. J. Toxicol. 27 (2), 183–188.
Randazzo, J., Vitale, D., Kirkpatrick, D., Burleson, E.G., Singal, M., 2013. Evaluation of nose-only inhalation exposure to aerosolized linalool in Sprague-Dawley rats. Toxicologist abstract 1541.
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., 1994. Insecticidal properties of monoterpenoid derivatives to the house fly (Diptera: Muscidae) and red flour beetle (Coleoptera: Tenebrionidae). Pesticide science 41 (3), 195–202.
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.
RIFM (Research Institute for Fragrance Materials, Inc.), 1958a. Toxicological screening of linalyl acetate, linalyl isobutyrate and geranyl acetate in rats. Class VIII. Unpublished report from Trubeck Laboratories, Inc. Report number 29144 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1958b. Toxicological screening of citronellol and linalool in rats. Class VI. Unpublished report from Trubeck Laboratories, Inc. Report number 29150 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1969. Acute toxicity, irritation, and sensitization studies on linalyl acetate. Unpublished report from BASF, July 29. Report number 4418 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Report on human maximization studies. RIFM report number 1801, May 31 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Report on human maximization studies. RIFM report number 1799, October 24A (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1977a. Irritation test on the rabbit eye with tridecene-2-nitrile (tridecenonitrile). Unpublished report from Givaudan, February 18. Report number 55960 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1977b. Oral intraperitoneal acute toxicity study in mice with tridecene-2-nitrile (tridecenonitrile). Unpublished report from Givaudan, April 21. Report number 55959 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1979. 29 Day percutaneous toxicity range finding with linalool in rats. RIFM report number 32943, May 24 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1980. 90 Day subchronic dermal toxicity wit linalool in rats. RIFM report number 4001, April 4 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1982a. Delayed contact hypersensitivity study in guinea pigs of linalyl acetate. Unpublished report from Takasago International Corporation, October 30. Report number 31606 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1982b. Skin irritation and capacity for allergenic sensitization of linalyl acetate determined by the open epicutaneous test (OET) on guinea pigs. Unpublished report from Givaudan, August 5. Report number 55949 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1982c. Report on human maximization studies. RIFM report number 1643, April 27A April 30 September 14 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1983a. Guinea pig skin sensitisation test with linalyl acetate. RIFM report number 46399, September 2 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1983b. Determination of phototoxicity of linalyl acetate in guinea pigs. Unpublished report from Givaudan, May 2. Report number 55946 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1983c. The rat topical application photoirritation test with linalyl acetate. Unpublished report from Quest International, August 25. Report number 46396 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1984. Ames Metabolic Activation Test with linalyl acetate. Unpublished report from Quest International, April 16. Report number 46395 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1987. Mutagenicity evaluation of linalyl acetate in the Ames Salmonella/microsome reverse mutation assay. Unpublished report by Lorillard Tobacco Company, January 30. Report number 36497 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. Antioxidant butylated hydroxyl toluene (BHT): a review of the toxicology and an assessment of the safety in use. RIFM report number 9804.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Reproductive and developmental toxicity screening test of coriander oil administered orally via gavage to Crl: CD(TM) (SD)BR female rats. Unpublished report from Lorillard Tobacco Company, April 12. Report number 36124 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1990. 28-Day oral toxicity study of coriander oil in rats. Unpublished report from Lorillard Tobacco Company, January 26. Report number 36125 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1991a. Determination of the ready biodegradability of linalyl acetate synthetic. Unpublished report from Givaudan, February 25. Report number 32451 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1991b. Determination of the partition coefficient (octanol/water) of linalyl acetate. Unpublished report from Givaudan, April 22. Report number 32453 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1994. The biodegradability of perfume ingredients in the sealed vessel test. Unpublished report from Quest International, October 03. Report number 49675 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996. [Submission to EPA] Dermal penetration potential of perfume materials, with letter dated 5/28/96. Unpublished report from Procter & Gamble, January 31. Report number 33463 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1997. Investigation of oxidation gases from paraffin aromatic candles in toxicological relevance to classes of damaging materials. Unpublished report from The Union of German Candle Manufacturers, October. Report number 18011 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1998a. Report on the metabolism of linalyl acetate in rat tissue & intestinal homogenates. Unpublished report by Flavor and Extract Manufacturers Association, November 28. Report number 34253 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1998b. Report on the metabolism of linalool in rat tissue & intestinal homogenates. Unpublished report by Flavor and Extract Manufacturers Association, March 24. Report number 34252 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1998c. 96-Hour acute toxicity study in carp with linalyl acetate. Unpublished report from Givaudan, December 23. Report number 55950(RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000. Evaluation of the ability of linalyl acetate to induce chromosome aberrations in cultured peripheral human lymphocytes. Unpublished report from Hoffmann-LaRoche, June 22. Report number 38576 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Methyl stearate: ready biodegradability closed bottle test. Unpublished report from Symrise, February 15. Report number 53664 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Linalyl acetate: local lymph node assay (LLNA) in mice. Unpublished report from Givaudan, 11 November. Report number 55948 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Airborne levels of selected fragrance materials in a simulated bathroom. RIFM report number 41708, January 10 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Indoor air quality evaluation of a plug-in air freshener. RIFM report number 43292, October 13 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2004a. Partition coefficient n-octanol/water of linalyl acetate. Unpublished report from Givaudan, November 24. Report number 51472 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2004b. Airborne levels of selected fragrance materials following a controlled exposure to a surrogate fine fragrance. RIFM Report number 47425, December 3 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2007a. In vitro human skin penetration of fragrance material linalool under both in-use and occluded conditions from an ethanol/water vehicle. RIFM report number 54455 October 3 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2007b. In vitro human skin penetration of fragrance material linalool under both in-use and occluded conditions from a diethyl phthalate (DEP) vehicle. RIFM report number 54456 October 3 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007c. In vitro human skin penetration of fragrance material linalool under both in-use and occluded conditions from a dipropylene glycol (DPG) vehicle. RIFM report number 54457 October 3 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2008a. In vitro human skin penetration of fragrance material linalool under both in-use and occluded conditions from an ethanol/diethyl phthalate vehicle. RIFM report number 54662 June 9 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2008b. In vitro human skin penetration of fragrance material linalool under both in-use and occluded conditions from an ethanol/dipropylene glycol vehicle. RIFM report number 54663 June 9 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Linalool: B220 assay research report: comparison of linalool and linalool with anti-oxidant. RIFM report number 63724, July 26 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. A two-week inhalation toxicity study of aerosolized linalool in the Spanish Dawley rat. RIFM report number 63821, September 6 (RIFM, Woodcliff Lake, NJ, USA).
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., et al., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
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. Abstract 683.
Rogers, R.E., Isola, D.A., Jeng, C.J., Lefebvre, A., Smith, L.W., 2005. Simulated inhalation levels of fragrance materials in a surrogate air freshener formulation. Environ. Sci. Technol. 39 (20), 7810–7816.
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, G., 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 Fragr. J. 22, 435–437.
Satoh, T., 1987. Role of carboxylesterases in xenobiotic metabolism. Rev. Biochem. Toxicol. 8 (1987), 155–181.
Schmitt, S., Schaefer, U., Sporer, F., Reichling, J., 2010. Comparative study on the in vitro human skin permeation of monoterpenes and phenylpropanoids applied in rose oil and in form of neat single compounds. Pharmazie 65 (2), 102–105.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. Ann. N. Y. Acad. Sci. 641 (1), 152–163.
Skold, M., Hagvall, L., Borje, A., Karlberg, A.-T., 2005. Autooxidation of linalool, linalyl acetate, and beta-carophyllene in air-exposed lavender oil. Identification of oxidation products and effect of skin sensitization. In: Contact Allergy to Autoxidized Fragrance Terpenes.
Skold, M., Hagvall, L., Karlberg, A.-T., 2008. Autoxidation of linalyl acetate, the main component of lavender oil, creates potent contact allergens. Contact Dermatitis 58 (1), 9–14.
Smith, L.W., Rogers, R.E., Black, M.S., Isola, D.A., 2004. Exposure characterizations of three fragranced products. Toxicol. Appl. Pharmacol. Abstract 249.
Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K., Go, G.B., 1973. Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res. 33 (12), 3069–3085.
Sugawara, Y., Hara, C., Tamura, K., Fujii, T., Nakamura, K.I., Masujima, T., et al., 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), 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), 155–160.
The OECD QSAR Toolbox (Version 3.0) [Software]. (Copyright 2012), Organization for Economic Co-operation and Development & European Chemicals Agency: http://www.qsartoolbox.org/.
Troy, W.R., 1977. Doctoral Dissertation: the comparative respiratory irritation potential of fourteen fragrance raw materials. ST. John's University, College of Pharmacy, New York.
USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA.
Van Duuren, B.L., Blazej, T., Goldschmidt, B.M., Katz, C., Melchionne, S., Sivak, A., 1971. Cocarcinogenesis studies on mouse skin and inhibition of tumor induction. J. Natl Cancer Inst. 46 (5), 1039–1044.
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.