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Short review

RIFM fragrance ingredient safety assessment, l-linalool, CAS Registry Number 126-91-0

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ABSTRACT

The use of this material under current use conditions is supported by the existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined using a suitable read across analog to have the most conservative systemic exposure derived NO[A]EL of 36 mg/kg/day. A dermal 90-day subchronic toxicity study conducted in rats resulted in a MOE of 2250 while considering 14.4% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

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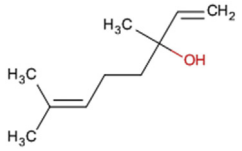
Name: l-Linalool
CAS Registry Number: 126-91-0



Abbreviation list:
2-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
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
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[a] **concludes that this material is safe under the limits described in this safety assessment.**
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015; #68218) which 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).

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined using a suitable read across analog to have the most conservative systemic exposure derived NO[A]EL of 36 mg/kg/day. A dermal 90-day subchronic toxicity study conducted in rats resulted in a MOE of 2250 while considering 14.4% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic	(Belsito et al., 2010)
Repeated Dose Toxicity: NOAEL = 36 mg/kg/day	(RIFM, 1980)
Developmental and Reproductive Toxicity: NOAEL = 200 mg/kg/day	(ECHA REACH Dossier: Linalool)
Skin Sensitization: Not Sensitizing	(RIFM, 2005)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC = 10 ppm or 63 mg/m^3	(RIFM, 2012)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: Read−across to linalool (CAS# 78-70-6); 80−100%	(RIFM, 1977a; RIFM, 1994b; RIFM, 1991a)
Bioaccumulation: Screening Level: 42.33 L/kg	(EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: Read-across to linalool: *Daphnia Magna* 48 h EC50: 20 mg/L (RIFM, 1988)	
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: Read-across to linalool: *Daphnia Magna* 48 h EC50: 20 mg/L	(RIFM, 1988)
RIFM PNEC is: 20 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe <1	

[a] 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.

1. Identification

1. **Chemical Name:** l-Linalool
2. **CAS Registry Number:** 126-91-0
3. **Synonyms:** (R)-3,7-Dimethyl-1,6-octadien-3-ol, l-Linalool, 1,6-Octadien-3-ol, 3,7-dimethyl-, (R)-,

3，7－ ジメチルー１，６ーオクタジエンー３ーオール, 3,7-Dimethylocta-1,6-dien-3-ol

, 3,7-Dimethylocta-1,6-dien-3-ol

4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25
6. **Specific Gravity:** 0.86000 to 0.86700 @ 25 °C[1]
7. **Vapor Pressure:** 0.0521 mm Hg @ 20 °C [EPI Suite 4.0], 0.0832 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless clear liquid with a medium, fresh, floral, woody, natural, deep and lavender odor[1]

3. Exposure

1. **Volume of Use (worldwide band):** >1000 metric tons per year	[IFRA, 2011]
2. **Average Maximum Concentration in Hydroalcoholics:** 0.31%	[IFRA, 2004]
3. **97.5**th **Percentile:** 2.86%	[IFRA, 2004]
4. **Dermal Exposure**[a]**:** 0.0729 mg/kg/day	[IFRA, 2004]
5. **Oral Exposure:** Not available	
6. **Inhalation Exposures**[b]**:** 0.006 mg/kg/day (Calculated)	[IFRA, 2004]
7. **Total Systemic Exposure (Dermal + Inhalation):** (0.0729 mg/kg/day × 14.4%) + 0.006 mg/kg/day = 0.016 mg/kg/day	

[a] 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., anti-perspirant, 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).
[b] 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.

6. **RIFM Number:** 5160

2. Physical data

1. **Boiling Point:** (calculated) 204.05 °C [EPI Suite]
2. **Flash Point:** 160.00 °F. TCC (71.11 °C)[1]
3. **Log K_{OW}:** 3.38 [EPI Suite]
4. **Melting Point**: (calculated) −11.39 °C [EPI Suite]
5. **Water Solubility:** (calculated) 683.7 mg/L [EPI Suite]

[1] http://www.thegoodscentscompany.com/data/rw1011632.html, retrieved 10/30/13.

4. Derivation of systemic absorption

1. **Dermal:** 14.4%

RIFM, 2007a; (data also available in RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008): A series of *in vitro* human skin penetration studies were conducted with 4% stereoisomer linalool (CAS # 78-70-6) 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 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:** Assume Dermal (14.4%) + Inhalation (100%) absorbed = (0.0729 mg/kg/day × 14.4%) + 0.006 mg/kg/day = 0.016 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)
2. **Analogues Selected**:
   a. **Genotoxicity:** Linalool (CAS # 78-70-6)
   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:** Linalool (CAS # 78-70-6)
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity:** Linalool (CAS # 78-70-6)
   g. **Environmental Toxicity:** Linalool (CAS # 78-70-6)
3. **Read-across Justification**: See Appendix below

Expert Judgment	Toxtree v. 2.6	OECD QSAR Toolbox v. 3.2
I[a]	III	I

[a] See Appendix below for explanation.

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

l-Linalool is reported to occur in the following foods[2]:

Apricot (Prunus armeniaca L.)	Ocimum species
Arctic bramble (Rubus arcticus L.)	Passion fruit (Passiflora species)
Cinnamomum species	Peach (Prunus persica L.)
Citrus fruits	Pineapple (Ananas comosus)
Coriander seed (Coriandrum sativum L.)	Plum (Prunus species)
Guava and feyoa	Raspberry, blackberry and boysenberry
Mace (Myristica fragrans Houttuyn)	Strawberry (Fragaria species)
Mangifera species	Tea
Nutmeg (Myristica fragrans Houttuyn)	

8. IFRA standard

IFRA Standard Specified - The material should only be used if it meets purity criteria or if it is used in conjunction with other materials. See Skin Sensitization.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 10/29/2015.

10. Summary

1. **Human Health Endpoint Summaries:**

10.1. Genotoxicity

Based on the current existing data and use levels, *l*-linalool does not present a concern for genetic toxicity.

10.1.1. Risk assessment

The genotoxic potential of l-linalool has been evaluated in the BlueScreen assay and was found to be negative both with and without metabolic activation. No other data are available for l-linalool, however, there are sufficient data for its stereoisomer, linalool (CAS # 78-70-6; see Section V). The genotoxic potential of linalool has been evaluated for mutagenicity in bacteria and in cultured mouse L5718Y tk ± cells, and for cytogenetics in CHO cells via SCE, a chromosome aberration study, and an *in vivo* micronucleus test. The Fragrance Material Review on linalool, summarizes available data including negative Ames studies in *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2 uvrA, a negative sister chromatid exchange assay in CHO cells, a negative test for induction of unscheduled DNA synthesis in rat primary hepatocytes, and a negative *in vivo* mouse micronucleus assay (Letizia et al., 2003). Additionally, the US NTP has shown linalool to be non-mutagenic in *S. typhimurium* strains TA100, 1535, 97, 98, 102, 104 up to 1000 μg/plate (NTP, 1999). Mammalian mutagenicity was evaluated in a mouse lymphoma assay which demonstrated a weak positive result for linalool, however, the authors emphasized that positive results in this assay are commonly observed for polar substances in the presence of S9 and may be associated with changes in physiologic culture conditions such as pH and osmolality (Heck et al., 1989). When a second mouse lymphoma study was conducted which took into account cytotoxicity, osmolality and pH, the results were negative (RIFM, 1994a). Linalool has been previously reviewed by RIFM's Expert Panel and it was concluded that there is sufficient mutagenicity and clastogenicity data indicating the material is not genotoxic (Bickers et al., 2003; Belsito et al., 2010). Since this evaluation by the panel, an *in vitro* micronucleus test demonstrated negative effects for linalool (DiSotto et al., 2011), further supporting a lack of genotoxic concern for linalool.

[2] 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.

Additional References: Eder et al., 1980; Eder et al., 1982; Ishidate et al., 1984; Lutz et al., 1980; Yoo, 1986; Rockwell and Raw, 1979; RIFM, 1983a,b; RIFM, 2001; Sasaki et al., 1989.

Literature Search and Risk Assessment Completed on: 04/05/13.

10.2. Repeated dose toxicity

The margin of exposure for *l*-linalool is adequate for the repeated dose toxicity endpoint at the current level of use.

10.2.1. Risk assessment

There are no repeat dose toxicity data on l-linalool. Stereoisomer linalool (CAS # 78-70-6; see Section V) 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). A dermal absorption study was conducted on linalool *in vitro* with human skin (RIFM, 2007a; (data also available in RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008)). Under the most severe conditions, occluded in a 70/30 ethanol/water vehicle, only 14.4% of linalool was absorbed. To account for bioavailability following dermal application, these data from the *in vitro* dermal absorption study 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, 36/0.016 or 2250.**

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

Literature Search and Risk Assessment Completed on: 04/05/13.

10.3. Developmental and reproductive toxicity

The margin of exposure for *l*-linalool is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.3.1. Risk assessment

There are no developmental toxicity data on l-linalool. Stereoisomer linalool (CAS # 78-70-6; see Section V) has a gavage developmental toxicity study in rats, which concluded a NOAEL of 1000 mg/kg/day for developmental toxicity, the highest dosage tested (Politano et al., 2008 (data also available in RIFM, 2006; Letizia et al., 2007)). A dermal absorption study was conducted on linalool *in vitro* with human skin (RIFM, 2007a; (data also available in RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008)). Under the most severe conditions, occluded in a 70/30 ethanol/water vehicle, only 14.4% of linalool was absorbed. **Therefore, the MOE for developmental toxicity is equal to the linalool NOAEL in mg/kg/day divided by the total systemic exposure, 1000/0.016 or 62500.**

There are no reproductive toxicity data on l-linalool. Read-across material dehydrolinalool (CAS # 29171-20-8; see Section V) 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: Linalool Read across Subs Key Toxicity to reproduction.003 (accessed 02/21/13)). The gavage developmental toxicity study in rats on stereoisomer 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; (data also available in RIFM, 2006; Letizia et al., 2007)). The dermal 90-day subchronic toxicity study on 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. A dermal absorption study was conducted on linalool *in vitro* with human skin (RIFM, 2007a). Under the most severe conditions, occluded in a 70/30 ethanol/water vehicle, only 14.4% of linalool was absorbed. **Therefore, the MOE for reproductive toxicity is equal to the dehydrolinalool NOAEL in mg/kg/day divided by the total systemic exposure, 200/0.016 or 12500.**

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

Literature Search and Risk Assessment Completed on: 04/05/13.

10.4. Skin Sensitization

Based on existing data for the read across material (linalool (CAS # 78-70-6)), l-linalool does not present a concern for skin sensitization.

10.4.1. Risk assessment

Based on existing data for the read across material (linalool (CAS # 78-70-6; see Section V)), l-linalool does not present a concern for skin sensitization. The isomer specificity of l-linalool would not be expected to impact on the potential for skin sensitization, and therefore l-linalool does not present a concern for skin sensitization. Linalool is not predicted to be directly reactive to skin proteins (Roberts et al., 2007; OECD toolbox v3.0). However, linalool is known to undergo auto-oxidation resulting in degradation products that may be protein reactive (Skold et al., 2004). In guinea pig test methods and the local lymph node assay (LLNA), positive and negative results have been reported (Basketter et al., 2002a, 2002b; Ishihara et al., 1986; Klecak, 1979, 1985; Sharp, 1978; Skold et al., 2004). In these LLNAs and guinea pig studies the positive results have been shown to be the result of sensitizing products of autoxidation and irritation (RIFM, 2010b; Skold et al., 2002; Skold et al., 2004). In human confirmatory studies, no reactions indicative of sensitization have been observed to linalool at the maximum tested concentration of 12.7% (14 998 μg/cm^2) (Greif, 1967; and RIFM, 1975, 1970).

Note: Whereas linalool is considered to be a non-sensitizer, autoxidation products of this material are known to be contact allergens. Similarly, l-linalool would be expected to autoxidize. l-Linalool, and natural products rich in l-linalool, are subject to an IFRA standard that defines a good manufacturing practice (GMP) specification limiting peroxide levels to 20 mmol/l with a recommendation to add an antioxidant at the time of production (IFRA, 2004).

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/05/13.

10.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, *l*-linalool would not be expected to present a concern for phototoxicity or photoallergenicity.

10.5.1. Risk assessment

There are no phototoxicity studies available for *l*-linalool in experimental models. UV/Vis absorption spectra (OECD test guideline 101) indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark, 1000 L mol^{-1} cm^{-1}, of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, *l*-linalool does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/24/15.

10.6. Local respiratory toxicity

The margin of exposure for *l*-linalool is adequate for the respiratory endpoint at the current level of use.

10.6.1. 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 l-linalool. A NOAEC of 10 ppm (63 mg/m^3) for the read across analog linalool (CAS# 78-70-6; See section V) was reported in a 2 week acute inhalation study conducted in rats; the highest dose tested (RIFM, 2012). The test substance-related effects were limited to non-adverse microscopic findings in the nasal cavity.

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

- (63 mg/m^3) (1 m^3/1000L) = 0.063 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague–Dawley rat X 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[3]) = 2409.75 mg/kg lw/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 2.86%. 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 0.265 mg/day as 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. 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 0.41 mg/kg lung weight/day resulting in a MOE of 5877 (i.e., [2409.75 mg/kg lw/day]/[0.41 mg/kg lung weight/day]).

The MOE is significantly greater than 100. Without the adjustment for specific uncertainty factors related to inter-species and intra-species variation the material exposure by inhalation at 12.70% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

Additional References: RIFM, 1977b; Jirovetz et al., 1991, 1990; Buchbauer et al., 1991; RIFM, 1997; Buchbauer et al., 1993; Perrucci et al., 1996, 1995a; Rice, 1994a; Silver, 1992; Karr, 1992; Regnault-Roger, 1995; Rice, 1994b; Perrucci et al., 1995b; Sugawara et al., 1998; Coats et al., 1991; Cometto-Muniz et al., 1998; Isola et al., 2003a; RIFM, 2003b; Rogers et al., 2003; RIFM, 2003a; Isola et al., 2003b; Isola et al., 2004a; Larsen et al., 1997; Smith et al., 2004; RIFM, 2004; 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, 2009; de Moura Linck et al., 2009.

Literature Search and Risk Assessment Completed on: 04/05/13.

2. **Environmental Endpoint Summary**:

10.7. Screening-level assessment

A screening level risk assessment of l-linalool 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, l-Linalool 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 identified l-linalool 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 I.

10.8. Risk assessment

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

10.9. Key studies

10.9.1. Biodegradation

Six studies are reported in the RIFM Database for Linalool (CAS # 78-70-6)

A study was conducted following OECD Guideline 302B. 722 mg/L of the test substance was incubated for 13 days. At the end of the study 90–100% biodegradation was observed (RIFM, 1977a).

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 97.1% biodegradation was observed (RIFM, 1994b).

[3] 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."

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 80% biodegradation was observed (RIFM, 1991a).

10.9.2. Ecotoxicity

An algae growth inhibition study was conducted. The growth rate (μ) and biomass (B) of *Scendedesmus subspicatus* was measured over a 96-hr period. At the end of the study, the $E_{\mu}C50$ was 141.4 mg/L, the $E_{B}C50$ was 86.0 mg/L, and the NOEC was 32.0 mg/L (RIFM, 1998a).

One *Daphnia* immobilization study is reported. The 48 h EC50 was reported as 20 mg/L (nominal concentration) (RIFM, 1998b).

Two acute fish toxicity studies are reported: a flow through study following DIN 38 412 using Golden Orfe. The reported 96 h LC50 was >21.5 mg/L and <46.4 mg/L (RIFM, 1989b). In a second study following OECD Test Guideline 203 using *Salmo gairdneri*, a 96 h LC50 of 27.8 mg/L was reported (RIFM, 1991b).

10.10. Other available data

L-Linalool has not been registered under REACH, but the read-across material linalool (CAS # 78-70-6) has been registered under REACH. No additional data are available at this time. An OECD SIDS dossier is also available for linalool; no additional key studies are needed to complete the safety assessment.

10.11. 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.

Note: The difference between the RIFM PNEC and the REACH PNEC is due to the use, in REACH, of an Assessment Factor of 100 for the same lowest endpoint that RIFM uses an Assessment Factor of 1000. It was previously acceptable to use the algae NOEC as a single chronic value (and thus the lower AF). In this current assessment a lower AF would require either a Daphnia or fish chronic alone or in combination with algae (or the use of all three species). None of this, however, changes the outcome of the risk assessment; all PEC/PNECs are <1.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	34.3 mg/L			1,000,000	0.034 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.191 mg/L	0.32 9mg/L	6.863 mg/L	10,000	0.0329 μg/L	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	19.704 mg/L	12.517 mg/L	12.769 mg/L			Neutral organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	27.8 mg/l					
Daphnia		20.0 mg/l		1,000	20.0 μg/l	
Algae		86.0 mg/l	32.0			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.90 (K_{ow} for linalool)	2.90 (K_{ow} for linalool)
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 20.0 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic

environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 04/05/13.

11. Literature Search[4]

- **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

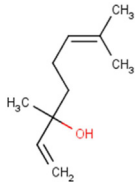
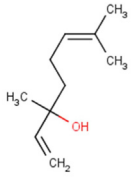
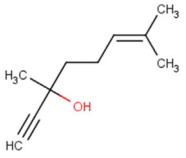
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.12.014.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.12.014.

Appendix

	Target Material	Read across Material	
Principal Name	l-Linalool	Linalool	Dehydrolinalool
CAS No.	126-91-0	78-70-6	29171-20-8
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/126-91-0.html	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/29171-20-8.html
Read-across endpoint		•Genotoxicity •Repeated Dose •Devel/Repro •Skin sensitization •Respiratory •Environmental	•Devel/Repro
Molecular Formula	C10H18O	C10H18O	C10H16O
Molecular Weight	154.25	154.25	152.24
Melting Point (°C, EPISUITE)	-11.39	-11.39	15.40
Boiling Point (°C,	204.05	204.05	212.37

[4] Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

	Target Material	Read across Material	
EPISUITE)			
Vapor Pressure (Pa @ 25°C, EPISUITE)	11.09	11.09	4.64
Log Kow (KOWWIN v1.68 in EPISUITE)	3.38	3.38	2.75
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	683.7	683.7	1084
J_{max} (mg/cm^2/h, SAM)	90.06108298	90.06108298	93.21980338
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.285034	4.285034	0.449174
Similarity (Tanimoto score)[1]		100%	63%
In silico Results for Target and Analog			
Genotoxicity			
DNA binding (OASIS v1.1)	•No alert found	•No alert found	
DNA binding (OECD)	•No alert found	•No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	•No alert found	•No alert found	

	Target Material	Read across Material	
DNA alerts for Ames, MN, CA (OASIS v1.1)	•No alert found	•No alert found	
In vitro mutagenicity (Ames test) alerts (ISS)	•No alert found	•No alert found	
In vivo mutagenicity (Micronucleus) alerts (ISS)	•No alert found	•No alert found	
Oncologic classification (OECD)	•Not classified	•Not classified	
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)
Skin Sensitization			
Protein binding (OASIS v1.1)	•No alert found	•No alert found	
Protein binding (OECD)	•No alert found	•No alert found	
Protein binding potency	•Not possible to classify according to these rules (GSH)	•Not possible to classify according to these rules (GSH)	

	Target Material	Read across Material	
(OECD)			
Protein binding alerts for skin sensitization (OASIS v1.1)	•No alert found	•No alert found	
Skin sensitization model (CAESAR v2.1.5)	Sensitizer(experimental activity)	Sensitizer(experimental activity)	
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See Supplemental data 1	See Supplemental data 2	See Supplemental data 3

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

Summary

There are insufficient toxicity data on l-Linalool (RIFM # 5160, CAS # 126-91-0). 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 analog 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)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- 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 (CAS # 78-70-6) is a stereoisomer of the target. Stereoisomers have the same atomic connectivity but differ in spatial arrangement of atoms or functional groups and usually behave in a similar chemical and toxicological manner.
- Dehydrolinalool (analog) was used as a read-across for l-Linalool (target) based on:
  - The target and analog belong to the generic class of alcohols, specifically, alcohol/branched chain/unsaturated/tertiary α,β.
  - The target and analog are terpene alcohols. They have the same number isoprene units and hydroxyl group.
  - The only difference is that the target has an alkene terminal while the analog has an alkyne terminal. The difference between structures does not essentially change physicochemical properties nor raise any additional structural alerts and therefore, the developmental and reproductive toxicity profiles are expected to be similar.
  - 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.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox both materials are predicted to have similar metabolites.

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1.Normal constituent of the body? **No**
Q2.Contains functional groups associated with enhanced toxicity? **No**
Q3.Contains elements other than C,H,O,N,divalent S? **No**
Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6.Benzene derivative with certain substituents? **No**
Q7.Heterocyclic? **No**
Q16.Common terpene? **Yes,** Low, (Class I)

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

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

Basketter, D.A., Wright, Z., Gilmour, N.J., Ryan, C.A., Gerberick, G.F., Robinson, M.K., Dearman, R.J., Kimber, I., 2002a. Prediction of human sensitization potency using local lymph node assay EC3 values. Toxicol. 66 (1-S), 240.

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

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, J.H., Sipes, I.G., Tagami, H., 2008. A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. Food Chem. Toxicol. 46 (11S), S1–S71.

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

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

Bickers, D., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, H.J., Sipes, I.G., Smith, R.L., Tagami, H., 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 esssential oil of lavender after inhalation. Z. Fur 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.H., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regul. Toxicol. Pharmacol. 36 (3), 246–252.

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

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

Cal, C.K., Kryzaniak, 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, 265–267 [Letter to the Editor].

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

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Central 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. Am. Cancer Soc. Symposium Ser. 449, 305–316.

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

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

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.

DiSotto, 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.

ECHA REACH Dossier: linalool: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d93c699-8de9-6b59-e044-00144f67d249/DISS-9d93c699-8de9-6b59-e044-00144f67d249_DISS-9d93c699-8de9-6b59-e044-00144f67d249.html

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1980. Mutagenic potential of allyl and allylic compounds. Structure-activity relationship as determined by alkylating and direct in vitro mutagenic properties. Biochem. Pharmacol. 29 (7), 993–998.

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1982. Correlation of alkylating and mutagenic activities of allyl and allylic compounds: standard alkylation test vs. kinetic investigation. Chemico-Biol. Interact. 38, 303–315.

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. Retrieved from http://www.epa.gov/opptintr/exposure/pubs/episuite.htm Research, 20(6), 482–487.

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. Perfumer Cosmet. 82, 54–57.

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. Toxicol. 9 (1), 257.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

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

Howes, M.-J.R., 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), 2004. Use Level Survey, June 2004.

IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.

Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22 (8), 623–636.

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

Isola, D., Smith, L.W., Ansari, R., Black, M.S., 2003a. Exposure characterization from a fragranced plug-in air freshener. Toxicol. 72 (S-1), 291.

Isola, D.A., Smith, L.W., Rogers, R.E., Black, M.S., 2003b. Exposure characterization of fragranced air fresheners. Allergy Clin. Immunol. Int. (Suppl. 1), 132.

Isola, D.A., Rogers, R.E., Myshaniuk, A., Jeng, C.-J., Ansari, R., Smith, L.W., 2004a. Exposure characterization from a surrogate fine fragrance. Toxicol. 78 (S-1), 107.

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

Jager, W., Buchbauer, G., Jirovetz, L., Fritzer, M., 1992. Percutaneous absorption of lavender oil from a massage oil. J. Soc. Cosmet. Chem. Jpn. 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. Effect of four monoterpenoids on growth and reproduction of the German cockroach (Blattodea: Blattellidae). J. Econ. Entomol. 85 (2), 424–429.

Klecak, G., 1979. The Open Epicutaneous Test (OET), a Predictive Test Procedure in the Guinea Pig for Estimation of Allergenic Properties of Simple Chemical Compounds, Their Mixtures and of Finished Cosmetic Preparations. International Federation Societies Cosmetic Chemists, 9/18/79.

Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol. 14, pp. 152–171.

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

Lalko, J., Brain, K.R., Green, D.M., Api, A.M., 2007. In vitro human skin penetration of the fragrance material linalool. Int. J. Toxicol. Former. J. Am. Coll. Toxicol. 26 (6), 608.

Lalko, J., Brain, K., Green, D., Api, A.M., 2008. In vitro human skin penetration of the fragrance material linalool. Toxicol. 102 (1), 319.

Lapczynski, A., Letizia, C.S., Api, A.M., 2008a. Addendum to Fragrance material review on linalool. Food Chem. Toxicol. 46 (11S), S190–S192.

Lapczynski, A., Letizia, C.S., Api, A.M., 2008b. Fragrance material review on d-linalool. Food Chem. Toxicol. 46 (11S), S193–S194.

Lapczynski, A., Bhatia, S.P., Letizia, C.S., Api, A.M., 2008c. Fragrance material review on l-linalool. Food Chem. Toxicol. 46 (11S), S195–S196.

Larsen, B., Bomboi-Mingarro, T., Brancaleoni, E., Calogirou, A., Cecinato, A., Coeur, C., Chatzianestis, I., Duane, M., Fratoni, M., Fugit, J.-L., Hansen, U., Jacob, V., Mimikos, N., Hoffmann, T., Owen, S., Perez-Pastor, R., Reichmann, A., Seufert, G., Staudt, M., Steinbrecher, R., 1997. Sampling and analysis of terpenes in air. An interlaboratory comparison. Atmos. Environ. 31 (S1), 35–49.

Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003. Fragrance material review on linalool. Food Chem. Toxicol. 41 (7), 943–964.

Letizia, C., Api, A.M., Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., 2007. Evaluation of the developmental toxicity of linalool in rats.

Toxicol. 96 (1), 92.
Lutz, D., Neudecker, T., Eder, E., 1980. Mutagenic effects of allylic alcohols and their corresponding aldehydes. Arch. Pharmacol. 311 (Suppl. I), R25.
Matsui, A.S., Rogers, J., Woo, Y.-K., Cutting, W.C., 1967. Effects of some natural products on fertility in mice. Med. Pharmacol. Exp. 16, 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., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneim. Drug. Res. 9, 516–519.
Meyer, F. (1965). Penetrating agents. Patent, British, 1,001,949, M49750IVa/30h, 7/20/61.
de Moura Linck, V., da Silva, A.L., Figueiró, M., Piato, Â.L., Herrmann, A.P., Birck, F.D., Elisabetsky, E., 2009. Inhaled linalool-induced sedation in mice. Phytomedicine 16 (4), 303–307.
Nakamura, A., Fujiwara, S., Matsumoto, I., Abe, K., 2009. Stress repression in restrained rats by (R)-(-)-linalool inhalation and gene expression profiling of their whole blood cells. J. Agric. Food Chem. 57, 5480–5485.
Nakamura, A., Fujiwari, S., Ishijima, T., Okada, S., Nakai, Y., Matsumoto, I., Misaka, T., Abe, K., 2010. Neuron differentiation-related genes are upregulated in the hypothalamus of odorant-inhaling rats subjected to acute restraint stress. J. Agric. Food Chem. 58 (13), 7922–7929.
NTP (National Toxicology Program), (1999): http://tools.niehs.nih.gov/cebs3/ntpViews/?studyNumber=002-02364-0001-0000-8
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), 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. Phytotherapy Res. 10 (1), 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. Former. J. Am. Coll. 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. Toxicol. 132 (1), 330.
Regnault-Roger, C., Hamraoui, A., 1995. Fumigant toxic activity and reproductive inhibition induced by monoterpenes on Acanthoscelides obtectus (Say) (Coleoptera), a bruchid of kidney bean (Phaseolus vulgaris L. J. Stored Prod. Res. 31 (4), 291–299.
Rice, P.J., Coats, J.R., 1994a. Insecticidal properties of monoterpenoid derivatives to the house fly (Diptera; Muscidae) and red flour beetle (Coleoptera: Tenebrionidae). Pesticide Sci. 41 (3), 195–202.
Rice, P.J., Coats, J.R., 1994b. Insecticidal properties of several monoterpenoids to the house fly (Diptera: Muscidae), red flour beetle (Coleoptera: Tenebrionidae) and southern corn rootworm (Coleoptera: Chrysomelidae). J. Econ. Entomology 87 (5), 1172–1179.
RIFM (Research Institute for Fragrance Materials, Inc.), 1970. The Contact Sensitizing Potential of Fragrance Materials in Humans. RIFM report number 1760. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Report on Human Maximization Studies. RIFM report number 1799. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1958. Toxicological Screening of Citronellol and Linalool in Rats. Class VI. Private Communication to FEMA. Unpublished report from Trubek Laboratories, Inc. RIFM report number 29150. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1977a. Determination of the Ultimate and Inherent Biodegradation of Linalool in a Batch Test with Activated Sludge (Zahn-Wellens Method). Unpublished report from BASF. RIFM report number 55319. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1977b. Doctoral Dissertation: the Comparative Respiratory Irritation Potential of Fourteen Fragrance Raw Materials. RIFM report number 9011. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979. 29 Day Percutaneous Toxicity Range Finding with Linalool in Rats. Report to RIFM. RIFM report number 32943. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980. 90 Day Subchronic Dermal Toxicity with Linalool in Rats. RIFM report number 4001. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1983a. Mutagenicity Evaluation of Linalool in the Ames Salmonella/microsome Plate Test. Unpublished report from Lorillard Tobacco Company. RIFM report number 35823. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1983b. Mutagenicity Evaluation of Linalool in an in Vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells. Unpublished report from Lorillard Tobacco Company. RIFM report number 35824. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1988a. Algae Inhibition Test with Linalool. Unpublished Report from BASF. RIFM report number 55312. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1988b. Acute Toxicity to Daphnia Magna of Linalool. Unpublished Report from BASF. RIFM report number 55316. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. 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. RIFM report number 36124. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Report on the Study of the Acute Toxicity of Linalool in Golden Orfe (Leuciscus idus L., Golden Variety). Unpublished report from BASF. RIFM report number 55318. 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. RIFM report number 36125. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1991a. Determination of Ready Biodegradability of Linalool. Unpublished Report from Givaudan-Roure. RIFM report number 32450. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1991b. Report on the Acute Toxicity Test of Linalool to Rainbow Trout(Salmo Gairdneri). Private Communication to FEMA. Unpublished report from Vial, A. RIFM report number 54391. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1994a. Mutagenicity Test on Linalool in the L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay. Unpublished report from Lorillard Tobacco Company. RIFM report number 35827. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1994b. The Biodegradability of Perfume Ingredients in the Sealed Vessel Test. Unpublished report from Quest International. RIFM report number 49675. 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. RIFM report number 18011. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1998. Report on the Metabolism of Linalool in Rat Tissue & Intestinal Homogenates. Report to FEMA. Unpublished report from Flavor and Extract Manufacturers Association. RIFM report number 34252. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Micronucleus Test in Bone Marrow Cells of the Mouse with Linalool. Private Communication to FEMA. Unpublished report from Hoffmann-LaRoche. RIFM report number 38577. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Indoor Air Quality Evaluation of a Plug-in Air Freshener. RIFM report number 43292. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Airborne Levels of Selected Fragrance Materials in a Simulated Bathroom. RIFM report number 41708. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Airborne Levels of Selected Fragrance Materials Following a Controlled Exposure to a Surrogate Fine Fragrance. RIFM report number 47425. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Repeated Insult Patch Test with Linalool. RIFM report number 49469. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Oral (Gavage) Developmental Toxicity Study of Linalool in Rats. RIFM report number 45726. 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. 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. 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. 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. 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/diproplylene Glycol Vehicle. RIFM report number 54663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008c. Vitro Human Skin Penetration of Fragrance Material Linalool under Both In-use and Occluded Conditions from a Petrolatum Vehicle. RIFM report number 54664. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2010a. Geraniol Extra: Reproduction/developmental Toxicity Screening Test in Wistar Rats. Dermal Administration. Unpublished report from BASF SE. RIFM report number 60844. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2010b. Linalool: B220 Assay

Research Report: Comparison of Linalool and Linalool with Anti-oxidant. RIFM report number 63724. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. A Two-week Inhalation Toxicity Study of Aerosolized Linalool in the Sprague Dawley Rat. RIFM report number 63821.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rockwell, P., Raw, I., 1979. A mutagenic screening of various herbs, spices, and food additives. Nutr. Cancer 1 (4), 10–15.
Rogers, R.E., Isola, D.A., Smith, L.W., Jeng, C.J., Dews, P., Myshaniuk, A., 2003. Characterization of potential human exposure to fragrances during residential consumer product use. J. Allergy Clin. Immunol. 111 (2), S239.
Rogers, R.E., Isola, D.A., Jeng, C.-J., Smith, L.W., Lefebvre, A., 2005. Simulated inhalation levels of fragrance materials in a surrogate air freshener formulation. Environ. Sci. Technol. 39 (20), 7810–7816.
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.
Sasaki, Y.F., Imanishi, H., Phta, T., Shirasu, Y., 1989. Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. Mutat. Res. Lett. 226 (1), 103–110.
Sato, K., Krist, S., Buchbauer, G., 2007. Antimicrobial effect of vapours of geraniol, (R)-(-)-linalool, terpineol, gamma-terpinene and 1,8-cinole on airborne microbes using an airwasher. Flavour Fragr. J. 22 (5), 435–437.
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.
Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. In: Annals of the New York Academy of Sciences, vol. 641, pp. 152–163.
Skold, M., Borje, A., Matura, M., Karlberg, A.-T., 2002. Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hyperperoxide. Contact Dermat. 46 (5), 267–272.
Skold, M., Borje, A., Harambasic, E., Karlberg, A.-T., 2004. Contact allergens formed on air exposure of linalool. Identification and quantification of primary and secondary oxidation products and the effect on skin sensitization. Chem. Res. Toxicol. 17 (12), 1697–1705.
Smith, L.W., Rogers, R.E., Black, M.S., Isola, D.A., 2004. Exposure characterizations of three fragranced products. Toxicol. Appl. Pharmacol. 197 (3), 189.
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., Aoki, T., 1998. Sedative effect on humans of inhalation of essential oil of linalool: sensory evaluation and physiological measurements using optically active linalools. Anal. Chim. Acta 365 (1–3), 293–299.
Tanida, M., Niijima, A., Shen, J., Nakamura, T., Nagai, K., 2006. Olfactory stimulation with scent of lavender oil affects autonomic neurotransmission and blood pressure in rats. Neurosci. Lett. 398 (1–2), 155–160.
USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v. 4.11. United States Environmental Protection Agency, Washington, DC, USA.
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.
Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. J. Osaka City Med. Cent. 34 (3–4), 267–288 ([Osaka-shi Igakkai Zasshi]).

Further reading

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.