Food and Chemical Toxicology 82 (2015) S49–S58

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, Linalyl hexanoate, CAS Registry Number 7779-23-9

A.M. Api [a], D. Belsito [b], S. Bhatia [a], M. Bruze [c], P. Calow [d], M.L. Dagli [e], W. Dekant [f], A.D. Fryer [g], L. Kromidas [a,*], S. La Cava [a], J.F. Lalko [a], A. Lapczynski [a], D.C. Liebler [h], Y. Miyachi [i], V.T. Politano [a], G. Ritacco [a], D. Salvito [a], J. Shen [a], T.W. Schultz [j], I.G. Sipes [k], B. Wall [a], D.K. Wilcox [a]

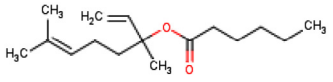
[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, United States*
[b] *Department of Dermatology, Member RIFM Expert Panel, Columbia University Medical Center, 161 Fort Washington Ave., New York, NY 10032, United States*
[c] *Department of Occupational & Environmental Dermatology, Member RIFM Expert Panel, Malmo University Hospital, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden*
[d] *Member RIFM Expert Panel, University of Nebraska Lincoln, 230 Whittier Research Center, Lincoln, NE 68583-0857, United States*
[e] *Department of Pathology, Member RIFM Expert Panel, School of Veterinary Medicine and Animal Science, University of Sao Paulo, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo CEP 05508-900, Brazil*
[f] *Department of Toxicology, Member RIFM Expert Panel, University of Wuerzburg, Versbacher Str. 9, Würzburg 97078, Germany*
[g] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, United States*
[h] *Member RIFM Expert Panel, Department of Biochemistry, Center in Molecular Toxicology, Vanderbilt University School of Medicine, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, United States*
[i] *Member RIFM Expert Panel, Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan*
[j] *Member RIFM Expert Panel, College of Veterinary Medicine, Department of Comparative Medicine, The University of Tennessee, 2407 River Dr., Knoxville, TN 37996-4500, United States*
[k] *Member RIFM Expert Panel, Department of Pharmacology, College of Medicine, University of Arizona, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, United States*

ARTICLE INFO

Article history:
Received 19 November 2014
Accepted 13 January 2015
Available online 28 January 2015

Version: 091514. This version replaces any previous versions.

Name: Linalyl hexanoate
CAS Registry Number: 7779-23-9



Abbreviation/Definition 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 97.5 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).

* Corresponding author. Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677 United States. Tel.: +1 201 689 8089 ext 110.
E-mail address: lkromidas@rifm.org (L. Kromidas).

http://dx.doi.org/10.1016/j.fct.2015.01.009

AF – Assessment 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* 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 genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as environmental assessment. Reproductive toxicity was based on the Threshold of Toxicological Concern (TTC) of 0.03 mg/kg/day for a Cramer Class I material. The estimated systemic exposure is determined to be below this value assuming 80% absorption from skin contact and 100% from inhalation. A systemic exposure below this TTC value is acceptable.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (RIFM, 2014a; RIFM, 2004a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day (Hagan et al., 1967)
Developmental and Reproductive Toxicity: Developmental NOAEL = 364 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC (Vollmuth et al., 1990)
Skin Sensitization: Not a sensitization concern (RIFM, 1982; RIFM, 2010; Skold et al., 2005)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (RIFM, 1983a; RIFM, 1983b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 96.9% (OECD 301B) Read – across to linalyl acetate CAS # 115-95-7 (RIFM, 1994)
Bioaccumulation: Screening Level: 7202 L/Kg (EPISUITE ver 4.1)
Ecotoxicity: Screening Level: LC50: 0.055 mg/l (Salvito et al., 2002)
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: LC50: 0.055 mg/l (Salvito et al., 2002)
RIFM PNEC is: 5.5E-05 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; Cleared at Screening Level

1. Identification

1 **Chemical Name:** Linalyl hexanoate
2 **CAS Registry Number:** 7779-23-9
3 **Synonyms:** 3,7-Dimethyl-1,6-octadien-3-yl hexanoate, 1,5-Dimethyl-1-vinylhex-4-enyl hexanoate, Hexanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester, Linalyl caproate, Linalyl capronate, Linalyl hexanoate, ｱﾙｶﾝ酸(C=1～6)ｼﾞﾒﾁﾙｵｸﾀｼﾞｴﾆﾙ, 1,5-Dimethyl-1-vinylhex-4-en-1-yl hexanoate
4 **Molecular Formula:** $C_{16}H_{28}O_2$
5 **Molecular Weight:** 252.4
6 **RIFM Number:** 5114

2. Physical data

1 **Boiling Point:** 295.92 °C (EPI Suite)
2 **Flash Point:** > 200 °F; CC (IFRA)
3 **Log K_{ow}:** 6.35 (EPI Suite)
4 **Melting Point**: 30.43 °C (EPI Suite)
5 **Water Solubility:** 0.08645 mg/L (EPI Suite)
6 **Specific Gravity:** 0.90000 @ 25.00 °C [http://www.thegoodscentscompany.com/data/rw1030571.html, retrieved 5/16/14]

7 **Vapor Pressure:** 0.00119 mm Hg @ 20 °C (EPI Suite 4.0), 0.00217 mm Hg @ 25 °C (EPI Suite)
8 **UV Spectra:** Not available
9 **Appearance/Organoleptic:** Colorless oily liquid. Peculiar dry-fruity and somewhat animal odor. The term, "metallic" is sometimes included in the odor description.

3. Exposure

1 **Volume of Use (worldwide band):** <1 metric tons per year (IFRA, 2011)
2 **Average Maximum Concentration in Hydroalcoholics:** 0.46% (IFRA, 2002)
3 **97.5th Percentile:** 1.15% (IFRA, 2002)
4 **Dermal Exposure*:** 0.0293 mg/kg/day (IFRA, 2002)
5 **Oral Exposure:** Not available
6 **Inhalation Exposures**:** 0.0018 mg/kg/day (IFRA, 2002)
7 **Total Systemic Exposure (Dermal + Inhalation):** (0.0293 mg/kg/day × 80% absorption) + 0.0018 mg/kg/day = 0.025 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., 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).

** 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:** 80% (predicted)

Using RIFM's *in silico* skin absorption model (Shen et al., 2014) that was approved by RIFM's Independent Expert Panel (Meeting, Miami, FL, January 13–14, 2014) the prediction results are:

	Parent	Metabolite	Metabolite
Name	Linalyl hexanoate	Linalool	Hexanoic acid
J_{max} (mg/cm^2/h)	0.88[a]		452.93[c]
Skin Absorption Class	40%	14.4%[b]	80%

[a] J_{max} was calculated based on estimated log K_{ow} = 5.41 (consensus model) and Solubility = 6.90 mg/L (consensus model).
[b] Human *in vitro* skin penetration study (RIFM, 2007a).
[c] J_{max} was calculated based on measured log K_{ow} = 1.92 (PhysProp Db) and Solubility = 1.03×10^4 mg/L (PhysProp Db).

Refined dermal exposure: 0.0293 mg/kg/day × 80% = 0.0234 mg/kg/day.

2 **Oral:** Data not available – not considered.
3 **Inhalation:** Assumed 100%
4 **Total:** Dermal (80%) + Inhalation (assume 100%) absorbed = (0.0293 mg/kg/day × 80%) + 0.0018 mg/kg/day = 0.025 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:** Linalyl isobutyrate (CAS # 78-35-3)
   c. **Developmental and Reproductive Toxicity:** Linalool (CAS # 78-70-6); dehydrolinalool (CAS # 29171-20-8); hexanoic acid (CAS # 142-62-1)
   d. **Skin Sensitization:** Linalyl acetate (CAS # 115-95-7)
   e. **Phototoxicity/Photoallergenicity:** Linalyl acetate (CAS # 115-95-7)
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** Linalyl acetate (CAS # 115-95-7)
3 **Read-across Justifications:** See Appendix below

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)

Linalyl hexanoate is not reported to occur in food by the VCF database* nor as a component of natural complex substances (NCS).

* 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

Pre-Registered for 2010; No dossier available as of 02/10/14.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Linalyl hexanoate was tested by the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity, indicating a lack of genotoxic potential (RIFM, 2014a). The mutagenicity of linalyl hexanoate was tested in a GLP compliant Ames assay conducted in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli strain* WP2 uvrA were treated with linalyl hexanoate in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of an exogenous mammalian activation system (S9). No increase in the mean frequency of revertant colonies was observed in any of the strains at the concentrations tested with or without metabolic activation (RIFM, 2004a). Under the conditions of the study, linalyl hexanoate was considered not mutagenic in bacteria.

The clastogenic activity of linalyl hexanoate was assessed in a GLP compliant *in vitro* micronucleus assay conducted in accordance with OECD TG 487. Human peripheral lymphocytes were treated with linalyl hexanoate in DMSO at concentrations ranging from 12.1 to 200 μg/ml without S9 and at concentrations ranging

from 168 to 2524 μg/ml with S9 mix. No statistically significant increase in the frequency of binucleated cells with micronuclei was observed in any of the treatment conditions (DiSotto et al., 2011; RIFM, 2014b). Under the conditions of the study, linalyl hexanoate was considered not clastogenic in mammalian cells.

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

Additional References: Di Sotto et al., 2008; RIFM, 1984; Heck et al., 1989; Di Sotto et al., 2011; Oda et al., 1979; RIFM, 1987; RIFM, 2000.

Literature Search and Risk Assessment Completed on: 03/17/14.

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. There are no repeated dose toxicity data on linalyl hexanoate. Read across material linalyl isobutyrate (CAS # 78-35-3; see Section 5) has a dietary 18-week chronic toxicity study conducted in rats, which determined the NOAEL to be 10,000 ppm, or 500 mg/kg/day, the highest dosage tested (Hagan et al., 1967). Therefore, the MOE is equal to the linalyl isobutyrate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.025 or 20,000.

Additional References: Letizia et al., 2003a; Bickers et al., 2003; Letizia et al., 2003b; Letizia et al., 2003c; Letizia et al., 2003d; RIFM, 1958a; 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., 2003e; Letizia et al., 2003f; RIFM, 1980; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003g; 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; Deuel et al., 1954; Mori, 1953; Moody et al., 1982; Pennanen et al., 1993; Scheuplein, 1966; Henning et al., 1970; Sani et al., 1987; Brown et al., 1984; Dawson, 1991; Dawson et al., 1996; Katz et al., 1994.

Literature Search and Risk Assessment Completed on: 03/31/14.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on linalyl hexanoate, but it is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6; see Section 5) and hexanoic acid (CAS # 142-62-1; see Section 5). In a gavage developmental toxicity study conducted in rats with linalool, the NOAEL for developmental toxicity was determined to be 1000 mg/kg/day, the highest dosage tested (Politano et al., 2008). A gavage reproduction and developmental screening study conducted in rats with hexanoic acid determined the developmental NOAEL to be 364 mg/kg/day, the highest dosage tested (Vollmuth et al., 1990; poster). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE is equal to the hexanoic acid NOAEL in mg/kg/day divided by the total systemic exposure, 364/0.025 or 14560.

There are no reproductive toxicity data on linalyl hexanoate, any read across materials, or its major metabolites, linalool (CAS # 78-70-6) and hexanoic acid (CAS # 142-62-1). However, read-across material to linalool, dehydrolinalool (CAS # 29171-20-8; see Section 5) has a reproductive toxicity screening study in rats. The NOAEL for males was determined to be 750 mg/kg/day, 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 02/19/13)). There are no reproductive toxicity data on hexanoic acid; therefore, a NOAEL for linalyl hexanoate could not be determined. When correcting for skin absorption, the total systemic exposure (25 μg/kg/day; see Section 4) is below the TTC for the Cramer Class I linalyl hexanoate (30 μg/kg bw/day).

Additional References: Letizia et al., 2003a; Bickers et al., 2003; Letizia et al., 2003b; Letizia et al., 2003c; Letizia et al., 2003d; RIFM, 1958a; 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., 2003e; Letizia et al., 2003f; RIFM, 1980; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003g; 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; Deuel et al., 1954; Mori, 1953; Moody et al., 1982; Pennanen et al., 1993; Scheuplein, 1966; Henning et al., 1970; Sani et al., 1987; Brown et al., 1984; Dawson, 1991; Dawson et al., 1996; Katz et al., 1994.

Literature Search and Risk Assessment Completed on: 03/31/14.

10.1.4. Skin sensitization

Based on the available data for the read across material linalyl acetate (CAS # 115-95-7), linalyl hexanoate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data for the read across analog linalyl acetate (CAS # 115-95-7; see Section 5), linalyl hexanoate does not present a concern for skin sensitization. Linalyl acetate and linalyl hexanoate are not predicted to significantly react to skin proteins (Roberts et al., 2007; OECD toolbox v3.0). However, linalyl acetate is known to undergo auto-oxidation resulting in degradation products that may be protein reactive (Sköld et al., 2008). In the local lymph node assay (LLNA), positive results were reported for various qualities of linalyl acetate with EC3 values in the range of 3.6% to 25% (900 to 6250 μg/cm^2) (RIFM, 2002; Sköld et al., 2008). These positive results were shown to be due to irritation or sensitizing products formed during autoxidation of linalyl acetate (RIFM, 2010; Skold et al., 2005; Sköld et al., 2008). In the human maximization test positive results were reported at concentrations of 10% linalyl acetate in petrolatum; however these results were also demonstrated to be the result of test sample impurities as testing of purified samples demonstrated no sensitization potential (RIFM, 1974; RIFM, 1982). In the human maximization test no reactions indicative of sensitization were observed at higher concentrations (12.5% and 20.0%) to linalyl acetate (Greif, 1967; RIFM, 1975). Based on the weight-of-evidence (WOE), linalyl acetate does not present a concern for skin sensitization.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/28/14.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and data for the read across material linalyl acetate (CAS # 115-95-7), linalyl hexanoate would not be expected to present a concern for phototoxicity.

10.1.5.1. Risk assessment. Based on the available UV/Vis spectra and data for the read across analog linalyl acetate (CAS # 115-95-7; see Section 5), linalyl hexanoate is not expected to present a concern for phototoxicity. The UV absorption spectra demonstrate that this material has little to no absorption in the UV range (320–400 nm). Though the UV spectra are not suitable for conducting a benchmark evaluation, in Guinea pig and rat studies no reactions indicative of phototoxic responses were observed to linalyl acetate (RIFM, 1983a; RIFM, 1983b).

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/28/14.

10.1.6. Local respiratory toxicity

The material, linalyl hexanoate, is below the exposure level for the inhalation TTC Cramer Class I limit for local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on linalyl hexanoate. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 1.15%. 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 inhalation combined exposure would be 0.15 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value. This value is below the Cramer Class I TTC level of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009) and is deemed safe for use at the reported use level.

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., 1994a; Silver, 1992; Karr et al., 1992; Regnault-Roger et al., 1995; Rice et al., 1994b; 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; Smyth et al., 1962.

Literature Search and Risk Assessment Completed on: 03/28/14.

10.2. Environmental endpoint summary

10.2.1. Analogs identified/justification

Linalyl acetate (CAS # 115-95-7) has been identified as read-across analogs for linalyl hexanoate based on structure and physical/chemical properties. Both materials are aliphatic esters with predicted K_{ow} of 4.39 and 6.3, for linalyl acetate and linalyl hexanoate respectively. Available biodegradation data for linalyl acetate shows a biodegradation of 96.9% after 28 days, confirming that the material is not persistent; therefore it should be assumed that linalyl hexanoate is also not to be persistent. This is also supported by the BIOWIN models for biodegradation.

10.2.2. Screening-level assessment

A screening level risk assessment of linalyl hexanoate 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 hexanoate was identified as a fragrance material with no 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 hexanoate as not persistent but possibly 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.

10.2.3. Risk assessment

Based on current VoU (2011), linalyl hexanoate does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. A 10 day chronic static renewal effluent toxicity test with *Daphnia magna* was conducted according to the EPA/600/4-90/027 and ASTM E729, 1997 methods. The LC50 was calculated to be greater than 0.26 mg/l and the NOECs were 0.26 mg/l for reproduction and survival (RIFM, 2005).

Short-term, 7 days, chronic static renewal effluent toxicity tests with immature fathead minnows, *Pimephales promelas*, were conducted according to the EPA/600/4-90/027 and ASTM E729, 1997 methods. The LC50 was calculated to be greater than 0.26 mg/l and the NOECs were 0.26 mg/l for both growth and survival (RIFM, 2005).

10.2.3.3. Other available data. Linalyl hexanoate has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

Since linalyl hexanoate has been cleared at the screening level, ecotoxicity data are included in this document for completeness only and are not use in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>0.055</u>			1,000,000	5.5E-05 µg/l	

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

Exposure	Europe	North America
Log K_{ow} used	6.35	
Biodegradation Factor Used	0	
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 5.5E^{-05} μg/L. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at screening level 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: 03/28/14.

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.

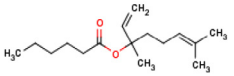
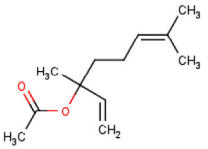
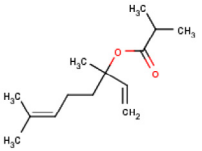
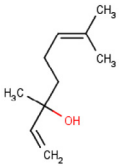
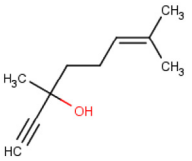
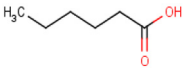
Conflict of interest

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 hexanoate	Linalyl acetate	Linalyl isobutyrate	Linalool	Dehydrolinalool	Hexanoic acid
CAS No.	7779-23-9	115-95-7	78-35-3	78-70-6	29171-20-8	142-62-1
Structure						
3D Structure	http://www.thegoodscentscompany.com/opl/7779-23-9.html	http://www.thegoodscentscompany.com/opl/115-95-7.html	http://www.thegoodscentscompany.com/opl/78-35-3.html	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/29171-20-8.html	http://www.thegoodscentscompany.com/opl/142-62-1.html
Read-across endpoint		• Skin sensitization • Phototoxicity • Environmental	• Repeated Dose	• Devel/Repro	• Devel/Repro	• Devel/Repro
Molecular Formula	C16H28O2	C12H20O2	C14H24O2	C10H18O	C10H16O	C6H12O2
Molecular Weight	252.4	196.29	224.35	154.25	152.24	116.16
Melting Point (°C, EPISUITE)	30.43	–2.09	8.99	–11.39	15.40	26.23
Boiling Point (°C, EPISUITE)	295.92	228.95	253.99	204.05	212.37	207.76
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.2893	17.47	10.97	11.09	4.64	37.06
Log K_{ow} (KOWWIN v1.68 in EPISUITE)	6.35	4.39	5.30	3.38	2.75	2.05
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	0.08645	20.12	0.9804	683.7	1084	5898
J_{max} (mg/cm²/h, SAM)	0.884152597	11.1668059	6.194908373	90.06108298	93.21980338	805.7900499
Henry's Law (Pa·m³/mol, Bond Method, EPISUITE)	546.7497	176.001525	310.25715	4.285034	0.449174	0.172354
Similarity (Tanimoto score)[a]		77%	71%	NA[b]	NA[b]	NA[b]
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	Non binder, non cyclic structure
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (good reliability)			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 (OECD)	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)				
Protein binding alerts for skin sensitization (OASIS v1.1)	• No alert found	• No alert found				
Skin sensitization model (CAESAR v2.1.6)	Sensitizer (good reliability)	Sensitizer (good reliability)				
Metabolism						
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data 2	See supplemental data 3	See supplemental data 4	See supplemental data 5	See supplemental data 6

[a] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).
[b] Metabolite of the target or analog of metabolite.

Summary

There are insufficient toxicity data on Linalyl hexanoate (CAS # 7779-23-9). 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 Jmax 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 and 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

- Linalyl acetate (analog) was used as a read-across for linalyl hexanoate (target) based on the following:
  - The target and analog belong to the generic class of aliphatic esters, specifically, esters/branched chain alcohol simple acid esters/tertiary alcohols.
  - They have the same alcohol part and similar carboxylic acid part.
  - The key difference is that the target is a hexanoate, while the analog is acetate. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for protein binding.
  - The target and read-across material are expected to be metabolized similarly. As per the OECD QSAR Toolbox they are predicted to have similar metabolites.
- Linalyl isobutyrate (analog) was used as a read-across analog for Linalyl hexanoate (target) based on the following:
  - The target and analog belong to the generic class of aliphatic esters, specifically, esters/branched chain alcohol simple acid esters/tertiary alcohols.
  - They have the same alcohol part and similar carboxylic acid part.
  - The key difference is that the target is a hexanoate, while the analog is an isobutyrate. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox they are predicted to have similar metabolites.
- Linalool, dehydrolinalool and hexanoic acid (read-across materials) were used as read-across for linalyl hexanoate (target) based on the following:
  - The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - Linalyl hexanoate is an ester formed by linalool and hexanoic acid. Dehydrolinalool is an analog of linalool.
  - The differences among the target and read-across materials can be mitigated by the fact that the target could readily hydrolyze to the metabolites. Therefore the toxicity profiles are expected to be that of the metabolites.
  - They all also show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a 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 QSAR Toolbox both the read-across materials are predicted as metabolites (see Metabolite # 2 & 3) of the target.

Appendix 2: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.01.009.

References

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.

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, J.H., et al., 2003. A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. Food Chem. Toxicol. 41 (7), 919–942.

Brown, N.A., Coakley, M.E., 1984. Valproic acid teratogenesis. II. Actions of related acids and potential antagonists and the role of coenzyme A. Teratology 29 (2), A20.

Buchbauer, G., Jirovetz, L., Jager, W., Dietrich, H., Plank, C., Singh, S.P., et al., 1991. Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. Z. Naturforsch. [C] 30, 395–396.

Buchbauer, G., Jirovetz, L., Jáger, 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. In ACS Symposium series-American Chemical Society (USA).

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.
Dawson, D.A., 1991. Additive incidence of developmental malformation for Xenopus embryos exposed to a mixture of ten aliphatic carboxylic acids. Teratology 44 (5), 531–546.
Dawson, D.A., Schultz, T.W., Hunter, R.S., 1996. Developmental toxicity of carboxylic acids to Xenopus embryos: a quantitative structure-activity relationship and computer-automated structure evaluation. Teratog. Carcinog. Mutagen. 16 (2), 109–124.
Deuel, H.J., Alfin-Slater, R., Weil, C.S., Smyth, H.F., Jr., 1954. Sorbic acid as a fungistatic agent for foods. I. Harmlessness of sorbic acid as a dietary component. Food Res. 19 (1–6), 1–12.
Di Sotto, A., Evandri, M.G., Mazzanti, G., 2008. Antimutagenic and mutagenic activities of some terpenes in the bacterial reverse mutation assay. Mutat. Res. 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. Oil Res. 20 (6), 482–487. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.
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), 257–272.
Henning, S.J., Hird, F.J.R., 1970. Concentrations and metabolism of volatile fatty acids in the fermentative organs of two species of kangaroo and the guinea-pig. Br. J. Nutr. 24 (01), 145–155.
Hood, R.L., Bailey, W.M., 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.
Isola, D., Smith, L.W., Ansari, R., Black, M.S., 2003a. Exposure characterization from a fragranced plug-in air freshener. Toxicologist Abstract 1416.
Isola, D., Smith, L.W., Rogers, R.E., Black, M.S., 2003b. Exposure characterization of fragranced air fresheners. Allergy Clin. Immunol. Int. Abstract P-10–12.
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.
Isola, D.A., 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 the American College of Toxicology – November 7–10, 2004.
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., Jäger, 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., Jäger, W., Buchbauer, G., Nikiforov, A., Raverdinno, 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.
Katz, G.V., Guest, D., 1994. Aliphatic carboxylic acids. Pattys Ind. Hyg. Toxicol. 4, 3523–3671.
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. Int. J. Toxicol. Abstract P-32.
Lalko, J., Brain, K.R., Green, D.M., Api, A.M., 2008. In vitro human skin penetration of the fragrance material linalool. Toxicologist Abstract 1555.
Lapczynski, A., Letizia, C.S., Api, A.M., 2008a. Addendum to fragrance material review on linalool. Food Chem. Toxicol. 46 (11), S190–S192.
Lapczynski, A., Letizia, C.S., Api, A.M., 2008b. Fragrance material review on d-linalool. Food Chem. Toxicol. 46 (11), S193–S194.
Lapczynski, A., Bhatia, S.P., Letizia, C.S., Api, A.M., 2008c. Fragrance material review on l-linalool. Food Chem. Toxicol. 46 (11), 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 hexanoate. Food Chem. Toxicol. 41 (7), 1001–1004.
Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003b. Fragrance material review on linalyl butyrate. Food Chem. Toxicol. 41 (7), 983–987.
Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003c. Fragrance material review on linalyl propionate. Food Chem. Toxicol. 41 (7), 1023–1027.
Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003d. Fragrance material review on linalyl acetate. Food Chem. Toxicol. 41 (7), 965–976.
Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003e. Fragrance material review on linalyl isovalerate. Food Chem. Toxicol. 41 (7), 1011–1015.
Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003f. Fragrance material review on linalyl isobutyrate. Food Chem. Toxicol. 41 (7), 1005–1010.
Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003g. Fragrance material review on linalool. Food Chem. Toxicol. 41 (7), 943–964.
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.
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, M49750IVa.
Meyer, F.R., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneimittelforschung 9, 516–519.
Moody, D.E., Reddy, J.K., 1982. Serum triglyceride and cholesterol contents in male rats receiving diets containing plasticizers and analogues of the ester 2-ethylhexanol. Toxicol. Lett. 10 (4), 379–383.
Mori, K., 1953. Production of gastric lesions in the rat by the diet containing fatty acids. Gan 44 (4), 421.
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., Hamono, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1979. Mutagenicity of food flavors in bacteria (1st report). Osaka-Furitsu Koshu Eisei Kenkyu Hokoku, 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 and excretion of linalool in the rat. Biochem. Soc. Trans. 2 (4), 612–615.
Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.M., Komulainen, H., 1993. Effects of 2-ethylhexanoic acid on reproduction and postnatal development in Wistar rats. Toxicol. Sci. 21 (2), 204–212.
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 Psoroptes cuniculi. Phytother. 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. 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., 1994a. Insecticidal properties of monoterpenoid derivatives to the house fly (Diptera: Muscidae) and red flour beetle (Coleoptera: Tenebrionidae). Pestic. 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. 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., August 11. Report number 29150 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Report on human maximization studies. RIFM Report number 1801, February 20 (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.), 1979. 29 Day percutaneous toxicity range finding with linalool in rats. RIFM Report number 32943, May 22 (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, April 4 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Report on human maximization studies. RIFM Report number 1643, January 20 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1983a. Determination of phototoxicity of linalyl acetate in guinea pigs. Unpublished report from Givaudan, May 24. Report number 55946 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1983b. 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. Private communication to FEMA. Unpublished report from Lorillard Tobacco Company, February 2. Report number 36497 (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, March 10. 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 and Gamble Company, June 3. 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 from FEMA, 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 from FEMA, July 17. Report number 34253 (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 Hoffman-LaRoche, June 22. Report number 38576 (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, November 11. 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 3 (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 20 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2004a. Salmonella typhimurium reverse mutation assay with linalyl propionate. Unpublished report from Givaudan, January 27. Report number 44310 (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.), 2005. 7-day chronic toxicity test results with LC50 and NOEC endpoints for 25 fragrance chemicals using ceriodaphnia dubia and fathead minnows. Unpublished report from SC Johnson, October 14. Report number 49950 (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, March 10 (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, March 10 (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, March 10 (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, September 6 (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, September 6 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2008c. In vitro human skin penetration of fragrance material linalool under both in-use and occluded conditions from a petrolatum vehicle. RIFM Report number 54664, September 6 (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 Sprague Dawley rat. RIFM Report number 63821, September 5 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Report on the testing of linalyl hexanoate in the BlueScreen HC Assay (-/+ S9 metabolic activation). RIFM Report number 67346, January (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. Report on the testing of linalyl hexanoate in the mammalian erythrocyte micronucleus test (-/+ S9 metabolic activation). RIFM Report number 67836 (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, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
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.
Sani, B.P., Allen, R.D., Moorer, C.M., McGee, B.W., 1987. Interference of retinoic acid binding to its binding protein by omega-6 fatty acids. Biochem. Biophys. Res. Commun. 147 (1), 25–30.
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, 435–437.
Scheuplein, R.J., 1966. Molecular Structure and Diffusional Processes Across Intact Epidermis. Harvard Medical School, Boston, MA.
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. Contact Allergy to Autoxidized Fragrance Terpenes.
Sköld, 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.
Smyth, H.F., Jr., Carpenter, C.P., Well, C.S., Pozzani, U.C., Striegel, J.A., 1962. Range-finding toxicity data: list VI. Am. Ind. Hyg. Assoc. J. 23 (2), 95–107.
Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K., Gori, 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.
Troy, W.R., 1977. Doctoral Dissertation: the comparative respiratory irritation potential of fourteen fragrance raw materials. Graduate Division, College of Pharmacy at St. Johns University.
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.
Vollmuth, T.A., Bennett, M.B., Hoberman, A.M., Christian, M.S., 1990. An evaluation of food flavoring ingredients using an in vivo reproductive and developmental toxicity screening test. Teratology 41, 597.
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.