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Short review

RIFM fragrance ingredient safety assessment, linalyl phenylacetate, CAS Registry Number 7143-69-3

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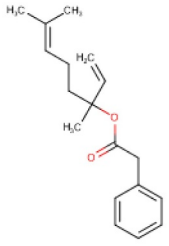
Version: 050118. This version replaces any previous versions.
Name: Linalyl phenylacetate
CAS Registry Number: 7143-69-3



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold

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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
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Linalyl phenylacetate was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on read-across analog linalyl cinnamate (CAS # 78-37-5) show that linalyl phenylacetate is not expected to be genotoxic. Data show that linalyl phenylacetate does not have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The developmental toxicity endpoint was completed using read-across analogs linalool (CAS # 78-70-6), dehydrolinalool (CAS # 29171-20-8), and phenylacetic acid (CAS # 103-82-2), which provided an MOE > 100. The repeated dose toxicity endpoint was completed using read-across linalyl cinnamate (CAS # 78-37-5), which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated for linalyl phenylacetate; data from read-across analog linalyl cinnamate (CAS # 78-37-5) were also considered. Linalyl phenylacetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current Volume of Use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2000a; RIFM, 2014a)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day. (Hagan et al., 1967)
Developmental and Reproductive Toxicity: Developmental NOAEL = 500 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC. (Vollmuth et al., 1990)
Skin Sensitization: Not sensitizing. (Klecak, 1985; RIFM, 1974; RIFM, 2000b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 89% (OECD 301F) RIFM (2004d)
Bioaccumulation: Screening-level: 4877 L/kg (EPI Suite; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.039 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.039 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC: 0.0039 µg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name:** Linalyl phenylacetate
2. **CAS Registry Number:** 7143-69-3
3. **Synonyms:** Benzeneacetic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester; 3,7-Dimethyl-1,6-octadien-3-yl phenylacetate; Linalyl α-toluate; 1,5-Dimethyl-1-vinylhex-4-en-1-yl phenylacetate; Linalyl phenylacetate
4. **Molecular Formula:** $C_{18}H_{24}O_2$
5. **Molecular Weight:** 272.39
6. **RIFM Number:** 550

2. Physical data

1. **Boiling Point:** 339.71 °C (EPI Suite)
2. **Flash Point:** > 200°F; CC (FMA)
3. **Log K_{OW}:** 6.09 (EPI Suite)
4. **Melting Point**: 77.26 °C (EPI Suite)
5. **Water Solubility:** 0.1105 mg/L (EPI Suite)
6. **Specific Gravity:** 0.9735 (EOA, 1974 Sample 74–101)
7. **Vapor Pressure:** < 0.001 mm Hg 20 °C (FMA), 0.0000373 mm Hg @ 20 °C (EPI Suite), 7.37e-005 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$).
9. **Appearance/Organoleptic:** A colorless or pale straw-colored viscous liquid with a mildly floral, intensely sweet Neroli-Rose type odor of greater tenacity and with variable amounts of honey-like undertones (Arctander, 1969)

3. Exposure

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00026% (RIFM, 2014b)
3. **Inhalation Exposure*:** 0.0000041 mg/kg/day or 0.00027 mg/day (RIFM, 2014b)
4. **Total Systemic Exposure** **: 0.000029 mg/kg/day (RIFM, 2014b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

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

4. Derivation of systemic absorption

1. **Dermal:** 80% (predicted)

RIFM's *in silico* skin absorption model (Shen et al., 2014), which was approved by the Expert Panel for Fragrance Safety (Meeting, Miami, FL, Jan 13–14, 2014), provided the following prediction results:

	Parent	Metabolite	Metabolite
Name	Linalyl phenylacetate	Linalool	Phenylacetic acid
J_{max} (mg/cm^2/h)	0.57[1]		201.12[3]
Skin Absorption Class	40%	14.4%[2]	80%

[1] J_{max} was calculated based on estimated log K_{ow} = 5.16 (consensus model) and Solubility = 6.17 mg/L (consensus model).
[2] Human *in vitro* skin penetration study (RIFM, 2007c).
[3] J_{max} was calculated based on measured log K_{ow} = 1.41 (PhysProp Db) and Solubility = 1.66*10^4 mg/L (PhysProp Db).

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

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:** Linalyl cinnamate (CAS # 78-37-5)
   b. **Repeated Dose Toxicity:** Linalyl cinnamate (CAS # 78-37-5)
   c. **Developmental and Reproductive Toxicity:** Linalool (CAS # 78-70-6); dehydrolinalool (CAS # 29171-20-8); phenylacetic acid (CAS # 103-82-2)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Linalool (CAS # 78-70-6); benzoic acid (CAS # 65-85-0)
   g. **Environmental Toxicity:** Linalyl cinnamate (CAS # 78-37-5)
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Linalyl phenylacetate is not reported to occur in foods by the VCF*.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 05/01/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, linalyl phenylacetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of linalyl phenylacetate was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the standard plate incorporation and modified preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were exposed to linalyl phenylacetate in ethanol at the concentrations of 33, 100, 333, 1000, 2500, and 5000 μg/plate with and without metabolic activation (S9 mix). No significant increase in revertant colony numbers of any of the 5 tester strains were observed following treatment with linalyl phenylacetate at any concentration level in the presence or absence of metabolic activation (RIFM, 2000a). Under the conditions of the study, linalyl phenylacetate was considered not mutagenic in the Ames assay.

There are no studies assessing the clastogenic activity of the target material. The clastogenicity of read-across material linalyl cinnamate (CAS # 78-37-5; see Section V) was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with linalyl cinnamate at concentrations ranging from 28.9 to 172 μg/mL in the approximate 24-h treatment, 28.9–138 μg/mL in the 3-h treatment without S9, and 36.2–400 μg/mL in the 3-h treatment with S9. No statistically significant increases in the frequency of binucleated cells with micronuclei (BNMN) were observed at any analyzed concentration in any treatment condition with or without S9 (RIFM, 2014a). Under the conditions of the study, linalyl cinnamate was considered not clastogenic in the *in vitro* micronucleus test, and this can be applied to linalyl phenylacetate.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/24/14.

10.1.2. Repeated dose toxicity

The margin of exposure for linalyl phenylacetate 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 phenylacetate. Read-across material linalyl cinnamate (CAS # 78-37-5; see Section V) has a dietary 17-week chronic toxicity study conducted in rats which determined the NOAEL to be 10000 ppm, or 500 mg/kg/day, the highest dosage tested (Hagan et al., 1967).

Therefore, the MOE is equal to the linalyl cinnamate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.000029 or 17,241,379.

In addition, the total systemic exposure for linalyl phenylacetate (0.029 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

10.1.2.2. Additional references. RIFM, 2003d; Bickers et al., 2003; RIFM, 2003c; RIFM, 2007a; Belsito et al., 2007; RIFM, 2003b; RIFM, 2007c; RIFM, 2007d; RIFM, 2007e; RIFM, 2008f; RIFM, 2008g; RIFM, 2008h; RIFM, 2007b; RIFM, 2008e; RIFM, 2003a; RIFM, 2008b; RIFM, 2008c; RIFM, 2008d; RIFM, 2008a; RIFM, 2010; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner et al., 1973; RIFM, 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990; Jirovetz et al., 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982; Chadha and Madyastha, 1984; RIFM, 1998; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959; Cal, 2006; Cal and Kryzaniak, 2006; Cal and Sznitowska, 2003; Meyer (1965); Boggs et al., 1963; Zaitsev and Rakhmanina, 1974; Sherwin and Kennard, 1919; Maganova and Saitsev, 1973; Zaitsev and Maganova, 1975; Davies et al., 1956; Dawson et al., 1996.

Literature Search and Risk Assessment Completed On: 04/02/14.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for linalyl phenylacetate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient toxicity reproductive data on linalyl phenylacetate or any read-across materials. The exposure is below the TTC.

10.1.3.1. Risk assessment. There are no developmental toxicity data on linalyl phenylacetate or any read-across materials. Linalyl phenylacetate is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6; see Section V) and phenylacetic acid (CAS # 103-82-2; see Section V). 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 phenylacetic acid determined the developmental NOAEL to be 500 mg/kg/day, based on reduced viability and pup bodyweight gain (Vollmuth et al., 1990). These effects occurred at maternally toxic dosages. The most conservative NOAEL was selected for this safety assessment.

Therefore, the MOE for developmental toxicity is equal to the phenylacetic acid NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.000029 or 17,241,379.

In addition, the total systemic exposure to linalyl phenylacetate (0.029 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental toxicity endpoint.

There are no reproductive toxicity data on linalyl phenylacetate or any read-across materials. Linalyl phenylacetate is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6) and phenylacetic acid (CAS # 103-82-2). There are no reproductive data on linalool. However, read-across material dehydrolinalool (CAS # 29171-20-8; see Section V) has a 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, decreased live birth index, and viability (ECHA REACH Dossier: Linalool [accessed 02/21/13]). The gavage developmental toxicity study in rats with linalool concluded a NOAEL of 500 mg/kg/day for maternal toxicity, based on reduced maternal bodyweight gain and feed consumption (Politano et al., 2008). The dermal 90-day subchronic toxicity study with linalool in rats (RIFM, 1980), in addition to the systemic endpoints, included organ weights (testes and ovaries) and histopathology (testes, epididymis, ovaries, pituitary, and thyroid), and no effects were observed. Together, these data indicate there is no concern for reproductive toxicity for the linalool metabolite. There are no reproductive toxicity data on phenylacetic acid; therefore, a NOAEL for linalyl phenylacetate could not be determined. When correcting for skin absorption (see Section IV), the current total systemic exposure (0.029 μg/kg/day) is below the TTC for linalyl phenylacetate (30 μg/kg bw/day).

10.1.3.2. Additional references. RIFM, 2003d; Bickers et al., 2003; RIFM, 2003c; RIFM, 2007a; Belsito et al., 2007; RIFM, 2003b; RIFM, 2007c; RIFM, 2007d; RIFM, 2007e; RIFM, 2008f; RIFM, 2008g; RIFM, 2008h; RIFM, 2007b; RIFM, 2008e; RIFM, 2003a; RIFM, 2008b; RIFM, 2008c; RIFM, 2008d; RIFM, 2008a; RIFM, 2010; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner et al., 1973; RIFM, 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990; Jirovetz et al., 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and

Madyastha, 1982; Chadha and Madyastha, 1984; RIFM, 1998; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959; Cal, 2006; Cal and Kryzaniak, 2006; Cal and Sznitowska, 2003; Meyer (1965); Boggs et al., 1963; Zaitsev and Rakhmanina, 1974; Sherwin and Kennard, 1919; Maganova and Saitsev, 1973; Zaitsev and Maganova, 1975; Davies et al., 1956; Dawson et al., 1996.

Literature Search and Risk Assessment Completed On: 04/02/14.

10.1.4. Skin sensitization

Based on the existing data, linalyl phenylacetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data, linalyl phenylacetate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; OECD toolbox v3.1). In guinea pig test methods, no results indicative of sensitization were observed (Klecak, 1985; RIFM, 2000b). Additionally, no reactions indicative of skin sensitization were observed in a human maximization test (RIFM, 1974).

Note: Linalyl phenylacetate could hydrolyze in skin to linalool and phenyl acetic acid. Autooxidation products of linalool are known to be contact allergens.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/14.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, linalyl phenylacetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for linalyl phenylacetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, linalyl phenylacetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/19/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level of linalyl phenylacetate is below the inhalation TTC Cramer Class I limit for local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on linalyl phenylacetate. Based on the Creme RIFM model, the inhalation exposure is 0.0000041 mg/kg bw/day. This exposure is 5609 times lower than the TTC for a Cramer Class I material (0.023 mg/kg bw/day) and is deemed safe for use at the reported use level.

As further weight of evidence, we took into consideration that linalyl phenylacetate metabolizes to phenylacetic acid (CAS # 103-82-2; see Section V) and linalool (CAS # 78-70-6; see Section V) in the respiratory tract.

There are no inhalation data on the metabolite phenylacetic acid. Data are available on read-across analog, benzoic acid (CAS # 65-85-0; see Section V). A NOAEC of 12.6 mg/m^3 is reported for the benzoic acid (RIFM, 2009). The NOAEC of benzoic acid expressed in mg/kg lung weight/day is:

- (12.6 mg/m^3) (1m^3/1000 L) = 0.0126 mg/L
- Minute ventilation 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
- (0.0126 mg/L) (61.2 L/d) = 0.77 mg/d
- (0.77 mg/d)/(0.0016 kg lung weight of rat*) = 481.3 mg/kg lw/day

For conservative purposes, the NOAEC of benzoic acid was used to calculate the MOE. Based on this NOAEC, the linalyl phenylacetate MOE is comparable to the benzoic acid NOAEC in mg/kg lw/day divided by the calculated combined inhalation exposure, 481.3/0.0000041 or 117,390,243.

A NOAEC of 10 ppm or 63 mg/m^3 was reported for linalool in a 2-week acute inhalation study. The test substance-related effects were limited to non-adverse microscopic findings in the nasal cavity (RIFM, 2012). Furthermore, there were no alterations in Bronchoalveolar Lavage Cytology (BALF) chemistry parameters, cytology, or cytokine levels that were associated with test substance exposure. Since the NOAEC of linalool is greater than that of benzoic acid, it results in an even higher MOE.

Based on the TTC and the MOE for linalool and benzoic acid, linalyl phenylacetate 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; UGCM, 1997; Buchbauer et al., 1993; Perrucci et al., 1996; Perrucci, 1995; Perrucci et al., 1995; Rice and Coats, 1994a; Rice and Coats, 1994b; Silver (1992); Karr and Coats, 1992; Regnault-Roger and Hamraoui, 1995; Rice and Coats, 1994a; Rice and Coats, 1994b; Perrucci, 1995; Perrucci et al., 1995; Sugawara et al., 1998; Coats et al., 1991; Cometto-Muniz et al., 1998; Isola et al., 2003a; RIFM, 2003e; Rogers et al., 2003; RIFM, 2003f; Isola et al., 2003b; RIFM, 2004a; Larsen et al., 1997; RIFM, 2004b; RIFM, 2004c; Isola et al., 2004; 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; ECHA REACH Dossier: Phenylacetic Acid; Engstrom (1984).

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of linalyl phenylacetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, linalyl phenylacetate was identified as a fragrance material with

potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

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

10.2.2. Risk assessment

Based on the current Volume of Use (2011), linalyl phenylacetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies. ***Biodegradation:*** No data available.

Ecotoxicity: No data available.

Other available data:

Linalyl phenylacetate has been pre-registered for REACH with no additional data at this time.

There is one biodegradation study in the RIFM DB for the read-across material linalyl cinnamate (CAS # 78-37-5):

The ready biodegradability of linalyl cinnamate was evaluated in a manometric respirometry test according to OECD 301F guidelines. 100 mg/L of the test material was incubated for 28 days. Biodegradation of 89% was observed (RIFM, 2004d).

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC(µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.101			1,000,000	0.00010	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.148	0.198	0.044L			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.409	0.740	0.140			Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.047	0.039	0.139	10,000	0.0039	Neutral organics SAR (baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	6.09	6.09
Biodegradation Factor Used	1	1
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 0.0039 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: 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
- 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://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.11.028.

Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material				
Principal Name	Linalyl phenylacetate	Linalyl cinnamate	Linalool	Dehydrolinalool	Phenylacetic acid	Benzoic acid
CAS No.	7143-69-3	78-37-5	78-70-6	29171-20-8	103-82-2	65-85-0
Structure						
3D Structure	http://www.thegoodscentscompany.com/opl/7143-69-3.html	http://www.thegoodscentscompany.com/opl/78-37-5.html	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/29171-20-8.html	http://www.thegoodscentscompany.com/opl/103-82-2.html	http://www.thegoodscentscompany.com/opl/65-85-0.html
Read-across endpoint	• Genotoxicity • Environmental • Local respiratory	• Repeated Dose • Developmental and reproductive • Developmental and reproductive	• Local respiratory			
Molecular Formula	$C_{18}H_{24}O_2$	$C_{19}H_{24}O_2$	$C_{10}H_{18}O$	$C_{10}H_{16}O$	$C_8H_8O_2$	$C_7H_6O_2$
Molecular Weight	272.39	284.4	154.25	152.24	136.15	122.12
Melting Point (°C, EPI Suite)	77.26	84.83	−11.39	15.40	59.25	48.85
Boiling Point (°C, EPI Suite)	339.71	355.04	204.05	212.37	266.58	249.51
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.009826	0.003573	11.09	4.64	0.5173	0.3973
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	6.09	6.37	3.38	2.75	1.43	1.87
Water Solubility (mg/L, @ 25 °C,	0.1105	0.05483	683.7	1084	1.348e+004	2493

WSKOW v1.42 in EPI Suite)						
J_{max} (mg/cm^2/h, SAM)	0.566988506	0.2031987	90.06108298	93.21980338	539.6200519	585.5878938
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	14.205765	4.156351	4.285034	0.449174	0.004481	0.010984
Similarity (Tanimoto score)[1]		71%	NA[2]	NA[3]	NA[2]	NA[3]
Genotoxicity						
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	No Alert found	No Alert found				
DNA Binding (OECD QSAR Toolbox v3.4)	Michael addition	No Alert found				
Carcinogenicity (ISS)	NON-Carcinogen (low reliability)	NON-Carcinogen (low reliability)				
DNA Binding (Ames, MN, CA, OASIS v1.1)	No Alert found	No Alert found				
In Vitro Mutagenicity (Ames, ISS)	No Alert found	No Alert found				
In Vivo Mutagenicity (Micronucleus, ISS)	No Alert found	No Alert found				
Oncologic Classification	No Alert found	Acrylate reactive				
Repeated Dose Toxicity						
Repeated dose (HESS)	Not categorized	Not categorized				
Developmental and Reproductive Toxicity						
ER binding (OECD)	Non-binder, without OH or NH_2 group		Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	Non-binder, without OH or NH_2 group	
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (low reliability)		NON-Toxicant (low reliability)	NON-Toxicant (low reliability)	Toxicant (good reliability)	
Local Respiratory Toxicity						
Respiratory Sensitization (OECD QSAR Toolbox v3.4)	No Alert found					No Alert found
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[4]

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).
[2] Metabolites of the target.
[3] Analog of the Metabolites of the target.
[4] Bridges et al., 1970.

Summary

There are insufficient toxicity data on linalyl phenylacetate (CAS # 7143-69-3). Hence, *in silico* evaluation was conducted to determine read-across materials. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, the read-across materials shown in the table above were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Phenylacetic acid (CAS # 103-82-2), linalyl cinnamate (CAS # 78-37-5), and dehydrolinalool (CAS # 29171-20-8) were used as read-across analogs for the target material linalyl phenylacetate (CAS # 7143-69-3) based on the following:
  - The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - Linalyl phenylacetate is an ester formed by linalool and phenylacetic acid. Linalyl cinnamate is an ester formed by linalool and cinnamic 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 reproductive and developmental toxicity profiles are expected to be similar to those of the metabolites.
  - Linalyl cinnamate is potentially more toxic than the target due to the presence of an alpha, beta unsaturated ester in the cinnamate. The use of the potentially more toxic analog for repeated dose, genotoxicity, and environmental toxicity is a conservative choice, and thus, is justified in this context.
  - Materials 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.

- Linalyl phenylacetate is given an alert of Michael addition for DNA binding by OECD QSAR Toolbox v3.4. This alert is due to the fact that phenyl acetic acid is a constituent of the ester. Aromatic rings will have propensity of undergoing oxidation forming epoxide, 1,2 dioxone, and then 1,2 dioxol. These species can undergo nucleophilic addition and are very good Michael acceptors. The target is a cinnamate ester and will have a different mechanism of reactivity due to conjugation of acid (alpha-beta unsaturation) with the aromatic moiety. The acid group in cinnamic acid will be more reactive compared to an aromatic ring. Therefore, the target probably is not given the same alert. The read-across analog with this structural feature is expected to be more reactive compared to the target. Other genotoxicity related alerts are negative for both the target and the read-across analog. Therefore, based on structural similarity and the data for the read-across analog, the alert for the target will be superseded by the read-across data.
- As per the OECD QSAR Toolbox, linalool and phenylacetic acid are predicted as metabolites (see metabolites in the table above) of the target.

- Linalool (CAS # 78-70-6) and benzoic acid (CAS # 65-85-0) were used as read-across analogs for the target material linalyl phenylacetate (CAS # 7143-69-3) based on the following:
  - The read-across materials are the major metabolite or analog of the metabolite of the target material.
  - The target is an ester formed by linalool and phenylacetic acid. Benzoic acid is an analog of phenylacetic acid. The only difference between them is in the length of the branch, which is not expected to alter the toxicity profiles.
  - The difference between the target and read-across materials could also be mitigated by the fact that the target could be readily hydrolyzed into the read-across materials. Therefore, the inhalation toxicity profiles are expected to be that of the metabolites.
  - As per the OECD QSAR Toolbox, they are predicted as metabolites (see metabolites in the table above) of the target material.

References

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

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II Published by the author: Montclair, NJ (USA).

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.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hannifin, J.M., Rogers, A.E., Saurat, J.H., Sipes, I.G., Tagami, H., 2007. A toxicologic and dermatologic assessment of related esters and alcohols of cinnamic acid and cinnamyl alcohol when used as fragrance ingredients. [Erratum Attached]. Food Chem. Toxicol. 45 (Suppl. 1), S1–S23.

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.

Boggs, D.E., Rosenberg, R., Waisman, H.A., 1963. Effects of phenylalanine, phenylacetic acid, tyrosine and valine on brain and liver serotonin in rats. PSEBM (Proc. Soc. Exp. Biol. Med.) 114 (2), 356–358.

Bridges, J.W., French, M.R., Smith, R.L., Williams, R.T., 1970. The fate of benzoic acid in various species. Biochem. J. 118, 47–51.

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. Zeitschrift Fur Nauturforschung. Zeitschrift fur Naturforschung, C: Bioscience 46 (11–12), 1067–1072.

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

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 [Letter to the Editor]. J. Dermatol. Sci. 42, 265–267.

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

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

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: American Cancer Society Symposium Series. 449, pp. 305–316.

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

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

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

Davies, G.E., Driver, G.W., Hoggarth, E., Martin, A.R., Paige, M.F.C., Rose, F.L., Wilson, B.R., 1956. Studies in the chemotherapy of tuberculosis: ethyl mercaptan and related compounds. Br. J. Pharmacol. 11, 351–356.

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.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Engstrom, K.M., 1984. Metabolism of inhaled ethylbenzene in rats. Scand. J. Work. Environ. Health 10 (2), 83–87.

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

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Chem. Toxicol. 5 (2), 141–157.

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. Poultry 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), 2011. Volume of Use Survey, 2011.

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

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

Isola, D.A., Rogers, R., Black, M.S., Smith, L.W., 2004. Exposure characterizations of three fragranced products. Int. J. 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. Fresen. J. Anal. Chem. 338 (8), 922–923.

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

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

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

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

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.

Maganova, N.B., Saitsev, A.N., 1973. Study of the embryotoxic action of some synthetic food flavorings. Vopr. Pitan. 32 (4), 50–54.
Meesters, R.J.W., Duisken, M., Hollender, J., 2007. Study on the cytochrome P450-mediated oxidative metabolism of the terpene alcohol linalool: indication of biological epoxidation. Xenobiotica 37 (6), 604–617.
Meyer, F. (1965). Penetrating Agents. Patent. British, 1,001,949, M49750IVa/30h, 7/20/61.
Meyer, F., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneim. Forsch. (Drug Res.) 9, 516–519.
Nakamura, A., Fujiwara, S., Matsumoto, I., Abe, K., 2009. Stress repression in restrained rats by (R)-(-)-linalool inhalation and gene expression profiling of their whole blood cells. J. Agric. Food Chem. 57, 5480–5485.
Nakamura, A., Fujiwari, S., Ishijima, T., Okada, S., Nakai, Y., Matsumoto, I., Misaka, T., Abe, K., 2010. Neuron differentiation-related genes are upregulated in the hypothalamus of odorant-inhaling rats subjected to acute restraint stress. J. Agric. Food Chem. 58 (13), 7922–7929.
OECD, 2012. The OECD QSAR Toolbox, V 3.4. Retrieved from. http://www.qsartoolbox.org/.
OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.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 Protect. 58 (5), 560–563.
Perrucci, S., Macchioni, G., Cioni, P.L., Flamini, G., Morelli, I., 1995. Structure/activity relationship of some natural monoterpenes as acaricides against Psoroptes cuniculi. J. Nat. Prod. 58 (8), 1261–1264.
Perrucci, S., Macchioni, G., Cioni, P.C., Flamini, G., Morelli, I., Taccini, F., 1996. The activity of volatile compounds from Lavandula angustifolia against Psoraptes cuniculi. Phytother Res. 10 (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.
Regnault-Roger, C., Hamraoui, A., 1995. Fumigant toxic activity and reproductive inhibition induced by monoterpenes on Acanthoscelides obtectus (Say) (Coleoptera), a bruchid of kidney bean (Phaseolus vulgaris L.). J. Stored Prod. Res. 31 (4), 291–299.
Rice, P.J., Coats, J.R., 1994a. Insecticidal properties of several monoterpenoids to the house fly (Diptera: Muscidae), red flour beetle (Coleoptera: Tenebrionidae) and southern corn rootworm (Coleoptera: Chrysomelidae). J. Econ. Entomol. 87 (5), 1172–1179.
Rice, P.J., Coats, J.R., 1994b. Insecticidal properties of monoterpenoid derivatives to the house fly (Diptera; Muscidae) and red flour beetle (Coleoptera: Tenebrionidae). Pestic. Sci. 41 (3), 195–202.
RIFM (Research Institute for Fragrance Materials, Inc), 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), 1974. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1779. 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. Report to RIFM. RIFM report number 4001. 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), 2000a. Salmonella typhimurium Reverse Mutation Assay of Linalyl Phenylacetate. Unpublished report from Givaudan. RIFM report number 42007. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2000b. Linalyl Phenylacetate: Contact Hypersensitivity in Albino guinea Pigs, Maximization-test. Unpublished report from Givaudan. RIFM report number 42047. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2003a. Fragrance Material Review on Linalool. RIFM report number 42696. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2003b. Fragrance Material Review on Linalyl Benzoate. RIFM report number 42698. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2003c. Fragrance Material Review on Linalyl Cinnamate. RIFM report number 42700. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2003d. Fragrance Material Review on Linalyl Phenylacetate. RIFM report number 42705. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2003e. 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), 2003f. 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), 2004a. Exposure Characterization from a Surrogate Fine Fragrance. RIFM report number 44448. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2004b. Exposure Characterizations of Three Fragranced Products. RIFM report number 45348. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2004c. 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), 2004d. Ready Biodegradability of Linalyl Cinnamate. Unpublished report from Givaudan. RIFM report number 57181. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2007a. Addendum to Fragrance Material Review on Linalyl Cinnamate. RIFM report number 54020. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2007b. In Vitro Human Skin Penetration of the Fragrance Material Linalool. RIFM report number 55159. 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 an Ethanol/water Vehicle. RIFM report number 54455. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2007d. 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), 2007e. 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. A Toxicologic and Dermatologic Assessment of Cyclic and Non-cyclic Terpene Alcohols when Used as Fragrance Ingredients. RIFM report number 56372. RIFM, Woodcliff Lake, NJ, USA.
RIFM, 2008b. Addendum to Fragrance Material Review on Linalool. RIFM report number 56410. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008c. Fragrance Material Review on D-linalool. RIFM report number 56422. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008d. Fragrance Material Review on L-linalool. RIFM report number 56428. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008e. In Vitro Human Skin Penetration of the Fragrance Material Linalool. RIFM report number 54430. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008f. 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), 2008g. 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), 2008h. In 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), 2009. A 4-week Inhalation Toxicity Study of Aerosolized Benzyl Alcohol and Benzoic Acid in Sprague-Dawley Rats. RIFM report number 58285. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. A Safety Assessment of Non-cyclic Alcohols with Unsaturated Branched Chain when Used as Fragrance Ingredients. The RIFM expert panel. RIFM report number 58982. 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. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Evaluation of Nose-only Inhalation Exposure to Aerosolized Linalool in Sprague-Dawley Rats. RIFM report number 64502. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2014a. Linalyl Cinnamate: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 68152. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2014b. Exposure Survey 04, July 2014.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Rogers, R.E., Isola, D.A., 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. Environmental Science and Technology. Environ. Sci. Technol. 39 (20), 7810–7816.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care

and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Sato, K., Krist, S., Buchbauer, G., 2007. Antimicrobial effect of vapours of geraniol, (R)-(-)-linalool, terpineol, gamma-terpinene and 1,8-cinole on airborne microbes using an airwasher. Flavour Fragrance J. 22 (5), 435–437.
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.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Cronin, M.T.D., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
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.
Sherwin, C.P., Kennard, K.S., 1919. Toxicity of phenylactic acid. J. Biol. Chem. 40, 259–264 The Journal of Biological Chemistry.
Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. Ann. N. Y. Acad. Sci. 641, 152–163.
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.
Troy, W.R., 1977. Doctoral Dissertation: the Comparative Respiratory Irritation Potential of Fourteen Fragrance Raw Materials. (Unpublished).
The Union of German Candle Manufacturers, 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. (Unpublished).
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
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 (5), 597–598.
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 humans capitis (Anoplura: Pediculicidae). Int. J. Parasitol. 35 (14), 1595–1600.
Zaitsev, A.N., Maganova, N.B., 1975. Embryotoxic action of some food aromatizers. Vopr. Pitan. 3, 64–68.
Zaitsev, A.N., Rakhmanina, N.L., 1974. Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vopr. Pitan. 6, 48–53.