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Short review

RIFM fragrance ingredient safety assessment, linalyl benzoate, CAS Registry Number 126-64-7

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ABSTRACT

The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog linalyl phenylacetate (CAS # 7143-69-3) show that this material does not have skin sensitization potential. The repeated dose toxicity endpoint was completed using linalyl cinnamate (CAS # 78-37-5) as a suitable read across analog, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using linalool (CAS # 78-70-6), dehydrolinalool (CAS # 29171-20-8), benzoic acid (CAS # 65-85-0) and sodium benzoate (CAS # 532-32-1) as suitable read across analogs, which provided a MOE > 100. The local respiratory toxicity endpoint was completed using linalool (CAS # 78-70-6) and benzoic acid (CAS # 65-85-0) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework along with data from the suitable read across analog linalyl cinnamate (CAS # 78-375).

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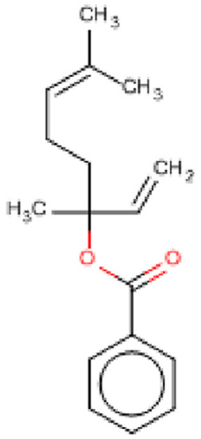

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* 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 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 conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog linalyl phenylacetate (CAS # 7143-69-3) show that this material does not have skin sensitization potential. The repeated dose toxicity endpoint was completed using linalyl cinnamate (CAS # 78-37-5) as a suitable read across analog, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using linalool (CAS # 78-70-6),

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(*continued*)

dehydrolinalool (CAS # 29171-20-8), benzoic acid (CAS # 65-85-0) and sodium benzoate (CAS # 532-32-1) as suitable read across analogs, which provided a MOE > 100. The local respiratory toxicity endpoint was completed using linalool (CAS # 78-70-6) and benzoic acid (CAS # 65-85-0) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework along with data from the suitable read across analog linalyl cinnamate (CAS # 78-375).

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2004a; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day (Hagan et al., 1967)
Developmental and Reproductive Toxicity: NOAEL = 146 mg/kg/day (CIR, 2001)
Skin Sensitization: Not sensitizing (RIFM, 1972, 1974; Klecak, 1985; RIFM, 2000)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC = 63 mg/m^3 (linalool) and 12.6 mg/m^3 (benzoic acid) (RIFM, 2012; RIFM, 2009)
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 89% (OECD 301F) Read-across to linalyl cinnamate (CAS # 78-37-5) (RIFM, 2004b)
Bioaccumulation: Screening Level: 3322 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 48 h *Daphnia magna* LC50: 0.061 mg/l (EpiSuite ver 4.1)
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: 0.061 mg/l (EPISUITE ver 4.1)
RIFM PNEC is: 0.0061 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe <1

1. Identification

1. **Chemical Name:** Linalyl benzoate
2. CAS Registry Number: 126-64-7
3. **Synonyms:** 3,7-Dimethyl-1,6-octadien-3-yl benzoate, Linalool benzoate, Linalyl benzoate, 1,6-Octadien-3-ol, 3,7-dimethyl-, benzoate, 安息香酸リナリル, 1,5-Dimethyl-1-vinylhex-4-en-1-yl benzoate
4. Molecular Formula: $C_{17}H_{22}O_2$
5. Molecular Weight: 258.36
6. RIFM Number: 457

2. Physical data

1. **Boiling Point:** 327.26 °C [EPI Suite]
2. **Flash Point:** >200 °F; CC [FMA database]
3. **Log K_{OW}:** 5.84 [EPI Suite]
4. **Melting Point**: 67.99 °C [EPI Suite]
5. **Water Solubility:** 0.218 mg/L [EPI Suite]
6. **Specific Gravity:** 0.9857 [RIFM database], 0.989 [FMA database]
7. **Vapor Pressure:** 0.0000923 mm Hg @ 20 °C [EPI Suite 4.0], 0.01 mm Hg 20 °C [FMA database], 0.000179 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Yellow to brownish yellow liquid, with a heavy odor, suggestive of tuberose. Almost colorless oily liquid, balsamic floral, bergamot fruity odor of good tenacity (Arctander Volume II, 1969).

3. Exposure

1. **Volume of Use (worldwide band):** <1 metric tons per year [IFRA, 2011]
2. **Average Maximum Concentration in Hydroalcoholics**: 1.50% [IFRA, 2002]
3. **97.5**th **Percentile**: 3.85% [IFRA, 2002]
4. **Dermal Exposure*:** 0.0981 mg/kg/day [IFRA, 2002]
5. **Oral Exposure**: Not available
6. **Inhalation Exposures**:** 0.0060 mg/kg/day or 0.36 mg/day [IFRA, 2002]
7. **Total Systemic Exposure (Dermal + Inhalation)**: 0.10 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:** Assumed 100%
2. **Oral:** Data not available – not considered.
3. **Inhalation**: Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.10 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
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2. **Analogues Selected**:
   a. **Genotoxicity**: None
   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); benzoic acid (CAS # 65-85-0); sodium benzoate (CAS # 532-32-1)
   d. **Skin Sensitization:** Linalyl phenylacetate (CAS # 7143-69-3)
   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

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 benzoate is reported to occur in the following foods*:

Mushroom

*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 06/1/2016.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.2. Risk assessment

Linalyl benzoate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2015). The mutagenic activity of linalyl benzoate was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance to OECD TG 471 using both the standard plate incorporation and modified preincubation methods. Salmonella typhimurium strains TA1535, TA1537, TA98, TA100, and TA102 were tested with linalyl benzoate in DMSO (dimethyl sulfoxide) at concentrations of 100, 333, 1000, 2500 and 5000 μg/plate in triplicate, in the presence and absence of metabolically active liver homogenate (S-9 mix). Cytotoxicity was observed in strains TA100 and TA1535 using the preincubation method at 5000 μg/plate in the absence of S-9. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any dose, either with or without metabolic activation (RIFM, 2004a,b,c). Under the conditions of the study, linalyl benzoate was considered not mutagenic.

The clastogenicity of linalyl benzoate 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 (HPBL) were treated with linalyl benzoate at concentrations ranging from 10 to 80 μg/mL (24 h treatment without S9), 5–640 μg/mL (3 h treatment without S9) and from 5 to 960 μg/mL (3 h treatment with S9). No statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at any analyzed concentration in any treatment condition with or without S9 (RIFM, 2014). Under the conditions of the study, linalyl benzoate was considered not clastogenic in the in vitro micronucleus test.

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

Additional References: None.

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

10.1.3. Repeated Dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on linalyl benzoate. Read across material linalyl cinnamate (CAS # 78-37-5; see Section V) has a dietary 17-week chronic toxicity study conducted on a group of 10 Osborne-Mendel rats/sex/group administered a target dose of linalyl cinnamate at 0, 50, 125, or 500 mg/kg/day. Body Weight, food intake and general condition were recorded weekly. Hematological examinations were conducted at the termination of the study. On completion of the study, all surviving animals were sacrificed and examined macroscopically. Organ weights were recorded and tissues were preserved for histopathologic examination. Detailed microscopic examinations were done on 6 or 8 animals evenly divided by sex, in the high dose group and control group. No effects were observed at any dosage. The NOAEL was determined to be 500 mg/kg/day, the highest dosage tested (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967).

Therefore, the MOE is equal to the linalyl cinnamate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.10 or 5000.

Additional References: Letizia et al., 2003a, 2003b; Bickers et al., 2003; Letizia et al., 2003b, 2003c; Bhatia et al., 2007; Belsito et al., 2007; RIFM, 2007a, 2007b, 2007c, 2008c, 2008b, 2008a; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003d; Lapczynski et al., 2008a, 2008b, 2008c; Belsito et al., 2008; Belsito et al., 2010; RIFM, 1958, 1979, 2012; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982, 1984; RIFM, 1998; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959; Cal, 2006a; Cal and Kryzaniak, 2006b; Cal and Sznitowska, 2003; Meyer, 1965; ECHA REACH Dossier: Benzoic acid; SCCNFP, 2002; WHO, 2000; Kreis et al., 1971; Bedford and Clarke, 1972; Hruban et al., 1966; Graham and Kuizenga, 1945; Shtenberg and Ignat'ev, 1970; RIFM, 2009; Sodemoto and Enomoto, 1980; Lemini et al., 1995; Kimmel et al., 1971; Ashby et al., 1997; Danish Ministry of the Environment, 1999; Laufersweiler et al., 2012; Bedford and Clarke, 1971; Benton et al., 1955; Schafer and Bowles, 1985; Dawson et al., 1996; Nishihara et al., 2000; Picard et al., 2001; Kolle et al., 2010; ECHA REACH Dossier: Sodium benzoate; Minor and Becker, 1971; Verrett

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et al., 1980; Daston et al., 1995; Peterka et al., 1986; Okubo and Kano, 2003.

Literature Search and Risk Assessment Completed on: 04/04/14.

10.1.5. Developmental and reproductive toxicity

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

10.1.6. Risk assessment

There are no developmental toxicity data on linalyl benzoate or any read across materials. Linalyl benzoate is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6; see Section V) and benzoic acid (CAS # 65-85-0; 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). The developmental toxicity data on benzoic acid are insufficient; however, sodium benzoate (CAS # 532-32-1; see Section V) has been tested for developmental toxicity in several species and via gavage and dietary routes. No developmental toxicity was observed in any species following gavage exposure, thus the NOAEL in rats and mice was determined to be 146 mg/kg/day, the highest dosage tested (CIR, 2001). After dietary exposure of sodium benzoate to rats, the developmental toxicity NOAEL was determined to be 2%, or 1167 mg/kg/day, based on perinatal mortality and organ abnormalities (OECD SIDS, 2001). 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 sodium benzoate NOAEL in mg/kg/day divided by the total systemic exposure, 146/0.10 or 1460.

There are no reproductive toxicity data on linalyl benzoate or any read across materials. Linalyl benzoate is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6) and benzoic acid (CAS # 65-85-0). 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 and 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 body weight gain and feed consumption (Politano et al., 2008; data also available in RIFM, 2006; Letizia et al., 2007). The dermal 90-day subchronic toxicity study 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. For the benzoic acid metabolite, a dietary chronic toxicity and 4-generation reproductive toxicity study conducted in rats determined the NOAEL for reproductive toxicity to be 1%, or 500 mg/kg/day, the highest dosage tested (Kieckebusch and Lang, 1960). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the dehydrolinalool NOAEL in mg/kg/day divided by the total systemic exposure, 200/0.10 or 2000.

Additional References: Letizia et al., 2003a, 2003b; Bickers et al., 2003; Letizia et al., 2003b, 2003c; Bhatia et al., 2007; Belsito et al., 2007; RIFM, 2007a, 2007b, 2007c, 2008c, 2008b, 2008a; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003d; Lapczynski et al., 2008a, 2008b, 2008c; Belsito et al., 2008; Belsito et al., 2010; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982, 1984; RIFM, 1998; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959; Cal, 2006a; Cal and Kryzaniak, 2006b; Cal and Sznitowska, 2003; Meyer, 1965; ECHA REACH Dossier: Benzoic acid; SCCNFP, 2002; WHO, 2000; Kreis et al., 1971; Bedford and Clarke, 1972; Hruban et al., 1966; Graham and Kuizenga, 1945; Shtenberg and Ignat'ev, 1970; RIFM, 2009; Sodemoto and Enomoto, 1980; Lemini et al., 1995; Kimmel et al., 1971; Ashby et al., 1997; Danish Ministry of the Environment, 1999; Laufersweiler et al., 2012; Bedford and Clarke, 1971; Benton et al., 1955; Schafer and Bowles, 1985; Dawson et al., 1996; Nishihara et al., 2000; Picard et al., 2001; Kolle et al., 2010; ECHA REACH Dossier: Sodium benzoate; Minor and Becker, 1971; Verrett et al., 1980; Daston et al., 1995; Peterka et al., 1986; Okubo and Kano, 2003;

Literature Search and Risk Assessment Completed on: 04/04/14.

10.1.7. Skin sensitization

Based on the available material specific data and read across to linalyl phenylacetate (CAS # 7143-69-3), linalyl benzoate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available data on linalyl benzoate and read across to linalyl phenylacetate (CAS # 7143-69-3; see Section V), linalyl benzoate does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not significantly 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 to either material (Klecak, 1985; RIFM, 2000). Additionally, no reactions indicative of skin sensitization were observed in the human maximization test to either material (RIFM, 1972, 1974).

Note: Linalyl benzoate could hydrolyze in skin to linalool and benzoic acid and autoxidation products of linalool are known to be contact allergens.

Additional References: None.

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

10.1.9. Phototoxicity/photoallergenicity

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

10.1.10. Risk assessment

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

Additional References: None.

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

10.1.10.1. Local respiratory toxicity. There are no inhalation data available on linalyl benzoate; however, linalyl benzoate is expected to metabolize to linalool (CAS # 78-70-6; see Section V) and benzoic acid (CAS # 65-85-0; see Section V) (Bickers et al., 2003). In an acute, two week inhalation study for linalool, a NOAEC of 63 mg/m^3

was reported by RIFM, 2012. Additionally, in a four week inhalation study for benzoic acid, a NOAEC of 12.6 mg/m^3 was reported by RIFM, 2009.

10.1.11. Risk assessment

The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a two week, acute inhalation study conducted in rats, a NOAEC of 63 mg/m^3 was reported for linalool (RIFM, 2012). Test substance-related effects were limited to non-adverse microscopic findings in the nasal cavity.

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

- (63 mg/m^3) (1m^3/1000 L) = 0.063 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.063 mg/L) (61.2 L/day) = 3.86 mg/day
- (3.86 mg/day)/(0.0016 kg lung weight of rat*) = 2412.5 mg/kg lung weight/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 3.85%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) the combined inhalation exposure would be 0.36 mg/day—as calculated using RIFM's 2-Box/MPPD *in silico* models, and based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics. To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.55 mg/kg lung weight/day resulting in a MOE of 4386 (i.e., [2412.5 mg/kg lung weight/day]/[0.55 mg/kg lung weight/day]).

In a four week inhalation study conducted in rats, a NOAEC of 12.6 mg/m^3 was reported for benzoic acid (RIFM, 2009). There were no test substance-related effects reported.

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

- (12.6 mg/m^3) (1m^3/1000 L) = 0.0126 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0126 mg/L) (61.2 L/day) = 0.771 mg/day
- (0.771 mg/day)/(0.0016 kg lung weight of rat*) = 481.9 mg/kg lung weight/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 3.85%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) the combined inhalation exposure would be 0.36 mg/day—as calculated using RIFM's 2-Box/MPPD *in silico* models, and based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics. To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.55 mg/kg lung weight/day resulting in a MOE of 876 (i.e., [481.9 mg/kg lung weight/day]/[0.55 mg/kg lung weight/day]).

For further weight of evidence, the inhalation exposure value (0.36 mg/day) 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). Based on the TTC and the MOE (>100) for the metabolites, linalool and benzoic acid, linalyl benzoate exposure by inhalation at 3.85% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd Ed. 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy", subsection, "Comparative Airway Anatomy."

Additional References: RIFM, 1977; Jirovetz et al., 1991; Buchbauer et al., 1991; RIFM, 1997; Buchbauer et al., 1993; Perrucci et al., 1996; Perrucci, 1995a; Rice and Coats, 1994a; Silver, 1992; Karr and Coats, 1992; Regnault-Roger and Hamraoui, 1995; Rice and Coats, 1994b; Perrucci et al., 1995b; Sugawara et al., 1998; Coats et al., 1991; Cometto-Muniz 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, 2004c; 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; de Moura Linck et al., 2009; Engstrom, 1984; Fraser et al., 2003.

Literature Search and Risk Assessment Completed on: 5/27/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of linalyl benzoate 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). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, linalyl benzoate 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 EPISUITE ver 4.1 did identify linalyl benzoate as possibly persistent and bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.2. Risk assessment

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

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10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.4. Other available data

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

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

RIFM, 2004b: The ready biodegradability of linalyl cinnamate was evaluated in Manometric Respirometry test according to the OECD 301F guidelines. 100 mg/l of the test material was incubated for 28 days. Biodegradation of 89% was observed.

10.2.5. 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.16 mg/l			1,000,000	0.000158 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.197 mg/l	0.272 mg/l	0.063 mg/l			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.428 mg/l	0.853 mg/l	0.165 mg/l			Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.075 mg/l	0.061 mg/l	0.197 mg/l	10,000	0.0061 μg/l	Neutral organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.84	5.84
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 0.0061 μg/L. The revised PEC/PNECs for EU and NA <1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

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

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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.09.023.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.09.023.

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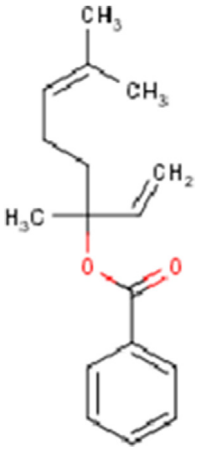
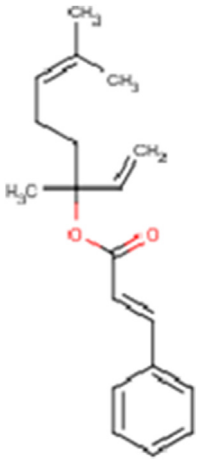
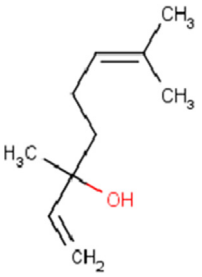
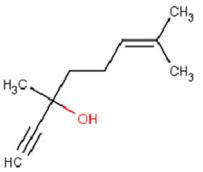
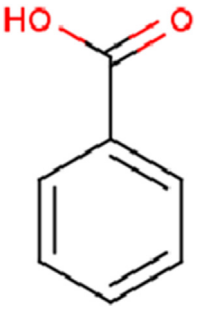
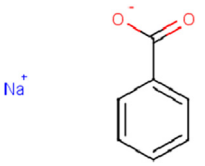
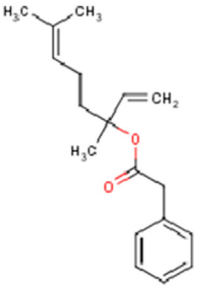
Appendix

	Target Material	Read across Material					
Principal Name	Linalyl benzoate	Linalyl cinnamate	Linalool	Dehydrolinalool	Benzoic acid	Sodium benzoate	Linalyl phenylacetate
CAS No.	126-64-7	78-37-5	78-70-6	29171-20-8	65-85-0	532-32-1	7143-69-3
Structure							
3D Structure	http://www.thegoodscentscompany.com/opl/126-64-7.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/65-85-0.html	http://www.thegoodscentscompany.com/opl/532-32-1.html	http://www.thegoodscentscompany.com/opl/7143-69-3.html
Read-across endpoint		•Repeated Dose •Environmental	•Devel/Repro •Respiratory	•Devel/Repro	•Devel/Repro •Respiratory	•Devel/Repro	•Skin sensitization
Molecular Formula	C17H22O2	C19H24O2	C10H18O	C10H16O	C7H6O2	C7H5NaO2	C18H24O2
Molecular Weight	258.36	284.4	154.25	152.24	122.12	122.12	272.39
Melting Point (°C, EPISUITE)	67.99	84.83	-11.39	15.40	48.85	48.85	77.26
Boiling Point (°C, EPISUITE)	327.26	355.04	204.05	212.37	249.51	249.51	339.71
Vapor Pressure (Pa @ 25°C, EPISUITE)	0.02386	0.003573	11.09	4.64	0.3973	0.3973	0.009826
Log Kow (KOWWIN v1.68 in EPISUITE)	5.84	6.37	3.38	2.75	1.87	1.87	6.09
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	0.218	0.05483	683.7	1084	2493	2493	0.1105
J_{max} (mg/cm^2/h, SAM)	0.580026941	0.2031987	90.06108298	93.21980338	585.5878938	585.5878938	0.566988506
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	34.845667	4.156351	4.285034	0.449174	0.010984	0.010984	14.205765
Similarity (Tanimoto score)[a]		64%	NA[b]	NA[c]	NA[b]	NA[c]	66%
Repeated Dose Toxicity							
Repeated dose (HESS)	Not categorized	Not categorized					
Developmental and Reproductive Toxicity							
ER binding (OECD)	Non binder, without OH or NH2 group		Non binder, non-cyclic structure	Non binder, non-cyclic structure	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group	

Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (moderate reliability)	NON-Toxicant (low reliability)	Toxicant (low reliability)	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 (moderate 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	No Metabolite Found	No Metabolite Found	See Supplemental Data 5

[a] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).
[b] Metabolites of the target
[c] Analog of the Metabolites of the target

Summary

There are insufficient toxicity data on linalyl benzoate (RIFM # 457, CAS # 126-64-7). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- 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 cinnamate (analog) was used as a read-across analog for linalyl benzoate (target) based on:
- The target and analog belong to the generic class of aliphatic esters, specifically, aryl alkyl acid ester/unsaturated/tertiary benzoates.
- They have the same alcohol part and similar carboxylic acid part.
- The key difference is that the target is a benzoate, while the analog is a cinnamate, which has an additional double bond in the branch. The cinnamate ester will have potential reactivity with nucleophiles and therefore presents greater potential toxicity than the target material. The use of the potentially more toxic analog for repeated dose and environmental toxicity is a conservative choice and thus is justified in this context.
- The target and analog show similar alerts for Repeated Dose (HESS) Categorization.
- The target and analog are expected to metabolize via similar pathway. As per the OECD Toolbox they are predicted to have similar metabolites.
- Linalool, dehydrolinalool, benzoic acid and sodium benzoate (read-across materials) were used as a read-across for linalyl benzoate (target) based on:
- The analogs are major metabolites of the target or are analogs of the major metabolites.
- Linalyl benzoate is an ester formed by linalool and benzoic acid. Dehydrolinalool is an analog of linalool and sodium benzoate is the salt of benzoic acid.
- 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 similar to those of the metabolites.

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- They all also show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
- As per the OECD Toolbox both the analogs are predicted as metabolites (see Metabolite # 2 & 3) of the target.
- Linalyl phenylacetate (analog) was used as a read-across analog for linalyl benzoate (target) based on:
- The target and analog belong to the generic class of aliphatic esters, specifically, aryl alkyl acid ester/unsaturated/tertiary benzoates.
- They have the same alcohol part and similar carboxylic acid part.
- The key difference is that the target is a benzoate, while the analog is a phenylacetate, which has a longer branch. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the skin sensitization profiles are expected to be similar.
- The target and analog show similar alerts for protein binding.
- The target and analog are expected to be metabolized similarly. As per the OECD Toolbox they are predicted to have similar metabolites.

Environmental Analogues Identified/Justification:

- Linalyl cinnamate (CAS # 78-37-5) has been identified as read-across analogs for linalyl benzoate based on structure and physical/chemical properties. Both materials are aromatic esters with predicted K_{ow} of 6.37 and 5.84, for linalyl cinnamate and linalyl benzoate, respectively. Available biodegradation data for linalyl cinnamate shows a biodegradation of 89% after 28 days, confirming that the material is not persistent; therefore it should be assumed that linalyl benzoate is also not persistent. This is also supported by the BIOWIN models for biodegradation.

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