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Short Review

RIFM fragrance ingredient safety assessment, Linalool, CAS registry number 78-70-6

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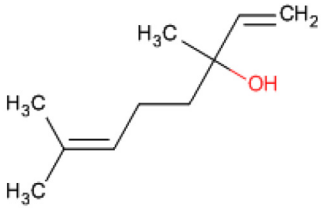

Abbreviation/Definition list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th 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).

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AF – Assessment Factor
DEREK – Derek nexus is an *in silico* tool used to identify structural alerts
DST – Dermal Sensitization Threshold
ECHA – European Chemicals Agency
EU – Europe/European Union
GLP – Good Laboratory Practice
IFRA – The International Fragrance Association
LOEL – Lowest Observable Effect Level
MOE – Margin of Exposure
MPPD – Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL – No Expected Sensitization Induction Level
NOAEC – No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
NOEC – No Observed Effect Concentration
OECD – Organisation for Economic Co-operation and Development
OECD TG – Organisation for Economic Co-operation and Development Testing Guidelines
PBT – Persistent, Bioaccumulative, and Toxic
PEC/PNEC – Predicted Environmental Concentration/Predicted No Effect Concentration
QRA – quantitative risk assessment
REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
TTC – Threshold of Toxicological Concern
UV/Vis Spectra – Ultra Violet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2014) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria such as, acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
* RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental assessment. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 36 mg/kg/day, based on a dermal 90-day subchronic toxicity study conducted in rats, that resulted in an MOE of 468, considering 14.4% absorption from skin contact and 100% from inhalation. An MOE of >100 is deemed acceptable.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (Belsito et al., 2010)
Repeated Dose Toxicity: NOAEL = 36 mg/kg/day (RIFM, 1980)
Developmental and Reproductive Toxicity: NOAEL = 200 mg/kg/day (ECHA REACH Dossier: Linalool)
Skin Sensitization: Not Sensitizing (RIFM, 2005)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (RIFM, 1982; RIFM, 1983)
Local Respiratory Toxicity: NOAEC = 10 ppm or 63 mg/m^3 (0.063 mg/L) (RIFM, 2012)

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 80–100% (RIFM, 1977a; RIFM, 1994a, 1994b; RIFM, 1991a)
Bioaccumulation: Screening Level: 42.33 L/kg (EPISUITE ver 4.1, 2000–2011)
Ecotoxicity: Critical Ecotoxicity Endpoint**:** *Daphnia Magna* 48 hr EC50: 20 mg/L (RIFM, 1998a)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) >1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: *Daphnia Magna* 48 h EC50: 20 mg/L (RIFM, 1998a)
RIFM PNEC is: 20 μg/L
Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Linalool
2. **CAS Registry Number**: 78-70-6
3. **Synonyms:** Coriandrol, 3,7-Dimethyl-1,6-octadien-3-ol, 2,6-Dimethyl-2,7-octadien-6-ol, Licareol, Linalol, Linalool, 1,6-Octadien-3-ol, 3,7-dimethyl-, 2,7-Octadien-6-ol, 2,6-dimethyl-, Linalyl alcohol, 3,7-ｼﾞﾒﾁﾙｰ1,6-ｵｸﾀｼﾞｴﾝｰ3-ｵｰﾙ, 3,7-Dimethylocta-1,6-dien-3-ol, Petinerol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25
6. **RIFM Number:** 128

2. Physical data

1. **Boiling Point:** 198 °C [IFRA], 0.2 mbar at 20 °C (RIFM, 1991b), 0.2 mbar at 20 °C (RIFM, 1991c), 204.05 °C [EPI Suite]
2. **Flash Point:** 160 °F; CC [IFRA]
3. **Log K_{ow}:** 3.28 ± 0.26 (Cal, 2006), Log Pow = 2.84 at 25 °C (RIFM, 1988b), Log Pow = 2.9 (RIFM, 1991b), Log Pow = 2.9 (RIFM, 1991b), 3.38 [EPI Suite]
4. **Melting Point:** less than 20 °C (RIFM, 1991a), less than 20 °C (RIFM, 1991b), <20 °C (RIFM, 1991c), –11.39 °C [EPI Suite]
5. **Water Solubility:** 683.7 mg/L [EPI Suite]

6. **Specific Gravity:** 0.861 g/mL at 20 °C (RIFM, 1991a), 0.860–0.864 [IFRA], 0.858–0.862 [IFRA], 0.861 g/mL at 20 °C (RIFM, 1991c), 0.862 (RIFM, 1989a), 0.861 g/mL at 20 °C (RIFM, 1991b), 0.86 g/mL (RIFM, 1994a)
7. **Vapor Pressure:** 0.0521 mm Hg @ 20 °C [EPI Suite 4.0], 0.05 mm Hg 20 °C [FMA], 0.0832 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Does not significantly absorb in the region of 290–700 nm
9. **Appearance/Organoleptic:** Colorless to very pale yellow liquid with a refreshing, floral, woody odor similar to that of bergamot oil and French lavender.

3. Exposure

1. **Volume of Use (worldwide band):** >1000 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 4.30% (IFRA, 2002)
3. **97.5th Percentile:** 12.70% (IFRA, 2002)
4. **Dermal Exposure*:** 0.3236 mg/kg/day (IFRA, 2002)
5. **Oral Exposure:** Not available
6. **Inhalation Exposures**:** 0.03 mg/kg/day (IFRA, 2002)
7. **Total Systemic Exposure (Dermal + Inhalation):** (0.3236 mg/kg/day × 14.4% absorption) + 0.03 mg/kg/day = 0.077 mg/kg/day

* Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in 10 of the most frequently used personal care and cosmetic products (i.e., antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

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

4. Derivation of systemic absorption

1. **Dermal:** 14.4%

RIFM, 2007a (data also available **RIFM**, 2007b; **RIFM**, 2007c; **RIFM**, 2008a; **RIFM**, 2008b; RIFM, 2008c Lalko et al., 2007; Lalko et al., 2008): A series of *in vitro* human skin penetration studies were conducted with 4% linalool under in-use (unoccluded) and occluded conditions in diethyl phthalate (DEP), dipropylene glycol (DPG), ethanol/water, petrolatum, ethanol/DEP or ethanol/DPG vehicles. Twelve active dosed diffusion cells were prepared from seven donors for each application condition (unoccluded, occluded, and an unoccluded control cell). Epidermal membranes were used, and their integrity was assessed by measuring the permeation rate of tritiated water over a period of 1 h. Permeation of linalool from a 5 μl/cm^2 dose was then measured at 12 time-points over 24 h. Occluded conditions reduced the loss of volatile application vehicles and test compounds but may have also increased skin hydration, factors which caused a significant increase in the permeation of linalool. Under unoccluded experimental conditions, there was a gradual but comprehensive evaporative loss. Total absorbed dose values from an unoccluded application ranged from 1.8% to 3.57% (DPG < ethanol/DPG < ethanol/DEP < DEP < petrolatum < ethanol/water). Total absorbed dose values from an occluded application ranged from 5.73% to 14.4% (DEP < ethanol/DEP < DPG < petrolatum < ethanol/DPG < ethanol/water). Conservatively, 14.4% dermal absorption was selected for this safety assessment.

2. **Oral:** Data not available – not considered.
3. **Inhalation**: Assumed 100%
4. **Total:** Dermal (14.4%) + Inhalation (assume 100%) absorbed = (0.3236 mg/kg/day × 14.4%) + 0.03 mg/kg/day = 0.077 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

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

* See appendix below for explanation.

2. **Analogues Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** Dehydrolinalool (CAS # 29171-20-8)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
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)

Linalool is reported to occur in food* and as a component in some natural complex substances (NCS):
Anise, star (Illicium verum Hook, F.)
Bergamot oil expressed
Citrus fruits
Clary (Salvia sclarea L.)
Coriander leaf (Coriandrum sativum L.)
Coriander seed (Coriandrum sativum L.)
Laurel (Laurus nobilis L.)
Lime oil distilled
Mentha arvensis oil
Mentha oils
Myrtle (Myrtus communis L.)
Myrtle berry
Salvia species
Star anise
Star anise (Illicium anisatum)
Thyme (Thymus species)
Thyme (Thymus vulgaris L.)
Thymus zygis L.

* 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

8.1. Standard specified

The material should only be used if it meets purity criteria or if it is used in conjunction with other materials. See Section 10.4 (IFRA, 2004).

9. REACH Dossier

Available; accessed on 02/21/13: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d93c699-8de9-6b59-e044-00144f67d249/DISS-9d93c699-8de9-6b59-e044-00144f67d249_DISS-9d93c699-8de9-6b59-e044-00144f67d249.html

10. Summary

1. Human Health Endpoint Summaries:

10.1. Genotoxicity

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

10.1.1. Risk assessment

The genotoxic potential of linalool has been evaluated for mutagenicity in bacteria and in cultured mouse L5718Y tk+/– cells, and by cytogenicity in Chinese hamster ovary (CHO) cells via SCE, a chromosome aberration study, and an *in vivo* micronucleus test. The Fragrance Material Review on linalool (Letizia et al., 2007), summarizes available data including negative Ames studies with *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537, TA1538, and *E. coil* strain WP2 uvrA, a negative sister chromatid exchange assay in CHO cells, a negative test for induction of unscheduled DNA synthesis in rat primary hepatocytes, and a negative *in vivo* mouse micronucleus assay. Additionally, the US NTP has shown linalool to be non-mutagenic in *S. typhimurium* strains TA100, 1535, 97, 98, 102, 104 up to 1000 μg/plate (NTP, 1999 study A67784). Mammalian mutagenicity was evaluated in one mouse lymphoma assay that demonstrated a weak positive result for linalool; however, the authors emphasized that positive results in this assay are commonly observed for polar substances in the presence of S9 and may be associated with changes in physiologic culture conditions such as pH and osmolality (Heck et al., 1989). When a second mouse lymphoma study was conducted which took into account cytotoxicity, osmolality and pH, the results were negative (RIFM, 1994b). Linalool was also reviewed by RIFM'S Expert Panel* and concluded that the mutagenicity and clastogenicity data are sufficient to indicate that linalool is not genotoxic (Bickers et al., 2003). More recently, an *in vitro* micronucleus test conducted using linalool demonstrated negative effects for mutagneticity and clastogenecity (DiSotto et al., 2011), further supporting a lack of genotoxic concern for linalool.

* 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.

Additional References: DiSotto et al., 2008; Mitic-Culafic et al., 2009; Lutz et al., 1980; Eder et al., 1982; Ishidate et al., 1984; Oda et al., 1978; Kuroda et al., 1984; Yoo, 1986; Mademtzoglou et al., 2011; Yoo, 1985

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

10.2. Repeated dose toxicity

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

10.2.1. Risk assessment

The repeated dose toxicity data on linalool are sufficient for the repeated dose toxicity endpoint. A dermal 90-day subchronic toxicity study conducted in rats determined the NOAEL to be 250 mg/kg/day, based on reduced body weights (RIFM, 1980). To account for bioavailability following dermal application, data from an *in vitro* dermal absorption study (RIFM, 2007a; see Section 4) were used to revise the NOAEL of 250 mg/kg/day to reflect the systemic dose. At a dermal penetration of 14.4% of the applied dose, the revised repeated dose toxicity NOAEL from the dermal study is 36 mg/kg/day. Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 36/0.077 or 468.

Additional References: Letizia et al., 2007; Lapczynski et al., 2008a; Lapczynski et al., 2008b; Lapczynski et al., 2008c; Bickers et al., 2003; Belsito et al., 2008; Belsito et al., 2010; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990; Jirovetz et al. 1991; Parke et al., 1974; Green et al., 1995; Meesters et al., 2007; Chadha et al., 1982; Chadha et al., 1984; FEMA, 1998; Jager et al., 1992; Schmitt et al., 2010; Meyer et al., 1959; Cal et al., 2006; Cal, 2006; Cal and Sznitowska 2003; Meyer, 1965; RIFM, 2010a; RIFM, 1989b; RIFM, 1990; Al-Said et al., 1987; Matsui et al., 1967

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

10.3. Developmental and reproductive toxicity

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

10.3.1. Risk assessment

The developmental toxicity data on linalool are sufficient for the developmental toxicity endpoint. A gavage developmental toxicity study was conducted in rats which concluded a NOAEL of 1000 mg/kg/day, the highest dosage tested (Politano et al., 2008). Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 1000/0.077 or 12987.

There are no reproductive toxicity data on linalool. Read-across material dehydrolinalool (CAS # 29171-20-8; see Section 5), has a gavage reproductive toxicity screening study in rats. The NOAEL was determined to be 750 mg/kg/day for males, the highest dosage tested, and 200 mg/kg/day for the offspring and dams, based on maternal clinical signs and decreased live birth index and viability (ECHA REACH Dossier: Linalool Read across Subs Key Toxicity to reproduction.003; accessed 02/21/13). A 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). The dermal 90-day subchronic toxicity study with linalool in rats (RIFM, 1980), in addition to assessing systemic endpoints, included organ weights (testes and ovaries) and histopathology (testes, epididymis, ovaries, pituitary, and thyroid) and no effects observed. Together, these data indicate there is no concern for reproductive toxicity. The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the dehydrolinalool NOAEL in mg/kg/day divided by the total systemic exposure, 200/0.077 or 2597.

Additional References: Letizia et al., 2007; Lapczynski et al., 2008a; Lapczynski et al., 2008b; Lapczynski et al., 2008c;

Bickers et al., 2003; Belsito et al., 2008; Belsito et al. 2010; RIFM, 1979; RIFM, 2012; Stoner et al. 1973; Randazzo et al. 2013; Hood et al. 1978; Howes et al. 2002; Jirovetz et al. 1990; Jirovetz et al. 1991; Parke et al. 1974; Green et al. 1995; Meesters et al. 2007; Chadha et al. 1982; Chadha et al. 1984; FEMA, 1998; Jager et al. 1992; Schmitt et al., 2010; Meyer et al. 1959; Cal and Kryzaniak 2006; Cal, 2006; Cal and Sznitowska 2003; Meyer, 1965; RIFM, 2010a; RIFM, 1989b; RIFM, 1990; Al-Said et al., 1987; Matsui et al., 1967

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

10.4. Skin sensitization

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

10.4.1. Risk assessment

Linalool is not predicted to be directly reactive to skin proteins (Roberts et al., 2007; OECD toolbox v3.0). However, linalool is known to undergo auto-oxidation resulting in degradation products that may be protein reactive (Skold et al., 2004a). In guinea pig test methods and the local lymph node assay (LLNA), positive and negative results have been reported (Basketter et al., 2002; Ishihara et al., 1986; Klecak, 1979, 1985; Sharp, 1978; Skold et al., 2004b). Various qualities of linalool have been evaluated. In these LLNAs and guinea pig studies, the positive results have been shown to be the result of irritation and sensitizing products of autoxidation (RIFM, 2010b; Skold et al., 2002; Skold et al., 2004a). In human confirmatory studies, no reactions indicative of sensitization have been observed to linalool at the maximum tested concentration of 12.7% (14,998 μg/cm^2) (Greif, 1967; RIFM, 1975; RIFM, 2005). Based on the available data, linalool does not present a concern for skin sensitization.

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

Additional References: None

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

10.5. Phototoxicity/photoallergenicity

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

10.5.1. Risk assessment

The UV absorption spectra demonstrate that this material has little to no absorption in the UV region (290–700 nm). Though the spectra are not suitable for conducting a benchmark evaluation, in Guinea pig and Human studies, no reactions indicative of phototoxic responses were observed (RIFM, 1982a; RIFM, 1983a). Based on the existing data, linalool does not present a concern for phototoxicity.

Additional References: None

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

10.6. Local respiratory toxicity

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

10.6.1. Risk assessment

The inhalation exposure estimated for combined exposure was considered along with toxicological data from the scientific literature to calculate the MOE from inhalation exposure to linalool when used in perfumery. Specifically, a NOAEC of 10 ppm (63 mg/m^3; the highest dose tested) was reported by Randazzo et al. (2013), in an acute 2 week inhalation study. The effects were limited to non-adverse microscopic findings in the nasal cavity.

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

- (63 mg/m^3) (1 m^3/1000 L) = 0.063 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat × duration of exposure of 360 minutes per day (Minutes/day) (according to GLP study guidelines) = 61.2 L/d
- (0.063 mg/L) (61.2 L/d) = 3.86 mg/d
- (3.86 mg/d)/(0.0016 kg lung weight of rat*) = 2409.75 mg/kg lw/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 12.70%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 1.18 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual using RIFM's 2-Box/MPPD *in silico* models. To compare this estimated exposure with the Randazzo 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, 1.81 mg/kg lung weight/day, resulting in an MOE of 1331 (i.e., [2409.75 mg/kg lw/day]/[1.81 mg/kg lung weight/day]).

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

* 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, 1977b; Jirovetz et al. 1991; Buchbauer et al., 1991; Jirovetz et al., 1990; RIFM, 1997; Buchbauer et al., 1993; Perrucci et al., 1996; Perrucci 1995; Rice and Coats, 1994; Silver, 1992; Karr and Coats, 1992; Regnault-Roger and Hamraoui, 1995; Rice and Coats, 1994; Perrucci et al., 1995; Sugawara et al., 1998; Coats et al., 1991; Cometto-Muniz et al., 1998; Isola et al., 2003a; RIFM, 2003a; RIFM, 2003b; Isola et al., 2003b; Isola et al., 2004a; Larsen et al., 1997; Smith et al., 2004; RIFM, 2004; Isola et al., 2004b; Barocelli et al., 2004; Rogers et al., 2003; Rogers et al., 2005; Kuroda et al., 1984; Tanida, et al., 2006; Yang et al., 2005; Corsi et al., 2007; Sato et al., 2007; Nakamura et al., 2010; Nakamura, et al., 2009; Matsubara et al., 2011

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

2. Environmental Endpoint Summary:

10.7. Analogues identified/justification

Not applicable.

10.8. Screening-level assessment

A screening level risk assessment of linalool was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chem-

ical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, linalool was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did identify linalool as being possibly persistent but not bio-accumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.9. Risk assessment

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

10.9.1. Biodegradation

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

A study was conducted following OECD Guideline 301B. 10 mg/L of the test substance was incubated for 28 days. At the end of the study 97.1% biodegradation was observed (RIFM, 1994a).

A study was conducted following OECD Guideline 301C. One hundred milligrams per liter of the test substance was incubated for 28 days. At the end of the study 80% biodegradation was observed (RIFM, 1991a).

10.9.2. Ecotoxicity

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

One *Daphnia* immobilization study is reported. The 48 h EC50 was reported as 20 mg/L (nominal concentration) (RIFM, 1988a).

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

10.10. Other available data

This material has been registered under REACH. No additional data are available at this time. An OECD SIDS dossier is also available; no additional key studies are needed to complete the safety assessment.

10.11. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening Level (Tier 1)	<u>34.3</u>			1,000,000	0.034	
ECOSAR Acute Endpoints (Tier 2) *Ver 1.11*	2.191	<u>0.329</u>	6.863	10,000	0.0329	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints (Tier 2) *Ver 1.11*	19.704	12.517	12.769			Neutral organics

Tier 3: Measured Data

	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	27.8					
Daphnia		<u>20.0</u>		1000	20.0	
Algae		86.0	32.0			

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

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

Exposure	Europe	North America
Log K_{ow} used	2.90	
Biodegradation Factor Used	1	
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000	>1000
Risk Characterization: PEC/PNEC	<1	<1

Note: Linalool is linked in the RIFM Database with l-linalool (CAS# 126-91-0). The additional regional volume does not alter the outcome of the risk assessment. The PEC/PNECs are <1.

The RIFM PNEC is 20.0 μg/L. The revised PEC/PNECs for EU and NA are <1 and, therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

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

11. Literature search*

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- NTP: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- PUBMED: http://www.ncbi.nlm.nih.gov/pubmed
- TOXNET: http://toxnet.nlm.nih.gov/
- IARC: (http://monographs.iarc.fr)
- OECD SIDS: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIS: http://www.epa.gov/hpv/hpvis/index.html
- US EPA Robust Summary: http://cfpub.epa.gov/hpv-s/
- Japanese NITE: http://www.safe.nite.go.jp/english/db.html

- Japan Existing Chemical Data Base: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Google: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

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

This is not an exhaustive list.

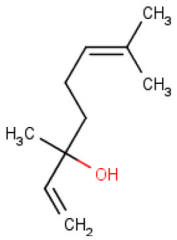
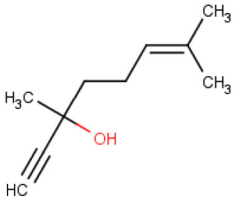
Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

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

Appendix 1

	Target Material	Read across Material
Principal Name	Linalool	Dehydrolinalool
CAS No.	78-70-6	29171-20-8
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/29171-20-8.html
Read-across endpoint		•Devel/Repro
Molecular Formula	C10H18O	C10H16O
Molecular Weight	154.25	152.24
Melting Point (°C, EPISUITE)	–11.39	15.40
Boiling Point (°C, EPISUITE)	204.05	212.37
Vapor Pressure (Pa @ 25 °C, EPISUITE)	11.09	4.64
Log K_{ow} (KOWWIN v1.68 in EPISUITE)	3.38	2.75
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	683.7	1084
J_{max} (mg/cm^2/h, SAM)	90.06108298	93.21980338
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.285034	0.449174
Similarity (Tanimoto score)[1]		63%
Developmental and Reproductive Toxicity		
ER binding (OECD)	Non binder, non-cyclic structure	Non binder, non-cyclic structure
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (low reliability)	NON-Toxicant (low reliability)
Metabolism		
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data 2

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

Summary

There are insufficient toxicity data on Linalool (CAS # 78-70-6). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

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

Conclusions/rationales

- Dehydrolinalool (analog) was used as a read-across for Linalool (target) based on:
  - The target and analog belong to the generic class of alcohols, specifically, alcohol/branched chain/unsaturated/tertiary α,β.
  - The target and analog are terpene alcohols. They have the same number of isoprene units and a hydroxyl group.
  - The only difference is that the target has an alkene terminal while the analog has an alkyne terminal. The difference between structures does not essentially change physicochemical properties nor raise any additional structural alerts and therefore, the developmental and reproductive toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox both materials are predicted to have similar metabolites.

Explanation of Cramer class

The Cramer class of the target material was determined based on Cramer decision tree (Cramer et al., 1978).

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

Appendix 2: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.01.005.

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