Food and Chemical Toxicology 130 (2019) 110610

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, linalyl anthranilate, CAS Registry Number 7149-26-0

A.M. Api[a], D. Belsito[b], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], L. Jones[a], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave, New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

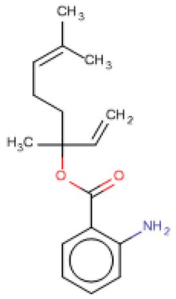
ARTICLE INFO

Keywords:
Genotoxicity
Repeated Dose, Developmental, and Reproductive Toxicity
Skin Sensitization
Phototoxicity/Photoallergenicity
Local Respiratory Toxicity
Environmental Safety

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2019.110610
Received 1 May 2018; Received in revised form 28 May 2019; Accepted 19 June 2019
Available online 22 June 2019

Version: 043018. This version replaces any previous versions.
Name: Linalyl anthranilate
CAS Registry Number: 7149-26-0



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
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 as 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 existing information supports the use of this material as described in this safety assessment.
Linalyl anthranilate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on the target material and the read-across analogs linalool (CAS # 78-70-6) and benzoic acid, 2-amino- (CAS # 118-92-3) show that linalyl anthranilate is not expected to be genotoxic. The reproductive and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). The repeated dose and developmental toxicity endpoints were completed using linalool (CAS # 78-70-6) and benzoic acid, 2-amino- (CAS # 118-92-3) as read-across analogs, which provided an MOE > 100. The skin sensitization endpoint was completed using the non-reactive DST (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints was completed based on UV spectra; linalyl anthranilate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; linalyl anthranilate 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 expected to be genotoxic. (Zeiger et al., 1987; RIFM, 2001; ECHA REACH Dossier: Anthranilic Acid; ECHA, 2012a)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day. (RIFM, 1980)
Developmental and Reproductive Toxicity: Developmental NOAEL = 1000 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC. (Politano et al., 2008)
Skin Sensitization: Not a sensitization concern. Exposure is below the DST.
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: Screening-level: 2.3882 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 6449 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-hour *Daphnia magna* EC50: 0.027 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, 2002)
Critical Ecotoxicity Endpoint: 48-hour *Daphnia magna* EC50: 0.027 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0027 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name:** Linalyl anthranilate
2. **CAS Registry Number:** 7149-26-0
3. **Synonyms:** 3,7-Dimethyl-1,6-octadien-3-yl anthranilate; 3,7-Dimethyl-1,6-octadien-3-yl 2-aminobenzoate; Linalyl 2-aminobenzoate; Linalyl o-aminobenzoate; 1,6-Octadien-3-ol, 3,7-dimethyl-, 2-aminobenzoate; 1,5-Dimethyl-1-vinylhex-4-en-1-yl 2-aminobenzoate; Linalyl anthranilate
4. **Molecular Formula:** $C_{17}H_{23}NO_2$
5. **Molecular Weight:** 273.38
6. **RIFM Number:** 412

2. Physical data

1. **Boiling Point:** 370.83 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA)
3. **Log K_{OW}:** 6.28 (EPI Suite)
4. **Melting Point**: 120.02 °C (EPI Suite)
5. **Water Solubility:** 0.076 mg/L (EPI Suite)
6. **Specific Gravity:** 0.99600 to 1.00600 @ 25.00 °C (http://www.thegoodscentscompany.com/data/rw1015571.html, retrieved 1/22/14)
7. **Vapor Pressure:** 0.00000228 mm Hg @ 20 °C (EPI Suite v4.0), 4.8e-006 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark.
9. **Appearance/Organoleptic:** A pale, straw-colored oily liquid with a sweet floral-fruity and comparatively powerful taste and a variety of green, fruity, grape-like, berry-like notes.

3. Exposure

1. **Volume of Use (worldwide band):** < 1 metric ton per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.042% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000028 mg/kg/day or 0.0019 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00034 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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, 2015, 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** 80%, read-across material linalool (CAS # 78-70-6)

RIFM, 2007b **(data also available in** RIFM, 2007c; RIFM, 2007d; RIFM, 2008f; RIFM, 2008g; RIFM, 2008h; RIFM, 2007a; RIFM, 2008e**)**: 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 7 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 for 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 (~97% evaporative loss over 24 h, with less than 7% recovery within the first hour of analysis). 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). The most conservative dermal penetration of 14.4% was determined. However, the total recovery reported was 8.01 ± 0.69 and 36.3 ± 2.9%, respectively, for the unoccluded and occluded applications. Since the evaporative loss was rapid and there was poor recovery of the test material, the study was not used towards the safety assessment.

Data from RIFM's *in silico* skin absorption model (RIFM, 2014) were used to predict the dermal penetration of 80% for linalool as shown below.

Name	Linalool
J_{max} (mg/cm^2/h)	101.980[1]
Skin Absorption Class	80%

[1] J_{max} was calculated based on measured log K_{ow} of 2.9 (RIFM, 1991) and water solubility of 1450 mg/L (RIFM, 1991).

2. **Oral:** Assumed 100%

3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate (Expert Judgment)

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

*See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** linalool (CAS # 78-70-6); benzoic acid, 2-amino- (CAS # 118-92-3)
   b. **Repeated Dose Toxicity:** linalool (CAS # 78-70-6) and benzoic acid, 2-amino- (CAS # 118-92-3)
   c. **Developmental and Reproductive Toxicity:** linalool (CAS # 78-70-6) and benzoic acid, 2-amino- (CAS # 118-92-3)
   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)

Linalyl anthranilate 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 2010; no dossier available as of 04/30/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, linalyl anthranilate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of linalyl anthranilate was assessed in a bacterial reverse mutation assay conducted similarly/equivalent to OECD TG 471 using the modified preincubation method. *S. typhimurium* strains TA98, TA100, TA1535, and TA97 were treated with linalyl anthranilate in dimethyl sulfoxide (DMSO) up to a concentration of 666 μg/plate (Zeiger et al., 1987). Under the conditions of this study, linalyl anthranilate was considered not mutagenic in bacteria.

There are no data assessing the clastogenic potential of linalyl anthranilate; however, the material benzoic acid, 2-amino- (anthranilic acid) (CAS # 118-92-3; see Section 5) was identified as a suitable read-across analog. The clastogenic activity of the anthranilate (i.e., salt of anthranilic acid) was assessed in an *in vivo* micronucleus study conducted in compliance with GLP regulations and in accordance to OECD TG 484. Groups of male and female ICR mice were treated with a single oral dose of the test article in 1% sodium carboxymethyl cellulose at 150, 1500, and 3000 mg/kg body weight in the males and 600, 1200, and 2400 mg/kg body weight in the female mice (ECHA, 2012a). Oral administration of the test item did not lead to a substantial increase of micronucleated polychromatic and normochromatic erythrocytes; the material, benzoic acid, 2-amino-, was considered not mutagenic in the *in vivo* micronucleus test, and this can be extended to linalyl anthranilate.

Additionally, the metabolite linalool (CAS # 78-70-6; see Section 5) was assessed for clastogenic potential in an *in vivo* micronucleus study conducted in compliance with GLP regulations and in accordance with OECD 474. Groups of male and female Swiss CD-1 mice were administered a single oral dose of linalool in corn oil at the concentrations 500, 1000, and 1500 mg/kg/body weight. Animals were euthanized 24 and 48 after dose administration, femurs were removed, and smears were prepared. No increase in the frequency of micronucleated polychromatic erythrocytes and no decrease in the ratio of polychromatic erythrocytes to normochromatic erythrocytes were observed (RIFM, 2001). It was concluded that linalool was not genotoxic in the micronucleus assay, and these results can be extended to the target substance, linalyl anthranilate.

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

Additional References: Kawachi et al., 1981; Foltinova and Grones, 1997; Miyagawa et al., 1995; Hughes et al., 2012; Fowler et al., 2012; 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, 1986; DiSotto et al., 2011.

Literature Search and Risk Assessment Completed On: 01/17/14.

10.1.2. Repeated dose toxicity

The margin of exposure for linalyl anthranilate 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 anthranilate. Linalyl anthranilate is expected to hydrolyze to linalool (CAS # 78-70-6; see Section 5) and benzoic acid, 2-amino- (anthranilic acid) (CAS # 118-92-3; see Section 5). The repeated dose toxicity data on linalool are sufficient for the repeated dose toxicity endpoint. A dermal 90-day (13-week) subchronic toxicity study was conducted in rats. Applications with linalool at doses of 250, 1000, and 4000 mg/kg/day were made daily to the clipped and shaved backs of the animals. The NOAEL was determined to be 250 mg/kg/day, based on reduced body weights among animals of the higher dose groups and mortality among the high-dose group animals (RIFM, 1980). An *in vitro* dermal penetration study was conducted with linalool (see Section 4) under occlusion and non-occlusion, resulting in significant evaporation of linalool and a dermal absorption value of 14.4% and 3.57% under occlusion and non-occlusion conditions (RIFM, 2007b). Since the evaporative loss from the skin absorption study was significantly high, the results from the study were not considered for the safety

assessment on linalool. The skin absorption model (SAM) prediction (RIFM, 2014; see Section 4) suggests a dermal absorption value of 80%. The more conservative SAM prediction for dermal absorption was considered in calculating dermal bioavailability for linalool. Thus, to account for bioavailability following dermal application, data from RIFM's *in silico* SAM were used to revise the NOAEL of 250 mg/kg/day to reflect the systemic dose. At a predicted dermal penetration of 80% of the applied dose, the revised linalool toxicity NOAEL from the dermal study is 200 mg/kg/day. In another study, Fischer 344 rats or B6C3F1 mice, when treated with metabolite anthranilic acid administered via diet at doses up to 30,000 ppm and 50,000 ppm, to rats and mice respectively for a period of 2 years, showed no evidence of carcinogenicity that could be related to treatment with anthranilic acid (NCI, 1978). The dietary dose in rats and mice was equivalent to 3000 mg/kg/day and 7500 mg/kg/day in rats and mice, respectively (as per the conversion factors for old rats available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). The most conservative NOAEL of 200 mg/kg/day from the 90-day dermal study on linalool was selected for the repeated dose toxicity endpoint.

Therefore, the linalyl anthranilate MOE for the repeated dose toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure to linalyl anthranilate, 200/0.00034 or 588235.

When correcting for skin absorption, the total systemic exposure to linalyl anthranilate (0.34 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Hagan et al., 1967; Bar and Griepentrog, 1967; OECD QSAR Toolbox (Dow Chemical, 1967 from MUNRO database); Stoner et al., 1973; Schafer and Bowles, 1985; Clark et al., 1980; Cutting et al., 1966; Verrett et al., 1980; RIFM, 1974; Grundschober (1977); Yamaori et al., 2005; Ekman and Strombeck, 1949; RIFM, 2003; RIFM, 2008b; RIFM, 2008c; RIFM, 2008d; Bickers et al., 2003; 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, 2006; Cal, 2003; Meyer (1965).

Literature Search and Risk Assessment Completed On: 02/16/17.

10.1.3. Developmental and reproductive toxicity

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

There are insufficient reproductive toxicity data on linalyl anthranilate or any read-across materials. The total systemic exposure to linalyl anthranilate is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental and reproductive toxicity data on linalyl anthranilate. Linalyl anthranilate is expected to hydrolyze to linalool (CAS # 78-70-6; see Section 5) and anthranilic acid (CAS # 118-92-3; see Section 5). The developmental toxicity data on linalool are sufficient for the developmental toxicity endpoint. A gavage developmental toxicity study was conducted on rats that received oral doses of linalool at 0, 250, 500, or 1000 mg/kg/day in corn oil on gestation days 7–17, which resulted in a NOAEL of 1000 mg/kg/day, the highest dosage tested, for developmental toxicity (Politano et al., 2008). There are no developmental toxicity data on metabolite anthranilic acid. Thus, the NOAEL of 1000 mg/kg/day from the OECD 414 developmental toxicity study was considered for the developmental toxicity endpoint.

Therefore, the linalyl anthranilate MOE for the developmental toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure to linalyl anthranilate, 1000/0.00034 or 2941176.

When correcting for skin absorption, the total systemic exposure to linalyl anthranilate (0.34 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no reproductive toxicity data on linalyl anthranilate. Linalyl anthranilate is expected to hydrolyze to linalool (CAS # 78-70-6; see Section 5) and anthranilic acid (CAS # 118-92-3; see Section 5). In a dermal 90-day (13-week) subchronic toxicity study with linalool in rats (RIFM, 1980), in addition to the systemic endpoint, organ weights (testes and ovaries) and histopathology (testes, epididymis, ovaries, pituitary, and thyroid) were performed on the reproductive organs, and no effects were observed. Together, these data indicate there is no concern for reproductive toxicity. However, since there are no sperm analysis data available for the males and no reproductive cycle analysis data for females, a NOAEL for the reproductive toxicity endpoint could not be determined. In addition, there are no reproductive toxicity data on metabolite anthranilic acid. When correcting for skin absorption, the total systemic exposure to linalyl anthranilate (0.34 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Hagan et al., 1967; Bar and Griepentrog, 1967; OECD QSAR Toolbox (Dow Chemical, 1967 from MUNRO database); Stoner et al., 1973; Schafer and Bowles, 1985; Clark et al., 1980; Cutting et al., 1966; Verrett et al., 1980; RIFM, 1974; Grundschober (1977); Yamaori et al., 2005; Ekman and Strombeck, 1949; RIFM, 2003; RIFM, 2008b; RIFM, 2008c; RIFM, 2008d; Bickers et al., 2003; 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.,

Table 1
Acceptable exposure limits for linalyl anthranilate based on non-reactive DST.

IFRA Category[a]	Examples of Product Type	Calculated QRA
1	Lip Products	0.026%
2	Deodorant/Antiperspirant	0.033%
3	Hydroalc., Shaved Skin	0.136%
4	Hydroalc., Unshaved Skin	0.407%
5	Women Facial Cream	0.214%
6	Mouthwash	0.652%
7	Intimate Wipes	0.068%
8	Hair Styling Aids Non-Spray	0.91%
9	Conditioners, Rinse-off	4.50%
10	Hard Surface Cleaners	2.5%
11	Candle (Non-Skin/Incidental Skin)	Not Restricted

Note: [a]For a description of the categories, refer to the QRA Informational Booklet (www.rifm.org/doc/QRAInfoJuly2011.pdf).

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, 2006; Cal, 2003; Meyer (1965).

Literature Search and Risk Assessment Completed On: 02/16/17.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. Based on the available data and application of the DST, linalyl anthranilate 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; Toxtree 2.5.0; OECD toolbox v3.1). In a human maximization test, no reactions to linalyl anthranilate were observed (RIFM, 1973). The reported exposure was benchmarked utilizing the non-reactive DST. The current 95th percentile dermal exposure is below the DST for non-reactive materials when evaluated in all QRA categories (Table 1).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/26/16.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, linalyl anthranilate 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 anthranilate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, linalyl anthranilate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for linalyl anthranilate were obtained. The spectra indicate minor 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: 09/07/16.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level of linalyl anthranilate is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on linalyl anthranilate. Based on the Creme RIFM model, the inhalation exposure is 0.0019 mg/day. This exposure is 247 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/16.

11. Environmental endpoint summary

11.1. Screening-level assessment

A screening-level risk assessment of linalyl anthranilate 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 anthranilate 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 v4.1 (US EPA, 2012a) identified linalyl anthranilate 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, 2012b). 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2. Risk assessment

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

Biodegradation: No data available.

Ecotoxicity: No data available.

11.3. Other available data

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

11.4. 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)**	0.023			1000000	2.3E-05	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.116	0.152	0.033			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.389	0.033	0.059			Anilines (Hindered)
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.382	0.644	0.120			Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.032	0.027	0.104	10000	0.0027	Neutral Organics SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	6.28	6.28
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 0.0027 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/17/14.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/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:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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. The links listed above were active as of 01/22/19.

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.2019.110610.

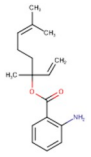
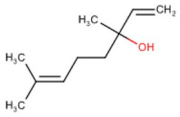
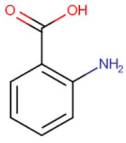
Appendix

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 were 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 anthranilate	Linalool	Benzoic acid, 2-amino-
CAS No.	7149-26-0	78-70-6	118-92-3
Structure			
Similarity (Tanimoto score)[1]		NA	NA
Read-across endpoint		• Repeated dose toxicity • Developmental and reproductive toxicity • Genotoxicity	• Repeated dose toxicity • Developmental and reproductive toxicity • Genotoxicity
Molecular Formula	$C_{17}H_{23}NO_2$	$C_{10}H_{18}O$	$C_7H_7NO_2$
Molecular Weight	273.38	154.25	139.15
Melting Point (°C, EPI Suite)	120.02	−11.39	94.08
Boiling Point (°C, EPI Suite)	370.83	204.05	307.70
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.00064	11.1	0.0105
Log Kow(KOWWIN v1.68 in EPI Suite)	6.28	2.9[1]	1.21
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.076	1590	3500
J_{max} (μg/cm^2/h, SAM)	0.770	121.085	29.603
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.302E + 000	2.18E + 000	3.88E-006
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• Radical mechanism via ROS formation • SN1, Nucleophilic attack	• No alert found	• Radical mechanism via ROS formation • SN1, Nucleophilic attack
DNA binding by OECD QSAR Toolbox (3.4)	• SN1, Nitrenium Ion formation	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (moderate reliability)	• Non-carcinogen (low reliability)	• Non-carcinogen (Experimental value)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• Primary aromatic amine, hydroxyl amine and its derived esters	• No alert found	• No alert found
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• H-acceptor-path3-H-acceptor • Primary aromatic amine, hydroxyl amine, and derived esters	• No alert found	• H-acceptor-path3-H-acceptor
Oncologic Classification	• Aromatic amine type compound	• Not classified	• Aromatic amine type compound
Repeated dose toxicity			
Repeated Dose (HESS)	• Allyl esters (Hepatoxicity) Class A	• Not categorized	• Not categorized
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Strong binder NH_2 group	• Non-binder, non-cyclic structure	• Weak binder NH_2 group

Developmental Toxicity Model by CAESAR v2.-1.6	• Non-toxicant (moderate reliability)	• Non-toxicant (low reliability)	• Toxicant (low reliability)
Metabolism			
OECD QSAR Toolbox (3.4) **Rat liver S9 metabolism simulator**	• See Supplemental Data	• NA	• NA

NA: Not applicable. Major metabolites or analogs of major metabolites of the target substance.
1. RIFM, 1991.
2. Patel et al., 2002

Summary

There are insufficient toxicity data on linalyl anthranilate (CAS # 7149-26-0). Hence *in silico* evaluation was conducted by determining suitable read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, suitable analogs linalool (CAS # 78-70-6), benzoic acid, 2-amino- (CAS # 118-92-3), and methyl anthranilate (CAS # 134-20-3) were identified as read-across materials with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target substance was not considered for the risk assessment, and therefore, metabolism data was not reviewed. Metabolism of the target material was predicted using the rat liver S9 metabolism simulator (OECD QSAR Toolbox v3.4). Target material is metabolized to linalool (CAS # 78-70-6) and anthranilic acid (CAS # 118-92-3) in the first step with 0.95 intrinsic probability and 0.28 pre-calculated probability. Hence, linalool (CAS 78-70-6) and anthranilic acid (CAS # 118-92-3) can be use as read-across for the target material. Read-across materials were out of domain for *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden and a justification is provided.

Conclusions

- Linalool (CAS # 78-70-6) and anthranilic acid (CAS # 118-92-3) are used as structurally similar read-across analogs for linalyl anthranilate (CAS # 7149-26-0) for the repeated dose, developmental, reproductive, and genotoxicity endpoints.
  - o The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - o Linalyl anthranilate (CAS # 7149-26-0) is an ester formed by linalool (CAS # 78-70-6) and anthranilic acid (CAS # 118-92-3).
  - o The structural difference in the target substance and the read-across analogs can be mitigated by the fact that linalyl anthranilate (CAS # 7149-26-0) could be metabolically hydrolyzed to linalool (CAS 78-70-6) and anthranilic acid (CAS # 118-92-3). Therefore, the toxicity profile of the target is expected to be that of its metabolites.
  - o The target substance and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the anthranilate fragment. The differences in the structure which are responsible for Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o The target substance and the read-across analogs have several genotoxicity alerts including carcinogen categorization by the ISS model. The data described in the genotoxicity section above show that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alerts will be superseded by the availability of the data.
  - o In spite of a structural alert due to the presence of a substituted amino group (Ashby and Tennant, 1988), the presence of the ortho carboxylic group might hinder the metabolic activation of the adjacent nitrogen substituent (Benigni et al, 2000).
  - o The target substance for repeated dose toxicity is categorized as an allyl esters substance with a hepatotoxicity alert by the HESS categorization scheme. It has been shown in the literature that allyl esters are metabolically hydrolyzed rapidly into alcohol and acid, and acids are excreted out from the human body relatively quickly with no toxic effects. The data described in the repeated dose section above for the allyl alcohol show that the margin of exposure of the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by availability of the data.
  - o The read-across analog is predicted to be a toxicant by the CAESAR model for developmental toxicity. The data described in the developmental toxicity section above shows that the read-across analog has adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - o The target substance is shown to have an ER binding alert. ER Binding is a molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity. It shows that the read-across analog is predicted to have similar reactivity compared to the target substance. The data described in the reproductive and developmental toxicity section shows that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of data.
  - o The target substance and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant.

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

Q1.Normal constituent of the body **No**
Q2.Contains functional groups associated with enhanced toxicity **No**
Q3.Contains elements other than C, H, O, N, divalent S **No**

Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate **No**
Q6.Benzene derivative with certain substituents **No**
Q7.Heterocyclic **No**
Q16.Common terpene (see Cramer, 1978 for explanation) **No**
Q17.Readily hydrolyzed to a common terpene **No**
Q19.Open chain **No**
Q23.Aromatic **Yes**
Q27.Rings with substituents **Yes**
Q28.More than one aromatic ring **No**
Q30. Aromatic ring with complex substituents **Yes**
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? **No**
Q32. Contains only the functional groups listed in Q30 or Q31 and either (a) a single fused non-aromatic carbocyclic ring or (b) aliphatic substituent chains longer than 5 carbon atoms or (c) a polyoxyethylene [(-OCH2CH2-)x, with x = 4] chain either on the aromatic ring or on an aliphatic side chain? **No**
Q22. Common component of food? **Yes**, Class Intermediate (Class II)

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.

Ashby, J., Tennant, R.W., 1988. Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. Mutat. Res. 204 (1), 17–115.

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel Fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Medizin Ernahr 8, 244–251.

Benigni, R., Giuliani, A., Franke, R., Gruska, A., 2000. Quantitative structure-activity relationships of mutagenic and carcinogenic aromatic amines. Chem. Rev. 100, 3697–3714.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of Cramer classification between Toxtree, the OECD QSAR Toolbox and expert judgment. Regulatory Toxicology and Pharmacology 71 (1), 52–62.

Bickers, D., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, H.J., Sipes, I.G., Smith, R.L., Tagami, H., 2003. A toxicological and dermatological assessment of linalool and related esters when used as fragrance ingredients. Food Chem. Toxicol. 41 (7), 919–942.

Cal, C.K., Kryzaniak, M., 2006b. 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. Control. Release 93 (3), 369–376.

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

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

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Benfenati, E., 2010, July. CAESAR models for developmental toxicity. In Chemistry Central Journal 4 (S1), S4 Springer International Publishing.

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.

Clark, R.L., Venkatasubramanian, K., Zimmerman, E.F., 1980. Cleft lip and palate caused by anthranilate methyl esters. Teratology 21 (2), 34a–35a.

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.

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

Cutting, W.C., Rogers, J., Roberts, J., Tabar, P., 1966. Antifertility effects of isatoic anhydride and derivatives. Med. Pharmacol. Exp. 15, 7–16.

DiSotto, A., Evandrib, M.G., Mazzanti, G., 2008. Antimutagenic and mutagenic activities of some terpenes in the bacterial reverse mutation assay. Mutat. Res. Genet. Toxicol. Environ. Mutagen 653 (1–2), 130–133.

DiSotto, A., Mazzanti, G., Carbone, F., Hrelia, P., Maffei, F., 2011. Genotoxicity of lavender oil, linalyl acetate, and linalool on human lymphocytes in vitro. Environ. Mol. Mutagen. 52 (1), 69–71.

ECHA, 2012a. Anthranilic Acid Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/6447/1.

ECHA, 2012b. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. European chemical agency read-across assessment framework. ECHA read-across assessment framework. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Eder, E., Henschler, D., Neudecker, T., 1982. Mutagenic properties of allylic and alpha, beta-unsaturated compounds: consideration of alkylating mechanisms. Xenobiotica 12 (12), 831–848.

Ekman, B., Strombeck, J.P., 1949. The effect of some splitproducts of 2,3'-azotoluene on the urinary bladder in the rat and their excretion on various diets. Acta Path. Microbiol. Scand. 26, 447–471.

Foltinova, P., Grones, J., 1997. Euglena gracilis as an eukaryotic test organism for detecting mutagens and antimutagens. Mutation Research. Genet. Toxicol. Environ. Mutagen 393 (1–2), 1–6.

Fowler, P., Smith, K., Young, J., Jeffrey, L., Kirkland, D., Pfuhler, S., Carmichael, P., 2012. Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type. Mutat. Res. Genet. Toxicol. Environ. Mutagen 742 (1–2), 11–25.

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

Grundschober, F., 1977. Toxicological assessment of flavouring esters. Toxicology 8, 387–390.

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 Cosmet. 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.

Hughes, C., Rabinowitz, A., Tate, M., Birrell, L., Allsup, J., Billinton, N., Walmsley, R.M., 2012. Development of a high-throughput Gaussia luciferase reporter assay for the activation of the GADD45a gene by mutagens, promutagens,clastogens, and aneugens. J. Biomol. Screen 17 (10), 1302–1315.

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

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

Jager, W., Buchbauer, G., Jirovetz, L., Fritzer, M., 1992. Percutaneous absorption of lavender oil from a massage oil. J. Soc. Cosmet. Chem. Jpn. 43 (1), 49–54.

Jirovetz, L., Buchbauer, G., Jager, W., Raverdino, V., Nikiforov, A., 1990. Determination of lavender oil fragrance compounds in blood samples. Fresenius J. Anal. Chem. 338 (8), 922–923.

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

Kawachi, T., Komatsu, T., Kada, T., Ishidate, M., Sasaki, M., Sugiyama, T., Tazima, Y., 1981. Results of recent studies on the relevance of various short-term screening tests in Japan. Appl. Methods Oncol. 3, 253–267.

Kuroda, K., Tanaka, S., Yu, Y.S., Ishibashi, T., 1984. Rec-assay of food additives. Nippon Kosnu Eisei Zasshi 31 (6), 277–281.

Lutz, D., Neudecker, T., Eder, E., 1980. Mutagenic effects of allylic alcohols and their corresponding aldehydes. Arch. Pharmacol. 311 (Suppl. l), R25.

Mademtzoglou, D., Akmoutsou, P., Kounatidis, I., Franzios, G., Drosopoulou, E., Vokou, D., Mavragani-Tsipidou, P., 2011. Applying the Drosophila wing spot test to assess the genotoxic impact of 10 essential oil constituents used as flavouring agents or cosmetic ingredients. Flavour Fragrance J. 26 (6), 447–451.

Meesters, R.J.W., Duisken, M., Hollender, J., 2007. Study on the cytochrome P450-mediated oxidative metabolism of the terpene alcohol linalool: indication of biological epoxidation. Xenobiotica 37 (6), 604–617.
Meyer, F., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneimittel-Forsch.(Drug Res.) 9, 516–519.
Meyer, F., 1965. Penetrating Agents. Patent. British, 1,001,949, M49750IVa/30h, 7/20/61.
Mitic-Culafic, D., Zegura, B., Nikolic, B., Vukovic-Gacic, B., Knezevic-Vukcevic, J., Filipic, M., 2009. Protective effect of linalool, myrcene and eucalyptol against t-butyl hydroperoxide induced genotoxicity in bacteria and cultured human cells. Food Chem. Toxicol. 47 (1), 260–266.
Miyagawa, M., Takasawa, H., Sugiyama, A., Inoue, Y., Murata, T., Uno, Y., Yoshikawa, K., 1995. The in vivo-in vitro replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative non-genotoxic (Ames-negative) mouse hepatocarcinogens. Mutat. Res. Genet. Toxicol. 343 (1), 157–183.
National Cancer Institute, 1978. Bioassay of Anthranilic Acid (Benzoic Acid, 2-amino-) for Possible Carcinogenicity. NCI-CG-TR-36. Unpublished.
Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen. 9, 177–181.
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/.
OECD, 2012. The OECD QSAR Toolbox, v3.4. http://www.qsartoolbox.org/.
Parke, D.V., Rahman, K.H.M.Q., Walker, R., 1974. The absorption, distribution & excretion of linalool in the rat. Biochem. Soc. Trans. 2 (4), 612–615.
Patel, H., ten Berge, W., Cronin, M.T.D., 2002. Quantitative structure-activity relationships (QSARs) for the prediction of skin permeation of exogenous chemicals. Chemosphere 48 (6), 603–613.
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.
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), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1802. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1974. In Vitro Study on the Hydrolysis of Eight Carboxylic Esters by Intestinal and Liver Enzymes. Unpublished Report from Naarden Inc. RIFM Report Number 8217. 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), 1991. Determination of the Partition Coefficient of Linalool. Unpublished Report from Givaudan. RIFM Report Number 51349. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1998. Report on the Metabolism of Linalool in Rat Tissue & Intestinal Homogenates. Report to FEMA. Unpublished Report from Flavor and Extract Manufacturers Association. RIFM Report Number 34252. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2001. Micronucleus Test in Bone Marrow Cells of the Mouse with Linalool. Private Communication to FEMA. Unpublished Report from Hoffmann-LaRoche. RIFM Report Number 38577. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc)., 2003. Fragrance Material Review on Linalool. RIFM Report Number 42696. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2007a. 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), 2007b. 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), 2007c. 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), 2007d. 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 (Research Institute for Fragrance Materials, Inc), 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), 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), 2014. An in Silico Skin Absorption Model for Fragrance Materials. RIFM Report Number 67839. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 12, August 2016.
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.
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.
Schafer Jr., E.W., Bowles Jr., W.A., 1985. Acute oral toxicity and repellency of 933 chemicals to house and deer mice. Arch. Environ. Contam. Toxicol. 14, 111–129.
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., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 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, 164–176.
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.
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.
Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., Thomas, C.A., 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol. Appl. Pharmacol. 56 (2), 265–273.
Yamaori, S., Yokozuka, H., Sasama, A., Funahashi, T., Kimura, T., Yamamoto, I., Watanabe, K., 2005. Hepatic metabolism of methyl anthranilate and methyl N-methylanthranilate as food flavoring agents in relation to allergenicity in the Guinea pig. J. Health Sci. 51 (6), 667–675.
Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. J. Osaka City Med. Cent. 34 (3–4), 267–288 [Osaka-shi Igakkai Zasshi].
Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ. Mutagen. 9 (S9), 1–110.