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Short review

RIFM fragrance ingredient safety assessment, linalyl isobutyrate, CAS registry number 78-35-3

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ABSTRACT

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 safety. Reproductive toxicity was based on the Threshold of Toxicological Concern (TTC) of 0.03 mg/kg/day for a Cramer Class I material. The estimated systemic exposure is determined to be below this value while assuming 80% absorption from skin contact and 100% from inhalation. A systemic exposure below the TTC value is acceptable.

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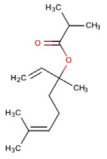
Abbreviation list

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

Version: 071615. This version replaces any previous versions.
Name: Linalyl isobutyrate
CAS Registry Number: 78-35-3



RIFM's Expert Panel[a] 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., 2015) 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).

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 safety. Reproductive toxicity was based on the Threshold of Toxicological Concern (TTC) of 0.03 mg/kg/day for a Cramer Class I material. The estimated systemic exposure is determined to be below this value while assuming 80% absorption from skin contact and 100% from inhalation. A systemic exposure below the TTC value is acceptable.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (RIFM, 2003a; RIFM, 2000)

Repeated Dose Toxicity: NOAEL = 500 mg/kg/day (Hagan et al., 1967)

Developmental and Reproductive Toxicity: Developmental NOAEL = 150 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC. (Vollmuth et al., 1990)

Skin Sensitization: Not a sensitization concern (RIFM, 2010; Greif, 1967; RIFM, 2002; RIFM, 1974b; Skold et al., 2005; Skold et al., 2008)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment
Persistence: Critical Measured Value: 96.9% (OECD 301B) Read - across to linalyl acetate CAS# 115-95-7
(RIFM, 1998a; RIFM, 1998b)
Bioaccumulation: Screening Level: 1448 L/Kg
(Episuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 96 h. Algae EC50: 0.132 mg/l
(Episuite ver 4.1)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment
Screening-Level: PEC/PNEC (North America and Europe) > 1
(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96 h. Algae EC50: 0.132 mg/l
(Episuite ver 4.1)
RIFM PNEC is: 0.0132 μg/L
- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

[a] 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.

1. Identification

1. **Chemical Name:** Linalyl isobutyrate
2. **CAS Registry Number**: 78-35-3
3. **Synonyms:** 3,7-Dimethyl-1,6-octadien-3-yl isobutanoate, 3,7-Dimethyl-1,6-octadien-3-yl 2-methylpropanoate, 1,5-Dimethyl-1-vinyl-4-hexenyl isobutyrate, Isobutyric acid, 1,5-dimethyl-1-vinyl-4-hexenyl ester, Linalool isobutyrate, Linalool 2-methylpropanoate, Linalyl isobutyrate, Propanoic acid, 2-methyl-, 1-ethenyl-1,5-dimethyl-4-hexenyl ester, ｱﾙｶﾝ酸(C=1～6)ｼﾞﾒﾁﾙｵｸﾀｼﾞｴﾆﾙ, 1,5-Dimethyl-1-vinylhex-4-en-1-yl 2-methylpropanoate
4. **Molecular Formula**: $C_{14}H_{24}O_2$
5. **Molecular Weight**: 224.34
6. **RIFM Number**: 508

2. Physical data

1. **Boiling Point:** >200 °C [FMA database], (calculated) 253.99 °C [EPI Suite]
2. **Flash Point:** >200 °F; CC [FMA database]
3. **Log K_{OW}:** 5.3 [EPI Suite]
4. **Melting Point**: 8.99 °C [EPI Suite]
5. **Water Solubility:** 0.9804 mg/L [EPI Suite]
6. **Specific Gravity:** 0.885 [FMA database]
7. **Vapor Pressure:** 0.0536 mm Hg @ 20 °C [EPI Suite 4.0], 0.01 mm Hg 20 °C [FMA], 0.0823 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minimal absorption in the region of 290–500 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Colorless to slightly yellow liquid with a floral, rosy, fresh, sweet odor more floral and less fruity than the n-butyrate, not quite as heavy and less plum like, more rosy yet overall fresh sweet and moderate tenacity (Arctander, 1969).

3. Exposure

1. **Volume of Use (worldwide band)**: <1 metric tons per year [IFRA, 2011]
2. **Average Maximum Concentration in Hydroalcoholics**: 0.48% [IFRA, 2002]
3. **97.5th Percentile**: 1.2% [IFRA, 2002]
4. **Dermal Exposure**[a]: 0.0306 mg/kg/day [IFRA, 2002]
5. **Oral Exposure**: Not available
6. **Inhalation Exposures**[b]: 0.0019 mg/kg/day [IFRA, 2002]
7. **Total Systemic Exposure (Dermal + Inhalation)**: (0.0306 mg/kg/day × 80%) + 0.0019 mg/kg/day = 0.026 mg/kg/day

[a] Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).
[b] Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

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

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

	Parent	Metabolite	Metabolite
Name	Linalyl isobutyrate	Linalool	Isobutyric acid
J_{max} (mg/cm^2/h)	6.19[a]		3228.89[c]
Skin Absorption Class	40%	14.4%[b]	80%

Linalool is not only a metabolite but a read across analog and its skin absorption of 14.4% is more reflective of that of linalyl isobutyrate. However, for conservative purposed 80% is considered.
Refined dermal exposure: 0.0306 mg/kg/day × 80% = 0.0245 mg/kg/day.
[a] J_{max} was calculated based on estimated log K_{ow} = 4.49 (consensus model) and Solubility = 60.02 mg/L (consensus model).
[b] Human In vitro skin penetration study (RIFM, 2007a).
[c] J_{max} was calculated based on measured log K_{ow} = 0.94 (Patel et al., 2002) and Solubility = 1.67*10^5 mg/L (PhysProp Db).

2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Assume Dermal (80%) + Inhalation (100%) absorbed = (0.0306 mg/kg/day × 80%) + 0.0019 mg/kg/day = 0.026 mg/kg/day

5. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert judgment	Toxtree v 2.6	OECD QSAR toolbox v 3.2
I	I	I

2. **Analogues Selected**:
   a. **Genotoxicity:** Linalyl acetate (CAS # 115-95-7)
   b. **Repeated Dose Toxicity**: None

c. **Developmental and Reproductive Toxicity:** Linalool (CAS # 78-70-6); dehydrolinalool (CAS # 29171-20-8); isobutyric acid (CAS # 79-31-2)
d. **Skin Sensitization:** Linalyl acetate (CAS # 115-95-7)
e. Phototoxicity/Photoallergenicity: None
f. **Local Respiratory Toxicity:** Linalool (CAS # 78-70-6); isobutyric acid (CAS # 79-31-2)
g. **Environmental Toxicity:** Linalyl acetate (CAS # 115-95-7)

3. **Read-across Justifications**: See Appendix below

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

Linalyl isobutyrate is reported to occur in the following foods[1]: Mangifera species.

7. IFRA standard

None

8. Reach dossier

Pre-registered for 2010; No dossier available as of 07/16/15

9. Summary

1. Human Health Endpoint Summaries:

9.1. Genotoxicity

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

9.2. Risk assessment

Linalyl isobutyrate was tested by the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity indicating a lack for genotoxic concern (RIFM, 2013). The mutagenic activity of linalyl isobutyrate was assessed in an Ames assay in compliance with GLP regulations and in accordance with OECD TG 471 using both the standard plate incorporation and modified preincubation methods. Salmonella typhimurium strains TA1535, TA1537, TA98, TA100, and TA102 were exposed to linalyl isobutyrate in DMSO (diemthyl sulfoxide) at concentrations of 100, 333, 1000, 2500 and 5000 μg/plate in the presence and absence of metabolic activation for all strains except TA 1535 which was tested in the dose range of 33.3–5000 μg/plate. No increases in revertant colonies were observed in any of the tester strains at any concentration (RIFM, 2003a). Under the conditions of the study, linalyl isobutyrate was considered not mutagenic in the Ames test (RIFM, 2003a).

There are no studies assessing the clastogenic activity of linalyl isobutyrate. Read across material linalyl acetate (CAS # 115-95-7; see Section 5) was assessed for clastogenic activity in a GLP compliant *in vitro* chromosome aberration study conducted in accordance with OECD TG 473. Human peripheral blood lymphocytes were exposed to linalyl acetate in DMSO in the presence and absence of metabolic activation at concentration up to 130 μg/ml in the absence of S-9 mix and 180 μg/ml in the presence of S-9. No statistically or biologically significant increase in the number of cells with chromosome aberrations was induced (RIFM, 2000). Under the conditions of the study, linalyl acetate was considered unable to induce chromosomal aberrations and this can be extended to linalyl isobutyrate.

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

Additional References: DiSotto et al., 2008; RIFM, 1984; Heck et al., 1989; DiSotto et al., 2011; Oda et al., 1978.

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

9.3. Repeated dose toxicity

The margin of exposure for the repeated dose toxicity endpoint is 19231.

9.4. Risk assessment

In a dietary 18-week chronic toxicity study conducted in rats with linalyl isobutyrate, the NOAEL was determined to be 500 mg/kg/day, the highest dosage tested (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967).

Additional References: Letizia et al., 2003a; Bickers et al., 2003; RIFM, 1958a; Letizia et al., 2003b; Stoner et al., 1973; Van Duuren et al., 1971; RIFM, 1998a; Jager et al., 1992; Meyer and Meyer, 1959; Meyer, 1965; Cal and Sznitowska, 2003; RIFM, 1996; Letizia et al., 2003c, 2003d, 2003e, 2003f; RIFM, 1980; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008a; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003g; Lapczynski et al., 2008a, 2008b, 2008c; Belsito et al., 2008; Belsito et al., 2010; RIFM, 1958b; RIFM, 1979; RIFM, 2012; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982, 1984; RIFM, 1998b; Schmitt et al., 2010; Cal, 2006; Cal and Kryzaniak, 2006; Katz and Guest, 1994; DiVincenzo and Hamilton, 1979; Thomas and Stalder, 1958; Kanazu and Yamaguchi, 1997; Bechtel and Cornish, 1975; Dryden and Hartman, 1971.

Literature Search and Risk Assessment Completed on: 03/21/14.

9.5. Developmental and reproductive toxicity

The margin of exposure for the developmental toxicity endpoint is 5769. The exposure is below the TTC for the reproductive toxicity endpoint.

9.6. Risk assessment

There are no developmental toxicity data on linalyl isobutyrate. Linalyl isobutyrate is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6; see Section 5) and isobutyric acid (CAS # 79-31-2; see Section 5). In a gavage developmental toxicity study conducted in rats with linalool, the NOAEL for developmental toxicity was determined to be 1000 mg/kg/day, the highest dosage tested (Politano et al., 2008 data also available in RIFM, 2006; Letizia et al., 2007). A gavage reproduction and developmental screening study conducted in rats with isobutyric acid determined the developmental NOAEL to be 150 mg/kg/day, the highest dosage tested (Vollmuth et al., 1990; poster). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure,

[1] 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.

150/0.026 or 5769.

There are no reproductive toxicity data on linalyl isobutyrate. Linalyl isobutyrate is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6) and isobutyric acid (CAS # 79-31-2). There are no reproductive data on linalool; however, read-across material dehydrolinalool (CAS # 29171-20-8; see Section 5) has a reproductive toxicity screening study in rats. The NOAELs were determined to be 750 mg/kg/day for males, the highest dosage tested, and 200 mg/kg/day for the offspring and dams, based on maternal clinical signs and decreased live birth index and viability (ECHA REACH Dossier: Linalool Read across Subs Key Toxicity to reproduction.003 (accessed 02/19/13)). There are no reproductive toxicity data on isobutyric acid; therefore, a NOAEL for linalyl isobutyrate could not be determined. When correcting for skin absorption, the current total systemic exposure (26 μg/kg/day) is below the TTC for linalyl isobutyrate (30 μg/kg bw/day).

Additional References: Letizia et al., 2003a; Bickers et al., 2003; RIFM, 1958a; Letizia et al., 2003b; Stoner et al., 1973; Van Duuren et al., 1971; RIFM, 1998a; Jager et al., 1992; Meyer and Meyer, 1959; Meyer, 1965; Cal and Sznitowska, 2003; RIFM, 1996; Letizia et al., 2003c, 2003d, 2003e, 2003f; RIFM, 1980; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003g; Lapczynski et al., 2008a, 2008b, 2008c; Belsito et al., 2008, 2010; RIFM, 1958b; RIFM, 1979; RIFM, 2012; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982, 1984; RIFM, 1998b; Schmitt et al., 2010; Cal, 2006; Cal and Kryzaniak, 2006; Katz and Guest, 1994; DiVincenzo and Hamilton, 1979; Thomas and Stalder, 1958; Kanazu and Yamaguchi, 1997; Bechtel and Cornish, 1975; Dryden and Hartman, 1971.

Literature Search and Risk Assessment Completed on: 03/21/14.

9.7. skin sensitization

Based on the available material specific data and read across to linalyl acetate (CAS # 115-95-7); linalyl isobutyrate does not present a concern for skin sensitization.

9.8. Risk assessment

Based on the available material specific data and read across to linalyl acetate (CAS # 115-95-7; see Section 5), linalyl isobutyrate does not present a concern for skin sensitization. Linalyl acetate and linalyl isobutyrate are not predicted to be directly reactive to skin proteins (Roberts et al., 2007 OECD toolbox v3.0). However, linalyl acetate is known to undergo auto-oxidation resulting in degradation products that may be protein reactive (Skold et al., 2008). In the local lymph node assay (LLNA), positive results have been reported to linalyl acetate with EC3 values in the range of 3.6%–25% (900–6250 μg/cm2) (RIFM, 2002; Skold et al., 2008). In the LLNA these positive results have been shown to be due to sensitizing products of autoxidation and irritation to linalyl acetate (RIFM, 2010; Skold et al., 2005, 2008). In the human maximization test positive results were reported at concentrations of 10% linalyl acetate in petrolatum; however these results were also demonstrated to be the result of test sample impurities as retesting of purified samples demonstrated no sensitization potential (RIFM, 1974a; RIFM, 1982). In the human maximization test no reactions indicative of sensitization were observed at higher concentrations (12.5% and 20.0%) to linalyl acetate (Greif, 1967; RIFM, 1975). Additionally, linalyl isobutyrate did not result in skin sensitization reactions in the human maximization test (RIFM, 1974b).

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

Additional References: None.

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

9.9. Phototoxicity/photoallergenicity

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

9.10. Risk assessment

The available UV/Vis spectra for linalyl isobutyrate indicate no absorbance between 290 and 500 nm. Molar absorption coefficient for λ max within this range is below 1000 L mol^{-1} cm^{-1}, the benchmark of concern for phototoxicity (Henry et al., 2009). Based on the lack of absorbance in the critical range, linalyl isobutyrate would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

9.11. Local respiratory toxicity

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

9.11.1. Risk assessment

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 1.2%. If the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) the inhalation combined exposure would be 0.11 mg/day, as calculated using the 97.5th percentile IFRA survey hydroalcoholic use value based on RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model.

There are no inhalation data available on linalyl isobutyrate. Linalyl isobutyrate metabolizes to linalool (CAS # 78-70-6; see Section 5) and isobutyric acid (CAS # 79-31-2; see Section 5) in the respiratory tract and a NOAEC of 10 ppm (63 mg/m^3) has been determined (RIFM, 2012) for linalool in a 2 week acute inhalation study where this was the highest dose tested. 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 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.063 mg/L) (61.2 L/d) = 3.856 mg/d
- (3.856 mg/d)/(0.0016 kg lung weight of rat[2]) = 2410 mg/kg lw/day

To compare the inhalation exposure (0.19 mg/day) with the linalool NOAEC expressed in mg/kg lung weight/day this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to

[2] 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."

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.407 mg/l			1,000,000	0.000407 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.357mg/l	0.521 mg/l	0.132 mg/l	10,000	0.0132 µg/l	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.459 mg/l	1.130 mg/l	0.229 mg/l			Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.202 mg/l	0.156 mg/l	0.408 mg/l			Neutral organics SAR (Baseline toxicity)

give, 0.30 mg/kg lung weight/day resulting in a MOE of 13388 (i.e., [2410 mg/kg lw/day]/[0.18 mg/kg lung weight/day].

For the metabolite isobutyric acid (CAS # 79-31-2, see Section 5) rats were exposed to a dose of 9.59 mg/l in an OECD 403 study (ECHA REACH Dossier: isobutyric acid). No mortality was observed for the extended exposure period of 8 h; there is no inhalation hazard for isobutyric acid under normal conditions of exposure.

For further weight of evidence, the inhalation exposure value (0.18 mg/day) is below the Cramer Class I TTC level of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009) and is deemed safe for use at the reported use level.

Based on the TTC, the MOE of the metabolite linalool, and the unlikely inhalation hazard for isobutyric acid, linalyl isobutyrate is deemed safe for use at the reported use level.

Additional References: RIFM, 1977; Jirovetz et al., 1991; Buchbauer et al., 1991; Jirovetz et al., 1990; RIFM, 1997; Buchbauer et al., 1993; Perrucci et al., 1996; Perrucci, 1995; Rice and Coats, 1994a; Silver, 1992; Karr and Coats, 1992; Regnault-Roger and Hamraoui, 1995; Rice and Coats, 1994b; Perrucci et al., 1995; Sugawara et al., 1998; Coats et al., 1991; Cometto-Muniz et al., 1998; Isola et al., 2003a; RIFM, 2003c; Rogers et al., 2003; 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., 2005; Kuroda et al., 2005; Tanida et al., 2006; Yang et al., 2005; Corsi et al., 2007; Sato et al., 2007; Nakamura et al., 2010, 2009; deMouraLinck, 2009; Bensafi et al., 2002.

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

2. Environmental Endpoint Summary:

9.12. Analogues identified/justification

Linalyl acetate (CAS # 115-95-7) has been identified as read-across analogs for linalyl isobutyrate based on structure and physical/chemical properties. Both materials are aliphatic esters with predicted Kow of 4.39 and 5.3 for linalyl acetate and linalyl isobutyrate respectively. Available biodegradation data for linalyl acetate shows a biodegradation of 96.9% after 28 days, confirming that the material is not persistent; therefore it should be assume that linalyl isobutyrate is also not to be persistent. This is also supported by the BIOWIN models for biodegradation.

9.13. Screening-level assessment

A screening level risk assessment of linalyl isobutyrate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate

the PNEC). Following the RIFM Environmental Framework, linalyl isobutyrate was identified as a fragrance material with potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC > 1).

A screening-level hazard assessment using EPISUITE ver 4.1 did identify linalyl isobutyrate as possibly persistent and bioaccumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

9.14. Risk assessment

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

9.15. Key studies

Biodegradation: No data available.

9.15.1. Ecotoxicity

RIFM, 2005: A 10 days chronic static renewal effluent toxicity test with *daphnia magna* was conducted according to the EPA/600/4–90/027 and ASTM E729, 1997 methods. The LC50 was calculated to be 2.94 mg/l and the NOECs were 1.47 mg/l for reproduction and 2.94 mg/l for survival.

RIFM, 2005: Short-term, 7 days, chronic static renewal effluent toxicity tests with immature fathead minnows, *Pimephales promelas*, were conducted according to the EPA/600/4–90/027 and ASTM E729, 1997 methods. The LC50 was calculated to be 2.94 mg/l and the NOECs were 1.47 mg/l for growth and 2.94 mg/l for survival.

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

The following biodegradation tests for linalyl acetate (CAS # 115-95-7) are available in RIFM Database:

RIFM, 1994: A sealed vessel test was conducted according to OECD Guideline 301B. Mineral salts medium inoculated with activated secondary effluent and 10 mg/l of linalyl acetate were incubated for 28 days. The biodegradation rate was 96.9%.

RIFM, 1991: A modified MITI Test was conducted according to the OECD 301C guidelines. Bottles containing approximately 100 mg/l of linalyl acetate and medium inoculated with 30 mg/l activated sludge were incubated for 28 days. The biodegradation rate at 28 days was 75%.

9.16. Risk assessment refinement

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

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.3	5.3
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 0.0132 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

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

10. Literature search[3]

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **CHA:** 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

This is not an exhaustive list.

Appendix C. Supplementary data

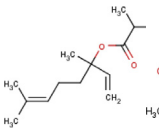
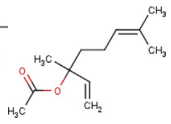
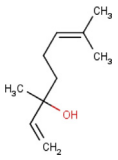
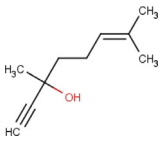
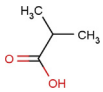
Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.09.013.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.06.014.

Appendix A

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

	Target material	Read across materials			
Principal name	Linalyl isobutyrate	Linalyl acetate	Linalool	Dehydrolinalool	Isobutyric acid
CAS No.	78-35-3	115-95-7	78-70-6	29171-20-8	79-31-2
Structure					
3D Structure	http://www.thegoodscentscompany.com/opl/78-35-3.html	http://www.thegoodscentscompany.com/opl/115-95-7.html	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/29171-20-8.html	http://www.thegoodscentscompany.com/opl/79-31-2.html
Read-across endpoint		• Genotoxicity • Skin sensitization • Environmental	• Devel/Repro • Respiratory	• Devel/Repro	• Devel/Repro • Respiratory
Molecular Formula	C14H24O2	C12H20O2	C10H18O	C10H16O	C4H8O2
Molecular Weight	224.35	196.29	154.25	152.24	88.11
Melting Point (°C, EPISUITE)	8.99	−2.09	−11.39	15.40	−8.29
Boiling Point (°C, EPISUITE)	253.99	228.95	204.05	212.37	153.79
Vapor Pressure (Pa @ 25 °C, EPISUITE)	10.97	17.47	11.09	4.64	436
Log Kow (KOWWIN v1.68 in EPISUITE)	5.30	4.39	3.38	2.75	1.00
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	0.9804	20.12	683.7	1084	4.918e + 004
J_{max} (mg/cm^2/h, SAM)	6.194908373	11.1668059	90.06108298	93.21980338	2771.973947
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	310.25715	176.001525	4.285034	0.449174	0.097809
Similarity (Tanimoto score)[a]		81%	NA[b]	NA[b]	NA[b]
Genotoxicity					
DNA binding (OASIS v1.1)	• No alert found	• Schiff base formers • Schiff base formers >> Direct acting Schiff base formers • Schiff base formers >> Direct acting Schiff base formers >> Specific Acetate Esters • SN1 • SN1 >> Carbenium ion formation • SN1 >> Carbenium ion formation >> Specific Acetate Esters • SN2 • SN2 >> Acylating agents • SN2 >> Acylating agents >> Specific Acetate Esters • SN2 >> SN2 at sp3-carbon atom • SN2 >> SN2 at sp3-carbon atom >> Specific Acetate Esters			
DNA binding (OECD)	• No alert found	• No alert found			
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found			
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found			
In vitro mutagenicity (Ames test) alerts (ISS)	• No alert found	• No alert found			
In vivo mutagenicity (Micronucleus) alerts (ISS)	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor			
Oncologic classification (OECD)	• Not classified	• Not classified			
Developmental and Reproductive Toxicity					
ER binding (OECD)	Non binder, non cyclic structure		Non binder, non cyclic structure	Non binder, non cyclic structure	Non binder, non cyclic structure
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (low reliability)		NON-Toxicant (low reliability)	NON-Toxicant (low reliability)	Toxicant (low reliability)
Skin Sensitization					
Protein binding (OASIS v1.1)	• No alert found	• No alert found			
Protein binding (OECD)	• No alert found	• No alert found			

(*continued on next page*)

(*continued*)

	Target material	Read across materials			
Principal name	Linalyl isobutyrate	Linalyl acetate	Linalool	Dehydrolinalool	Isobutyric acid
CAS No.	78-35-3	115-95-7	78-70-6	29171-20-8	79-31-2
Protein binding potency (OECD)	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)			
Protein binding alerts for skin sensitization (OASIS v1.1)	• No alert found	• No alert found			
Skin sensitization model (CAESAR v2.1.5)	Sensitizer (good reliability)	Sensitizer (good reliability)			
Metabolism					
Rat liver S9 metabolism simulator (OECD)	See Supplemental data 1	See Supplemental data 2	See Supplemental data 3	See Supplemental data 4	No Metabolites found

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

Summary:

There are insufficient toxicity data on linalyl isobutyrate (RIFM # 508, CAS # 78-35-3). 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 SuiteTM v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale

- Linalyl acetate (analog) was used as a read-across analog for linalyl isobutyrate (target) based on:
  - The target and analog belong to the generic class of aliphatic esters, specifically, esters/branched chain alcohol simple acid esters/tertiary alcohols.
  - They have the same alcohol part and similar carboxylic acid part.
  - The key difference is that the target is an isobutyrate, while the analog is an acetate. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - The target and analog show similar alerts for protein binding.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox they are predicted to have similar metabolites.
- Linalool, dehydrolinalool and isobutyric acid (analogs) were used as a read-across for linalyl isobutyrate (target) based on:
  - The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - Linalyl isobutyrate is an ester formed by linalool and isobutyric acid. Dehydrolinalool is an analog of linalool
  - The differences among the target and read-across materials can be mitigated by the fact that the target could readily hydrolyze to the metabolites. Therefore the toxicity profiles are expected to be that of the metabolites
  - They all also show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - As per the OECD QSAR Toolbox linalool and isobutyric acid are predicted as metabolites (see Metabolites # 3 & 4) of the target.

Environmental analog justification:

Linalyl acetate (CAS # 115-95-7) has been identified as read-across analogs for linalyl isobutyrate based on structure and physical/chemical properties. Both materials are aliphatic esters with predicted K_{ow} of 4.39 and 5.3, for linalyl acetate and linalyl isobutyrate, respectively. Available biodegradation data for linalyl acetate shows a biodegradation of 96.9% after 28 days, confirming that the material is not persistent; therefore it should be assume that linalyl isobutyrate is also not to be persistent. This is also supported by the BIOWIN models for biodegradation.

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