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Short review

RIFM fragrance ingredient safety assessment, Linalyl isovalerate, CAS Registry Number 1118-27-0

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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 equal to this value while assuming 100% absorption from skin contact and inhalation. A systemic exposure at or below the TTC value is acceptable.

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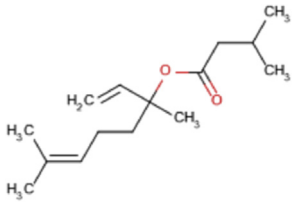
Abbreviation list

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: 071515. This version replaces any previous versions.
Name: Linalyl isovalerate
CAS registry number: 1118-27-0



RIFM's expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's criteria document (Api et al., 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).
*RIFM's expert Panel is an independent body that selects its own members and establishes its own operating procedures. The expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: **The use of this material under current use conditions is supported by the existing information**.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental 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 equal to this value while assuming 100% absorption from skin contact and inhalation. A systemic exposure at or below the TTC value is acceptable.

Human health safety assessment

Genotoxicity: Not genotoxic	(RIFM, 2004a; DiSotto, 2011)
Repeated dose toxicity: NOAEL = 500 mg/kg/day	(Hagan et al., 1967)
Developmental and reproductive toxicity: Developmental NOAEL = 600 mg/kg/day. No reproductive NOAEL. Exposure is at the TTC.	(Politano, 2008; ECHA REACH Dossier: Isovaleric acid)
Skin sensitization: Not a sensitization concern	(RIFM, 2010; RIFM, 1982; Skold, 2008)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV spectra, RIFM DB)
Local respiratory toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 96.9% (OECD 301B) Read – across to linalyl acetate CAS # 115-95-7	(RIFM, 1994)
Bioaccumulation: Screening Level: 3054 L/kg	(EPISUITE ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 0.162 mg/l	(Salvito et al., 2002)
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: Fish LC50: 0.162 mg/l	(Salvito et al., 2002)
RIFM PNEC is: 0.000162 μg/L	

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; Cleared at Screening Level

1. Identification

1. **Chemical Name:** Linalyl isovalerate
2. **CAS Registry Number:** 1118-27-0
3. **Synonyms:** 3,7-Dimethyl-1,6-octadien-3-yl isovalerate, 3,7-Dimethyl-1,6-octadien-3-yl 3-methylbutanoate, Isovaleric acid, 3,7-dimethyl-1,6-octadien-3-yl ester, Linalyl isovalerate, Linalyl isovalerianate, Linalyl isopentanoate, Linalyl 3-methylbutanoate, ｱﾙｶﾝ(C=1～6)酸ｼﾞﾒﾁﾙｵｸﾀﾋﾞｴﾆﾙ, 1,5-Dimethyl-1-vinylhex-4-en-1-yl 3-methylbutanoate
4. **Molecular Formula:** $C_{15}H_{26}O_2$
5. **Molecular Weight:** 238.37
6. **RIFM Number:** 638

2. Physical data

1. **Boiling Point:** 270.82 °C [EPI Suite]
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 5.79 [EPI Suite]
4. **Melting Point**: 19.54 °C [EPI Suite]
5. **Water Solubility:** 0.3135 mg/l [EPI Suite]
6. **Specific Gravity:** 1.4505 [RIFM]
7. **Vapor Pressure:** 0.00542 mm Hg @ 20 °C [EPI Suite 4.0], 0.00883 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorption in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1}).
9. **Appearance/Organoleptic:** Colorless, oily liquid with a sweet, fruity, citrusy odor, rich, apple like, clary-sage and tea like undertones and moderate tenacity. Apple-like sweet and powerful taste, remotely reminiscent of peach and plum (Arctander, 1969).

3. Exposure

1.**Volume of Use (worldwide band):** <1 metric tons per year	[IFRA, 2011]
2.**Average Maximum Concentration in Hydroalcoholics:** 0.40%	[IFRA, 2002]
3.**97.5**th **Percentile:** 1.1%	[IFRA, 2002]
4.**Dermal Exposure**[a]: 0.0280 mg/kg/day	[IFRA, 2002]
5.**Oral Exposure:** Not available	
6.**Inhalation Exposures**[b]: 0.0016 mg/kg/day	[IFRA, 2002]
7.**Total Systemic Exposure (Dermal + Inhalation):** 0.030 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, 2002; Ford, 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:** Assumed 100%
2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.030 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 propionate (CAS # 144-39-8); linalyl acetate (CAS # 115-95-7)
   b. **Repeated Dose Toxicity:** Linalyl isobutyrate (CAS # 78-35-3)
   c. **Developmental and Reproductive Toxicity:** Linalool (CAS # 78-70-6); dehydrolinalool (CAS # 29171-20-8); isovaleric acid (CAS # 503-74-22)
   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 isovalerate is reported to occur in the following foods[1]:
Salvia species.
Wormwood oil (Artemisia absinthium L.)

7. IFRA standard

None.

8. REACH dossier

Pre-Registered for 2010; No dossier available as of 07/15/15.

[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.

9. Summary

9.1. Human health endpoint summaries

9.1.1. Genotoxicity

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

9.1.2. Risk assessment

Linalyl isovalerate was tested in using the BlueScreen and was found negative for both cytotoxicity and genotoxicity indicating a lack of genotoxic potential (RIFM, 2013). There are no additional studies assessing the mutagenic potential of linalyl isovalerate. Read across can be made to linalyl propionate (CAS # 144-39-8; see Section 5) which was assessed for mutagenicity in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the preincubation and plate incorporation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with linalyl propionate in DMSO (dimethyl sulfoxide) at the concentrations 33, 100, 333, 1000, 2500 and 5000 μg/plate in the presence and absence of metabolic activation (S-9). In the preincubation test, the experiment was repeated with strain TA102 at the additional concentrations range of 10 and 666 μg/plate because only three out of the original six concentrations were analyzable without metabolic activation. No increase in the number of revertant colonies was observed in any of the tester strains at any concentration (RIFM, 2004a). Under the conditions of the study, linalyl propionate was considered not mutagenic in the Ames assay and this can be extended to linalyl isovalerate.

No studies are available that assess the clastogenic activity of linalyl isovalerate. The material linalyl acetate (CAS # 115-95-7; see Section 5) was identified as read across and was assessed in an *in vitro* micronucleus assay conducted equivalent to OECD TG 487. In five independent experiments, human peripheral lymphocytes were treated with linalyl acetate in DMSO at concentrations of 0.5, 1, 3, 10, 30, 100 and 300 μg/ml. Linalyl acetate had no effects on micronuclei formation in the test treated samples (DiSotto et al., 2011). Under the conditions of the study, linalyl acetate was considered not clastogenic in the *in vitro* micronucleus test and this can be extended to linalyl isovalerate (DiSotto et al., 2011). Additionally, read across material linalool (CAS # 78-70-6; see Section 5) was assessed for clastogenicity in an *in vivo* mouse micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. Male and female mice were dosed up to 1500 mg/kg body weight of linalyl acetate in corn oil via a single oral exposure (gavage) for 24 and 48 h. No increase in the frequency of micronucleated polychromatic erythrocytes was observed in the polychromatic erythrocytes of the bone marrow of Linalool treated animals compared to the vehicle treated animals adding weight of evidence against the clastogenic potential of the target material *in vivo* (RIFM, 2001).

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

Additional References: RIFM, 2013; DiSotto, 2008; RIFM, 1984; Heck, 1989; DiSotto, 2011; Oda, 1978; RIFM, 1987; RIFM, 2000.

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

9.1.3. Repeated dose toxicity

The margin of exposure for the repeated dose toxicity endpoint is 16,667.

9.1.4. Risk assessment

There are no repeated dose toxicity data on linalyl isovalerate. Read across material linalyl isobutyrate (CAS # 78-35-3; see Section 5) has a dietary 18-week chronic toxicity study conducted in rats, which determined the NOAEL to be 500 mg/kg/day, the highest dosage tested (Hagan et al., 1967; Bar and Griepentrog, 1967).

Additional References: Letizia et al., 2003a, 2003b; Bickers, 2003; Letizia et al., 2003c, 2003d, 2003e; RIFM, 1958a; Stoner, 1973; VanDuuren, 1971; RIFM, 1998a; Jager, 1992; Meyer, 1959, 1965; Cal, 2003; RIFM, 1996; Letizia, 2003f; RIFM, 1980; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008a; Lalko, 2007; Lalko, 2008; Letizia et al., 2003g; Lapczynski et al., 2008a, 2008b, 2008c; Belsito, 2008; Belsito, 2010; RIFM, 1958b; RIFM, 1979; RIFM, 2012; Randazzo et al., 2013; Hood, 1978; Howes, 2002; Jirovetz et al., 1990, 1991; Parke, 1974; Green and Tephly, 1996; Meesters, 2007; Chadha, 1982, 1984; RIFM, 1998b; Jager, 1992; Schmitt, 2010; Cal, 2006; 2006b; Amoore, 1978; RIFM, 1957; Dawson, 1996, 1991.

Literature Search and Risk Assessment Completed on: 03/31/14.

9.1.5. Developmental and Reproductive Toxicity

The margin of exposure for the developmental toxicity endpoint is 20,000. The exposure is at the TTC for the reproductive toxicity endpoint.

9.1.6. Risk assessment

There are no developmental toxicity data on linalyl isovalerate. Linalyl isovalerate is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6; see Section 5) and isovaleric acid (CAS # 503-74-22; 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, 2007). Isovaleric acid has an OECD 414 gavage developmental toxicity conducted in rats which determined the NOAEL for developmental toxicity to be 600 mg/kg/day, the only dosage tested (ECHA REACH Dossier: Isovaleric acid Exp Supporting Developmental toxicity/teratogenicity.001 (accessed 02/20/14)). 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, 600/0.030 or 20,000.**

There are no reproductive toxicity data on linalyl isovalerate but is expected to metabolize via hydrolysis to linalool (CAS # 78-70-6) and isovaleric acid (CAS # 503-74-22). 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 data on isovaleric acid; therefore, a NOAEL for linalyl isovalerate could not be determined. The total systemic exposure (30 μg/kg/day) is at the TTC for linalyl isovalerate (30 μg/kg bw/day).

Additional References: Letizia et al., 2003a; Bickers, 2003; Letizia, 2003b; Letizia et al., 2003c; RIFM, 1958a; Letizia, 2003d; Letizia, 2003e; Stoner, 1973; VanDuuren, 1971; RIFM, 1998a; Jager, 1992; Meyer, 1959, 1965; Cal, 2003; RIFM, 1996; Letizia, 2003f; RIFM, 1980; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008a; Lalko, 2007; Lalko, 2008; Letizia, 2003g; Lapczynski et al., 2008a, 2008b, 2008c; Belsito, 2008; Belsito, 2010; RIFM, 1958b; RIFM, 1979; RIFM, 2012, Randazzo et al., 2013; Hood, 1978; Howes, 2002; Jirovetz et al., 1990, 1991; Parke, 1974; Green and Tephly, 1996; Meesters, 2007; Chadha, 1982, 1984; RIFM, 1998b; Jager, 1992; Schmitt, 2010; Cal, 2006; Cal and Kryzaniak, 2006; Amoore et al., 1978; RIFM, 1957; Dawson, 1996, 1991

Literature Search and Risk Assessment Completed on: 03/31/14.

9.1.7. Skin sensitization

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

9.1.8. Risk assessment

Based on the available material specific data and read across to linalyl acetate (CAS # 115-95-7; see Section 5), linalyl isovalerate does not present a concern for skin sensitization. Linalyl acetate and linalyl isovalerate 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/cm^2) (RIFM, 2002; Skold, 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, 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, 1974; 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 isovalerate did not result in skin sensitization reactions in the human maximization test (RIFM, 1975).

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

9.1.9. Phototoxicity/Photoallergenicity

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

9.1.10. Risk assessment

There are no phototoxicity studies available for linalyl isovalerate in experimental models. UV/Vis absorption spectra (OECD test guideline 101) indicate no significant absorption between 290 and 700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, linalyl isovalerate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

9.1.11. Local respiratory toxicity

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

9.1.12. 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 by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model.

There are no inhalation data available on linalyl isovalerate. Linalyl isovalerate metabolizes to linalool (CAS # 78-70-6; see Section 5) and isovaleric acid (CAS # 503-74-2; see Section 5) in the respiratory tract and therefore, a NOAEC of 10 ppm (63 mg/m^3) was 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 X 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 give, 0.30 mg/kg lung weight/day resulting in a MOE of 13,388 (i.e., [2410 mg/kg lw/day]/[0.18 mg/kg lung weight/day]).

For the metabolite isovaleric acid (CAS # 503-74-2) there are no inhalation data. However, for its read across analog isobutyric acid (CAS # 79-31-2, see Section 5) a NOAEC of 9.59 mg/l in an OECD 403 study is reported by ECHA. This NOAEC treated similarly as the linalool NOAEC, resulted in an MOE of 2,717,166.

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 and the MOE of the metabolite linalool (which is more conservative than the MOE of isobutyric acid), linalyl isovalerate is deemed safe for use at the reported use level.

Additional References: RIFM, 1977; Jirovetz et al., 1991; Buchbauer, 1991; Jirovetz, 1990; RIFM, 1997; Buchbauer, 1993; Perrucci, 1996, 1995; Rice, 1994a; Silver, 1992; Karr, 1992; Regnault-Roger, 1995; Rice, 1994b; Perrucci, 1995b; Sugawara, 1998; Coats, 1991; Cometto-Muniz, 1998; Isola, 2003a; RIFM, 2003b; Rogers, 2003; RIFM, 2003a; Isola, 2003b; Isola, 2004a; Larsen, 1997; Smith, 2004; RIFM, 2004b; Isola, 2004b; Barocelli, 2004; Rogers, 2005; Kuroda, 2005; Tanida, 2006; Yang, 2005; Corsi et al., 2007; Sato, 2007; Nakamura, 2010, 2009; deMouraLinck, 2009; Bensafi et al., 2002.

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

9.2. Environmental endpoint summary

9.2.1. Analogues identified/Justification

Linalyl acetate (CAS # 115-95-7) has been identified as read-across analogs for linalyl isovalerate based on structure and physical/chemical properties. Both materials are aliphatic esters with predicted K_{ow} of 4.39 and 5.79, for linalyl acetate and linalyl isovalerate 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 isovalerate is also not to be persistent. This is also supported by the BIOWIN models for biodegradation.

[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".

9.2.2. Screening-level assessment

A screening level risk assessment of linalyl isovalerate 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 isovalerate was identified as a fragrance material with no 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 isovalerate 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., US EPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

9.2.3. Risk assessment

Based on current VoU (as of 2011), linalyl isovalerate does not present a risk to the aquatic compartment in the screening level assessment.

9.2.4. Key studies

Biodegradation: No data available

9.2.5. Ecotoxicity

RIFM, 2005: A 10 day 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 greater than 0.94 mg/l and the NOECs were 0.24 mg/l for reproduction and 0.94 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 greater than 0.94 mg/l and the NOECs were 0.94 mg/l for both growth and survival.

Other available data: Linalyl isovalerate 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%.

9.2.6. Risk assessment refinement

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

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.162 mg/l			1,000,000	0.000162 μg/l	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.79	5.79
Biodegradation factor used	0	0
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 0.000162 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

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

10. Literature search[3]

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/

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

- **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

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.08.025.

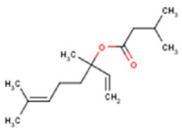
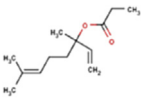
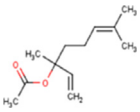
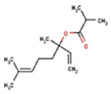
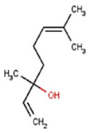
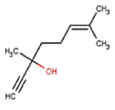
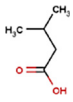
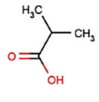
Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.08.025.

Summary

There are insufficient toxicity data on linalyl isovalerate (RIFM # 638, CAS # 1118-27-0). 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

Appendix

	Target material	Read across material						
Principal Name	Linalyl isovalerate	Linalyl propionate	Linalyl acetate	Linalyl isobutyrate	Linalool	Dehydrolinalool	Isovaleric acid	Isobutyric acid
CAS No.	1118-27-0	144-39-8	115-95-7	78-35-3	78-70-6	29171-20-8	503-74-2	79-31-2
Structure								
3D Structure	http://www.thegoodscentscompany.com/opl/1118-27-0.html	http://www.thegoodscentscompany.com/opl/144-39-8.html	http://www.thegoodscentscompany.com/opl/115-95-7.html	http://www.thegoodscentscompany.com/opl/78-35-3.html	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/29171-20-8.html	http://www.thegoodscentscompany.com/opl/503-74-2.html	http://www.thegoodscentscompany.com/opl/79-31-2.html
Read-across endpoint		• Genotoxicity	• Genotoxicity • Skin sensitization • Environmental	• Repeated Dose	• Devel/Repro • Respiratory	• Devel/Repro	• Devel/Repro	• Respiratory
Molecular formula	C15H26O2	C13H22O2	C12H20O2	C14H24O2	C10H18O	C10H16O	C5H10O2	C4H8O2
Molecular Weight	238.37	210.32	196.29	224.35	154.25	152.24	102.13	88.11
Melting point (°C, EPISUITE)	19.54	8.82	−2.09	8.99	−11.39	15.40	3.61	−8.29
Boiling point (°C, EPISUITE)	270.82	247.05	228.95	253.99	204.05	212.37	175.25	153.79
Vapor Pressure (Pa @ 25 °C, EPISUITE)	1.177	4.253	17.47	10.97	11.09	4.64	152	436
Log Kow (KOWWIN v1.68 in EPISUITE)	5.79	4.88	4.39	5.30	3.38	2.75	1.49	1.00
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	0.3135	2.643	20.12	0.9804	683.7	1084	2.924e+004	4.918e+004
J_{max} (mg/cm^2/h, SAM)	2.221527523	9.253768793	11.1668059	6.194908373	90.06108298	93.21980338	1057.323634	2771.973947
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	411.7848	233.65545	176.001525	310.25715	4.285034	0.449174	0.129797	0.097809
Similarity (Tanimoto score)[a]		81%	77%	71%	NA[b]	NA[b]	NA[b]	NA[b]
Genotoxicity								
DNA binding (OASIS v1.1)	• No alert found	• No alert found	• Schiff base formers • Schiff base formers >> Direct acting Schiff base formers • Schiff base formers >> Direct acting Schiff base					

(*continued*)

	Target material	Read across material						
			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	• No alert found					
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	• No alert found					
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found	• No alert found					
In vitro mutagenicity (Ames test) alerts (ISS)	• No alert found	• No alert found	• No alert found					
In vivo mutagenicity (Micronucleus) alerts (ISS)	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor					
Oncologic classification (OECD)	• Not classified	• Not classified	• Not classified					
Repeated Dose Toxicity								
Repeated dose (HESS)	Not categorized			Not categorized				
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 (good reliability)	
Skin Sensitization								
Protein binding (OASIS v1.1)	•No alert found		•No alert found					
Protein binding (OECD)	•No alert found		•No alert found					
Protein binding potency (OECD)	•Not possible to classify according to these rules (GSH)		•Not possible to classify according to these rules (GSH)					
Protein binding alerts for skin sensitization (OASIS v1.1)	•No alert found		•No alert found					
Skin sensitization model (CAESAR v2.1.5)	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	See Supplemental data 5	See Supplemental data 6	See Supplemental data 7	No metabolites found

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

endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Linalyl propionate and linalyl acetate (analogs) were used as read-across for linalyl isovalerate (target) based on:
  - The target and analogs 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 isovalerate, while the analogs are propionate and acetate. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the genotoxicity profiles are expected to be similar.
  - The target and the read-across materials show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - The target and analog show similar alerts for protein binding.
  - The target and read-across materials are expected to be metabolized similarly. As per the OECD QSAR Toolbox both the materials are predicted to have similar metabolites.
- Linalyl isobutyrate (analog) was used as a read-across analog for linalyl isovalerate (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 isovalerate, while the analog is an isobutyrate. 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 Repeated Dose (HESS) Categorization.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox they are predicted to have similar metabolites.
- Dehydrolinalool, isovaleric acid and linalool (analogs) were used as a read-across for linalyl isovalerate (target) based on:
  - The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - Linalyl isovalerate is an ester formed by linalool and isovaleric acid. Dehydrolinalool is an analog of linalool, in which, the vinyl group was dehydrolized and formed an ethylene group.
  - The differences among the target and read-across materials can be mitigated by the fact that the target could readily hydrolyze to the metabolites. Therefore the reproductive and developmental toxicity profiles are expected to be 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 isovaleric acid are predicted as metabolites (see Metabolites # 3 & 4) of the target.
- Linalool and Isobutyric acid (read-across materials) were used as read-across analog for linalyl isovalerate (target) based on:
  - The read-across materials are the major metabolite or analog of the metabolite of the target.
  - The target is an ester formed by linalool and isovaleric acid. Isobutyric acid is a suitable analog of isovaleric acid. The only difference between them is in the length of the alkyl chain, which is not expected to alter the toxicity profiles.
  - The difference between target and read-across materials could also be mitigated by the fact the target could readily hydrolyzed into the read-across materials. Therefore, the inhalation toxicity profiles are expected to be that of the metabolites.
  - As per the OECD QSAR Toolbox linalool is predicted as metabolites (see Metabolites # 3) of the target

Environmental analogues justification

- Linalyl acetate (CAS # 115-95-7) has been identified as read-across analogs for linalyl isovalerate based on structure and physical/chemical properties. Both materials aliphatic esters with predicted K_{ow} of 4.39 and 5.79, for linalyl acetate and linalyl isovalerate 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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