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Short review

RIFM fragrance ingredient safety assessment, isophytol, CAS Registry Number 505-32-8

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Genotoxicity
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Local respiratory toxicity
Environmental toxicity

1. Identification

1. Chemical Name: Isophytol
2. CAS Registry Number: 505-32-8
3. Synonyms: Isophytol, 3,7,11,15-Tetramethyl-1-hexadecen-3-ol, 1-Hexadecen-3-ol,3,7,11,15-tetramethyl-, 脂肪族不飽和アルコール(C=9～24), 3,7,11,15-Tetramethylhexadec-1-en-3-ol
4. Molecular Formula: $C_{20}H_{40}O$
5. Molecular Weight: 296.54
6. RIFM Number: 1180

2. Physical data

1. Boiling Point: 334.88 °C [EPI Suite]
2. Flash Point: >200 °F; CC [FMA database]
3. Log K_{OW}: >6.0 (upper limit of validity of method) [RIFM, 1999b], 8.23 [EPI Suite]
4. Melting Point: 70.18 °C [EPI Suite]
5. Water Solubility: 0.003893 mg/L [EPI Suite]
6. Specific Gravity: 0.852 [FMA database]
7. Vapor Pressure: <0.001 mm Hg 20 °C [FMA database], (calculated) 0.00000734 mm Hg @ 20 °C [EPI Suite 4.0], (calculated) 1.41e-005 mm Hg @ 25 °C [EPI Suite]
8. UV Spectra: Does not absorb in the region of 290–400 nm; molar absorption for this range is below the benchmark (1000 L mol^{-1} cm^{-1})
9. Appearance/Organoleptic: Colorless clear viscous liquid with a low/mild, floral, herbal, and green odor.* *http://www.thegoodscentscompany.com/data/rw1045431.html, retrieved 12/17/13

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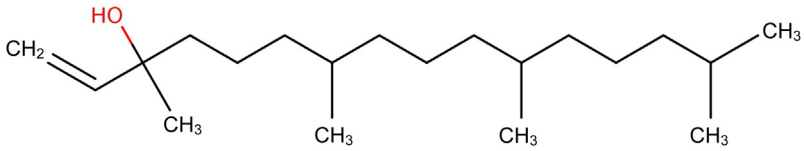
Version: 050515. This version replaces any previous versions.
Name: Isophytol
CAS Registry Number: 505-32-8



Abbreviation list:2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence
RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2014) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria such as, acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential as well as environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 25 mg/kg/day, based on an OECD 415 gavage one-generation reproductive toxicity study in rats, that resulted in a MOE of 1923 while assuming 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment

Genotoxicity: Not genotoxic	(OECD SIDS, 2003: Isophytol; RIFM, 1990; RIFM, 1989a)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day	(OECD SIDS, 2003: Isophytol)
Developmental and Reproductive Toxicity: NOAEL = 500 mg/kg/day	(OECD SIDS, 2003: Isophytol)
Skin Sensitization: Not sensitizing	(OECD SIDS, 2003: Isophytol; RIFM, 1970a; RIFM, 1970b; RIFM, 1981)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB; RIFM, 1982)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 62%–80%	(RIFM, 1999a; RIFM, 1989b)
Bioaccumulation: Screening Level: 840.4 L/kg	(EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: *Daphnia* EC50: 0.13 mg/L	(ECHA REACH dossier accessed 14 May 2013; see Section 9)
Conclusion: Not PBT or vPvB as per IFRA ENV Stds	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) > 1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: *Daphnia* EC50: 0.13 mg/L	(ECHA REACH dossier accessed 14 May 2013; see Section 9)
RIFM PNEC is: 0.026 μg/L	
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1	

3. Exposure

1. Volume of Use (worldwide band): 1–10 metric tons per year	[IFRA, 2011]
2. Average Maximum Concentration in Hydroalcoholics: 0.44%	[IFRA, 2007]
3. 97.5th Percentile: 0.47%	[IFRA, 2007]
4. Dermal Exposure[a]: 0.0120 mg/kg/day	[IFRA, 2007]
5. Oral Exposure: Not available	
6. Inhalation Exposures[b]: 0.001 mg/kg/day	[IFRA, 2007]
7. Total Systemic Exposure (Dermal + Inhalation): 0.013 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 = 0.013 mg/kg/day

5. Computational toxicology evaluation

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

Expert judgment	Toxtree (v. 2.6)	OECD QSAR toolbox (v. 3.2)
I[a]	III	I

[a] See Appendix below for explanation.

2. Analogues Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Developmental and Reproductive Toxicity: None
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read-across Justification: None

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)

Isophytol is reported to occur in the following foods[1] and in some natural complex substances (NCS):

Camomile.

Turpentine oil (Pistacia terebinthus)

8. IFRA standard

None

9. Reach dossier: two dossiers available accessed on 5/5/2015

Individual submission: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d803561-4c54-470b-e044-00144f67d249/DISS-9d803561-4c54-470b-e044-00144f67d249_DISS-9d803561-4c54-470b-e044-00144f67d249.html.

Joint submission: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d814129-3dca-56d7-e044-00144f67d249/DISS-9d814129-3dca-56d7-e044-00144f67d249_DISS-9d814129-3dca-56d7-e044-00144f67d249.html.

10. Summary

1. Human Health Endpoint Summaries:

10.1. Genotoxicity

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

10.2. Risk assessment

The genotoxic potential of isophytol has been evaluated for mutagenicity in bacteria, and clastogenicity *in vivo*. While one

[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.

Ames assay showed equivocal results (Zeiger, 2000) two other Ames assays, conducted according to OECD TG 471, demonstrated negative results. In one study, four strains of *Salmonella typhimurium* were treated up to 5000 μg/plate, both with and without metabolic activation via the standard plate test and preincubation test methods (RIFM, 1989c). In another study, two strains of *S. typhimurium* were treated up to 5000 μg/plate both with and without metabolic activation via a modified Ames preincubation test, i.e. the Liquid suspension assay (RIFM, 1991). In yet another Ames test performed by NTP (http://tools.niehs.nih.gov/cebs3/ntpViews/?studyNumber=002-02323-0001-0000-3), isophytol was considered to be negative, even though some equivocal (5/87) and weakly positive (1/87) results were observed, no dose–response relationship was present. Based on these tests, the mutagenic potential of isophytol to bacteria is considered negative.

The clastogenic potential of isophytol was evaluated in a mouse micronucleus test conducted according to OECD TG 474 (OECD SIDS, 2003: Isophytol). Mice treated with a single oral dose of 2000 mg/kg bw did not show any increase in the frequency of micronucleated polychromatic erythrocytes among total polychromatic erythrocytes at 24 or 48 h after dosing.

These data indicate that isophytol does not have the potential to be genotoxic.

Additional References: Zeiger, 2000.

Literature Search and Risk Assessment Completed on: 05/17/13.

10.3. Repeated dose toxicity

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

10.4. Risk assessment

The repeated dose toxicity data on isophytol are sufficient for the repeated dose toxicity endpoint. An OECD 407 gavage 28-day subchronic toxicity study conducted in rats determined the NOAEL to be 500 mg/kg/day, based on minor reversible clinical chemistry and organ weight findings (OECD SIDS, 2003: Isophytol). When rats were dosed for a longer period of time (52–108 days) in an OECD 415 gavage one-generation reproductive toxicity study, the LOAEL for general parental toxicity was determined to be 250 mg/kg/day, based on renal changes in males and females (OECD SIDS, 2003: Isophytol). The NOAEL was derived by dividing the LOAEL by a safety factor of 10, which is equal to 25 mg/kg/day. 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, 25/0.013 or 1923.

Additional References: McGinty, 2010a; Belsito, 2010; OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-; McGinty, 2010b; RIFM, 1994; RIFM, 1980; Politano, 2008; RIFM, 2006; Letizia et al., 2007; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko, 2007; Lalko, 2008; Letizia, 2003; Lapczynski, 2008a, 2008b, 2008c; Bickers, 2003; Belsito, 2008; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner, 1973; Randazzo, 2013; Hood, 1978; Howes, 2002; Jirovetz, 1990, 1991; Parke, 1974; Green and Tephly, 1996; Meesters, 2007; Chadha, 1982, 1984; RIFM, 1998; Jager, 1992; Schmitt, 2010; Meyer, 1959, Cal, 2006; Cal and Kryzaniak, 2006; Cal and Sznitowska, 2003; Meyer, 1965; RIFM, 2010; Lapczynski, 2008d; McGinty, 2010c; Hanley, 1997; Blair, 2000; Elliott, 1980; Longenecker, 1939.

Literature Search and Risk Assessment Completed on: 05/17/13.

10.5. Developmental and reproductive toxicity

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

10.6. Risk assessment

The developmental toxicity data on isophytol are sufficient for the developmental toxicity endpoint. In an OECD 415 gavage one-generation reproductive toxicity study conducted in rats the NOAEL for developmental toxicity was determined to be 500 mg/kg/day, based on clinical signs and decreased pup body weight during the lactation period (OECD SIDS, 2003: Isophytol). Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.013 or 38462.

The reproductive toxicity data on isophytol are sufficient for the reproductive toxicity endpoint. In an OECD 415 gavage one-generation reproductive toxicity study conducted in rats the NOAEL for reproductive toxicity was determined to be 500 mg/kg/day, based on increased pre-coital time, decreased fertility index, decreased conception rate, and postnatal loss (OECD SIDS, 2003: Isophytol). Therefore, the MOE for reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.013 or 38462.

Additional References: McGinty, 2010a; Belsito, 2010; OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-; McGinty, 2010b; RIFM, 1994; RIFM, 1980; Politano, 2008; RIFM, 2006; Letizia et al., 2007; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko, 2007; Lalko, 2008; Letizia, 2003; Lapczynski, 2008a, 2008b, 2008c; Bickers, 2003; Belsito, 2008; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner, 1973; Randazzo, 2013; Hood, 1978; Howes, 2002; Jirovetz, 1990, 1991; Parke, 1974; Green and Tephly, 1996; Meesters, 2007; Chadha, 1982, 1984; RIFM, 1998; Jager, 1992; Schmitt, 2010; Meyer, 1959, 1965; RIFM, 2010; Lapczynski, 2008d; McGinty, 2010c; Hanley, 1997; Blair, 2000; Elliott, 1980; Longenecker, 1939.

Literature Search and Risk Assessment Completed on: 05/17/13.

10.7. Skin sensitization

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

10.8. Risk assessment

The chemical structure of isophytol indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree 2.5.0; OECD toolbox v3.0). In Guinea pig studies (RIFM, 1970a; and RIFM, 1970d; OECD SIDS, 2003: Isophytol) and a human maximization test (RIFM, 1981) isophytol was not observed to result in reactions indicative of sensitization. Based on existing data, isophytol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/19/13.

10.9. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, Isophytol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.10. Risk assessment

The available spectrum demonstrates that isophytol does not absorb between 290 and 400 nm. The molar absorption coefficient for λ max between 290 and 400 nm is below the benchmark (1000 L mol^{-1} cm^{-1}) considered to be of concern for phototoxic effects (Henry, 2009). Experimental data in Guinea pigs (RIFM, 1982) show that 5, 10, 30 and 50% solutions of isophytol in acetone followed by exposure to UV light did not result in phototoxic reactions. Based on the available UV spectrum and experimental data from an available *in vivo* phototoxicity study conducted in Guinea pigs, isophytol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/19/13.

10.11. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, isophytol, is below the exposure level for the inhalation TTC Cramer Class I limit for local effects.

10.12. Risk assessment

The inhalation data available on isophytol are insufficient to assess the local respiratory endpoint.

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.47%. 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 0.06 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value. This value is below the Cramer Class I TTC level of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009) and is deemed safe for use at the reported use level.

Additional References: RIFM, 1969; Tsuchiya, 1992.

Literature Search and Risk Assessment Completed on: 09/19/13.

11. Environmental endpoint summary

11.1. Screening-level assessment

A screening level risk assessment of isophytol was performed following the RIFM Environmental Framework (Salvito, 2002) that 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 (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, isophytol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC>1).

A screening-level hazard assessment using EPISUITE ver 4.1 did identify Isophytol as being possibly persistent but not 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.

Risk Assessment: Based on current VoU from 2011, Isophytol presents a risk to the aquatic compartment.

11.2. Key studies

11.2.1. Biodegradation

There are 2 biodegradation studies in the RIFM Database.

A study was conducted following OECD Test Guideline 301F. 100 mg/L of the test substance was incubated for a period of 29 days. The test material underwent 62% biodegradation after 29 days (60% after 28 days) (RIFM, 1999b).

A study was conducted following OECD Test Guideline 301F. 84 mg/L of the test substance was incubated for 28 days. At the end of 28 days biodegradation of 70–80% was observed (RIFM, 1989c).

11.2.2. Ecotoxicity

Four studies are reported in the RIFM Database.

An algae growth inhibition study was conducted following German standard DIN 38412 part 9 using *Scenedesmus subspicatus*. Based on the reported test concentrations the 72 h EC50 values (growth rate and biomass) were determined to be greater than 500 mg/L (RIFM, 1988a).

A *Daphnia* immobilization study following German standard DIN 38412 L 1 was reported. The reported 48 h EC50 was 0.2 mg/L (RIFM, 1988b).

In a second report (RIFM, 1992) nominal loadings of isophytol with and without solvents and mechanical methods (e.g., stirring and centrifuging) to improve solubility of the test material were employed. In 5 different test designs, 48 h EC50s ranged from 0.11 mg/L (no solvent; oily film present in test chambers) to 20.3 mg/L (no vehicle; media stirred for 4 h, let stand for ca. 17 h and centrifuged). This report is presented for completeness, but was not used in the calculation of the PNEC for Isophytol.

A static acute fish toxicity study was performed using *Leucsius idus* following German standard DIN 38 412. The reported 96 h LC50 was >10,000 mg/L (nominal concentration) (RIFM, 1989b). However, in the REACH dossier (see Section 9) the water solubility following OECD Test Guideline 105 is reported as 5.8 mg/L (accessed 05/14/13). Therefore, this report is presented for completeness, but was not used in the calculation of the RIFM PNEC for Isophytol.

11.3. Other available data

This material has been registered under REACH in 2 dossiers (accessed 05/14/13).

In one dossier, there is an additional *Daphnia magna* study following OECD Test Guideline 202 reported. The 48 EC50 is 0.13 mg/L. No other additional data are available in either dossier. The REACH PNEC is 0.0002 mg/L based on the fish, *Daphnia*, and algae studies reported above.

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)**	0.0015 mg/L			1,000,000	0.0000015 μg/L	
aECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.671 mg/L	0.157 mg/L	0.010 mg/L			Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.00062 mg/L	0.00062 mg/L	0.005 mg/L	10,000	0.000062 μg/L	Neutral Organic
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish						
Daphnia		0.13 mg/L		5,000	0.026 μg/L	
Algae		>500 mg/L				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	8.23	8.23
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	<1	<1

The RIFM PNEC is 0.026 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: 05/17/13.

12. Literature Search[2]

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- NTP: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- PUBMED: http://www.ncbi.nlm.nih.gov/pubmed
- TOXNET: http://toxnet.nlm.nih.gov/
- IARC: (http://monographs.iarc.fr)
- OECD SIDS: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIS: http://www.epa.gov/hpv/hpvis/index.html
- US EPA Robust Summary: http://cfpub.epa.gov/hpv-s/
- Japanese NITE: http://www.safe.nite.go.jp/english/db.html
- Japan Existing Chemical Data Base: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Google: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

This is not an exhaustive list.

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

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

Explanation of Cramer class:

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

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

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