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Short review

RIFM fragrance ingredient safety assessment, 2-methyl-3-buten-2-ol, CAS Registry Number 115-18-4

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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. Repeated dose, developmental, and reproductive toxicities were determined to have the most conservative systemic exposure derived NO[A]EL of 50 mg/kg/day, based on OECD gavage toxicity studies in rats, that resulted in a MOE of 4545455 after considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

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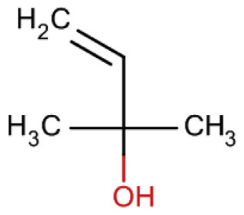

Abbreviation list:**2-Box Model** – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper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

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. Repeated dose, developmental, and reproductive toxicities were determined to have the most conservative systemic exposure derived NO[A]EL of 50 mg/kg/day, based on OECD gavage toxicity studies in rats, that resulted in a MOE of 4545455 after considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment

Genotoxicity: Not Genotoxic (RIFM, 1989a; RIFM, 1992a)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day (OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-)
Developmental and Reproductive Toxicity: NOAEL = 50 mg/kg/day (OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-)
Skin Sensitization: Not sensitizing (RIFM, 1991)
Phototoxicity/**Photoallergenicity**: Not phototoxic/photoallergenic (UV spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 67% (REACH dossier accessed 14 May 2013; see Section 9)

(*continued on next page*)

(*continued*)

Bioaccumulation: Screening Level: 2.4 L/Kg	(EPISUITE 4.1)
Ecotoxicity: Screening Level: 734 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: 734 mg/L	
RIFM PNEC is: 0.734 μg/L	
• **Revised PEC/PNECs** (**2011 IFRA VoU**): North America and Europe Not Applicable, cleared at Screening Level	

1. Identification

1. **Chemical Name**: 2-Methyl-3-buten-2-ol
2. CAS Registry Number: 115-18-4
3. **Synonyms**: 3-Buten-2-ol, 2-methyl-, 1,1,-Dimethyl-2-propenol, 2-Methyl-3-buten-2-ol, アルケニルアルコール(C = 5~8), 2-Methylbut-3-en-2-ol
4. **Molecular Formula**: $C_5H_{10}O$
5. **Molecular Weight**: 86.13
6. **RIFM Number**: 6122

2. Physical data

1. **Boiling Point**: 93.27 °C [EPI Suite]
2. **Flash Point**: 56.00 °F TCC (13.33 °C)[1]
3. **Log K_{OW}**: 1.08 [EPI Suite]
4. **Melting Point**: −62.39 °C [EPI Suite]
5. **Water Solubility**: 48,740 mg/L [EPI Suite]
6. **Specific Gravity**: 0.81800 to 0.82700 @ 25.00 °C[1]
7. **Vapor Pressure**: 17 mm Hg @ 20 °C [EPI Suite 4.0], 23.4 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra**: Does not significantly absorb in the region of 290–700 nm; molar absorption coefficient is below the benchmark.
9. **Appearance/Organoleptic**: Colorless mobile liquid with powerful, oily-herbaceous, somewhat earthy, fungus-like odor of considerable radiance (Arctander, 1969).

3. Exposure

1. **Volume of Use** (**worldwide band**): <1 metric tons per year	[IFRA, 2011]
2. **Average Maximum Concentration in Hydroalcoholics**: 0.002%	[IFRA, 2007]
3. **97.5**th **Percentile**: 0.0005%	[IFRA, 2007]
4. **Dermal Exposure**[a]: 0.00001 mg/kg/day	[IFRA, 2007]
5. **Oral Exposure**: Not available	
6. **Inhalation Exposures**[b]: 0.0000008 mg/kg/day	[IFRA, 2007]
7. **Total Systemic Exposure** (**Dermal** + **Inhalation**): 0.000011 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.

[1] http://www.thegoodscentscompany.com/data/rw1040251.html, retrieved 04/15/15.

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 = 0.000011 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification**: Class III, High

Expert judgment	Toxtree (v 2.6.0)	OECD QSAR toolbox (v. 3.2)
III	III	III

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 Justifications**: 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)

2-Methyl-3-buten-2-ol is reported to occur in the following foods[2]:

[2] 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.

Acerola (Malpighia)	Grape (Vitis species)
Beer	Hop (Humulus lupulus)
Beli, bael (Aegle marmelos Correa)	Lamb's lettuce (Valerianella locusta)
Black currants (Ribes nigrum L.)	Litchi (Litchi chinensis Sonn.)
Cabbage (Brassica oleracea)	Mangifera species
Cardamom (Ellettaria cardamomum Maton.)	Mate (Ilex paraguayensis)
Cherimoya (Annona cherimolia Mill.)	Melon
Chicken	Milk and milk products
Citrus fruits	Papaya (Carica papaya L.)
Coffee	Passion fruit (passiflora speices)
Endive (Cichorium endivia L.)	Pepino fruit (Solanum muricatum)
Ginger (Zingiber species)	Pineapple (Ananas comosus)
Pork	Plum (Prunus species)
Pulasan (Nephelium ramboutan-ake (Labill.) Leenh.)	Salvia species
Rambutan (Nephelium lappaceum L.)	Tamarind (Tamarindus indica L.)
Raspberry, blackberry and boysenberry	Tea
Rooibos tea (Aspalathus linearis)	Tomato (Lycopersicon esculentum Mill.)
	Vaccinium species
	Vinegar

8. IFRA Standard

None.

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

Individual submission: http://apps.echa.europa.eu/registered/data/dossiers/DISS-07466439-2090-3142-e053-1cdf090ac6ca/DISS-07466439-2090-3142-e053-1cdf090ac6ca_DISS-07466439-2090-3142-e053-1cdf090ac6ca.html.

Joint submission: http://apps.echa.europa.eu/registered/data/dossiers/DISS-d01993ee-7bab-3ef6-e044-00144f67d249/DISS-d01993ee-7bab-3ef6-e044-00144f67d249_DISS-d01993ee-7bab-3ef6-e044-00144f67d249.html.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 2-Methyl-3-buten-2-ol does not present a concern for genetic toxicity.

10.1.2. Risk assessment

The genotoxic potential of 2-methyl-3-buten-2-ol has been evaluated for mutagenicity in an Ames study conducted according to OECD TG 471. *Salmonella typhimurium* strains TA 1535, TA100, TA1537 and TA 98 were treated with 2-methyl-3-buten-2-ol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of an exogenous, metabolically activated system (S9). No increase in the number of revertant colonies was observed in any strain or dose with or without S9 (RIFM, 1989a). Under the conditions of the study, 2-methyl-3-buten-2-ol was considered not mutagenic in the Ames study.

The clastogenic potential of 2-methyl-3-buten-2-ol was evaluated in an *in vivo* mouse micronucleus test conducted according to OECD TG 474. Male and female NMRI mice were dosed with 2-methyl-3-buten-2-ol dissolved in aqua dest (10 ml/kg body weight, b.w.) via a single oral administration at the concentrations of 500, 1000 and 1500 mg/kg b.w. No inhibition of erythropoiesis determined from the ratio of polychromatic to normochromatic erythrocytes was detected (RIFM, 1992a). Under the conditions of the study, 2-methyl-3-buten-2-ol does not have any clastogenic effect.

The above data demonstrate that 2-Methyl-3-buten-2-ol does not have the potential to be genotoxic.

Additional References: RIFM, 1991; RIFM, 2013.

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

10.1.3. Repeated dose toxicity

The margin of exposure for 2-methyl-3-buten-2-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

The repeated dose toxicity data on 2-methyl-3-buten-2-ol are sufficient for the repeated dose endpoint. An OECD 407 gavage 28-day subchronic toxicity study conducted in rats determined the NOAEL to be 50 mg/kg/day, based on increased liver weights and hypertrophy of hepatocytes (OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-). **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.000011 or 4545455**.

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

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

10.1.5. Developmental and reproductive toxicity

The margin of exposure for 2-methyl-3-buten-2-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

The developmental and reproductive toxicity data on 2-methyl-3-buten-2-ol are sufficient for the developmental and reproductive toxicity endpoints. An OECD 421 gavage reproduction/developmental toxicity screening test conducted in rats determined the developmental toxicity NOAEL to be 50 mg/kg/day, based on reduced pup viability, and the reproductive toxicity NOAEL to be 50 mg/kg/day, based on clinical signs, decreased male body weight gain, and decreased female feed consumption during lactation (OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-). **Therefore, the MOE for developmental and reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.000011 or 4545455**.

Additional References: McGinty et al., 2010a; Belsito et al., 2010; RIFM, 1994; RIFM, 1980; Politano et al., 2008; RIFM, 2006; Letizia et al., 2007; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003; Lapczynski et al., 2008a, 2008b, 2008c; Bickers et al., 2003; Belsito et al., 2008; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982; Chadha and Madyastha, 1984; RIFM, 1998; Jager

et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959, 1965; RIFM, 2010; Lapczynski et al., 2008d; McGinty et al., 2010b; Hanley et al., 1997; Blair et al., 2000; Howes et al., 2002; Elliott and Lachance, 1980; Longenecker et al., 1939; OECD SIDS, 2003: Isophytol; McGinty et al., 2010c; Cal, 2003; Cal, 2006a; Cal, 2006b.

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

10.1.7. Skin sensitization

Based on the existing data, 2-methyl-3-buten-2-ol does not present a concern for skin sensitization.

10.1.8. Risk assessment

The chemical structure of 2-methyl-3-buten-2-ol indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.0) and in a guinea pig maximization study the material was not observed to result in reactions indicative of sensitization (RIFM, 1991). Based on the existing data, 2-methyl-3-buten-2-ol does not present a concern for skin sensitization.

Additional References: Belsito, 2010.

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

10.1.9. Phototoxicity/photoallergenicity

Based on the available UV spectra, 2-methyl-3-buten-2-ol does not present a concern for phototoxicity/photoallergenicity.

10.1.10. Risk assessment

Based on the available UV spectra, 2-methyl-3-buten-2-ol does not present a concern for phototoxicity. The available spectra for 2-methyl-3-buten-2-ol demonstrates that this material has limited to no absorption in the region of 290–700 nm. The molar absorption coefficient for λ max between 290 and 700 nm is well below the benchmark (1000 L mol^{-1} cm^{-1}) considered to be of concern for phototoxic effects (Henry et al., 2009). While there are no phototoxicity studies available on 2-methyl-3-buten-2-ol, the UV spectrum demonstrate that this material does not present a concern for phototoxicity/photoallergenicity.

Additional References: None.

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

10.1.11. Local respiratory toxicity

The margin of exposure for 2-methyl-3-buten-2-ol could not be calculated due to lack of appropriate data. The 2-methyl-3-buten-2-ol exposure level is below the inhalation TTC Cramer Class III* limit for local effects.

10.1.12. Risk assessment

There are no inhalation data available on 2-methyl-3-buten-2-ol to address local respiratory toxicity. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.0005%. 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 0.000046 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 III[3] TTC level of 0.47 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.

Key Studies: None.

Additional References: Helmig et al., 1999; RIFM, 1989; RIFM, 1972.

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 2-Methyl-3-buten-2-ol 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, 2-Methyl-3-buten-2-ol 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 not identify 2-methyl-3-buten-2-ol as being possibly bioaccumulative or persistent 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.

10.2.2. Risk assessment

Based on current VoU from 2011, 2-Methyl-3-buten-2-ol presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key Studies

10.2.3.1. Biodegradation. None available in the RIFM Database but as discussed below 2-methyl-3-buten-2-ol is expected to be 67% biodegradable.

10.2.3.2. Ecotoxicity. There are 4 studies in the RIFM Database.

There are 2 algae inhibition studies. In one study using *Scenedesmus subspicatus*, an EC50 could not be calculated. Protocol details are limited. A 72 h EC20 was reported as 300.7 mg/L (RIFM, 1989b). In another study following OECD Test Guideline 201 and also using *S. subspicatus*, the reported 72 h EC50 was >500 mg/L (RIFM, 1992b).

A *Daphnia magna* immobilization study was performed following Method C2 of Annex V to Directive 79/831 EEC using nominal concentrations of 2-methyl-3-buten-2-ol. The reported EC50 was ≥500 mg/L (RIFM, 1988a).

An acute fish study following German guideline DIN 38 412 using *Leuciscus idus* under flow through conditions reported a 96 h LC50 of >2200 and <4600 mg/L (RIFM, 1988b).

[3] For the respiratory endpoint Cramer Class II defaults to the Cramer Class III value (Api et al., 2015).

10.2.4. Other available data

This material has been registered under REACH. Additional data are reported below. These data were accessed on 14 May 2013. A biodegradation study is reported following OECD Test Guideline 301F. At the end of 28 days 67% biodegradation was observed. The 10-day window was not met. The aquatic toxicity studies are reported above.

10.2.5. Risk assessment refinement

Ecotoxicological data and PNEC derivation.

Endpoints used to calculate PNEC are underlined.

	LC50 (fish)	EC50 (Daphnia)	EC50 (algae)	AF	PNEC	Chemical class
RIFM Framework Screening Level (**Tier 1**)	734 mg/L			1,000,000	0.734 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.08	1.08
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: **PEC/PNEC**	<**1**	<**1**

The RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.734 μg/L μg/L. The revised PEC/PNECs for EU and NA are <1, 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: 05/17/13.

11. Literature Search[4]

- **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.

[4] 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.2015.07.009.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., et al., 2015. Criteria for the research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vol. I and vol II. Published by the author, Montclair, NJ (USA).

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, J.H., Sipes, I.G., Tagami, H., 2008. A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. Food Chem. Toxicol. 46 (11S), S1–S71.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., et al., 2010. A safety assessment of non-cyclic alcohols with unsaturated branched chain when used as fragrance ingredients: the RIFM expert panel. Food Chem. Toxicol. 48 (Suppl. 3), S1–S42.

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

Blair, R.M., Fang, H., Branham, W.S., Hass, B.S., Dial, S.L., Moland, C.L., Tong, W., Shi, L., Perkins, R., Sheehan, D.M., 2000. The estrogen receptor relative binding affinities of 188 natural and xenochemicals: structural diversity of ligands. Toxicol. Sci. Former. Fundam. Appl. Toxicol. 54 (1), 138–153.

Cadby, P.A., Troy, W.R., Vey, M.G.H., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regul. Toxicol. Pharmacol. 36 (3), 246–252.

Cal, K., Sznitowska, M., 2003. Cutaneous absorption and elimination of three acyclic terpenes-in vitro studies. J. Control. Release 93 (3), 369–376.

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

Cal, K., Kryzaniak, M., 2006b. Stratum corneum absorption and retention of linalool and terpinen-4-ol applied as gel or oily solution in humans [Letter to the Editor] J. Dermatol. Sci. 42, 265–267.

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

Chadha, A., Madyastha, K.M., 1982. Omega-hydroxylation of acyclic monoterpene alcohols by rat lung microsomes. Biochem. Biophys. Res. Commun. 108 (3), 1271–1277.

Chadha, A., Madyastha, K.M., 1984. Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. Xenobiotica 14 (5), 365–374.

Elliott, J.G., Lachance, P.A., 1980. Effects of vitamin A and ascorbic acid on in vitro cholesterol biosynthesis in the rat. J. Nutr. 110 (7), 1488–1496.

Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software]. (Copyright 2000-2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Retrieved from http://www.epa.gov/opptintr/exposure/pubs/episuite.htm Research, 20(6), 482–487.

Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance ingredients. Regul. Toxicol. Pharmacol. 31 (2), 166–181.

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

Hanley, K., Jiang, Y., Crumrine, D., Bass, N.M., Appel, R., Elias, P.M., Williams, M.L., Feingold, K.R., 1997. Activators of the nuclear hormone receptors PPAR alpha and FXR accelerate the development of the fetal epidermal permeability barrier. J. Clin. Investig. 100 (3), 705–712.

Helmig, D., Klinger, L.F., Guenther, A., Vierling, L., Geron, C., Zimmerman, P., 1999. Biogenic volatile organic compound emissions (BVOCs). I. Identifications from three continental sites in the U.S. Chemosphere 38 (9), 2163–2187.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B: Biol. 96 (1), 57–62.
Hood, R.L., McBailey, W., Svoronos, D., 1978. The effect of dietary monoterpenes on the cholesterol level of eggs. Poult. Sci. 57, 304–306.
Howes, M.-J.R., Houghton, P.J., Barlow, D.J., Pocock, V.J., Milligan, S.R., 2002. Assessment of estrogenic activity in some common essential oil constituents. J. Pharm. Pharmacol. 54 (11), 1521–1528.
IFRA (International Fragrance Association), 2007. Use Level Survey, February 2007.
IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.
Jager, W., Buchbauer, G., Jirovetz, L., Fritzer, M., 1992. Percutaneous absorption of lavender oil from a massage oil. J. Soc. Cosmet. Chem. Jpn. 43 (1), 49–54.
Jirovetz, L., Buchbauer, G., Jager, W., Raverdino, V., Nikiforov, A., 1990. Determination of lavender oil fragrance compounds in blood samples. Fresenius' J. Anal. Chem. 338 (8), 922–923.
Jirovetz, L., Jager, W., Buchbauer, G., Nikiforov, A., Raverdino, V., 1991. Investigations of animal blood samples after fragrance drug inhalation by gas chromatography/mass spectrometry with chemical ionization and selected ion monitoring. Biol. Mass Spectrom. 20 (12), 801–803.
Lalko, J., Brain, K.R., Green, D.M., Api, A.M., 2007. In vitro human skin penetration of the fragrance material linalool. Int. J. Toxicol. Former. J. Am. Coll. Toxicol. 26 (6), 608.
Lalko, J., Brain, K., Green, D., Api, A.M., 2008. In vitro human skin penetration of the fragrance material linalool. Toxicol. 102 (1), 319.
Lapczynski, A., Letizia, C.S., Api, A.M., 2008a. Addendum to fragrance material review on linalool. Food Chem. Toxicol. 46 (11S), S190–S192.
Lapczynski, A., Letizia, C.S., Api, A.M., 2008b. Fragrance material review on d-linalool. Food Chem. Toxicol. 46 (11S), S193–S194.
Lapczynski, A., Bhatia, S.P., Letizia, C.S., Api, A.M., 2008c. Fragrance material review on l-linalool. Food Chem. Toxicol. 46 (11S), S195–S196.
Lapczynski, A., Bhatia, S.P., Letizia, C.S., Api, A.M., 2008d. Fragrance material review on nerolidol (isomer unspecified). Food Chem. Toxicol. 46 (11S), S247–S250.
Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003. Fragrance material review on linalool. Food Chem. Toxicol. 41 (7), 943–964.
Letizia, C., Api, A.M., Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., 2007. Evaluation of the developmental toxicity of linalool in rats. Toxicol. 96 (1), 92.
Longenecker, H.E., Musulin, R.R., Tully III, R.H., King, C.G., 1939. An acceleration of vitamin C synthesis and excretion by feeding known organic compounds to rats. J. Biol. Chem. 129, 445–453.
McGinty, D., Letizia, C.S., Api, A.M., 2010a. Addendum to fragrance material review on nerolidol (isomer unspecified). Food Chem. Toxicol. 48 (Suppl. 3), S43–S45.
McGinty, D., Letizia, C.S., Api, A.M., 2010b. Fragrance material review on isophytol. Food Chem. Toxicol. 48 (Suppl. 3), S76–S81.
McGinty, D., Letizia, C.S., Api, A.M., 2010c. Fragrance material review on 2-methyl-3-buten-2-ol. Food Chem. Toxicol. 48 (Suppl. 3), S97–S100.
Meesters, R.J.W., Duisken, M., Hollender, J., 2007. Study on the cytochrome P450-mediated oxidative metabolism of the terpene alcohol linalool: indication of biological epoxidation. Xenobiotica 37 (6), 604–617.
Meyer, F., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneim. Drug. Res. 9, 516–519.
Meyer, F. (1965). Penetrating agents. Patent, British, 1,001,949, M49750IVa/30h, 7/20/61.
OECD SIDS report, 1995. 3-Buten-2-ol, 2-methyl-. Retrieved on 5/5/2015 from: http://www.chem.unep.ch/irptc/sids/OECDSIDS/115184.pdf.
OECD SIDS report, 2003. Isophytol retrieved 5/5/2015: http://www.chem.unep.ch/irptc/sids/OECDSIDS/505328.pdf.
Parke, D.V., Rahman, K.H.M.Q., Walker, R., 1974. The absorption, distribution & excretion of linalool in the rat. Biochem. Soc. Trans. 2 (4), 612–615.
Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., Api, A.M., 2008. Evaluation of the developmental toxicity of linalool in rats. Int. J. Toxicol. Former. J. Am. Coll. Toxicol. 27 (2), 183–188.
Randazzo, J., Vitale, D., Kirkpatrick, D., Burleson, E.G., Singal, M., 2013. Evaluation of nose-only inhalation exposure to aerosolized linalool in Sprague-Dawley rats. Toxicol. 132 (1), 330.
RIFM (Research Institute for Fragrance Materials, Inc.), 1958. Toxicological Screening of Citronellol and Linalool in Rats. Class VI. Private Communication to FEMA. Unpublished report from Trubek Laboratories, Inc.. RIFM report number 29150. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Trade Toxicology of 2-methyl-3-buten-2-ol. Unpublished report from BASF. RIFM report number 55332. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979. 29 Day Percutaneous Toxicity Range Finding with Linalool in Rats. Report to RIFM. RIFM report number 32943. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980. 90 Day Subchronic Dermal Toxicity with Linalool in Rats. Report to RIFM. RIFM report number 4001. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1988a. Determination of the Acute Effect of 2-methyl-3-buten-2-ol on Daphnia Magna Straus. Unpublished report from BASF. RIFM report number 55331. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1988b. Report on the Study of the Acute Toxicity of 2-methyl-3-buten-2-ol in Golden Orfe (Leuciscus idus L., Golden Variety). Unpublished report from BASF. RIFM report number 55333. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. Study on the Acute Inhalation Toxicity of 2-methyl-3-buten-2-ol as a Vapor in Rats. Unpublished report from BASF. RIFM report number 55325. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Algae Test with 2-methy-3-buten-2-ol. Unpublished Report from BASF. RIFM report number 55326. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989c. Report on the Study of 2-methyl-3-buten-2-ol in the Ames Test. Unpublished report from BASF. RIFM report number 55328. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1991a. Report on the Maximization Test for the Sensitizing Potential of 2-methyl-3-buten-2-ol in Guinea Pigs. Unpublished report from BASF. RIFM report number 55335. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1991b. Report on the Study of 2-methylbuten-3-ol- in the Liquid Suspension Assay Modified Salmonella/mammalian-microsome Mutagenicity Test. Unpublished report from BASF. RIFM report number 65713. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1992a. Algae Inhibition Test with 2-methyl-3-buten-2-ol. Unpublished report from BASF. RIFM report number 55327. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1992b. Cytogenetic Study 2-methyl-3-buten-2-ol in Mice. Unpublished report from BASF. RIFM report number 55334. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1994. Repeated Dose Oral Toxicity Study with 2-methyl-3-buten-2-ol in Wistar Rats. Unpublished report from BASF. RIFM report number 55324. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1998. Report on the Metabolism of Linalool in Rat Tissue & Intestinal Homogenates. Report to FEMA. Unpublished report from Flavor and Extract Manufacturers Association. RIFM report number 34252. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Oral (Gavage) Developmental Toxicity Study of Linalool in Rats. RIFM report number 45726. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007a. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from an Ethanol/water Vehicle. RIFM report number 54455. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007b. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from a Diethyl Phthalate (DEP) Vehicle. RIFM report number 54456. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007c. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from a Dipropylene Glycol (DPG) Vehicle. RIFM report number 54457. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2008a. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from an Ethanol/diethyl Phthalate Vehicle. RIFM report number 54662. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2008b. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from an Ethanol/diproplylene Glycol Vehicle. RIFM report number 54663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2008c. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from a Petrolatum Vehicle. RIFM report number 54664. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Nerolidol: Combined Repeated Dose Toxicity Study with the Reproduction/developmental Toxicity Screening Test in Wistar Rats Administration via the Diet. Unpublished report from BASF. RIFM report number 64878. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. A Two-week Inhalation Toxicity Study of Aerosolized Linalool in the Sprague Dawley Rat. RIFM report number 63821. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. 2-Methyl-3-buten-2-ol: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 66404. RIFM, Woodcliff Lake, NJ, USA.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schmitt, S., Schaefer, U., Sporer, F., Reichling, J., 2010. Comparative study on the in vitro human skin permeation of monoterpenes and phenylpropanoids applied in rose oil and in form of neat single compounds. Pharmazie 65 (2), 102–105.
Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K., Go, G.B., 1973. Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res. 33 (12), 3069–3085.