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Short review

RIFM fragrance ingredient safety assessment, terpineol, CAS Registry Number 8000-41-7

A.M. Api [a, *], D. Belsito [b], S. Bhatia [a], D. Botelho [a], D. Browne [a], M. Bruze [c], A. Burton Jr. [d], J. Buschmann [e], P. Calow [f], M.L. Dagli [g], M. Date [a], W. Dekant [h], C. Deodhar [a], A.D. Fryer [i], K. Joshi [a], L. Kromidas [a], S. La Cava [a], J.F. Lalko [a], A. Lapczynski [a], D.C. Liebler [j], Y. Miyachi [k], D. O'Brien [a], R. Parakhia [a], A. Patel [a], T.M. Penning [l], V.T. Politano [a], G. Ritacco [a], J. Romine [a], D. Salvito [a], T.W. Schultz [m], J. Shen [a], I.G. Sipes [n], Y. Thakkar [a], Y. Tokura [o], S. Tsang [a], J. Wahler [a], B. Wall [a], D.K. Wilcox [a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany*
[f] *Member RIFM Expert Panel, Humphrey School of Public Affairs, University of Minnesota, 301 19th Avenue South, Minneapolis, MN 55455, USA*
[g] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo CEP 05508-900, Brazil*
[h] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany*
[i] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA*
[j] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, USA*
[k] *Member RIFM Expert Panel, Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan*
[l] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA 19104-3083, USA*
[m] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA*
[n] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA*
[o] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan*

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* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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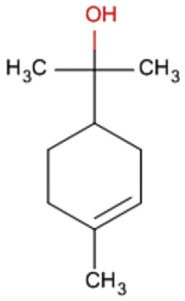
Version: 041717. This version replaces any previous versions.
Name: Terpineol
CAS Registry Number: 8000-41-7
Additional CAS Numbers*:
10482-56-1 p-Menth-1-en-8-ol (S)
7785-53-7 d-.α.-Terpineol
98-55-5 α-Terpineol
*These materials are included in this assessment because they are a mixture of isomers.



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
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

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.
Each endpoint discussed in this safety assessment 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).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic, provided a MOE >100 for the repeated dose, developmental and reproductive toxicity endpoints, and it does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (ECHA REACH Dossier: Terpineol)
Repeated Dose Toxicity: NOAEL = 578 mg/kg/day (ECHA REACH Dossier: Terpineol)
Developmental Toxicity: NOAEL = 200 mg/kg/day **and Reproductive Toxicity:** NOAEL = 250 mg/kg/day (ECHA REACH Dossier: Terpineol)
Skin Sensitization: Not sensitizing (ECHA REACH Dossier: Terpineol; RIFM, 1964)

(*continued on next page*)

(*continued*)

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: 105.7% (OECD 301B)	(RIFM, 1994)
Bioaccumulation: Screening Level: 67.8 L/Kg	(EpiSuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 72 h Algae EbC50: 17 mg/l	(ECHA REACH Dossier: Terpineol)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 72 h Algae EbC50: 17 mg/l	(ECHA REACH Dossier: Terpineol)
RIFM PNEC is: 17 μg/L	
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1	

1. Identification

Chemical Name: Terpineol	Chemical Name: d-.α.-Terpineol	Chemical Name: *p*-Menth-1-en-8-ol (S)	Chemical Name: α-Terpineol
CAS Registry Number: 8000-41-7 **Synonyms:** *p*-Menthenol (mixed isomers); Terpineol; Terpineol pure; α-テルピネオール; 2-(4-Methylcyclohex-3-en-1-yl)propan-2-ol	**CAS Registry Number:** 7785-53-7 **Synonyms:** 3-Cyclohexene-1-methanol,.α.,.α.,4-trimethyl-, (R)-; 2-(4-Methylcyclohex-3-en-1-yl) propan-2-ol; (R)-.α.,.α.,4-Trimethylcyclohex-3-ene-1-methanol	**CAS Registry Number:** 10482-56-1 **Synonyms:** 3-Cyclohexene-1-methanol,α,α,4-trimethyl-, (S)-; 2-(4-Methylcyclohex-3-en-1-yl)propan-2-ol; (−)-.α.-Terpineol	**CAS Registry Number:** 98-55-5 **Synonyms:** 3-Cyclohexene-1-methanol,.α.,.α.,4-trimethyl-; 1-*p*-Menthen-8-ol; *p*-Menth-1-en-8-ol; 2-(4-Methylcyclohex-3-en-1-yl)propan-2-ol; 1-Methyl-4-isopropyl-1-cyclohexen-8-ol; α-Terpilenol; Terpineol schlechthin; α、β 又はγ-テルピネオール
Molecular Formula: $C_{10}H_{18}O$ **Molecular Weight:** 154.25 **RIFM Number:** 148	**Molecular Formula:** $C_{10}H_{18}O$ **Molecular Weight:** 154.53 **RIFM Number:** 5365	**Molecular Formula:** $C_{10}H_{18}O$ **Molecular Weight:** 154.53 **RIFM Number:** 5386	**Molecular Formula:** $C_{10}H_{18}O$ **Molecular Weight:** 154.25 **RIFM Number:** 6100

2. Physical data*

1. **Boiling Point:** 217 °C [FMA database], (calculated) 214.38 °C [EPI Suite]
2. **Flash Point:** 192 °F; CC [FMA database]
3. **Log K_{OW}:** 2.6 at 30 °C [RIFM, 1996], 3.33 [EPI Suite]
4. **Melting Point**: 12.36 °C [EPI Suite]
5. **Water Solubility:** 2.5 g/L at 20 ± 0.5 °C [RIFM, 1992], (calculated) 371.7 mg/L [EPI Suite]
6. Specific Gravity: 0.931 [FMA database]
7. **Vapor Pressure:** 0.0108 mm Hg @ 20 °C [EPI Suite 4.0], 0.1 mm Hg 20 °C [FMA database], 0.0196 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance in the region of 290–700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless or white crystals with a soft and pleasant, sweet, almost floral odor of moderate tenacity (Arctander, 1969)

*Physical data are identical for all materials included in this assessment.

3. Exposure***

1. **Volume of Use (worldwide band):** >1000 metric tons per year (IFRA , 2011)
2. 95th Percentile Concentration in Hydroalcoholics: 0.12% (RIFM, 2016b)
3. **Inhalation Exposure*:** 0.0010 mg/kg/day or 0.074 mg/day (RIFM, 2016b)
4. **Total Systemic Exposure**:** 0.0067 mg/kg/day (RIFM, 2016b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015 and Safford et al., 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics, inhalation exposure and total exposure.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. Inhalation: Assumed 100%

5. Computational toxicology evaluation

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

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

*See Appendix 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

RIFM, 2016a: Previous studies on terpineol, indicate that the male reproductive system is a target following gavage and dietary administration to rats (see section IX; reproductive toxicity section). This was proposed to occur due to varying peak plasma concentrations required for adverse effects following gavage and dietary administration of terpineol. Thus a toxicokinetic comparison study was conducted to determine the underlying differences following gavage and dietary administration of terpineol. All studies were conducted according to the OECD 417 guidelines. A single dose gavage toxicokinetic study was conducted on [^{14}C]-alpha-terpineol at doses of 75, 250 and 750 mg/kg/day to Crl:CD (SD) male rats. In another study, daily dietary non-radiolabeled terpineol (650, 2200 and 6500 ppm, equivalent to 53.2–74.4, 211–274, 424–736 mg/kg/day respectively based on actual food consumption) was administered to male Crl:CD (SD) rats for 13 days followed by dietary [^{14}C]-alpha-terpineol administration on day 14.

Gavage: The absorption, distribution, metabolism and excretion of [isopropyl methyl-^{14}C]-alpha-terpineol in corn oil were studied after single gavage doses of 75, 250 and 750 mg/kg to male rats. Radiolabeled alpha-terpineol and non-radiolabeled terpineol multiconstituent were combined in corn oil to achieve the desired specific activity of the dosed material. The dosing, grouping and scheduled euthanasia times are as shown below in Table 1. Concentrations of radioactivity in tissues were highest in the kidney and liver at each dose level. The tissue:plasma ratios were generally less than one other than for kidney and liver (all euthanasia times) and fat (at the later euthanasia times).

Diet: The absorption, distribution, metabolism and excretion of [isopropyl methyl-^{14}C]-alpha-terpineol were studied after repeat daily dietary administration at 650, 2200 and 6500 ppm for 14 days to male rats. Non-radiolabelled alpha-terpineol was combined with powdered VRF1 diet and mixed to achieve homogenous treated diet. The daily intake based on food consumption was 53.2–74.4, 211–274, 424–736 mg/kg/day mg/kg/day. The animals were offered a diet treated with non-radiolabelled test substance for 13 days followed by treated diet fortified with [^{14}C]-alpha-terpineol on Day 14. The dosing, grouping and scheduled euthanasia times are as shown in Table 2. Concentrations of radioactivity in tissues were highest in the kidney and liver at each dose level. Overall tissue accumulation after single dietary administration of radioactivity was low with only a small proportion of the dose retained in tissues at 168 h (<1% dose). Concentrations in tissues generally increased to maximum concentrations at 24 h post administration before declining over time at all dose levels. Tissue:plasma ratios were generally less than one with the exception of kidney, liver and abdominal fat (all sacrifice times).

The rate of systemic exposure of rats to alpha-terpineol, characterized by Cmax, increased approximately proportionately with increasing dose over the dose range 75–750 mg/kg in the plasma for both routes of administration. Peak plasma concentrations were reached within 1–1.5 h of administered dose in rats administered [^{14}C]-alpha-terpineol as compared to 24 h in rats administered equivalent amounts of [^{14}C]-alpha-terpineol via diet. Peak plasma concentrations in the rats gavaged with radioactive alpha-terpineol had 9-10 times higher levels of radioactivity as compared to rats fed the radioactive diet of alpha-terpineol as shown in Table 3.

Following single oral doses or repeated daily dietary administration of non-radiolabeled alpha-terpineol for 13 days followed by dietary administration of [^{14}C]-alpha-terpineol, most of the radioactivity (>90% via gavage and >70% via diet)) was eliminated in urine and feces within 48 h . Excretion was mainly via the urine. The following tables (Tables 4 and 5) summarize the excretion of radioactivity during 0–168 h after administration. Results are expressed as % dose.

Unchanged [^{14}C]-alpha-terpineol was identified as the major component in fecal extracts and there were no unidentified metabolites >5% dose in the urine or feces in both cases as shown below. The proposed pathway of metabolism is as shown below.

Table 1
Gavage study dosing, grouping and scheduled euthanasia times.

	Excretion/Distribution (Groups 1–3)	Plasma and whole-blood kinetics experiment (Groups 4 to 6)	Tissue distribution experiments (Groups 7 to 9)
Animals	4 per group	12 per group further divided into 3 subgroups of 4 each	9 per group
Euthanasia times	168 h after dosing	**subgroup 1:** pre-does 1,4,24,96 h **subgroup 2:** 0.25,2,6,48,120 hours **subgroup 3:**0.5,3,12,77,168 hours	

Dose	75 mg/kg (Hours)	250 mg/kg (Hours)	750 mg/kg (Hours)
T_{max}	0.25	1	1
Half T_{max}	1.5	3	6
Latest quantifiable	24	24	48

Table 2
Diet study dosing, grouping and scheduled euthanasia times.

	Excretion/Distribution (Groups 1–3)	Plasma and whole-blood kinetics experiment (Groups 4 to 6)	Tissue distribution experiments (Groups 7 to 9)
Animals	4 per group	12 per group further divided into 3 subgroups of 4	9 male animals group
Euthanasia times	168 h after dosing	subgroup 1: pre-does 1, 4, 24, 96 h subgroup 2: 0.25, 2, 6, 48, 120 hours subgroup 3: 0.5, 3, 12, 77, 168 hours	

Dose	650 ppm Hours	2200 ppm Hours	6500 ppm Hours
Sacrifice times	4, 24 and 48 hours	12, 24 and 48 hours	1, 24 and 48 hours

Table 3
Radioactivity levels.

	Gavage	Dietary	Gavage	Dietary	Gavage	Dietary
	75 mg/kg/day		250 mg/kg/day		750 mg/kg/day	
Tmax (h)	1.5	24	1	24	1	24
Cmax (μg eq/g)	25.3	2.57	84.5	9.35	246	27.2
Factor	10		9		9	

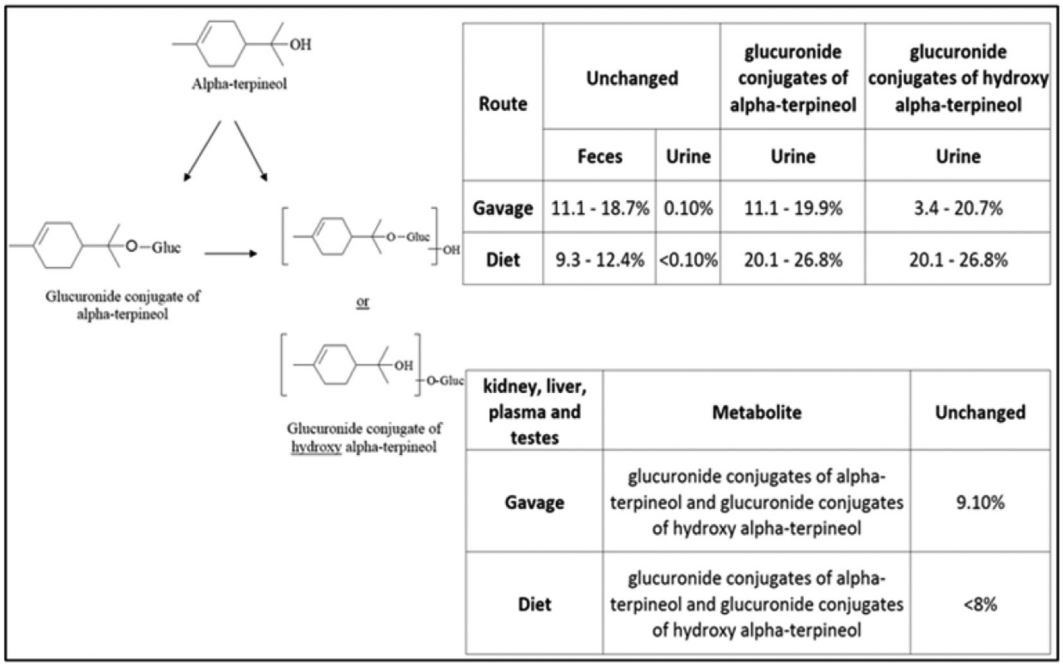
Table 4
Excretion of radioactivity during 0–168 h after administration.

	75 mg/kg	250 mg/kg	750 mg/kg
Urine	65.85	66.53	61.48
Cage wash	1.38	1.60	0.65
Faeces	26.78	27.50	33.08
Carcass	0.05	0.05	0.13
G.I.T.	0.03	0.00	0.00
Total	93.10	95.68	95.33

Table 5
Excretion of radioactivity during 0–168 h after administration.

	650 ppm (75 mg/kg)	2200 ppm (250 mg/kg)	6500 ppm (750 mg/kg)
Urine	65.57	67.69	73.64
Cage wash	7.86	5.48	5.03
Faeces	17.70	19.55	14.78
G.I.T. & Carcass	0.10	0.17	0.09
Total	89.23	92.89	93.54

Results of Toxicokinetic studies demonstrate that the percent drug excreted unchanged in the urine and feces (Fig 1) was similar in the rats administered dietary and single dose gavage alpha-terpineol. There was a 9–10 fold reduction in Cmax among rats administered dietary alpha-terpineol as compared to the rats administered alpha-terpineol via gavage. Tissue distribution data suggest high partitioning of radioactivity in the abdominal fat, liver and kidney tissue in dietary rats vs the kidney and liver in gavaged rats. Four major metabolites in urine were identified by mass spectrometry as glucuronide conjugates of alpha-terpineol or



Route	Unchanged		glucuronide conjugates of alpha-terpineol	glucuronide conjugates of hydroxy alpha-terpineol
	Feces	Urine	Urine	Urine
Gavage	11.1 - 18.7%	0.10%	11.1 - 19.9%	3.4 - 20.7%
Diet	9.3 - 12.4%	<0.10%	20.1 - 26.8%	20.1 - 26.8%

kidney, liver, plasma and testes	Metabolite	Unchanged
Gavage	glucuronide conjugates of alpha-terpineol and glucuronide conjugates of hydroxy alpha-terpineol	9.10%
Diet	glucuronide conjugates of alpha-terpineol and glucuronide conjugates of hydroxy alpha-terpineol	<8%

Fig. 1. Results of Toxicokinetic studies.

glucuronide conjugates of hydroxy alpha-terpineol in both cases. The results concluded that the peak plasma concentrations remained 9–9.8 times lower for rats on dietary treatment as compared to oral gavage. The results suggest that the adverse male reproductive toxicity effects observed following gavage administration of terpineol was mediated by high plasma concentration of terpineol following bolus gavage administration. The absence of adverse male reproductive toxicity effects among animals administered terpineol via diet suggests that continuous administration of equivalent doses of terpineol may not result in adverse male reproductive toxicity. The absence of adverse male reproductive toxicity among animals treated with dietary terpineol may be mediated by ~10X lower plasma concentrations of terpineol as compared to animals treated with equivalent doses via gavage.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Terpineol is reported to occur in the following foods* and in some natural complex substances (NCS):

Apple brandy (Calvados)Cherry brandy Citrus fruits Laurel (Laurus nobilis L.)Mentha oils Mushroom Ocimum species Pear brandy Plum brandy Salvia species Thyme (Thymus species) Wine.

d-.α.-Terpineol and *p*-menth-1-en-8-ol (S) are reported to occur in the following foods*:

Citrus fruits.

Mastic (Pistacia lentiscus).

α-Terpineol is reported to occur in the following foods* and in some natural complex substances (NCS):

Acerola (Malpighia)Allium speciesAlpinia speciesAngelica (Angelica archangelica L.)Anise (Pimpinella anisum L.)Anise brandyApple brandy (Calvados)Apple fresh (Malus species)Apple processed (Malus species)Apricot (Prunus armeniaca L.)Arctic bramble (Rubus arcticus L.)ArtichokeAshanti pepper (Piper guineense Schum and Thom)Avocado (Persea americana Mill.)Babaco fruit (Carica pentagona Heilborn)BeansBeefBeerBeli, Bael (Aegle marmelos Correa)Bilberry wineBlack currants (Ribes nigrum L.) Brown algaeBuchu oilBullock's heart (Annona reticulata L.)Calabash nutmeg (Monodora myristica Dunal)Calamus (sweet flag) (Acorus calamus L.)California pepper (Schinus molle L.)CamomileCape gooseberry (Physalis peruviana L.)Capsicum speciesCardamom (Ellettaria cardamomum Maton.)Carrot (Daucus carota L.)Celery (Apium graveolens L.)Cheese, various typesCherimoya (Annona cherimolia Mill.)CherryChickenChinese quince (Pseudocydonia sinensis Schneid)Cider (apple wine)Cinnamomum speciesCitrus fruitsCloudberry (Rubus chamaemorus L.)Cloves (Eugenia caryophyllata Thunberg)CocoaCoffeeCoriander leaf (Coriandrum sativum L.)Coriander seed (Coriandrum sativum L.)Crowberry (Empetrum nigrum coll.)Cumin seed (Cuminum cyminum L.)Curcuma speciesCurry (Bergera koenigii L.)Custard apple, atemoya (Annona atemoya)Date (Phoenix dactylifera L.)Dill (Anethum species)Dwarf quince (Chaenomeles japonica)Elderberry (Sambucus nigra L.)Endive (Cichorium endivia L.)Eucalyptus oil (Eucalyptus globulus Labill)Fennel (Foeniculum vulg., ssp. capillaceum; var.) GinGinger (Zingiber species)Grape (Vitis species)Grape brandyGuava and feyoaGuava wineHog plum (Spondias mombins L.) HoneyHop (Humulus lupulus)Juniperus communisKatsuobushi (dried bonito)Kiwifruit (Actinidia chinensis, syn. A. deliciosa) Kumazasa (Sasa albo-marginata)Laurel (Laurus nobilis L.)Lemon balm (Melissa officinalis L.)Lemon grass oilLicorice (Glycyrrhiza glabra L.)Litchi (Litchi chinensis Sonn.)Litchi wineLoganberry (Rubus ursinus var. loganobaccus)Loquat (Eriobotrya japonica Lindl.)Lovage (Levisticum officinale Koch)Macadamia nut (Macadamia integrifolia)Mace (Myristica fragrans Houttuyn)Maize (Zea mays L.)MaltMangifera speciesMangosteen (Garcinia mangostana L.)Mastic (Pistacia lentiscus)Mate (Ilex paraguayensis) Matsutake (Tricholoma matsutake)MelonMentha oilsMilk and milk products Mountain papaya (C. candamarcensis, C. pubescens) MushroomMyrtle (Myrtus communis L.)Naranjilla fruit (Solanum quitoense Lam.)NectarineNutmeg (Myristica fragrans Houttuyn) Ocimum speciesOkra (Hibiscus esculentus L.)Olive (Olea europaea) Origanum (Spanish) (Coridothymus cap.(L.) Rchb.)Papaya (Carica papaya L.)Parsley (Petroselium species)Parsnip root (Pastinaca sativa L.)Passion fruit (passiflora species)Peach (Prunus persica L.) Peanut (Arachis hypogaea L.)Pear (Pyrus communis L.)Peas (Pisum sativum L.)Pecan (Carya illinoensis Koch)Pepper (Piper nigrum L.) Pimento (allspice) (Pimenta dioica L. Merr.)Pineapple (Ananas comosus)Piper betle l. cultivarsPistachio oil (Pistacia vera)Pistacia atlanticaPistacia palaestina (Pistacia terebinthus L.)Plum (Prunus species)Plum brandyPlum winePomegranate juice (Punica granatum L.)Potato (Solanum tuberosum L.)Potato chips (American) Quince, marmelo (Cydonia oblonga Mill.)Raspberry brandyRaspberry, blackberry and boysenberryRhubarbRice (Oryza sativa L.) Rooibos tea (Aspalathus linearis)Rosemary (Rosmarinus officinalis L.)Salvia speciesSatureja speciesSea buckthorn (Hippophaë rhamnoides L.)SherrySoursop (Annona muricata L.)Star aniseStarfruit (Averrhoa carambola L.)Strawberry (Fragaria species)Strawberry wineSweet grass oil (Hierochloe odorata)Sweet marjoram (Origanum majorana L.)Sweetsop, sugar apple (Annona squamosa L.) Syzygium speciesTamarind (Tamarindus indica L.)Tapereba, caja fruit (Spondias lutea L.)Tarragon (Artemisia dracunculus L.)TeaTequila (Agave tequilana)Thyme (Thymus species)Tomato (Lycopersicon esculentum Mill.)Turpentine oil (Pistacia terebinthus) Vaccinium speciesVanillaWater yam (Dioscorea alata)Wild marjoram (Origanum vulgare L.)WineWormwood oil (Artemisia absinthium L.)Xylopia species.

*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.

8. IFRA standard

None.

9. REACH dossier

Terpineol and α-terpineol have dossiers available; accessed on 06/18/13. d-.α.-Terpineol and *p*-menth-1-en-8-ol (S) are preregistered for 2010, no dossier available as of 04/17/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.2. Risk assessment. The mutagenic activity of terpineol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were

treated with terpineol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA REACH Dossier: Terpineol). Under the conditions of the study, terpineol was not mutagenic in the Ames test.

The clastogenic activity of terpineol was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with terpineol in DMSO at concentrations up to 650 μg/ml in the presence and absence of metabolic activation (S9) at the 3 h and 20 h time points. Terpineol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (ECHA REACH Dossier: Terpineol). Under the conditions of the study, terpineol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on all available data, terpineol does not present a concern for genotoxic potential.

Additional References: Carneiro et al., 1997; Gomes-Carneiro et al., 1998.

Literature Search and Risk Assessment Completed on: 10/18/2016.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on terpineol for the repeated dose toxicity endpoint. There are no repeated dose toxicity data on any of the other combined materials. In a GLP/OECD 413 guideline study, Crl:CD (SD) male and female rats (10/sex/group) were exposed to terpineol multiconstituent by snout-only inhalation route at 0.202, 0.572 and 2.23 mg/L (actual levels) for 13 weeks (6 h/day; 5 days/week), corresponding to 0, 52, 148 or 578 mg/kg/day according to standard minute volume and body weight parameters for Sprague-Dawley rats. The MMAD were between 0.52 and 1.6 μM and the respective GSD was between 2.99 and 1.75. A 4 week treatment free recovery group of 10/sex/group of control and high dose group animals was also included. The nasal cavity was identified as a target organ for local effects. Significant reduction in mean group bodyweight gain among males of the high dose group was observed. Examination of recovery phase animals showed no changes in the nasal pharynx respiratory epithelium, suggesting complete recovery after 4 weeks which is therefore not considered adverse. The group mean reticulocyte percentage and the absolute reticulocyte count were significantly lower than control values for males of the high dose group. Thus the NOAEL for the repeated dose toxicity endpoint was determined to be 2.23 mg/L, the highest dose tested, equivalent to 578 mg/kg/day according to standard minute volume and body weight parameters for Sprague-Dawley rats (ECHA, REACH Dossier on terpineol). In another study, an OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in Sprague-Dawley rats. There were 3 treatment groups. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. Main phase males and toxicity phase females were dosed daily for a minimum of five consecutive weeks. An additional 5 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for five weeks and then given two weeks of recovery before termination. The repeated dose toxicity NOAEL was determined to be 750 mg/kg/day, the highest dose tested. Although there were alterations in liver weight, clinical chemistry and histopathological alterations, all the effects were reversible. The effects on the kidney were male rat specific effects and had no significance towards human health (Lehman-McKeeman and Caudill, 1992; and Lehman-McKeeman et al., 1990). Testis weight was markedly low in males receiving 750 mg/kg/day and there was also an indication of low epididymal weights at this dose. There were adverse findings related to treatment with test material on the male reproductive parameters reported among the animals of the high dose group. However the effects on the male reproductive system and organs will be discussed in the reproductive toxicity section of the safety assessment (ECHA REACH Dossier: terpineol). In another study, terpineol multiconstituent No. 2 was administered to 10 male Sprague-Dawley rats for 90 days via diet. The test item was dissolved in corn oil, mixed in Ssniff powder feed at the dose level of 12000 ppm (equivalent to 622.65 mg/kg bw/day) and fed to male Sprague-Dawley rats (10/dose) daily ad libitum for 13 weeks. The body weights were significantly reduced in rats receiving test item at 12000 ppm. This decrease was associated with a decrease in the food intake throughout the treatment period. There was no other test material related adverse effect reported among the treated males (ECHA, REACH Dossier on terpineol). The most conservative NOAEL of 578 mg/kg/day from the 90 day inhalation toxicity study was selected for the repeated dose toxicity endpoint. Therefore, the terpineol MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpineol NOAEL by the total systemic exposure to terpineol, 578/0.0067 or 86269.

In addition, the total systemic exposure to terpineol (6.7 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2008a; RIFM, 2008b; Boutin et al., 1985; Boutin et al., 1981; Meyer and Meyer, 1959, 1965; Godwin and Michniak, 1999.

Literature Search and Risk Assessment Completed on: 10/31/2016.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on terpineol for the developmental and reproductive toxicity endpoints. There are no developmental and reproductive toxicity data on any of the other combined materials.

An OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in Sprague-Dawley rats. There were 3 treatment groups. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. Main phase males and toxicity phase females were dosed daily for a minimum of five consecutive weeks. An additional 5 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for five weeks and then given two weeks of recovery before termination. There were no adverse effects towards the development of the fetus up to 250 mg/kg/day. At 750 mg/kg/day, no females became pregnant. It is considered that the testicular and epididymal effects observed in males receiving 750 mg/kg/day would have been

sufficient to prevent fertilization. Thus the NOAEL for the developmental toxicity endpoint was determined to be more than 250 mg/kg/day. In another study, terpineol multiconstituent diluted in corn oil was administered by gavage to groups of mated female Sprague-Dawley rats (20 mated females/dose) at the dose levels of 0, 60, 200, 600 mg/kg bw/day from Days 6–19 after mating. The test was conducted according to the OECD 414 protocol. Embryo-fetal growth was slightly reduced by maternal treatment as evidenced by reduced mean male and female fetal weight at 600 mg/kg bw/day. In addition, mean placental weight in this dose group was slightly low with differences attaining statistical significance. Mean placental, litter and fetal weights at 60 or 200 mg/kg/day were unaffected by maternal treatment with terpineol. The incidence of major and minor abnormalities and skeletal variants showed no relationship to maternal treatment with terpineol. Thus the NOAEL for the developmental toxicity was determined to be 200 mg/kg/day (ECHA, REACH dossier on terpineol). The most conservative NOAEL of 200 mg/kg/day was selected for the developmental toxicity endpoint. **Therefore, the terpineol MOE for the developmental toxicity endpoint can be calculated by dividing the terpineol NOAEL by the total systemic exposure to terpineol, 200/0.0067 or 89552.**

In addition, the total systemic exposure to terpineol (6.7 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

An OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in Sprague-Dawley rats. There were 3 treatment groups. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. Main phase males and toxicity phase females were dosed daily for a minimum of five consecutive weeks. An additional 5 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for five weeks and then given two weeks of recovery before termination. Testis weight was markedly low in males receiving 750 mg/kg/day and there was also an indication of low epididymal weights at this dose. This effect was also seen in the recovery group males. At 750 mg/kg/day, reduced numbers or complete absence of spermatozoa, accompanied by the presence of degenerate spermatogenic cells in duct(s) were observed in the epididymides and were still present following the 2-week recovery period. Spermatocele granuloma (ta) that were seen in two males receiving 750 mg/kg/day and one receiving 60 mg/kg/day were not seen at the end of the recovery period. The significance of this change in the single male receiving 60 mg/kg/day is uncertain as spermatocele granuloma (ta) can occur spontaneously in rats of this age and considering the absence of other degenerative changes in the testes or epididymides of this animal. Moderate to severe seminiferous tubular atrophy/degeneration was seen in the testes of all animals dosed at 750 mg/kg/day, accompanied by minimal to moderate spermatid giant cells and minimal to slight seminiferous tubular vacuolation. Similar findings were still evident following the 2-week recovery period but at a lower incidence and severity suggesting a degree of recovery. There were no alterations in the female reproductive cycles or the reproductive organs up to the highest dose tested. Thus the NOAEL for the reproductive toxicity endpoint was determined to be 250 mg/kg/day based on impairment of male fertility at 750 mg/kg/day (ECHA, REACH Dossier on terpineol). In another investigatory study, succeeding the OECD 422 screening test, was performed to compare the toxicity of terpineol to the male reproductive system when administered by dietary or oral gavage routes. Three groups of Crl:CD (SD) male rats (five/dose) were administered terpineol daily by dietary and/or oral gavage routes at the following doses:

Group 1: dietary 7500 ppm + supplementary gavage dose 300 mg/kg/day,
Group 2: dietary 10000 ppm + supplementary gavage dose 150 mg/kg/day, and
Group 3: 750 mg/kg/day by gavage only.

Necropsy data indicated that decreases in reproductive organ weights and changes to macroscopic appearance were most marked in the animals receiving terpineol multiconstituent at 750 mg/kg/day. Sperm analysis showed that motile sperm with normal morphology were present in 4/5 males of Group 2 and 1/5 males of Group 1. The outliers in each group were at the extreme of achieved overall exposure for the group suggesting that absolute exposure was important, although the route of exposure and consequently potential to exceed threshold levels was of greater significance. Microscopic examination indicated there were relatively fewer changes in the testes and epididymides in the animals which were given terpineol multiconstituent by the dietary route with oral gavage supplementation (Groups 1 and 2), whereas there were significant changes in those which received it solely by oral gavage (Group 3). The results of dietary administration suggest that exposure via the dietary route of administration reduces the testicular and sperm toxicity of the test material compared to dosing by oral gavage. The results of this study, in part, support the hypothesis that a high peak plasma level is necessary to induce the observed toxic effects (ECHA, REACH dossier on terpineol). In another repeated dose oral dietary toxicity study terpineol multiconstituent No. 2 was administered to 10 male Sprague-Dawley rats for 90 days. The test item was dissolved in corn oil, mixed in Ssniff powder feed at the dose level of 12000 ppm and fed to male Sprague-Dawley rats (10/dose) daily ad libitum for 13 weeks. Rats in the control group were fed basal diet only without any test item admixtures. Histopathological examination of the testes and the epididymides were carried out. There were no test item-related histological changes observed in the testis and the epididymis. Thus the NOAEL for male reproductive and systemic toxicity was determined to be 12000 ppm (622.65 mg/kg bw/day) or higher the only dose tested (ECHA, REACH dossier on terpineol). The most conservative NOAEL of 250 mg/kg/day was selected for the reproductive toxicity endpoint. Therefore, the terpineol MOE for the reproductive toxicity endpoint can be calculated by dividing the terpineol NOAEL by the total systemic exposure to terpineol, 250/0.0067 or 29851.

In addition, the total systemic exposure to terpineol (6.7 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2008a; RIFM, 2008b; Boutin et al., 1985; Boutin et al., 1981; Meyer and Meyer, 1959, 1965; Godwin and Michniak, 1999.

Literature Search and Risk Assessment Completed on: 10/31/2016.

10.1.4. Skin sensitization

Based on existing data for terpineol and the specific isomer α-terpineol, terpineol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on existing data for terpineol and the specific isomer α-terpineol (see Section I), terpineol does not present a concern for skin sensitization. Both materials are predicted to be non-reactive to skin proteins and therefore would not be likely to act as a skin sensitizer (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). However, it should be noted that as cyclic terpenes, these materials could be reasonably anticipated to undergo autoxidation resulting in potentially sensitizing degradation products. Nevertheless, in guinea pig sensitization tests, no reactions indicative of sensitization were observed with terpineol (ECHA Dossier; Klecak, 1979; RIFM, 1982). Additionally, in human confirmatory studies no sensitization reactions were observed to terpineol (RIFM, 1961; Greif, 1967; RIFM, 1964). Based on weight of evidence from animal and human data terpineol does not present a concern for skin sensitization.

Additional References: RIFM, 1961; Friedrich et al., 2007; Hausen et al., 1999; Klecak, 1979.

Literature Search and Risk Assessment Completed on: 08/23/13.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for terpineol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, terpineol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/13/16.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are limited inhalation data available on terpineol. Based on the Creme RIFM model, the inhalation exposure is 0.074 mg/day. This exposure is 18.9 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Rice and Coats, 1994; Ellis and Baxendale, 1997; Regnault-Roger and Hamraoui, 1995; Sato et al., 2007; Perrucci et al., 1995; Helmig et al., 1999a, 1999b.

Literature Search and Risk Assessment Completed on: 10/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of terpineol 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). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, terpineol 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 terpineol 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., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.1.2. Risk assessment. Based on current volume of use (2011), terpineol presents a risk to the aquatic compartment in the screening level assessment.

10.2.2. Key studies

10.2.3.1. Biodegradation. RIFM, 1994: A biodegradation of terpineol was evaluated according to the OECD 301B method. Biodegradation on day 28 was 105.7%.

RIFM, 1997: A biodegradation study was conducted using activated sludge in a manometric respirometry test according to the OECD 301F method. The test material underwent an average 87% biodegradation after 28 days.

RIFM, 2007: Ready biodegradability of terpineol was evaluated in a CO_2 headspace test according to the OECD 310 guidelines. Test material was biodegraded 80% at day 28.

10.2.3.2. ***Ecotoxicity:*** *No data available.* Other available data:

Terpineol is registered under REACH and full dossier is available with additional information (accessed 08/19/13):

A 96 h semi-static fish (*Danio rerio*) acute study according to the OECD 203 method was reported with LC50 of 62 mg/l.

Daphnia magna acute study according to the OECD 202 method was reported. Under static conditions the 48 h EC50 was 73 mg/l.

An algae acute study according to the OECD 201 method was reported. The 72 h EC50 was biomass was 17 mg/l and for growth was 68 mg/l.

11. Risk assessment refinement

The REACH PNEC has been derived based on fish LC50 of 62 mg/l. However, for more conservative approach an algae biomass EC50 of 17 mg/l is used in this assessment.

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)**	62.54 mg/L			1,000,000	0.0625 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	8.004 mg/L	5.495 mg/L	4.651 mg/L	10,000	0.4651 µg/L	Neutral organics
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	62 mg/L					
Daphnia		73 mg/L				
Algae		17 mg/L		1000	17 µg/l	

Exposure information and PEC calculation (following RIFM Framework: Salvito et al., 2002; #40315).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.6	2.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000*	100-1000+
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined volumes for all CAS#.

Based on available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 17 µg/L. The revised PEC/PNECs for EU and NA are < 1 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: 08/23/13.

12. Literature search*

- **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

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

This is not an exhaustive list.

Appendix

Explanation of cramer class:

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

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

Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6.Benzene derivative with certain substituents? **No**
Q7.Heterocyclic? **No**
Q16.Common terpene Yes? **Low (Class I)**

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.07.042.

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