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Short Review

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

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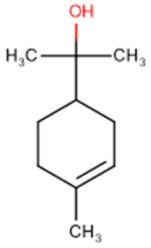


Name: Terpineol
CAS Registry Number: 8000-41-7
Additional CAS Numbers*:
10482-56-1 *p*-Menth-1-en-8-ol (S)
7785-53-7 d-α-Terpineol
98-55-5 α-Terpineol
*These materials are included in this assessment because they are a mixture of isomers.

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
NOEL - No Observed Effect Level
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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

(*continued on next column*)

(*continued*)

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes 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 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., 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 endpoint 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 with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Terpineol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that terpineol is not genotoxic. Data on terpineol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for terpineol for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; terpineol is not expected to be photoirritating/photoallergenic. Data on terpineol provide a calculated MOE >100 for the local respiratory endpoint. The environmental endpoints were evaluated; terpineol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: p-Menth-1-en-8-ol; ECHA, 2013)
Repeated Dose Toxicity: NOAEL = 578 mg/kg/day.	(ECHA REACH Dossier: 4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene; ECHA, 2017b)
Reproductive Toxicity: Developmental toxicity NOAEL = 200 mg/kg/day. Fertility: NOAEL = 250 mg/kg/day.	(ECHA REACH Dossier: 4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene; ECHA, 2017b)
Skin Sensitization: No concern for skin sensitization.	(Anderson et al., 2009)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 20 mg/m^3.	(ECHA REACH Dossier: 4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene; ECHA, 2017b)

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 105.7% (OECD 301B)	(RIFM, 1994)
Bioaccumulation:	
Screening-level: 67.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 72-h Algae EbC50: 17 mg/L	(ECHA REACH Dossier: p-Menth-1-en-8-ol; ECHA, 2013)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 72-h Algae EbC50: 17 mg/L	(ECHA REACH Dossier: p-Menth-1-en-8-ol; ECHA, 2013)
RIFM PNEC is: 17 μg/L	

- Revised PEC/PNECs (2019 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	**CAS Registry Number:** 7785-53-7	**CAS Registry Number:** 10482-56-1	**CAS Registry Number:** 98-55-5
Synonyms: *p*-Menthenol (mixed isomers); Terpineol pure; α-テルピネオール; 2-(4-Methylcyclohex-3-en-1-yl) propan-2-ol; Terpineol	**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	**Synonyms:** 3-Cyclohexene-1-methanol,α,α,4-trimethyl-, (S)-; 2-(4-Methylcyclohex-3-en-1-yl) propan-2-ol; (−)-α-Terpineol	**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-テレピネオール
Molecular Formula: $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$
Molecular Weight: 154.25 g/mol	**Molecular Weight:** 154.53 g/mol	**Molecular Weight:** 154.53 g/mol	**Molecular Weight:** 154.25 g/mol
RIFM Number: 148	**RIFM Number:** 5365	**RIFM Number:** 5386	**RIFM Number:** 6100

2. Physical data

1. **Boiling Point:** 217 °C (Fragrance Materials Association [FMA]), 214.38 °C (EPI Suite)
2. **Flash Point:** 192 °F; Closed cup (FMA), 88 °C (Globally Harmonized System)
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:** 371.7 mg/L (EPI Suite)
6. **Specific Gravity:** 0.931 (FMA)
7. **Vapor Pressure:** 0.0108 mm Hg at 20 °C (EPI Suite v4.0), 0.1 mm Hg at 20 °C (FMA), 0.0196 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. >1000 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient* (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.18% (RIFM, 2019)
2. **Inhalation Exposure**:** 0.00059 mg/kg/day or 0.044 mg/day (RIFM, 2019)
3. **Total Systemic Exposure***:** 0.0044 mg/kg/day (RIFM, 2019)

*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 fine fragrance, inhalation exposure, and total exposure.

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	III	I

*See the Appendix below for details.

2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification:** None

7. Metabolism

RIFM, 2016: Previous studies on terpineol indicate that the male reproductive system is a target following gavage and dietary administration to rats (see 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 OECD 417 guidelines. A single-dose gavage toxicokinetic study was conducted on [^{14}C]-α-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, and 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]-α-terpineol administration on day 14.

Gavage: The absorption, distribution, metabolism, and excretion of [isopropyl methyl-^{14}C]-α-terpineol in corn oil were studied after single gavage doses of 75, 250, and 750 mg/kg were administered to male rats. Radiolabeled α-terpineol and non-radiolabeled terpineol multi-constituent were combined in corn oil to achieve the desired specific activity of the dosed material. The dosing, grouping, and scheduled euthanasia times are shown below in Table 1 (see Table 1 below). Concentrations of radioactivity in tissues were highest in the kidney and liver at each dose level. The tissue:plasma ratios were generally less than 1, other than for the 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]-α-terpineol were studied after repeated daily dietary administration at 650, 2200, and 6500 ppm for 14 days in male rats. Non-radiolabeled α-terpineol was combined with a powdered VRF1

Table 1
Dosing, grouping, and scheduled sacrifice times from metabolism study on terpineol administered via gavage in male rats (RIFM, 2016).

Table 1	Excretion/ Distribution (Groups 1-3)	Plasma and whole-blood kinetics experiments (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
Sacrifice times	168 hours after dosing	**Subgroup 1:** Pre-dose, 1, 4, 24, 96 hours **Subgroup 2:** 0.25, 2, 6, 48, 120 hours **Subgroup 3:** 0.5, 3, 12, 72, 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

diet and mixed to achieve a homogenous treated diet. The daily intake based on food consumption was 53.2–74.4, 211–274, and 424–736 mg/kg/day. The animals were offered a diet treated with non-radiolabeled test material for 13 days, followed by a treated diet fortified with [^{14}C]-α-terpineol on day 14. The dosing, grouping, and scheduled sacrifice times are shown in Table 2 (see Table 2 below). 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 overtime at all dose levels. Tissue:plasma ratios were generally less than 1, with the exception of the kidney, liver, and abdominal fat (all euthanasia times).

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

Following single oral doses or repeated daily dietary administration of non-radiolabeled α-terpineol for 13 days followed by dietary administration of [^{14}C]-α-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 urine. The following tables (see Table 4 and 5 below) summarize the excretion of radioactivity during 0–168 h after administration. Results are expressed as % dose.

Unchanged [^{14}C]-α-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 shown below.

The results of toxicokinetic studies demonstrate that the percent of drug excreted unchanged in the urine and feces (Fig. 1) was similar in the rats administered dietary and single-dose gavage α-terpineol. There was a 9- to 10-fold reduction in Cmax among rats administered dietary α-terpineol as compared to the rats administered α-terpineol via gavage.

Table 2
Dosing, grouping, and scheduled sacrifice times from metabolism study on terpineol administered via diet in male rats (RIFM, 2016).

Table 2	Excretion/ Distribution (Groups 1-3)	Plasma and whole-blood kinetics experiments (Groups 4 to 6)	Tissue distribution experiments (Groups 7 to 9)
Animals	4 per group	12 male animals per group further divided into subgroups of 4	9 male animals per group
Sacrifice times	168 hours after dosing	**Subgroup 1:** Pre-dose, 1, 4, 24, 96 hours **Subgroup 2:** 0.25, 2, 6, 48, 120 hours **Subgroup 3:** 0.5, 3, 12, 72, 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
Peak plasma concentrations in rats administered radioactive α-terpineol via gavage versus peak plasma concentrations in rats administered radioactive α-terpineol via diet (RIFM, 2016).

Table 3	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
And 5: Excretion of radioactivity from rats administered α-terpineol via gavage (Table 4) or via diet (Table 5) (RIFM, 2016).

Table 4	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	650 ppm (75 mg/kg)	2200 ppm (250 mg/kg)	6500 ppm (750 mg/kg)
Urine	63.57	67.69	73.64
Cage wash	7.86	5.48	5.03
Faeces	17.70	19.55	14.78
GIT & Carcass	0.10	0.17	0.09
Total	89.23	92.89	93.54

Tissue distribution data suggest high partitioning of radioactivity in the abdominal fat, liver, and kidney tissue in dietary rats versus the kidney and liver in gavaged rats. Four major metabolites in urine were identified by mass spectrometry as glucuronide conjugates of α-terpineol or glucuronide conjugates of hydroxy α-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 the gavage administration of terpineol were mediated by the 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 approximately 10x lower plasma concentrations of terpineol as compared to animals treated with equivalent doses via gavage.

Additional References: None.

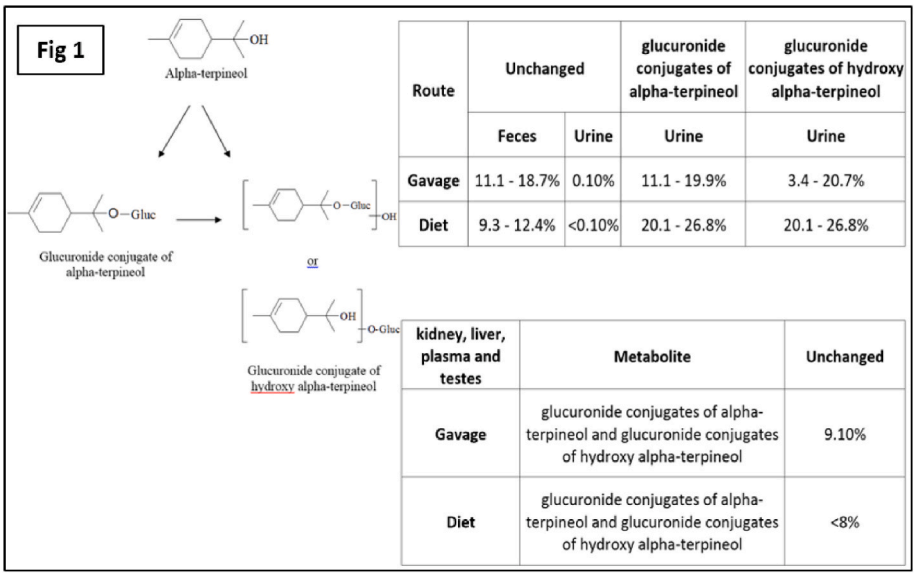
8. Natural occurrence

Terpineol (CAS # 8000-41-7) is reported to occur in the following foods by the VCF*:

Apple brandy (*Calvados*)	Ocimum species
Cherry brandy	Pear brandy
Citrus fruits	Salvia species
Mentha oils	Thyme (*Thymus* species)
Mushroom	Wine

p-Menth-1-en-8-ol (S) (CAS # 10482-56-1) and d-α-terpineol (CAS # 7785-53-7) are reported to occur in the following foods by the VCF*:

Citrus fruits
Mastic (*Pistacia lentiscus*)
Tea



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 on rats administered dietary and single-dose gavage α-terpineol (RIFM, 2016).

α-Terpineol (CAS # 98-55-5) is reported to occur in the following foods by the VCF*:

Acerola (*Malpighia*)	Chicken
Allium species	Citrus fruits
Asafoetida oil	Fish
Beer	Honey
Camomile	Litchi wine

*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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. These are partial lists.

9. Reach dossier

Terpineol (CAS # 8000-41-7) is pre-registered for 2010; no dossier available as of 03/16/22. Available for p-menth-1-en-8-ol (S) (CAS # 10482-56-1) (ECHA, 2019); accessed on 03/16/22. d-α-Terpineol (CAS # 7785-53-7) is pre-registered for 2010; no dossier available as of 03/16/22. Available for α-terpineol (CAS # 98-55-5) (ECHA, 2013); accessed on 05/31/22.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of defined isomer α-terpineol has been evaluated in a bacterial reverse mutation assay conducted in an equivalent manner to OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with α-terpineol (solvent not specified) at concentrations up to 1000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, α-terpineol was not mutagenic in the Ames test.

The clastogenicity of isomeric mixture terpineol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with terpineol in dimethyl sulfoxide (DMSO) at concentrations up to 1543 μg/mL in the dose range finding (DRF) study; the main study was conducted at concentrations up to 650 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2013). Under the conditions of the study, terpineol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 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: 05/20/22.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on terpineol (multi-constituent) and α-terpineol (pure isomer) for the repeated dose toxicity endpoint.

In a GLP- and OECD 413-compliant study, groups of 10 Crl:CD(SD) rats/sex/dose were exposed to terpineol multi-constituent by snout-only inhalation at concentrations of 0.202, 0.572, and 2.23 mg/L (corresponding to doses of 0, 52, 148, or 578 mg/kg/day according to standard minute volume and body weight parameters for Sprague Dawley rats) for 13 weeks (6 h/day, 5 days/week). An additional 10 Crl:CD(SD) rats/sex/dose were treated with 0 or 578 mg/kg/day terpineol and maintained for 4 weeks after the treatment period as recovery groups. No mortality occurred throughout the study. No treatment-related adverse effects were observed in food consumption, blood chemistry,

ophthalmoscopy, organ weights, or macropathology. Bodyweight gain was reduced in males at the low dose and in both sexes at the mid and high doses (statistically significant only in high-dose males). However, this effect was not dose-dependent and was fully reversed in all groups during the recovery period. Reticulocyte percentage and absolute reticulocyte count were significantly reduced in males at the mid dose and in both sexes at the high dose (statistically significant only in males). This effect was fully reversed during the recovery period. Based on no toxicologically relevant adverse effects seen up to the highest dose, the NOAEC for the repeated dose toxicity endpoint was determined to be 2.23 mg/L (equivalent to a NOAEL of 578 mg/kg/day) (ECHA, 2017b; uses terpineol data as read-across).

In a GLP- and OECD 408-compliant study, groups of 10 Crl:Sprague-Dawley CD IGS rats/sex/dose were administered α-terpineol via diet at doses of 0, 50, 150, and 500 mg/kg/day for 90 days. No mortality occurred throughout the study period. There were no treatment-related adverse effects on clinical signs, body weights, food consumption, hematology, clinical chemistry, thyroid hormone, urinalysis, organ weights, or macroscopic or microscopic examinations. Based on no adverse effects seen up to the highest dose, the repeated dose toxicity NOAEL for this study was considered to be 500 mg/kg/day (RIFM, 2021).

In an OECD 422-compliant study, groups of 10 Sprague Dawley rats/sex/dose were administered terpineol via gavage at doses of 0, 60, 250, and 750 mg/kg/day (except for the control and high-dose groups containing the only 5 males/dose). Males were treated for a minimum of 5 weeks. Females were treated for 2 weeks before pairing, throughout mating, gestation, and until day 6 of lactation. Additional groups of 10 rats/sex/dose at 0 or 750 mg/kg/day were maintained for 2 weeks after the treatment period as recovery groups. No treatment-related mortality was observed. No treatment-related adverse effects were observed in clinical signs, sensory reactivity findings, grip strength values, motor activity, body weights, food consumption, hematology, urinalysis, and clinical chemistry. Thus, the repeated dose NOAEL for this study was considered to be 750 mg/kg/day (ECHA, 2018).

The most robust NOAEL of 578 mg/kg/day was selected from the 90-day, OECD 413-compliant toxicity study for the repeated dose toxicity endpoint.

Therefore, the terpineol MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to terpineol, 578/0.0044, or 131363.

In addition, the total systemic exposure to terpineol (4.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/06/22.

11.1.3. Reproductive toxicity

The MOE for terpineol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity and fertility data on terpineol (multi-constituent) and α-terpineol (pure isomer) for the reproductive toxicity endpoints.

In an OECD 422-compliant study, groups of 10 Sprague Dawley rats/sex/dose were administered terpineol via gavage at doses of 0, 60, 250, and 750 mg/kg/day (except for the control and high-dose groups containing only 5 males/dose). Males were treated for a minimum of 5 weeks. Females were treated for 2 weeks before pairing, throughout mating, gestation, and until day 6 of lactation. An additional 10 rats/sex/dose at 0 or 750 mg/kg/day were maintained for 2 weeks after the treatment period as recovery groups. There were no treatment-related adverse effects on estrous cycles, precoital interval, mating, or gestation length. Testes and epididymis weights were significantly lower in high-dose males; these effects were not reversed during the recovery period. Reduced numbers or complete absence of spermatozoa, accompanied by the presence of degenerate spermatogenic cells in ducts, were observed in the epididymides of high-dose males; these effects were not reversed during the recovery period. Seminiferous tubular atrophy/degeneration of the testes was observed in high-dose males. There were no adverse effects on fetal development up to 250 mg/kg/day. At 750 mg/kg/day, no females became pregnant, which was considered to be due to the prevention of fertilization by the testicular and epididymal effects observed in males receiving 750 mg/kg/day. Thus, based on no adverse effects observed up to the highest dose, the developmental toxicity NOAEL for this study was determined to be 750 mg/kg/day. Based on testicular and epididymis effects observed at 750 mg/kg/day, the fertility NOAEL for this study was considered to be 250 mg/kg/day (ECHA, 2017b; uses terpineol data as read-across).

In an OECD 414-compliant study, groups of 20 mated female Sprague Dawley rats/dose were administered terpineol multi-constituent via gavage (vehicle: corn oil) at doses of 0, 60, 200, and 600 mg/kg/day from days 6–19 after mating. Male and female fetal weights were significantly reduced at the high dose. Placental weights were slightly but significantly reduced at the high dose. There were no treatment-related major and minor abnormalities or skeletal variations. Thus, based on reduced fetal weights and placental weights at 600 mg/kg/day, the developmental toxicity NOAEL for this study was determined to be 200 mg/kg/day (ECHA, 2017b).

In a GLP- and OECD 408-compliant study, groups of 10 Crl:Sprague-Dawley CD IGS rats/sex/dose were administered α-terpineol via diet at doses of 0, 50, 150, and 500 mg/kg/day for 90 days. Sperm parameters were assessed. There were no treatment-related changes to epididymal sperm count or homogenization-resistant spermatid (HRS) count. There were no statistically significant effects on the percentage of mobile or abnormal sperm; however, 3 males at the high dose had 0% motile sperm, and another male at the high dose had a notably reduced percentage of motile sperm compared to the others in the same group. The sperm in these 4 males were noted to have excessive fragmentation (heads separated from tails), which correlated with reduced motility. However, there were no macroscopic or microscopic findings in these males that could be associated with sperm changes. Based on the abnormalities found in the sperm analysis at 500 mg/kg/day, the male fertility NOAEL for this study was considered to be 150 mg/kg/day (RIFM, 2021).

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 in mg/kg/day by the total systemic exposure to terpineol, 200/0.0044 or 45454.

In the OECD 422 and OECD 408 studies, adverse effects on sperm parameters were observed at the highest doses of 750 mg/kg/day and 500 mg/kg/day, respectively. However, these effects were not observed in either study at the mid doses of 250 mg/kg/day and 150 mg/kg/day, respectively. Because no adverse effects were observed up to 250 mg/kg/day across the 2 studies, the NOAEL of 250 mg/kg/day from the OECD 422 study was selected for the fertility endpoint. Therefore, the terpineol MOE for the fertility endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to terpineol, 250/0.0044 or 56818.

In addition, the total systemic exposure to terpineol (4.4 μg/kg bw/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/07/22.

11.1.4. Skin sensitization

Based on the existing data, terpineol (CAS 8000-41-7) and its

isomers, including d-α-terpineol (CAS # 7785-53-7), *p*-menth-1-en-8-ol (S) (CAS # 10482-56-1), and α-terpineol (CAS # 98-55-5), present no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, terpineol and its isomers are not considered a skin sensitizer. The data are summarized in Table 6 (see Table 6 below). The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), isomer *p*-menth-1-en-8-ol (S) in 4:1 acetone:olive oil was found not to be sensitizing up to 50% (12500 μg/cm^2) (Anderson et al., 2009). In a guinea pig maximization test and closed epicutaneous test, no reactions indicative of sensitization were observed with terpineol (ECHA, 2019; Ishihara et al., 1986). Additionally, in a human maximization test and Confirmation of No Induction in Humans test (CNIH) with terpineol, no sensitization reactions were observed at 12% (8280 μg/cm^2) in petrolatum and 12.5% in ethanol (9689 μg/cm^2), respectively (Greif, 1967; RIFM, 1964).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, terpineol and its isomers do not present a concern for skin sensitization.

Additional References: RIFM, 1961; Friedrich et al., 2007; Hausen et al., 1999; Klecak (1979); RIFM, 1982; RIFM, 1962.

Literature Search and Risk Assessment Completed On: 05/22/22.

Photoirritation/Photoallergenicity:

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

11.1.4.2. Risk assessment. There are no photoirritation studies available for terpineol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, terpineol does not present a concern for photoirritation or photoallergenicity.

11.1.4.3. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/13/22.

11.1.5. Local Respiratory Toxicity

The MOE for terpineol is adequate for the respiratory endpoint at the current level of use.

11.1.5.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. An OECD 413, 13-week inhalation study in CRL:CD rats identified a Lowest Observed Adverse Effect Concentration (LOAEC) of 200 mg/m^3 (ECHA, 2017b; uses terpineol data as read-across). In this study, 10 rats/sex/group were exposed to terpineol via nose-only inhalation for 6 h a day, 5 days per week for 13 weeks. The test concentrations were 0, 200, 600, and 2000 mg/m^3. Standard evaluations included mortality, clinical observations, body weight, hematology, clinical chemistry, and gross and microscopic pathology. After 13 weeks of treatment, related effects were observed in the nasal turbinates and nasal pharynx. Minimal to slight severity hyperplasia of the mucous cells in nasal turbinates was observed in males from all the terpineol exposure groups (0/10, 9/10, 9/10, 10/10) and the females from all the terpineol exposure groups (0/10, 4/10, 8/10, 8/10). Minimal degeneration of olfactory epithelium, respiratory epithelium, and inflammation of the respiratory epithelium in the nasal turbinates was observed in the males and females of the high-dose group. Minimal hyperplasia of the mucous cells in the nasal pharynx was observed in the males and females of the mid- and high-dose groups. Based on the observations in the respiratory tract, the LOAEC is identified at 200 mg/m^3. Therefore, by using a safety adjustment factor of 10, a local effects NOAEC of 20 mg/m^3 is calculated for the subchronic inhalation exposure of terpineol.

This NOAEC expressed in mg/kg lung weight/day is:

- (20 mg/m^3) × (1m^3/1000L) = 0.02 mg/L
- Minute ventilation of 0.17 L/min* for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.02 mg/L) × (61.2 L/d) = 1.224 mg/day
- (1.224 mg/day)/(0.0016 kg lung weight of rat**) = 765 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.044 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.068 mg/kg lung weight/day resulting in

Table 6
Summary of existing data on terpineol and *p*-menth-1-en-8-ol (S).

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA Weighted Mean EC3 Value μg/cm^2	GPMT[d]	Buehler[d]
No evidence of sensitization[f]	9689	8280	NA	NA	12500	Negative	NA
	***In vitro* Data[e]**				***In silico* protein binding alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	NA	NA	NA		No alert found	Radical reactions	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Studies conducted according to the OECD TG 406 are included in the table.

[e] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[f] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

a MOE of 11250 (i.e., [765 mg/kg lung weight of rat/day]/[0.068 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.044 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

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

Literature Search and Risk Assessment Completed On: 05/20/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of terpineol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of 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 EPI Suite v4.11 (US EPA, 2012a) identified terpineol as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative, as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), terpineol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 1994**: The biodegradation of terpineol was evaluated according to the OECD 301B method. The 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 of 87% biodegradation after 28 days.

RIFM, 2007: The ready biodegradability of terpineol was evaluated in a CO_2 headspace test according to the OECD 310 guidelines. Biodegradation of 80% was observed on day 28.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. α-Terpineol (CAS # 98-55-5) is registered under REACH, and the following information is available (ECHA, 2013):

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

A *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 for biomass was 17 mg/L and for growth was 68 mg/L.

11.2.1.3. 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.

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

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*	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined volumes for all CAS #s.

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; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 05/18/22.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	62.54			1000000	0.0625	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	8.004	5.495	4.651	10000	0.4651	Neutral organics
Tier 3: Measured Data, including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	62					
Daphnia		73				
Algae		17		1000	17	

- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 11/01/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix

Explanation of Cramer Classification

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. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and 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? (see Cramer et al., 1978 for detailed explanation). Yes. Class Low (Class I).

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