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Short review

RIFM fragrance ingredient safety assessment, dihydro-α-terpineol, CAS Registry Number 498-81-7

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1. Identification

Chemical Name: Dihydro-α-terpineol	**Chemical Name:** Terpineol, dihydro-
CAS Registry Number: 498-81-7	**CAS Registry Number:** 58985-02-7
Synonyms: Cyclohexanemethanol,.α.,.α., 4-trimethyl-; Dihydro-α-terpineol; 1-Methyl-4-isopropylcyclohexane-8-ol; Dihydro Terpineol; *cis*-p-メンタン-8-オール; p-メンタン-8-オール; 2-(4-Methylcyclohexyl)propan-2-ol	**Synonyms:** Menthanol ou *para*-menthanol
Molecular Formula: $C_{10}H_{20}O$	**Molecular Formula:** $C_{10}H_{20}O$
Molecular Weight: 156.27	**Molecular Weight:** 156.27
RIFM Number: 261	**RIFM Number:** 6991

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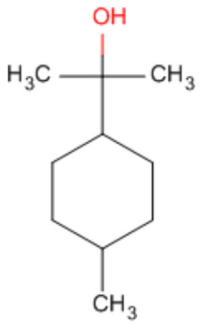
Version: 041717. This version replaces any previous versions.
Name: Dihydro-α-terpineol
CAS Registry Number: 498-81-7
Additional CAS Numbers*:58985-02-7 Terpineol, dihydro-*This material was included in this assessment because they are a mixture of isomers.



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 from the suitable read across analog 2-hydroxy-alpha, alpha,4-trimethylcyclohexanemethanol (CAS# 42822-86-6) show that this material is not genotoxic, provided a MOE > 100 for the repeated dose toxicity endpoint, and it does not have skin sensitization potential. The developmental and reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). 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. (RIFM, 1986a; RIFM, 2000a)
Repeated Dose Toxicity: NOEL = 67 mg/kg/day (RIFM, 2000b)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not sensitizing (RIFM, 1972; RIFM, 1985; RIFM, 1986b; RIFM, 1999b; RIFM, 1995c,d)

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(*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: 91.8% (OECD 301B)	(RIFM, 1994)
Bioaccumulation: Screening Level: 83.48 L/kg	(EPISUITE ver 4.1)
Ecotoxicity: Screening Level: *Daphnia* LC50: 4.43 mg/L	(EPISUITE ver 4.1)
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: *Daphnia* LC50: 4.43 mg/L	(EPISUITE ver 4.1)
RIFM PNEC is: 0.443 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe <1	

2. Physical data*

1. **Boiling Point:** >401 °F [FMA database], (calculated) 207.88 °C [EPI Suite]
2. **Flash Point:** 179 °F; CC [FMA database]
3. **Log K_{OW}:** 3.1 to 3.3 at 35 °C [RIFM, 1999c], 3.42 [EPI Suite]
4. **Melting Point**: 1.7 °C [EPI Suite]
5. **Water Solubility:** 278 mg/L [EPI Suite]
6. **Specific Gravity:** 0.907 [FMA database]
7. **Vapor Pressure:** 0.0282 mm Hg @ 20 °C [EPI Suite 4.0], 0.04 mm Hg 20 °C [FMA database], 0.0457 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A liquid with a woodier, pine-like odor than terpineol.

*Physical data is identical for both materials included in this assessment.

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:**0.86% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0015 mg/kg/day or 0.11 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0097 mg/kg/day (RIFM, 2016)

*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 4. 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:** 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v.2.6	OECD QSAR Toolbox
I*	III	I

*See Appendix below for explanation.

2. **Analogs Selected:**
   a. **Genotoxicity:** 2-Hydroxy-alpha, alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6)
   b. **Repeated Dose Toxicity:** 2-Hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

Dihydro-α-terpineol is reported to occur in the following foods*:

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Citrus fruits

Terpineol, dihydro-is reported to occur in the following foods*:

Agastache 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

Dihydro-α-terpineol and terpineol, dihydro-are pre-registered for 2010; no dossier available as of 4/17/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.2. Risk assessment

Dihydro-α-terpineol was assessed for genotoxic potential in the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity (RIFM, 2013). There are no data assessing the mutagenic potential of dihydro-α-terpineol. The material 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6; see Section 5) has been identified as an acceptable analog to use for read across. 2-Hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol has been evaluated for mutagenicity in a GLP compliant bacterial reverse mutagenicity study in accordance with OECD TG 471 using the standard plate incorporation method. *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol in DMSO (dimethyl sulfoxide) at concentrations of 0.1–25.0 μl/plate (equivalent to 100–2500 μg/plate) with and without metabolic activation and was unable to induce an increase in revertant colonies (RIFM, 1986a,b). Additional studies using up to 5000 μg/plate confirm this result (RIFM, 1995c,d). Under the conditions of the study, the test material is not considered to be mutagenic.

There are no data assessing the clastogenic potential of dihydro-α-terpineol. Again read across can be made to the analog 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6; see Section 5) which was assessed for clastogenicity in an OECD 473 in vitro chromosomal aberration study in Chinese hamster V79 cells. The cells were exposed for 4 and 18 h at concentrations of 25, 50, and 100 μg/ml in the absence of metabolic activation (S9 mix), for 28 h at concentrations of 12.5, 25, and 75 μg/ml in the absence of S9 mix and for 4 h at concentrations of 100, 200, 300, and 400 μg/ml in the presence of S9 mix. It was concluded that 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol did not induce structural chromosome aberrations (RIFM, 2000a,b).

The read across analog 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol does not present a genotoxic concern and this can be applied to dihydro-α-terpineol.

Additional References: RIFM, 1995c,d.

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

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on dihydro-α-terpineol. Read across material, 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6; see Section 5) has an OECD 407 gavage 28-day subchronic toxicity study in rats. The NOEL was determined to be 200 mg/kg/day, based on liver weights, hematology and clinical chemistry effects (RIFM, 2000a,b).

A default safety factor of 3 was used when deriving a NOEL from the 28 day OECD 407 study. The safety factor has been approved by RIFM's Independent Expert Panel*.

Thus the derived NOEL for the repeated dose toxicity data is 200/3 or 67 mg/kg/day.

*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Therefore, the dihydro-α-terpineol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol NOEL in mg/kg/day by the total systemic exposure to dihydro-α-terpineol, 67/0.0097 or 6907.

In addition, the total systemic exposure to dihydro-α-terpineol (9.7 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; RIFM, 1995a; RIFM, 1995b; RIFM, 2008c.

Literature Search and Risk Assessment Completed on: 02/14/2017.

10.1.5. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on dihydro-α-terpineol or any read across materials. The total systemic exposure to dihydro-α-terpineol is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.6. Risk assessment

There are no developmental or reproductive toxicity data on dihydro-α-terpineol or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to dihydro-α-terpineol (9.7 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental or reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2008a; RIFM, 2008b; RIFM, 1995a; RIFM, 1995b; RIFM, 2008c.

Literature Search and Risk Assessment Completed on: 02/14/2017.

10.1.7. Skin sensitization

Based on the available data and read across to 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6), dihydro-α-terpineol does not present a concern for skin

sensitization.

10.1.8. Risk assessment

Based on the available data and read across to 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6; see Section 5), dihydro-α-terpineol does not present a concern for skin sensitization. Both dihydro-α-terpineol and 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol are not predicted to be reactive to skin proteins and therefore would present a low concern for skin sensitization (Roberts et al., 2007; Toxtree 2.5.0; OECD Toolbox v3.1). In guinea pig test methods conducted on 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol no results indicative of sensitization concern were observed (RIFM, 1986a,b; and RIFM, 1999a; RIFM, 1995c,d). In human studies no results indicative of a sensitization potential were reported with dihydro-α-terpineol and 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (RIFM, 1985; RIFM, 1972).

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/26/16.

10.1.9. Phototoxicity/photoallergenicity

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

10.1.10. Risk assessment

There are no phototoxicity studies available for dihydro-α-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 $L \cdot mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on lack of absorbance, dihydro-α-terpineol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.11. Local Respiratory Toxicity

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

10.1.12. Risk assessment

There are no inhalation data available on dihydro-α-terpineol. Based on the Creme RIFM model, the inhalation exposure is 0.11 mg/day. This exposure is 12.7 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: None.

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 dihydro-α-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, dihydro-α-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 dihydro-α-terpineol as being possibly persistent but not bio-accumulative 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 bio-accumulation, 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 1.

10.2.2. Risk assessment

Based on current volume of use (2011), dihydro-α-terpineol does present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM , 1994:** Biodegradation was evaluated by the sealed vessel test according to the OECD 301B method. Vessels containing mineral salts medium inoculated with filtered activated secondary effluent were incubated with 10 mg/L of dihydro-alpha-terpineol for 28 days. The biodegradation rate after 28 days was 91.8%.

RIFM, 1999: Biodegradation was evaluated by the Manometric Respirometry Test which was conducted according to OECD Guideline 301F. Mineral medium inoculated with fresh activated sludge was incubated with 100 mg/L of dihydro-alpha-terpineol for 32 days. The biodegradation rate was 66%, 75%, and 76% after 10, 28 and 32 days, respectively.

10.2.4. Ecotoxicity

Not Available.

10.2.5. Other available data

Dihydro-α-terpineol has been pre-registered for REACH with no additional data available at this time.

10.2.6. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	15.59 mg/l			1,000,000	0.01559 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.851 mg/l	4.434 mg/l	5.674 mg/l	10,000	0.443 μg/L	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.3	3.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10-100*	1-10*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined volumes for both CAS#.

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

The RIFM PNEC is 0.443 μg/L. The revised PEC/PNECs for EU and North America: <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 11/01/13.

11. 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

Read across justification

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012)

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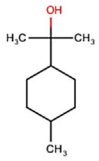
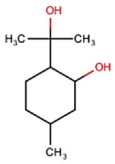
	Target material	Read across material
Principal Name	Dihydro-α-terpineol	2-Hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol
CAS No.	498-81-7	42822-86-6
Structure		
Similarity (Tanimoto score)[1]		0.578
Read across endpoint		• Genotoxicity • Skin sensitization • Repeated dose
Molecular Formula	$C_{10}H_{20}O$	$C_{10}H_{20}O_2$
Molecular Weight	156.27	172.27
Melting Point (°C, EPISUITE)	1.70	46.57
Boiling Point (°C, EPISUITE)	207.88	264.67
Vapor Pressure (Pa @ 25°C, EPISUITE)	6.1	0.0638
Log Kow (KOWWIN v1.68 in EPISUITE)	3.1[1]	2.29
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in	278	670.7

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	Target material	Read across material
EPISUITE)		
J_{max} (mg/cm^2/h, SAM)	139.895	93.452
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.52E-005	5.56E-007
Genotoxicity		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non carcinogen (low reliability)	• Non carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Skin Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found

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	Target material	Read across material
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

1. RIFM, 1999

Summary

There are insufficient toxicity data on dihydro-α-terpineol (CAS # 498-81-7). Hence *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analog 2-hydroxy-alpha, alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6) was identified as a proper read across material with data for its respective toxicity endpoints.

Conclusion/Rational

- 2-Hydroxy-alpha, alpha,4-trimethylcyclohexanemethanol (CAS # 42822-86-6) could be used as a structurally similar read across analog for target material dihydro-α-terpineol (CAS # 498-81-7) for skin senzitization, genotoxicity, and repeated dose toxicity endpoints.
  - The target substance and the read across analog are structurally similar and belong to a class of saturated cyclic tertiary terpene alcohols.
  - The target substance and the read across analog have cycloalkyl branched tertiary alcohol fragment common among them.
  - The key difference between the target material and the read across is that the read across analog is a diol while the target substance has a mono hydroxy group. One of the hydroxy groups in the read across analog is a secondary OH and can undergo metabolic transformation to form a ketone. This makes the read across analog more reactive from a biochemical reactivity perspective compared to the target substance as confirmed by OECD QSAR Toolbox structural alerts.
  - The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the cycloalkyl branched tertiary alcohol fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevant from a toxic endpoint perspective.
  - The target substance and the read across analog have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the skin senzitization, genotoxicity, and repeated dose toxicity endpoints.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for the skin senzitization, genotoxicity, and repeated dose toxicity endpoints are consistent between the target substance and the read across analog. The CAESAR model v.2.1.6 predicts the target and the read across analog to be sensitizer. Other protein binding alerts for both of the substances are negative. The data described in the skin sensitization section above shows that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore this alert will be superseded by the availability of data.
  - The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator.
  - The structural alerts for the skin senzitization, genotoxicity, and repeated dose toxicity endpoints are consistent between the metabolites of the read across analog and the target substance.
  - The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant.

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? No
- Q17. Readily hydrolysed to a common terpene? No
- Q19. Open chain? No
- Q23. Aromatic? No
- Q24. Monocarbocyclic with simple substituents? Yes
- Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)? No – Low, (Class I)

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.05.063.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.05.063.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renkers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research institute for fragrance materials, inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of Cramer classification between Toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

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

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.

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

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.

OECD, 2012. The OECD QSAR Toolbox, V. 3.1. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. The Contact-sensitization Potential of Fragrance Materials by Maximization Testing in Humans. Report to RIFM. RIFM report number 1804. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1985. 2-Hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (Geranodyle): Repeat Insult Patch Test. Unpublished report from Givaudan. RIFM report number 57086. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1986a. Capacity for Allergenic Sensitization Determined by the Intradermal Test with Freund's Complete Adjuvant (FCAT) on Guinea Pigs with 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (Geranodyle). Unpublished report from Givaudan. RIFM report number 57085. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1986b. Mutagenicity Evaluation of 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (Geranodyle) in the Ames Salmonella/microsome Plate Assay. Unpublished report from Givaudan. RIFM report number 57087. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1994. The Biodegradability of Dihydro-alpha-terpineol in the Sealed Vessel Test. Unpublished report from Quest International Ltd. RIFM report number 34973. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995a. 7-Day Oral (Gavage) Dose Rangefinding Study of 4-cyclohexyl-2-methyl-2-butanol in the Rat. Unpublished report from Firmenich Incorporated. RIFM report number 36752. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995b. 4-Cyclohexyl-2-methyl-2-butanol: 4 Week Oral (Gavage) Toxicity Study in the Rat. Unpublished report from Firmenich Incorporated. RIFM report number 36754. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995c. Mutagenicity Test of Geranodyle. Private Communication to FEMA. Unpublished report from Kajiura, Y. RIFM report number 43642. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995d. Primary Skin Irritation Study, Phototoxicity Study and Delayed Contact Hypersensitivity Test of Geranodyle in Guinea Pigs. Private Communication to FEMA. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Kajiura, Y. & Kinosakie, A. RIFM report number 43643.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999a. Geranodyle: Study of Skin Sensitization in Albino Guinea Pigs; Maximization-test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 43443.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999b. Ready Biodegradability of Dihydro-alpha-terpineol. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51422.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999c. Partition Coefficient N-octanol/water of Dihydro-alpha-terpineol (Dihydro Terpineol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51423.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. Geranodyle: 28-Day Oral Toxicity (Gavage) Study in the Wistar Rat. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 41536.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells with Geranodyle. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 43444.

RIFM (Research Institute for Fragrance Materials, Inc.), 2008a. A Toxicologic and Dermatologic Assessment of Cyclic and Non-cyclic Terpene Alcohols when Used as Fragrance Ingredients. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 56372.

RIFM (Research Institute for Fragrance Materials, Inc.), 2008b. Fragrance Material Review on Dihydro-alpha-terpineol. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 56387.

RIFM (Research Institute for Fragrance Materials, Inc.), 2008c. Fragrance Material Review on Geranodyle. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 56393.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Dihydro-alpha -terpineol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65333.

RIFM (Research Institute for Fragrance Materials), 2016. Use Level Survey, August 2016.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., …, Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.

USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, V. 4.11 Washington, DC, USA. United States Environmental Protection Agency.