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Short review

RIFM fragrance ingredient safety assessment, 2-Hydroxy-α,α,4-trimethylcyclohexanemethanol, CAS Registry Number 42822-86-6

A.M. Api [a, *], D. Belsito [b], S. Bhatia [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], P. Calow [f], M.L. Dagli [g], W. Dekant [h], A.D. Fryer [i], L. Kromidas [a], S. La Cava [a], A. Lapczynski [a], D.C. Liebler [j], D. O'Brien [a], R. Parakhia [a], T.M. Penning [k], V.T. Politano [a], G. Ritacco [a], D. Salvito [a], T.W. Schultz [l], J. Shen [a], I.G. Sipes [m], 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 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*
[l] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996- 4500, USA*
[m] *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*

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1. Identification

1 **Chemical Name:** 2-Hydroxy-α,α,4-trimethylcyclohexanemethanol.
2 **CAS Registry Number:** 42822-86-6.
3 **Synonyms:** Geranodyle; *p*-Menthane-3,8-diol; Cyclohexanemethanol,2-hydroxy-α,α,4-trimethyl-; 2-(2′Hydroxypropan-2′-yl)-5-methylcyclohexanol; 2-Hydroxy-α,α,4-trimethylcyclohexanemethanol; *p*-メンタン-3,8-ジオール; 2-(1-Hydroxy-1-methylethyl)-5-methylcyclohexanol.
4 **Molecular Formula:** $C_{10}H_{20}O_2$.
5 **Molecular Weight:** 172.27.
6 **RIFM Number:** 6431.

2. Physical data

1 **Boiling Point:** 264.67 °C [EPI Suite].
2 **Flash Point:** >93 °C [GHS].
3 **Log K_{OW}:** 1.8–4.0 [RIFM, 1999b], 2.29 [EPI Suite].
4 **Melting Point**: 46.57 °C [EPI Suite].
5 **Water Solubility:** 670.7 mg/L [EPI Suite].
6 **Specific Gravity:** 0.97600 to 0.98200 @ 25.00 °C*.
7 **Vapor Pressure**: 0.000239 mmHg @ 20 °C [EPI Suite 4.0], 0.29 Pa @ 25 C [RIFM, 2000c], 2.14 × 10(-3) Pa @ 25 C [RIFM, 2000c], 0.000479 mm Hg @ 25 °C [EPI Suite].
8 **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} cm^{-1}).

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

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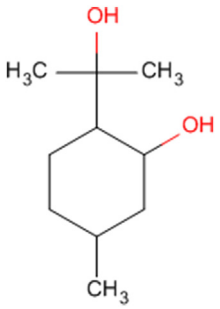
Version: 091516. This version replaces any previous versions.
Name: 2-Hydroxy-α,α,4-trimethylcyclohexanemethanol **CAS Registry Number**: 42822-86-6



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) 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

RIFM's Expert Panel* 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).
*RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential and provided a MOE >100 for the repeated dose endpoint. 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 along with data on the target material. The environmental endpoint was completed as described in the RIFM Framework.

Human health safety assessment.
Genotoxicity: Not genotoxic. (RIFM, 1995a; 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, 1995b; RIFM, 1999a,c; RIFM, 1985a)
Phototoxicity/photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB; RIFM, 1995b; RIFM, 1985b; RIFM, 1985c)
Local respiratory toxicity: No NOAEC available. Exposure is below the TTC.
Environmental safety assessment
Hazard assessment:
Persistence: Critical Measured Value: 94% (OECD 301C) (RIFM, 1996)
Bioaccumulation: Screening Level: 14.95 l/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 96 h Algae EC50: 37.99 mg/l (EpiSuite ver 4.1)

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(*continued*)

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: 96 h Algae EC50: 37.99 mg/l	(EpiSuite ver 4.1)
RIFM PNEC is: 3.799 μg/L	
•Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1	

9 **Appearance/Organoleptic:** A yellow to orange, clear, liquid. The odor is described as floral, rose, geraniol with herbal, green lavender and tea like nuances.*

* http://www.thegoodscentscompany.com/data/rw1375461.html#toorgano, Retrieved 7/14/2015.

3. Exposure

1 **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2011).

2 **95th Percentile Concentration in Hydroalcoholics**: 0.13% (RIFM, 2015).

3 **Inhalation Exposure***: 0.00033 mg/kg/day or 0.024 mg/day (RIFM, 2015).

4 **Total Systemic Exposure****: 0.00037 mg/kg/day (RIFM, 2015).

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

** 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).

4. Derivation of systemic absorption

1 Dermal: 3.5%

Reifenrath et al., 2009 **(data also available in** Olson et al., 2003**):** An *in vitro* skin absorption study was conducted with 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol using pig skin. Carbon-14-labeled 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol formulated in lotion and in an ethanol solution was applied to excised pig skin in an *in vitro* flow-through test system predictive of skin absorption in humans. Twenty-four hours after application, radiolabel recovered from the dermis and receptor fluid was summed to determine percent absorption. At a dose of approximately 80 μg/cm^2 of 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol in the lotion, a value of 3.5± 0.8% of applied dose was obtained with pig skin. The corresponding value for 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol in ethanol (90 μg/cm^2) was not significantly different (3.0± 1.2%). Most of the applied dose was found to evaporate from pig skin (77± 8% for the lotion and 87± 1% for ethanol solution), thus limiting percutaneous absorption values.

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 v 3.2
I*	III	I

*See Appendix below for explanation.

2 **Analogues Selected**.

a **Genotoxicity**: None.

b **Repeated Dose Toxicity**: None.

c **Developmental and Reproductive Toxicity**: None.

d **Skin Sensitization**: None.

e **Phototoxicity/Photoallergenicity**: None.

f **Local Respiratory Toxicity**: None.

g **Environmental Toxicity**: None.

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

6. Metabolism

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

7. Natural occurrence (discrete chemical) or composition (NCS)

2-Hydroxy-α,α,4-trimethylcyclohexanemethanol is reported to occur in the following foods* and in some natural complex substances (NCS):

Passion fruit (Passiflora 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

Pre-registered for 2010; No dossier available as of 09/15/2016.

10. Summary

1 **Human Health Endpoint Summaries**:

10.1. Genotoxicity:

Based on the current existing data and use levels, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol does not present a concern

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for genetic toxicity.

10.1.1. Risk assessment

The mutagenic activity of 2-hydroxy-α,α,4-trimethylcyclohexanemethanol was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and Escherichia Coli strain WP2uvrA were treated with 2-hydroxy-α,α,4-trimethylcyclohexanemethanol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of S9 mix. No significant increase in the number of revertant colonies was observed in the tester strains at any dose (RIFM, 1995a; RIFM, 1995b). Under the conditions of the study, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol was considered not mutagenic in bacteria.

The clastogenic activity of 2-hydroxy-α,α,4-trimethylcyclohexanemethanol was assessed in an *in vitro* chromosome aberration assay conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster V79 cells were treated with 2-hydroxy-α,α,4-trimethylcyclohexanemethanol in DMSO at concentrations up to 400 μg/ml for 4 h with or without S9 and 28 h without S9. 2-Hydroxy-α,α,4-trimethylcyclohexanemethanol did not induce an increase in structural aberrations compared to vehicle control (RIFM, 2000d; RIFM, 2000e; RIFM, 2000f). Under the conditions of the study, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol was considered not clastogenic in mammalian cells.

Based on the available data, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol does not present a concern for genotoxic potential.

Additional References: RIFM, 1986a; RIFM, 1986b.

Literature Search and Risk Assessment Completed on: 2/25/15.

10.2. Repeated Dose Toxicity

The margin of exposure for 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.2.1. Risk Assessment

The repeated dose toxicity data on 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol are sufficient for the repeated dose toxicity endpoint. An OECD 407 gavage 28-day subchronic toxicity study conducted in rats determined the NOEL to be 200 mg/kg/day, based on increased liver weights, hematology, and clinical chemistry effects (RIFM, 2000d; RIFM, 2000e; RIFM, 2000f).

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

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

Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 67/0.00037 or 181081.

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

In addition, the total systemic exposure, for 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol (0.37 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the repeated dose toxicity endpoint.

Additional References: Bhatia et al., 2008; Belsito et al., 2008.

Literature Search and Risk Assessment Completed on: 02/17/15.

10.3. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol or any read across materials. The total systemic exposure is below the TTC.

10.3.1. Risk assessment

There are no developmental or reproductive toxicity data on 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure (0.37 μg/kg/day) is below the TTC (30 μg/kg/day).

Key Studies: None.

Additional References: Bhatia et al., 2008; Belsito et al., 2008.

Literature Search and Risk Assessment Completed on: 02/17/15.

10.4. Skin sensitization

Based on the existing data, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol does not present a concern for skin sensitization.

10.4.1. Risk assessment

The chemical structure of 2-hydroxy-α, α,4-trimethylcyclohexanemethanol indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In guinea pig sensitization studies no reactions indicative of sensitization were observed (RIFM, 1986a; RIFM, 1986b; RIFM, 1995a,b; RIFM, 1999a,b,c). A confirmatory human repeat insult patch test on 51 subjects with 2% or 1000 μg/cm2 2-hydroxy-α,α,4-trimethylcyclohexanemethanol did not result in sensitization reactions in any of the subjects tested (RIFM, 1985a; RIFM, 1985b; RIFM, 1985c). Based on weight of evidence from the structural analysis, predictive animal studies and a confirmatory human study, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/08/15.

10.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available *in vivo* experimental data, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.5.1. Risk assessment

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). Phototoxicity and photoallergenicity of 2-hydroxy-α,α,4-trimethylcyclohexanemethanol were evaluated in guinea pigs; there were no reactions indicative of either phototoxicity or photoallergenicity (RIFM, 1995a; RIFM, 1995b; RIFM, 1985a; RIFM, 1985b). Based on lack of absorbance and *in vivo* study data, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/08/16.

10.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

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10.6.1. Risk assessment

There are no inhalation data available on 2-hydroxy-α,α,4-trimethylcyclohexanemethanol. Based on the Creme RIFM model, the inhalation exposure is 0.024 mg/day. This exposure is 58.3 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: 7/2016.

2 Environmental Endpoint Summary:

10.7. Screening-level assessment

A screening level risk assessment of 2-hydroxy-α,α,4-trimethylcyclohexanemethanol 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, 2-hydroxy-α,α,4-trimethylcyclohexanemethanol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify 2-hydroxy-α,α,4-trimethylcyclohexanemethanol as either being possibly persistent nor 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.

10.7.1. Risk assessment:

Based on current Volume of Use (2011), 2-hydroxy-α,α,4-trimethylcyclohexanemethanol presents a risk to the aquatic compartment in the screening level assessment.

Key Studies:

10.8. Biodegradation:

RIFM, 1996: The test was conducted to evaluate the biodegradability of the test material by microorganisms according to the OECD 301C method. Average percentage biodegradation of the test material after 28 days was 73% and 94% by BOD and TOC, respectively.

RIFM, 1999a,b,c: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F. Mineral medium inoculated with activated sludge from a biological wastewater treatment plant was incubated with 100 mg/l of 2-hydroxy-α,α,4-trimethylcyclohexanemethanol. 2-Hydroxy-α,α,4-trimethylcyclohexanemethanol underwent 77% biodegradation after 37 days (75% after 28 days).

10.9. Ecotoxicity

RIFM, 2000a: The acute toxicity of the test material to zebra fish (*Brachydanio rerio*) was determined in a 96 h semi-static study according to the OECD 203 method. The 96-h LC50 was based on mean measured concentration was 62 mg/l.

RIFM, 2000b: An algal growth inhibition test was conducted according to OECD 201 guideline. The 72 h EC50 was calculated to be 34 mg/l (biomass) and 52 mg/l (growth rate).

RIFM, 2000c: The acute toxicity of the test material to *Daphnia magna* was evaluated according to the OECD 202 I method under static conditions. The 48-h EC50 value based on total mean measured test material concentration was 68 mg/l.

10.9.1. Other available data:

2Hydroxy-α,α,4-trimethylcyclohexanemethanol has been pre-registered for REACH with no additional data at this time.

10.9.2. Risk assessment refinement:

Since 2-hydroxy-α,α,4-trimethylcyclohexanemethanol has passed the screening criteria (Tier 2), measured data has been included in this document for completeness only and has not been used in PNEC derivation.

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)**	4.228 mg/l			1,000,000	0.004228 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	78.46 mg/l	45.74 mg/l	37.99 mg/l	10,000	3.799 μg/l	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.0	4.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 3.799 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: 2/24/15.

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.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.10.009.

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? 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 Class Low (Class I).

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