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Short Review

RIFM fragrance ingredient safety assessment, benzenepropanol, α, γ, γ-trimethyl-, CAS Registry Number 2035-93-0

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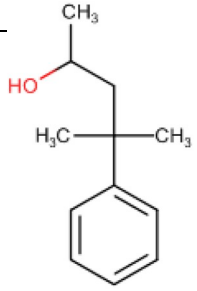
Version: 121218. This version replaces any previous versions.

Name: Benzenepropanol, α, γ, γ-trimethyl
CAS Registry Number: 2035-93-0



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
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
DST - Dermal Sensitization Threshold

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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
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
QRA - Quantitative Risk Assessment
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

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 et al., 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.

Benzenepropanol, α, γ, γ-trimethyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that benzenepropanol, α, γ, γ-trimethyl- is not genotoxic. Data on benzenepropanol, α, γ, γ-trimethyl- provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for benzenepropanol, α, γ, γ-trimethyl- for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; benzenepropanol, α, γ, γ-trimethyl- is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material, and the exposure to benzenepropanol, α, γ, γ-trimethyl- is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; benzenepropanol, α, γ, γ-trimethyl- was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic	(ECHA REACH dossier: 4-Methyl-4-phenylpentan-2-ol; ECHA, 2016)
Repeated Dose Toxicity: NOAEL = 33.33 mg/kg/day	(ECHA REACH dossier: 4-Methyl-4-phenylpentan-2-ol; ECHA, 2016)
Reproductive Toxicity: NOAEL = 400 mg/kg/day	(ECHA REACH Dossier: 4-Methyl-4-phenylpentan-2-ol; ECHA, 2016)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: 4-Methyl-4-phenylpentan-2-ol; ECHA, 2016)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 47% (OECD 301F)	RIFM (2015a)
Bioaccumulation:	
Screening-level: 41.63 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 46.52 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 46.52 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.04652 μg/L	

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Benzenepropanol, α, γ, γ-trimethyl-
2. **CAS Registry Number:** 2035-93-0
3. **Synonyms:** 2-Pentanol, 4-methyl-4-phenyl-; 4-Phenyl-4,4-dimethyl-2-butanol; SymDeo MPP; Vetikol; Benzenepropanol, α, γ, γ-trimethyl-
4. **Molecular Formula:** Not Available
5. **Molecular Weight:** 178.27
6. **RIFM Number:** 1016
7. **Stereochemistry:** Isomer not specified. One chiral center and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 251.8 °C at 1013 hPa (RIFM, 2015a)
2. **Flash Point:** 108.5 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2014)
3. **Log K_{OW}:** 2.82 at 23.8 °C (RIFM, 2015b)
4. **Melting Point**: −59.0 °C at 1013 hPa (RIFM, 2015a)
5. **Water Solubility:** Not available
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** Not available
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Face Moisturizer:** 0.28% (RIFM, 2017)

No reported use in hydroalcoholics

3. **Inhalation Exposure*:** 0.00021 mg/kg/day or 0.015 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.024 mg/kg/day (RIFM, 2017)

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II*, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II	I	II

*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). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **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

No relevant data available for inclusion in this safety assessment. Additional References: None.

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

Benzenepropanol, α, γ, γ-trimethyl- is not reported to occur in foods by the VCF*.

*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.

8. IFRA standard

None.

9. REACH Dossier

Available; accessed 10/08/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, benzenepropanol, α, γ, γ-trimethyl- does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of benzenepropanol, α, γ, γ-trimethyl- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and TA102 were treated with benzenepropanol, α, γ, γ-trimethyl- in solvent dimethyl sulfoxide (DMSO) at concentrations up to 5 μL/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2016). Under the conditions of the study, benzenepropanol, α, γ, γ-trimethyl- was not mutagenic in the Ames test.

The clastogenicity of benzenepropanol, α, γ, γ-trimethyl- 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 benzenepropanol, α, γ, γ-trimethyl-in dimethyl sulfoxide (DMSO) at concentrations up to 1780 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, 2016). Under the conditions of the study, benzenepropanol, α, γ, γ-trimethyl- was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for benzenepropanol, α, γ, γ-trimethyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on benzenepropanol, α, γ, γ-trimethyl- (or 4-methyl-4-phenylpentan-2-ol, CAS 2035-93-0). In an OECD 407 and GLP-compliant 28-day toxicity study, 5 Wistar Crl:WI BR strain rats/sex/dose were orally administered 4-methyl-4-phenylpentan-2-ol (benzenepropanol, α, γ, γ-trimethyl-) at doses of 0, 100, 400, and 1000 mg/kg/day. Recovery groups of 5 animals/sex/dose were maintained for 2 weeks at 0 and 1000 mg/kg/day doses. No treatment-related mortalities were reported during the study at any of the doses. During study week 1, alterations of gait and posture were observed within 2 h of dose administration in some animals receiving 400 and 1000 mg/kg/day doses, especially in females. Although the general well-being of the animals was not influenced by the test substance, the alterations of gait and posture are indicative of short-term neurological effects. Food consumption was lower in the 1000 mg/kg/day group only during the first week of treatment, but no subsequent change was reported during the study. No treatment-related alterations of bodyweight gain, hematology, and biochemical parameters were reported during the study. In males, absolute and relative weights of kidney and liver were significantly increased at 1000 mg/kg/day dose, while relative kidney weight increased at 400 mg/kg/day dose. In females, relative liver weight increased significantly at the 1000 mg/kg/day group as well as the recovery group for this dose. However, no treatment-related pathological macroscopic or histological findings were reported in either sex. Based on the alterations of liver and kidney weights combined with neurological effects at 400 and 1000 mg/kg/day doses, **the NOAEL for repeated dose toxicity was determined to be 100 mg/kg/day**.

A default safety factor of 3 was used when deriving a NOAEL from the OECD 407 (28-day) studies. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33.33 mg/kg/day.

Therefore, the benzenepropanol, α, γ, γ-trimethyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzenepropanol, α, γ, γ-trimethyl- NOAEL in mg/kg/day by the total systemic exposure to benzenepropanol, α, γ, γ-trimethyl-, 33.33/0.024 or 1389.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/21/18.

10.1.3. Reproductive toxicity

The MOE for benzenepropanol, α, γ, γ-trimethyl- is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on benzenepropanol, α, γ, γ-trimethyl- that can be used to support the reproductive toxicity endpoint. An OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar rats. Groups of 20 rats/sex/dose were administered test material 4-methyl-4 phenylpentan-2-ol (benzenepropanol, α, γ, γ-trimethyl-) via oral gavage at doses of 0, 40, 120, or 400 mg/kg/day in corn oil. Males were dosed for 6 weeks (2 weeks prior to mating and continued through the mating period until approximately 80% of the females had delivered), while females were dosed for 7 weeks (2 weeks prior to mating, during mating and pregnancy period until lactation day [LD] 3). A statistically significant decrease in bodyweight gain was observed during gestation days (GDs) 14–20 among mid-dose dams. This finding was not associated with any change in the corresponding maternal food intake and, thus, was not considered to be toxicologically significant. At 40 mg/kg/day, a statistically significant decrease in male and female fertility was observed, which resulted from pregnancy failure in a single dam, which was considered to be incidental and not toxicologically relevant. A significant decrease in the implantation index (%) was observed at 120 mg/kg/day, which was contributed by a significant increase in the pre-implantation loss (%). Though the percentage of pre-implantation loss was outside of the historical control range, the same effect was not observed in the high-dose group animals; hence, this finding was considered incidental due to the lack of dose-response. A significant decrease in the mean total number of pups per litter was observed at 120 mg/kg/day on LD 4, which was presumed to be contributed by pup mortality/cannibalism during LDs 0 through 4. This finding was within the historical controls, with no dose-response relationship, and thus was not considered to be toxicologically relevant. No external abnormalities were observed in live or dead pups in any of the groups. There were no treatment-related adverse effect reported on fertility or the development of pups in a dose-response manner, thus the NOAEL for reproductive toxicity was considered to be 400 mg/kg/day, the highest dose tested (ECHA, 2016). **Therefore, the benzenepropanol, α, γ, γ-trimethyl- MOE for the reproductive toxicity endpoint can be calculated by dividing the benzenepropanol, α, γ, γ-trimethyl- NOAEL in mg/kg/day by the total systemic exposure to benzenepropanol, α, γ, γ-trimethyl-, 400/0.024 or 16667.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/06/18.

10.1.4. Skin sensitization

Based on the existing data, benzenepropanol, α, γ, γ-trimethyl- does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, benzenepropanol, α, γ, γ-trimethyl- is not considered a skin sensitizer under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), benzenepropanol, α, γ, γ-trimethyl- was found to be non-sensitizing up to 100% (ECHA, 2016).

Based on weight of evidence (WoE) from structural analysis and an animal study, benzenepropanol, α, γ, γ-trimethyl- does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/18.

10.1.5. Phototoxicity/photoallergenicity

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

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

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/14/18.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for benzenepropanol, α, γ, γ-trimethyl- is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on benzenepropanol, α, γ, γ-trimethyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.015 mg/day. This exposure is 31.33 times lower than the Cramer Class III* TTC value of 0.47 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/01/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of benzenepropanol, α, γ, γ-trimethyl- was performed following the RIFM Environmental Framework (Salvito et al., 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, benzenepropanol, α, γ, γ-trimethyl- was identified as a fragrance material with no 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 benzenepropanol, α, γ, γ-trimethyl- 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). 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.

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), benzenepropanol, α, γ, γ-trimethyl- presents no risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 2015e: The ready biodegradability of the test material was evaluated according to OECD 301F. Under the conditions of this study, biodegradation of 47% was observed after 28 days.

RIFM, 2016a: The ready biodegradability of the test material was evaluated according to OECD 301F. Under the conditions of this study, biodegradation of 7.1% was observed after 28 days.

10.2.1.2.2. Ecotoxicity. RIFM, 2015d: A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 method, and the 48-h EC50 was reported to be 39.8 mg/L.

RIFM, 2016b: A 96-h fish (*Gobiocypris rarus*) acute toxicity study was conducted according to the OECD 203 method, and the LC50 was reported to be 36.12 mg/L.

RIFM, 2015c: An algae growth inhibition study was conducted according to the OECD 201 method, and the 72-h ErC50 was reported to be 57.6 mg/L.

10.2.1.2.3. Other available data. Benzenepropanol, α, γ, γ-trimethyl- has been registered under REACH and no additional data is available at this time.

10.2.2. Risk assessment refinement

Since benzenepropanol, α, γ, γ-trimethyl- has passed the screening criteria, measured data is included 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	46.52			1000000	0.04652	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.82	2.82
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	Not reported
Risk Characterization: PEC/PNEC	**< 1**	**N/A**

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

The RIFM PNEC is 0.04652 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/20/18.

11. 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **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 05/31/19.

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 between 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.

1N,2N,3N,43N,5N,6N,42N,7N,16N,17N,19N,23Y,27Y,28N,30N,18N
Should be 30Y, 31N, 32Y, II See corrected path in G 101.

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, and divalent S? No
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? 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)? No
Q17. Readily hydrolyzed to a common terpene? No
Q23. Aromatic? Yes
Q27. Rings with substituents? No
Q28. More than one aromatic ring? No
Q30. Aromatic ring with complex substituents? No
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No
Q32. Contains only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms or c) a polyoxyethylene (n ≥ 4) on the aromatic or aliphatic side chain? Yes, Class II, Class Intermediate

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