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Short Review

RIFM fragrance ingredient safety assessment, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate, CAS Registry Number 81752-87-6

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Phototoxicity/photoallergenicity
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ABSTRACT

The existing information supports the use of this material as described in this safety assessment. Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is not genotoxic. Data on methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate provide a calculated Margin of Exposure (MOE) >100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards,

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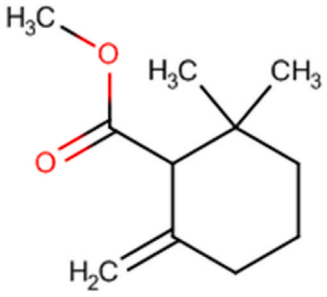
and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Version: 032620. This version replaces any previous versions.
Name: Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate
CAS Registry Number: 81752-87-6



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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly

(*continued on next column*)

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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.

Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is not genotoxic. Data on methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1991; RIFM, 1997b)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM (1998)
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.	
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	RIFM (1992b)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Screening-level: 2.73 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 180.5 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h algae EC50: 0.972 mg/L	(ECOSAR; US EPA, 2012b)
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: 0.972 mg/L (ECOSAR; US EPA, 2012b)	
RIFM PNEC is: 0.0972 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate

2. **CAS Registry Number:** 81752-87-6
3. **Synonyms:** Cylcohexanecarboxylic acid, 2,2-dimethyl-6-methylene-, methyl ester; Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate
4. **Molecular Formula:** $C_{11}H_{18}O_2$
5. **Molecular Weight:** 182.26
6. **RIFM Number:** 6360
7. **Stereochemistry:** Stereoisomer not specified. One chiral center and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** 204.8–210.1 °C at 987.6 mbar (RIFM, 1992a), 217.99 °C (EPI Suite)
2. **Flash Point:** 78 °C (Globally Harmonized System), 78 °C (RIFM, 1992a)
3. **Log K_{OW}:** 1.27 × 10^4, log10 Pow 4.10 (RIFM, 1997a), 3.92 (EPI Suite)
4. **Melting Point**: less than 252±0.5 K (RIFM, 1997a), 18.62 °C (EPI Suite)
5. **Water Solubility:** 23.88 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.145 mm Hg at 25 °C (EPI Suite), 0.0961 mm Hg at 20 °C (EPI Suite v4.0)
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. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.12% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0097 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0015 mg/kg/day (RIFM, 2017)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

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

7. Metabolism

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

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

Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate 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.

9. REACH dossier

Available; accessed 03/26/20.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate 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, and TA1537 were treated with methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate in dimethyl sulfoxide (DMSO) at

concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1991). Under the conditions of the study, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was not mutagenic in the Ames test.

The clastogenicity of methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate 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 methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate in DMSO at concentrations up to 1820 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 (RIFM, 1997b). Under the conditions of the study, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate. In a GLP-compliant subchronic study, 5 Sprague Dawley Crl:CD BR rats/sex/dose were administered methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate via gavage at doses of 0, 15, 150, and 1000 mg/kg/day for 28 days. Clinical signs, body weight, food and water consumption, hematology, blood chemistry, organ weights, gross necropsy, and histopathology were examined. No mortality was observed during the study period. No treatment-related effects were observed in clinical observations, body weight, food consumption, water consumption, hematology, or blood chemistry. Relative liver weights were increased in males at the mid dose and in both sexes at the high dose (dose-dependent); absolute liver weights were increased in females at the mid dose and in both sexes at the high dose (dose-dependent). Centrilobular hepatocyte enlargement was observed in both sexes at the high dose. Periportal glycogen vacuolation of hepatocytes was also observed in high-dose males. However, these liver effects were considered adaptive changes. Absolute kidney weights were increased in males at the high dose. Speckled kidneys were observed in males at the mid and high doses. Accumulations of globular eosinophilic material (hyaline droplets) were observed in males at the mid and high doses, but this is consistent with hydrocarbon nephropathy, which is specific to male rats and thus not relevant to human health. Based on no adverse effects observed up to the highest dose, the NOAEL for this study was considered to be 1000 mg/kg/day (RIFM, 1998).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 1000/3, or 333 mg/kg/day.

Therefore, the methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate NOAEL in mg/kg/day by the total systemic exposure to Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate, 333/0.0015, or 222000.

In addition, the total systemic exposure to methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate (1.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: 04/03/20.

11.1.3. Reproductive Toxicity

There are insufficient reproductive toxicity data on methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate or any read-across materials. The total systemic exposure to methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate or any read-across materials that can be used to support the reproductive toxicity endpoints. The total systemic exposure (1.5 μg/kg/day) is below the TTC for methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/09/20.

11.1.4. Skin Sensitization

Based on the existing data, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2; TIMES-SS v2.28.16). In a guinea pig maximization test, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate did not lead to skin sensitization reactions when tested up to 100% (RIFM, 1992b).

Based on weight of evidence (WoE) from structural analysis and animal studies, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate 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: 05/06/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, methyl-2,2-dimethyl-6-

methylene-1-cyclohexanecarboxylate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate 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, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. 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} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate. Based on the Creme RIFM Model, the inhalation exposure is 0.0097 mg/day. This exposure is 144 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: 05/04/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (IFRA, 2015), methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. **RIFM, 1997d**: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 based on nominal concentrations was reported to be greater than 2.0 mg/L.

RIFM, 1997c: The acute fish (rainbow trout) toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value based on a time-weighted average was reported to be greater than 1.5 mg/L.

RIFM, 1983: The algae growth inhibition test was conducted according to the OECD 201 guideline under constant illumination and shaking. The EC50 values based on time-weighted mean measured concentration for cell growth and growth rate were reported to be > 0.63 mg/L.

11.2.1.3. Other available data. Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate has been registered for REACH with no additional data available at this time.

11.2.2. Risk assessment refinement

Since methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

Risk 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)**	3.66			1000000	0.00366	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.831	3.098	0.972	10000	0.0972	Ester
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.797	1.897	2.947			Neutral Organics SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.1	4.1
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0972 μg/L. The revised PEC/PNECs for EU and NA are <1. Therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 05/08/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA 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 09/30/20.

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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