Food and Chemical Toxicology 144 (2020) 111495

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

# RIFM fragrance ingredient safety assessment, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester, CAS Registry Number 478695-70-4

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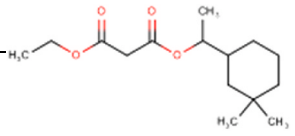
Version: 090919. This version replaces any previous versions.

Name: Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester
CAS Registry Number: 478695-70-4



**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
**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 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

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https://doi.org/10.1016/j.fct.2020.111495
Received 26 February 2020; Received in revised form 12 May 2020; Accepted 2 June 2020
Available online 04 July 2020

**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 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.**

Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester is not genotoxic and provide a calculated MOE $> 100$ for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester is below the TTC (30 μg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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. (RIFM, 2003b; Wesley and Maibach, 2003)

**Repeated Dose Toxicity:** RIFM (2003h)
NOAEL = 333.3 mg/kg/day.

**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.

**Skin Sensitization:** Not a concern for skin sensitization at the current, declared use levels. (RIFM, 2004b; RIFM, 2003i)

**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: 89% (OECD 301 B) RIFM (2003f)

**Bioaccumulation:** Screening-level: 403.5 L/kg (EPI Suite v4.11; US EPA, 2012a)

**Ecotoxicity:** Screening-level: 96-hr Algae EC50: 0.-615 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-hr Algae EC50: 0.-615 mg/L (ECOSAR; US EPA, 2012b)

**RIFM PNEC is:** 0.0615 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

## 1. Identification

1. **Chemical Name:** Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester
2. **CAS Registry Number:** 478695-70-4
3. **Synonyms:** Applelide; Musk nouvelle; Propanedioic acid, 1-[1-(3,3-dimethylcyclohexyl)ethyl] 3-ethyl ester; Edenolide; Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester
4. **Molecular Formula:** $C_{15}H_{26}O_4$
5. **Molecular Weight:** 270.36
6. **RIFM Number:** 6491
7. **Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 479–538 K @ 101.62–102.33 kPa (RIFM, 2003e)
2. **Flash Point:** 1.12 × 10-7 at a pH of 7 (RIFM, 2003e), 141 ± 2 °C (RIFM, 2003g)
3. **Log $K_{OW}$:** 7.98 × 10 (4) log10 Pow 4.90 (RIFM, 2003e)
4. **Melting Point:** > 253 ± 0.5 K (RIFM, 2003e)
5. **Water Solubility:** Not Available
6. **Specific Gravity:** 1.00 @ 20.0 ± 0.5 °C (RIFM, 2003e)
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. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.48% (RIFM, 2018b)
2. Inhalation Exposure*: 0.00094 mg/kg/day or 0.064 mg/day (RIFM, 2018b)
3. Total Systemic Exposure**: 0.011 mg/kg/day (RIFM, 2018b)

*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 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 et al., 2015, 2017; Safford et al., 2015, 2017).

## 5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%

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

## 6. Computational toxicology evaluation

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

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

*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 the 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

## 7. Metabolism

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

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

Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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

No dossier available as of 09/09/19.

## 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 and use levels, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester does not present a concern for genetic toxicity.

*11.1.1.1. Risk assessment.* Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester was assessed in the BlueScreen assay and found positive for both cytotoxicity without metabolic activation (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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, and *Escherichia coli* strain WP2uvrA were treated with propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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, 2003b). Under the conditions of the study, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester was not mutagenic in the Ames test.

The clastogenic activity of propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in Arachis oil via the oral route to groups of male CD-1 mice. Doses of 500, 1000, or 2000 mg/kg were administered. Mice from 500 to 1000 mg/kg were euthanized at 24 h after dosing, and mice from 2000 mg/kg dose level were euthanized at 24 and 48 h after dosing, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2003a). Under the conditions of the study, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester does not present a concern for genotoxic potential.

**Additional References:** RIFM, 2003a.

**Literature Search and Risk Assessment Completed On:** 10/16/19.

#### *11.1.2. Repeated dose toxicity*

*11.1.2.1. Risk assessment.* There are sufficient data to support the test material for the repeated dose toxicity endpoint. In an OECD 407 and GLP compliant subchronic toxicity study, 5 Sprague Dawley Crl:CD (SD) IGS rats/sex/dose were administered propanedioic acid, 1-(3,3-dimethylcyclohexyl)ethyl, ethyl ester in Arachis oil BP by gavage at dose levels of 0, 15, 150, and 1000 mg/kg/day for 28 days. An additional 5 rats/sex/group were maintained for 14 days as a recovery group at 0 and 1000 mg/kg/day. No treatment-related mortality was reported during the study. No treatment-related adverse effects were reported for any of the tested parameters. Transient hunched posture and tiptoe gate were reported in animals of the high-dose group, but these effects were not reported during the recovery period. In addition, increased liver weights (absolute and relative) combined with centrilobular hepatocyte enlargement were reported in high-dose group animals. Since these effects were reversed during the recovery period, these were considered to be an adaptive physiological response to the increased metabolic load of high-dose treatment. Increased relative weights of the kidneys and globular accumulation of eosinophilic material in high-dose group males were attributed to α-2u-globulin nephropathy. This is a species- and sex-specific effect, often observed as a response to hydrocarbon treatment in rats. Hence, this was not considered to be a human health hazard. Based on the absence of any treatment-related adverse effects up to the highest tested dose, the NOAEL for repeated dose endpoint is considered to be 1000 mg/kg/day (RIFM, 2003h).

A default safety factor of 3 is used when deriving a NOAEL from the OECD 407 studies (ECHA, 2012). The safety factor has been approved

by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333.3 mg/kg/day.

Therefore, the MOE can be calculated by dividing the NOAEL (in mg/kg/day) by the total systemic exposure (in mg/kg/day), 333.3/0.011, or 30300.

In addition, the total systemic exposure to 3-ethylphenol (11 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:** 10/10/19.

*11.1.3. Reproductive toxicity*

There are no reproductive toxicity data on propanedioic acid, 1-(3,3-dimethylcyclohexyl)ethyl, ethyl ester, or on any read-across materials. The total systemic exposure to propanedioic acid, 1-(3,3-dimethylcyclohexyl)ethyl, ethyl ester 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 propanedioic acid, 1-(3,3-dimethylcyclohexyl)ethyl, ethyl ester, or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to propanedioic acid, 1-(3,3-dimethylcyclohexyl)ethyl, ethyl ester (11 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/09/19.

*11.1.4. Skin sensitization*

Based on the existing data, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester does not present a concern for skin sensitization under the current, declared levels of use.

*11.1.4.1. Risk assessment.* Based on the existing data, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester is not considered a skin sensitizer. 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 v 4.3). Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester was found to be negative in an *in vitro* direct peptide reactivity assay, KeratinoSens, and U937-CD86 test (RIFM, 2016a; RIFM, 2016b; RIFM, 2017) and found to be positive in an *in vitro* human cell line activation test (RIFM, 2018a). In a murine local lymph node assay, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester was not found to be sensitizing up to 100% (RIFM, 2004b). Additionally, in a confirmatory human repeat insult patch test with 4% or 2000 μg/cm$^2$ of propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester in 3:1 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2003i).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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:** 10/20/19.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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 propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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:** 09/30/19.

*11.1.6. Local Respiratory Toxicity*

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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 propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester. Based on the Creme RIFM Model, the inhalation exposure is 0.064 mg/day. This exposure is 21.9 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:** 10/08/19.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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, propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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 propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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 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 $\geq$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.

| | | | | | | |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 1.09 | | | 1000000 | 0.00109 | |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 1.333 | 2.131 | 0.615 | 10000 | 0.0615 | Esters |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 1.388 | 0.989 | 1.880 | | | Neutral Organic SAR (Baseline toxicity) |

*11.2.2. Risk assessment*

Based on the current Volume of Use (2015), propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester presents a risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies*

*11.2.2.1.1. Biodegradation.* RIFM, 2003f: The ready biodegradability of the test material was evaluated using the $CO_2$ evolution test according to the OECD 301B guideline. Biodegradation of 89% was observed after 28 days.

*11.2.2.1.2. Ecotoxicity.* RIFM, 2004a: The acute fish (*Oncorhynchus mykiss*) toxicity test was conducted according to the OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on the time-weighted mean measured concentrations was reported to be 0.79 mg/L (95% CI: 0.57–1.1 mg/L).

RIFM, 2003c: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on the nominal test concentrations was reported to be 3.4 mg/L (95% CI: 2.9–3.9 mg/L).

RIFM, 2003d: The algae growth inhibition test was conducted according to the OECD 201 guideline. The 72-h EC50 value based on geometric mean measured concentrations for growth was reported to be 0.46 mg/L (95% CI: 0.4–0.52 mg/L).

RIFM, 2005: The *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under static conditions. The 21-day NOEC value based on time-weighted mean concentration was reported to be 1.13 mg/L.

*11.2.2.1.3. Other available data.* Propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester has not been registered for REACH at this time.

*11.2.3. Risk assessment refinement*

Since propanedioic acid, 1-(3,3-dimethylcyclohexyl) ethyl, ethyl ester 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.

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

| Exposure | Europe | North America |
|---|---|---|
| Log $K_{ow}$ Used | 4.9 | 4.9 |
| 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** |

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

The RIFM PNEC is 0.0615 µg/L. The revised PEC/PNECs for EU and NA are $<$ 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 10/07/19.

## 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**
- **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 01/31/20.

## 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.

## 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,5N,6N,7N,16N,17Y(18Y)(19Y,20Y,21N,18N)(19Y,20Y,21N,18N).

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? Yes
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories)? No, Low (Class I)

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