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Short Review

# RIFM fragrance ingredient safety assessment, 1,2-cyclopentanedione, 3,4,4-trimethyl-, CAS Registry Number 33079-56-0

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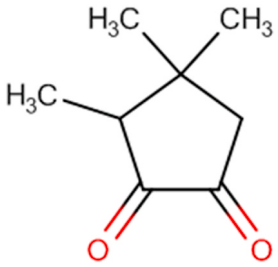


**Abbreviation/Definition List:**

**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, 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
**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 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).

(*continued on next column*)

(*continued*)

*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.**

1,2-Cyclopentanedione, 3,4,4-trimethyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 3,4-dimethyl-1,2-cyclopentadione (CAS # 13494-06-9) show that 1,2-cyclopentanedione, 3,4,4-trimethyl- is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the threshold of toxicological concern (TTC) for a Cramer Class III material, and the exposure to 1,2-cyclopentanedione, 3,4,4-trimethyl- is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm$^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on data; 1,2-cyclopentanedione, 3,4,4-trimethyl- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1,2-cyclopentanedione, 3,4,4-trimethyl- 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 expected to be genotoxic. (RIFM, 2014c; RIFM, 2015)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** Not a concern for skin sensitization under the current, declared use levels; the exposure is below the DST.
**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic. RIFM (1982)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:**
Screening-level: 2.68 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
**Bioaccumulation:**
Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:**
Screening-level: Fish LC50: 5365 mg/L (RIFM Framework; Salvito, 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, 2002)
**Critical Ecotoxicity Endpoint:** Fish LC50: 5365 mg/L (RIFM Framework; Salvito, 2002)
**RIFM PNEC is:** 5.365 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

## 1. Identification

1. **Chemical Name:** 1,2-Cyclopentanedione, 3,4,4-trimethyl-
2. **CAS Registry Number:** 33079-56-0
3. **Synonyms:** 3,4,4-Trimethylcyclopentane-1,2-dione; 1,2-Cyclopentanedione, 3,4,4-trimethyl-
4. **Molecular Formula:** $C_8H_{12}O_2$
5. **Molecular Weight:** 140.18
6. **RIFM Number:** 6388
7. **Stereochemistry:** One chiral center and 2 stereoisomers.

## 2. Physical data

1. **Boiling Point:** 228.22 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log $K_{OW}$:** 0.33 (EPI Suite)
4. **Melting Point**: 37.65 °C (EPI Suite)

5. **Water Solubility:** 43,600 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0573 mm Hg at 20 °C (EPI Suite v4.0), 0.0955 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm under neutral and acidic conditions, with peak absorbance at approximately 290 nm. Minor absorbance between 290 and 700 nm under basic conditions, with peak absorbance at 300 nm. Molar absorption coefficients under neutral and basic conditions (3086.5 and 1819.0 L $mol^{-1}$ · $cm^{-1}$, respectively) are above the benchmark (1000 L $mol^{-1}$ · $cm^{-1}$). The molar absorption coefficient under basic conditions (382.2 L $mol^{-1}$ · $cm^{-1}$) is below the benchmark (1000 L $mol^{-1}$ · $cm^{-1}$).
9. **Appearance/Organoleptic:** Not Available

## 3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000047% (RIFM, 2016)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or 0.0000032 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0000006 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015a, 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, 2017; Safford, 2015a, 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 III*, High (Expert Judgment)

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v3.2 |
|---|---|---|
| III | III | 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 the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** 3,4-Dimethyl-1,2-cyclopentadione (CAS # 13494-06-9)
   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: See Appendix below

## 7. Metabolism

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

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

1,2-Cyclopentanedione, 3,4,4-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.

## 9. REACH dossier

Pre-registered for 2010; no dossier available as of 10/27/20.

## 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, 1,2-cyclopentanedione, 3,4,4-trimethyl- does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* 1,2-Cyclopentanedione, 3,4,4-trimethyl- was assessed in the BlueScreen assay and found negative for both genotoxicity and cytotoxicity (positive: <80% relative cell density) with and without metabolic activation (RIFM, 2014b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an equally reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

Read-across material 3,4-dimethyl-1,2-cyclopentadione was assessed in the BlueScreen assay and found positive for cytotoxicity and negative for genotoxicity with metabolic activation and found positive for both cytotoxicity and genotoxicity without metabolic activation. These positive results were observed at cytotoxic concentrations that were within the acceptable ranges for the BlueScreen assay (positive: <80% relative cell density) (RIFM, 2014a). 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 read-across material.

There are no studies assessing the mutagenic and clastogenic activity of 1,2-cyclopentanedione, 3,4,4-trimethyl-; however, read-across can be made to 3,4-dimethyl-1,2-cyclopentadione (CAS # 13494-06-9; see Section VI).

The mutagenic activity of 3,4-dimethyl-1,2-cyclopentadione 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3,4-dimethyl-1,2-

cyclopentadione in sterile distilled water 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, 2014c). Under the conditions of the study, 3,4-dimethyl-1,2-cyclopentadione was not mutagenic in the Ames test, and this can be extended to 1,2-cyclopentanedione, 3,4,4-trimethyl-.

The clastogenic activity of 3,4-dimethyl-1,2-cyclopentadione was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 3,4-dimethyl-1,2-cyclopentadione in Eagle's minimal essential medium with HEPES buffer (MEM) at concentrations up to 1262 μg/mL in the dose range finding (DRF) study, and micronuclei analysis was conducted up to 1262 μg/mL in the presence and absence of metabolic activation. 3,4-Dimethyl-1,2-cyclopentadione did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, 3,4-dimethyl-1,2-cyclopentadione was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 1,2-cyclopentanedione, 3,4,4-trimethyl-.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/19/20.

*11.1.2. Repeated dose toxicity*

There are insufficient repeated dose toxicity data on 1,2-cyclopentanedione, 3,4,4-trimethyl- or any read-across materials. The total systemic exposure to 1,2-cyclopentanedione, 3,4,4-trimethyl- is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on 1,2-cyclopentanedione, 3,4,4-trimethyl- or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.0006 μg/kg/day) is below the TTC for 1,2-cyclopentanedione, 3,4,4-trimethyl- (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/12/20.

*11.1.3. Reproductive toxicity*

There are insufficient reproductive toxicity data on 1,2-cyclopentanedione, 3,4,4-trimethyl- or any read-across materials. The total systemic exposure to 1,2-cyclopentanedione, 3,4,4-trimethyl- is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

*11.1.3.1. Risk assessment.* There are no reproductive toxicity data on 1,2-cyclopentanedione, 3,4,4-trimethyl- or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.0006 μg/kg/day) is below the TTC for 1,2-cyclopentanedione, 3,4,4-trimethyl- (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/19/20.

*11.1.4. Skin sensitization*

Based on the existing data, 1,2-cyclopentanedione, 3,4,4-trimethyl- does not present a concern for skin sensitization under the current, declared levels of use.

*11.1.4.1. Risk assessment.* The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a confirmatory human repeat insult patch test (HRIPT) with 10% of 1,2-cyclopentanedione, 3,4,4-trimethyl- in dipropylene glycol (patch size not provided), no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1982). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm$^2$ (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 1,2-cyclopentanedione, 3,4,4-trimethyl- that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/04/

**Table 1**
Maximum acceptable concentrations for 1,2-cyclopentanedione, 3,4,4-trimethyl- that present no appreciable risk for skin sensitization based on reactive DST.

| IFRA Category[a] | Description of Product Type | Maximum Acceptable Concentrations in Finished Products Based on Reactive DST | Reported 95th Percentile Use Concentrations in Finished Products |
|---|---|---|---|
| 1 | Products applied to the lips | 0.0049% | NRU[b] |
| 2 | Products applied to the axillae | 0.0015% | $1.6 \times 10^{-6}$% |
| 3 | Products applied to the face using fingertips | 0.029% | NRU[b] |
| 4 | Fine fragrance products | 0.027% | $4.7 \times 10^{-5}$% |
| 5 | Products applied to the face and body using the hands (palms), primarily leave-on | 0.0070% | $9.0 \times 10^{-7}$% |
| 6 | Products with oral and lip exposure | 0.016% | NRU[b] |
| 7 | Products applied to the hair with some hand contact | 0.056% | $9.5 \times 10^{-7}$% |
| 8 | Products with significant ano-genital exposure | 0.0029% | No Data[c] |
| 9 | Products with body and hand exposure, primarily rinse-off | 0.054% | $3.1 \times 10^{-6}$% |
| 10 | Household care products with mostly hand contact | 0.19% | NRU[b] |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate | 0.11% | No Data[c] |
| 12 | Products not intended for direct skin contact, minimal or insignificant transfer to skin | Not restricted | $6.9 \times 10^{-5}$% |

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.

[b] No reported use.

[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

20.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available human study data, 1,2-cyclopentanedione, 3,4,4-trimethyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.1. Risk assessment.* UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is above the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In a photo-HRIPT, topical application of 10% 1,2-cyclopentanedione, 3,4,4-trimethyl- in white petrolatum followed by UV exposure did not cause any reactions; 1, 2-cyclopentanedione, 3,4,4-trimethyl- was not considered phototoxic or photoallergenic (RIFM, 1982). Based on the available human study data, 1,2-cyclopentanedione, 3,4,4-trimethyl- 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 significant absorbance in the range of 290–700 nm, under neutral and acidic conditions, with peak absorbance at 290 nm and returning to baseline by 330 nm. The molar absorption coefficients for neutral and acidic conditions were 3086.5 L $mol^{-1}$ · $cm^{-1}$ and 1819.0 L $mol^{-1}$ · $cm^{-1}$, respectively, and these values are above the benchmark of concern for phototoxic effects, 1000 L $mol^{-1}$ · $cm^{-1}$ (Henry, 2009). Under basic conditions, there was minor absorbance at 300 nm. The molar absorption coefficient under basic conditions was 382.2 L $mol^{-1}$ · $cm^{-1}$, which is below the benchmark for phototoxic effects.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/19/20.

*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 1,2-cyclopentanedione, 3,4,4-trimethyl- is below the Cramer Class III TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are no inhalation data available on 1,2-cyclopentanedione, 3,4,4-trimethyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.0000032 mg/day. This exposure is 146,875 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/28/20.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of 1,2-cyclopentanedione, 3,4,4-trimethyl- 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, 1,2-cyclopentanedione, 3,4,4-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 1,2-cyclopentanedione, 3,4,4-trimethyl- as possibly persistent but not 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).

*11.2.2. Risk assessment*

Based on the current Volume of Use (2015), 1,2-cyclopentanedione, 3,4,4-trimethyl- presents no risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies.* **Biodegradation**: No data available.

**Ecotoxicity**: No data available.

**Other available data**: 1,2-Cyclopentanedione, 3,4,4-trimethyl- has been pre-registered for REACH with no additional information available at this time.

*11.2.3. Risk assessment refinement*

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

Endpoints used to calculate PNEC are underlined.

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{OW}$ Used | 0.33 | 0.33 |
| Biodegradation Factor Used | 0 | 0 |
| 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 further assessment is necessary.

The RIFM PNEC is 5.365 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 02/24/20.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 5365 | | | 1000000 | 5.365 | |

## 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 10/27/20.

## 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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112177.

## Appendix

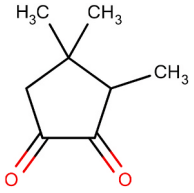
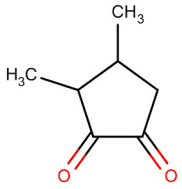
*Read-across Justification*

*Methods*

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.

- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

| | Target Material | Read-across Material |
|---|---|---|
| **Principal Name** | 1,2-Cyclopentanedione, 3,4,4-trimethyl- | 3,4-Dimethyl-1,2-cyclopentadione |
| **CAS No.** | 33079-56-0 | 13494-06-9 |
| **Structure** |  |  |
| **Similarity (Tanimoto Score)** | | 1.00 |
| **Endpoint** | | • Genotoxicity |
| **Molecular Formula** | $C_8H_{12}O_2$ | $C_7H_{10}O_2$ |
| **Molecular Weight** | 140.18 | 126.16 |
| **Melting Point (°C, EPI Suite)** | 37.65 | 26.50 |
| **Boiling Point (°C, EPI Suite)** | 228.22 | 219.34 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 12.73 | 24.53 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 43600.00 | 121100.00 |
| **Log $K_{OW}$** | 0.33 | −0.12 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 75.23 | 139.72 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 0.03 | 0.02 |
| **Genotoxicity** | | |
| **DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)** | AN2\|AN2 ≫ Schiff base formation\|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds | AN2\|AN2 ≫ Schiff base formation\|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds |
| **DNA Binding (OECD QSAR Toolbox v4.2)** | Schiff base formers\|Schiff base formers ≫ Direct Acting Schiff Base Formers\|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ α-β-dicarbonyl | Schiff base formers\|Schiff base formers ≫ Direct Acting Schiff Base Formers\|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ α-β-dicarbonyl |
| **Carcinogenicity (ISS)** | No alert found | No alert found |
| **DNA Binding (Ames, MN, CA, OASIS v1.1)** | AN2\|AN2 ≫ Schiff base formation\|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds | AN2\|AN2 ≫ Schiff base formation\|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds |
| ***In Vitro* Mutagenicity (Ames, ISS)** | No alert found | No alert found |
| ***In Vivo* Mutagenicity (Micronucleus, ISS)** | H-acceptor-path3-H-acceptor | H-acceptor-path3-H-acceptor |
| **Oncologic Classification** | Dicarbonyl-Type Compounds | Dicarbonyl-Type Compounds |
| **Metabolism** | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)** | • See Supplemental Data 1 | • See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on 1,2-cyclopentanedione, 3,4,4-trimethyl- (CAS # 33079-56-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 3,4-dimethyl-1,2-cyclopentadione (CAS # 13494-06-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

*Conclusions*

- 3,4-Dimethyl-1,2-cyclopentadione (CAS # 13494-06-9) was used as a read-across analog for the target material 1,2-cyclopentanedione, 3,4,4-trimethyl- (CAS # 33079-56-0) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of ketones.
  - o The target material and the read-across analog share a 1,2-cyclopentanedione ring and a methyl substituent on 3 and 4 positions.
  - o The key difference between the target material and the read-across analog is that the target material has an additional methyl group on the 4 position compared to the read-across analog. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have Schiff base formation alerts by the DNA binding model of the QSAR Toolbox. A multi-step Schiff base mechanism has been proposed for compounds containing α-β di-carboxyl groups. 1,2-Dicarbonyl chemicals have been shown to be able to undergo a second Schiff base reaction and thus cross-link protein chains. The read-across analog showed dose-related activity against

strain TA100, and the metabolic activation system (S9) did not have a significant effect on activity. A possible molecular mechanism could be suggested for the base-pair mutagenic activity of these compounds associated with interactions with the guanine residues of DNA [1]. The mutagenicity of another series of dicarbonyl compounds was also studied by employing the Ames test. The following sequence of mutagenic activities was obtained: glyoxal > methylglyoxal > phenylglyoxal ≫ 1,2-cyclohexanedione ≫ diacetyl >3,4-hexanedione was obtained. In the aldehyde and ketone series, the mutagenic activity decreased as the size of the substituent increased (for example, compare glyoxal with phenylglyoxal and diacetyl with 3,4-hexanedione). The structural domain of the target material and the read-across analog is in the middle of the series suggesting that the mutagenetic activity of the materials is expected at the intermediate range. The data on the read-across analog confirm that the material poses no concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data for the read-across analog, the *in silico* alert is superseded by the data.

- The target material and the read-across analog have an alert of H-acceptor-path3-H-acceptor. This is due to the fact that both materials contain 2 H acceptors (C═O) separated by 2 atoms. This alert explores the possibility that a chemical interacts with DNA and/or proteins via non-covalent binding, such as DNA intercalation or groove-binding (Snyder et al., 2006). Among the descriptors potentially accounting for non-covalent interactions, the present molecular framework representing 2 bonded atoms connecting 2 H bond acceptors (calculated with software Leadscope Enterprise 2.4.15–6) resulted in an increased sensitivity/specificity for what concerns the micronucleus training set. The data on the read-across analog confirm that the material poses no concern for genetic toxicity. Therefore, based on the structural similarity between the target and the read-across analog, and the data for the read-across analog, the *in silico* alert is superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

*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.

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
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? No
Q22 Common component of food? No
Q23 Aromatic? No
Q24 Monocarbocyclic with simple substituents? No
Q25 Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26 Monocycloalkanone or a bicyclo compound? No
Q33 Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulfonate or sulfamate? No, Class High (Class III).

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