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RIFM fragrance ingredient safety assessment, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde, CAS Registry Number 4501-58-0

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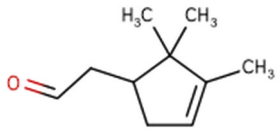
Name: 2,2,3-Trimethyl-3-cyclopentene-1-acetaldehyde
CAS Registry Number: 4501-58-0



Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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 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 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.
2,2,3-Trimethyl-3-cyclopentene-1-acetaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7) show that 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde 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 I material, and the exposure to 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across analog α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde (CAS # 65114-03-6) provided a No Expected Sensitization Induction Level (NESIL) of 500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on (ultraviolet/visible) UV/Vis spectra; 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde 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, 2003; 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: NESIL = 500 μg/cm^2.	RIFM (2001)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 69% (OECD 301D)	RIFM (2000)
Bioaccumulation:	
Screening-level: 70.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 14.88 mg/L	(RIFM Framework; Salvito, 2002)

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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: 14.88 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.01488 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 2,2,3-Trimethyl-3-Cyclopentene-1-acetaldehyde
2. **CAS Registry Number:** 4501-58-0
3. **Synonyms:** 3-Cyclopentene-1-acetaldehyde, 2,2,3-trimethyl-, (1R)-; Campholenic aldehyde; (R)-2,2,3-Trimethylcyclopent-3-ene-1-acetaldehyde; (2,2,3-Trimethylcyclopent-3-en-1-yl)acetaldehyde; 2,2,3-Trimethyl-3-Cyclopentene-1-acetaldehyde
4. **Molecular Formula:** $C_{10}H_{160}$
5. **Molecular Weight:** 152.23
6. **RIFM Number:** 44
7. **Stereochemistry:** Stereoisomer not specified. One chiral center present, and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** 73 °C at 105 mm Hg (Fragrance Materials Association [FMA]), 207.99 °C (EPI Suite)
2. **Flash Point:** 76 °C (Globally Harmonized System), 151 °F; CC (FMA)
3. **Log K_{OW}:** 3.31 (EPI Suite)
4. **Melting Point**: 11.46 °C (EPI Suite)
5. **Water Solubility:** 111.2 mg/L (EPI Suite)
6. **Specific Gravity:** 0.920 (FMA)
7. **Vapor Pressure:** 0.162 mm Hg at 20 °C (EPI Suite v4.0), 0.242 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm under basic conditions, no absorbance between 290 and 700 nm under other conditions; molar absorption coefficient (22 L mol^{-1} • cm^{-1} under basic conditions) 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 v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00037% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0000011 mg/kg/day or 0.000083 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00082 mg/kg/day (RIFM, 2018)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 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, 2015, 2017; Safford, 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	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** 4-(2,6,6-Trimethyl-2-cyclohexen)-2-methyl-butanal (CAS # 65405-84-7)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** α,2,2,3-Tetramethylcyclopent-3-ene-1-butyraldehyde (CAS # 65114-03-6)
   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

2,2,3-Trimethyl-3-Cyclopentene-1-acetaldehyde is reported to occur in the following foods by the VCF*:

Calabash nutmeg (*Monodora myristica* Dunal)	*Mangifera* species
Capsicum species	Mastic (*Pistacia lentiscus*)
Cherimoya (*Annona cherimolia* Mill.)	Pistachio oil (*Pistacia vera*)
Citrus fruits	Pistacia atlantica
Eucalyptus oil (*Eucalyptus globulus* Labill)	Turpentine oil (*Pistacia terebinthus*)

*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 on 11/24/21 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for

2,2,3-trimethyl-3-Cyclopentene-1-acetaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.038
2	Products applied to the axillae	0.011
3	Products applied to the face/body using fingertips	0.23
4	Products related to fine fragrances	0.021
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.054
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.054
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.054
5D	Baby cream, oil, talc	0.054
6	Products with oral and lip exposure	0.13
7	Products applied to the hair with some hand contact	0.44
8	Products with significant ano-genital exposure (tampon)	0.023
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.42
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.5
10B	Aerosol air freshener	1.5
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.83
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 2,2,3-trimethyl-3-Cyclopentene-1-acetaldehyde, the basis was a skin sensitization NESIL of 500 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2,2,3-Trimethyl-3-cyclopentene-1-acetaldehyde was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with metabolic activation, negative for cytotoxicity without metabolic activation, 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 on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde; however, read-across can be made to 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7; see Section VI).

The mutagenic activity of 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal 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 TA102 were treated with 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal 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, 2003). Under the conditions of the study, 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal was not mutagenic in the Ames test, and this can be extended to 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde.

There are no data assessing the clastogenic activity of 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde however, read-across can be made to 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7; see Section VI).

The clastogenic activity of 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal 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 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal in DMSO at concentrations up to 1500 μg/mL in the presence and absence of S9 for 3 h and in the absence of metabolic activation for 24 h. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at the 2 lowest evaluated concentrations (45.8 and 62.8 μg/mL) in the 3-h treatment without S9 and at 86.1 μg/mL with S9. However, the increases were within the historical control range, and no dose response was observed; hence, these increases were considered to be biologically non-relevant. Additionally, no increase in binucleated cells with micronuclei was observed when tested up to cytotoxic concentrations in the 24 treatments in the absence of S9 (RIFM, 2015). Under the conditions of the study, 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde.

Based on the data available, 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal does not present a concern for genotoxic potential, and this can be extended to 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde.

Additional References: None

Literature Search and Risk Assessment Completed On: 06/04/21

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (0.82 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 05/06/21

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde or any read-across materials. The total systemic exposure to 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde 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

Table 1
Data summary for α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde as read-across for 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
NA[a]	NA	500	NA	NA	500

NOEL = No observed effect level; CNIH= Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (0.82 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 05/30/21

11.1.4. Skin sensitization

Based on the existing data and read-across material α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde (CAS # 65114-03-6), 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde is considered a skin sensitizer with a defined NESIL of 500 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde. Based on the existing data and read-across material α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde (CAS # 65114-03-6; see Section VI), 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde is a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde was not found to be sensitizing up to 50% (RIFM, 2012). In a Buehler test 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde did present reactions indicative of sensitization (EPA, 1997; ECHA, 2013). In a human maximization test, skin reactions were observed with 4% (2760 μg/cm^2) 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (RIFM, 1978). However, no reactions were observed at the same dose in another test (RIFM, 1979). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 500 μg/cm^2 of read-across material α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde, no reactions indicative of sensitization were observed in any of the 109 volunteers (RIFM, 2001). Based on weight of evidence from structural analysis, animal and human studies and data on read-across material α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde is a moderate sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 500 μg/cm2 (Table 1). Section 10 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al.

Additional References: None

Literature Search and Risk Assessment Completed On: 06/04/21

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde 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 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.6. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm under basic conditions. No absorbance was noted under neutral and acidic conditions. The molar absorption coefficient (22 L mol^{-1} • cm^{-1} under basic conditions) is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None

Literature Search and Risk Assessment Completed On: 06/01/21

11.1.7. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.7.1. Risk assessment. There are no inhalation data available on 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.000083 mg/day. This exposure is 16867 times lower than the Cramer Class I TTC value of 1.4 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: 06/03/21

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde 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, 2,2,3-Trimethyl-3-Cyclopentene-1-acetaldehyde 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) did not identify 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 2000: The biodegradability of the test material was determined using the closed bottle test according to the OECD 301D method. Under the conditions of the study, biodegradation of 69% was observed after 28 days.

11.2.2.2. Ecotoxicity. RIFM, 2000: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h geometric mean EC 0/EC 100 (arithmetic mean of analytical values) was reported to be 13.3 mg/L, based on mean measured concentration.

11.2.2.3. Other available data. 2,2,3-Trimethyl-3-cyclopentene-1-acetaldehyde has been registered under REACH with no additional data at this time.

11.2.2.4. Risk assessment refinement. Since 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde 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, 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.31	3.31
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 0.01488 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 VoU.

Literature Search and Risk Assessment Completed On: 05/18/21

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 12/10/21.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	14.88			1000000	0.01488	

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.2022.113024.

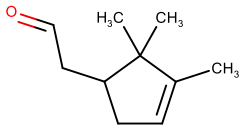
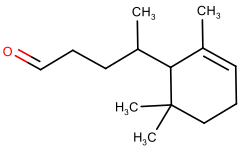
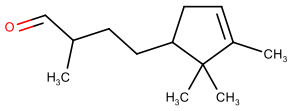
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical 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 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	2,2,3-Trimethyl-3-cyclopentene-1-acetaldehyde	4-(2,6,6-Trimethyl-2-cyclohexen)-2-methylbutanal	α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde
CAS No.	4501-58-0	65405-84-7	65114-03-6
Structure			
Similarity (Tanimoto Score)		0.67	0.73
SMILES	CC1=CCC(CC=O)C1(C)C	CC(CCC=O)C1C(C)=CCCC1(C)C	CC(CCC1CC=C(C)C1(C)C)C=O
Endpoint		Genotoxicity	Skin sensitization
Molecular Formula	$C_{10}H_{16}O$	$C_{14}H_{24}O$	$C_{13}H_{22}O$
Molecular Weight	152.237	208.345	194.318
Melting Point (°C, EPI Suite)	11.46	43.04	33.79
Boiling Point (°C, EPI Suite)	207.99	270.68	252.25
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.23E+01	8.35E-01	2.64E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.11E+02	1.44E+00	4.47E+00
Log K_{OW}	3.31	5.2	4.71
J_{max} (μg/cm^2/h, SAM)	12.20	0.23	0.68
	3.04E+01	9.43E+01	7.10E+01

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)			
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
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 ≫ Mono aldehydes	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	Simple aldehyde	Simple aldehyde	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	Simple aldehyde	Simple aldehyde	
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds	
Skin Sensitization			
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Protein Binding (OECD)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls		Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls
Protein Binding Potency	Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)		Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)
Protein-binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.		Alert for Schiff base formation identified.
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (CAS # 4501-58-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties and expert judgment, 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7) and α,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde (CAS # 65114-03-6) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 4-(2,6,6-Trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7) was used as a read-across analog for the target material 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (CAS # 4501-58-0) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of cyclic aliphatic aldehydes.
  - o The target material and the read-across analog share an aldehyde moiety attached to a cycloalkene structure.
  - o The key difference between the target material and the read-across analog is that the target material has a 5-membered cyclopentene ring substituted with a 2-carbon aliphatic aldehyde, whereas the read-across analog has a 6-membered cyclohexene ring substituted with a 4-carbon aliphatic aldehyde. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these cycloalkene-substituted aliphatic aldehydes. 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 comparison of their toxicological properties.

- o Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target material and $\leq 40\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- 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 several DNA-binding alerts and a carcinogenicity alert by the ISS model. They also have an *in vivo* and *in vitro* mutagenicity alert and are classified as aldehyde-type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genetic toxicity, based on the current existing data and use levels. Therefore, the alert is superseded by the availability of the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- α,2,2,3-Tetramethylcyclopent-3-ene-1-butyraldehyde (CAS # 65114-03-6) was used as a read-across analog for the target material 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (CAS # 4501-58-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of cyclic aliphatic aldehydes.
  - o The target material and the read-across analog share an aldehyde moiety attached to the cycloalkene structure.
  - o The key difference between the target material and the read-across analog is that the target material has a 2-carbon aliphatic aldehyde attached to a trimethyl cyclopentene, whereas the read-across analog has a 4-carbon aliphatic aldehyde attached to a similar trimethyl cyclopentene. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these cycloalkene-substituted aliphatic aldehydes. Differences between the structures that affect the Tanimoto score are toxicologically insignificant. The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target material and $\leq 40\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - 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 several protein-binding alerts for Schiff base formation. In addition, the read-across analog also has an alert for skin sensitization reactivity by Toxtree. Data shown in the skin sensitization section above are consistent with *in silico* alerts.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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