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RIFM fragrance ingredient safety assessment, 2,4,4,7-Tetramethyl-6-octen-3-one, CAS Registry Number 74338-72-0

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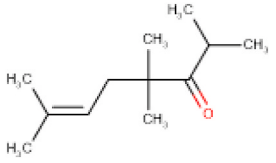
CAS Registry Number: 74,338-72-0



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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.,

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2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach

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., 2020)

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.

2,4,4,7-Tetramethyl-6-octen-3-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2,4,4,7-tetramethyl-6-octen-3-one is not genotoxic. Data on 2,4,4,7-tetramethyl-6-octen-3-one provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material and the exposure to 2,4,4,7-tetramethyl-6-octen-3-one is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data from read-across analog 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81,786-75-6) provided a NESIL of 4400 μg/cm^2 for 2,4,4,7-tetramethyl-6-octen-3-one. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2,4,4,7-tetramethyl-6-octen-3-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2,4,4,7-tetramethyl-6-octen-3-one 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1994a; RIFM, 1996f)

Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (RIFM, 1996i)

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

Skin Sensitization: NESIL = 4400 μg/cm^2. RIFM, (2012a)

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: 8% (OECD 301F) RIFM, (1996a)

Bioaccumulation:

Screening-level: 177 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: 48-h *Daphnia magna* LC50: 1.934 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, 2002)

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 1.934 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.1934 μg/L

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

1. Identification

1. **Chemical Name:** 2,4,4,7-Tetramethyl-6-octen-3-one
2. **CAS Registry Number:** 74,338-72-0
3. **Synonyms:** Claritone; 2,4,4,7-Tetramethyl-6-octen-3-one
4. **Molecular Formula:** $C_{12}H_{22}O$
5. **Molecular Weight:** 182.3
6. **RIFM Number:** 6851
7. Stereochemistry:

2. Physical data

1. **Boiling Point:** 184 ± 1 °C - 185 °C (RIFM, 1996c), 214 °C (mean) - 214.1 °C (RIFM, 1999)
2. **Flash Point:** 83 °C (RIFM, 1996e), half-life >1 year at 25 °C; <10% hydrolysis after 5 days (RIFM, 1996h), 82 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.5 at 20 ± 0.5 °C (RIFM, 1996d)
4. **Melting Point**: −52 to −46 °C to −46.4 °C (RIFM, 1996b)
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.105 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide Band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.21% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0010 mg/kg/day or 0.077 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0056 mg/kg/day (RIFM, 2017)

*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 II*, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	III

*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 detail.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 3,5,6,6-Tetramethyl-4-methyleneheptan-2-one (CAS # 81,786-75-6)
   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

2,4,4,7-Tetramethyl-6-octen-3-one is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH Dossier

Available; accessed on 10/09/20 (ECHA, 2012b).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,4,4,7-tetramethyl-6-octen-3-one 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)	0.34
2	Products applied to the axillae	0.10
3	Products applied to the face/body using fingertips	2.0
4	Products related to fine fragrances	1.9
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.48
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.48
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.48
5D	Baby cream, oil, talc	0.16
6	Products with oral and lip exposure	0.45
7	Products applied to the hair with some hand contact	3.9
8	Products with significant ano-genital exposure (tampon)	0.16
9	Products with body and hand exposure, primarily rinse-off (bar soap)	3.7
10A	Household care products with mostly hand contact (hand dishwashing detergent)	10
10B	Aerosol air freshener	13
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.16
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 2,4,4,7-tetramethyl-6-octen-3-one, the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 4400 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2,4,4,7-tetramethyl-6-octen-3-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2,4,4,7-tetramethyl-6-octen-3-one 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 TA1538 were treated with 2,4,4,7-tetramethyl-6-octen-3-one 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, 1994a). Under the conditions of the study, 2,4,4,7-tetramethyl-6-octen-3-one was not mutagenic in the Ames test.

The clastogenicity of 2,4,4,7-tetramethyl-6-octen-3-one was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung (V79) cells were treated with 2,4,4,7-tetramethyl-6-octen-3-one in DMSO at concentrations up to 500 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (RIFM, 1996f). Under the conditions of the study, 2,4,4,7-tetramethyl-6-octen-3-one was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, 2,4,4,7-tetramethyl-6-octen-3-one does not present a concern for genotoxic potential.

Additional References: None

Literature Search and Risk Assessment Completed On: 11/03/20

11.1.2. Repeated dose toxicity

The margin of exposure for 2,4,4,7-tetramethyl-6-octen-3-one is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2,4,4,7-tetramethyl-6-octen-3-one to support the repeated dose toxicity endpoint. An OECD 407/GLP oral gavage 28-day toxicity study was conducted in Sprague Dawley rats. Groups of 5 rats/sex/dose were administered 2,4,4,7-tetramethyl-6-octen-3-one daily via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day for 28 days. The liver weights among both high-dose males and females were statistically significantly increased, and higher kidney weights were also observed in male rats of the high-dose group. Enlarged and discolored livers in both sexes (4 males and 1 female) and enlarged kidneys in males were observed at necropsy in the highest dose group. Correspondingly, centrilobular hepatocellular hypertrophy was observed among animals of the high-dose group during histopathological evaluation. In the kidneys of some males dosed at 200 and 1000 mg/kg/day, an increase in the severity of hyaline droplet formation in the cortical tubules, accompanied by minimal to moderate granular cast formation, medullary tubule dilation, and tubular basophilia indicated α-2u-globulin nephropathy. The authors of the study report determined the NOAEL to be 50 mg/kg/day. However, these kidney changes were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). The liver weight increases can be considered to be adaptive as there was a lack of histopathological evidence of liver cell damage and clinical chemistry alterations (Hall, 2012). Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 1996i).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 study (ECHA, 2012a). 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 mg/kg/day.

Therefore, the 2,4,4,7-tetramethyl-6-octen-3-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,4,4,7-tetramethyl-6-octen-3-one NOAEL in mg/kg/day by the total systemic exposure to 2,4,4,7-tetramethyl-6-octen-3-one, 333/0.0056, or 59,464.

In addition, the total systemic exposure to 2,4,4,7-tetramethyl-6-octen-3-one (5.6 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3. Derivation of reference dose (RfD)

Section X 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. (RIFM, 2020b) and a reference dose of 3.33 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for 2,4,4,7-tetramethyl-6-octen-3-one to was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

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

Additional References: None

Literature Search and Risk Assessment Completed On: 11/16/20

11.1.4. Reproductive toxicity

There are insufficient reproductive toxicity data on 2,4,4,7-tetramethyl-6-octen-3-one or any read-across materials. The total systemic exposure to 2,4,4,7-tetramethyl-6-octen-3-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.4.1. Risk assessment. There are no reproductive toxicity data on 2,4,4,7-tetramethyl-6-octen-3-one or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (5.6 μg/kg/day) is below the TTC (Kroes, 2007; Laufersweiler, 2012) for 2,4,4,7-tetramethyl-6-octen-3-one (9 μg/kg bw/day).

Additional References: None

Literature Search and Risk Assessment Completed On: 11/05/20

11.1.5. Skin sensitization

Based on the existing data and read-across to 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81,786-75-6), 2,4,4,7-tetramethyl-6-octen-3-one is considered a skin sensitizer with a defined NESIL of 4400 μg/cm^2.

11.1.5.1. Risk assessment. Limited skin sensitization studies are available for 2,4,4,7-tetramethyl-6-octen-3-one. Based on the existing data and read-across analog 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81,786-75-6; see Section VI), 2,4,4,7-tetramethyl-6-octen-3-one is considered a skin sensitizer. 2,4,4,7-Tetramethyl-6-octen-3-one and read-across analog 3,5,6,6-etramethyl-4-methyleneheptan-2-one are not predicted to react with skin proteins directly (Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, 2,4,4,7-tetramethyl-6-octen-3-one did not present reactions indicative of sensitization (RIFM, 1994b). However, in murine local lymph node assays (LLNAs), 2,4,4,7-tetramethyl-6-octen-3-one and read-across material 3,5,6,6-tetramethyl-4-methyleneheptan-2-one were found to be sensitizing with EC3 values of 73.1% (18,275 μg/cm^2) and 64% (16,000 μg/cm^2), respectively (RIFM, 2011; ECHA, 2013; RIFM, 2012b). In a Confirmation of No Induction in Humans test (CNIH) with 10% of 2,4,4,7-tetramethyl-6-octen-3-one in 1:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1997c). In an additional CNIH with 8% (4408 μg/cm^2) of read-across material 3,5,6,6-tetramethyl-4-methyleneheptan-2-one in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 100 volunteers (RIFM, 2012a).

Based on WoE from structural analysis, animal and human studies, and data on the read-across material, 3,5,6,6-tetramethyl-4-methyleneheptan-2-one, 2,4,4,7-tetramethyl-6-octen-3-one is a weak sensitizer with a WoE NESIL of 4400 μg/cm^2 (see Table 1). Section X provides the

Table 1
Data summary for 3,5,6,6-tetramethyl-4-methyleneheptan-2-one as read-across analogs for 2,4,4,7-tetramethyl-6-octen-3-one.

LLNA Weighted Mean EC3 Value $\mu g/cm^2$ (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) $\mu g/cm^2$	NOEL-HMT (Induction) $\mu g/cm^2$	LOEL[b] (Induction) $\mu g/cm^2$	WoE NESIL[c] $\mu g/cm^2$
16,000 [1]	Weak	4408	N/A	N/A	4400

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.

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. (RIFM, 2020b) and a reference dose of 3.33 mg/kg/day.

Additional References: RIFM, 1996j.

Literature Search and Risk Assessment Completed On: 11/03/20

11.1.6. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2,4,4,7-tetramethyl-6-octen-3-one would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6.1. Risk assessment. There are no phototoxicity studies available for 2,4,4,7-tetramethyl-6-octen-3-one in experimental models. UV/Vis absorption spectra indicate no significant 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, 2,4,4,7-tetramethyl-6-octen-3-one does not present a concern for phototoxicity or photoallergenicity.

11.1.7. 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, 2009).

Additional References: None

Literature Search and Risk Assessment Completed On: 11/03/20

11.1.8. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2,4,4,7-tetramethyl-6-octen-3-one is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.8.1. Risk assessment. There are no inhalation data available on 2,4,4,7-tetramethyl-6-octen-3-one. Based on the Creme RIFM Model, the inhalation exposure is 0.077 mg/day. This exposure is 6.1 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None

Literature Search and Risk Assessment Completed On: 11/05/20

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,4,4,7-tetramethyl-6-octen-3-one 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, 2,4,4,7-tetramethyl-6-octen-3-one 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) identified 2,4,4,7-tetramethyl-6-octen-3-one as possibly being 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, 2012a). 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), 2,4,4,7-tetramethyl-6-octen-3-one presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. **RIFM, 1996a:** The ready biodegradability of the test material was evaluated in the manometric respirometry test according to the OECD 301F method. The test material at 30 and 100 mg/L was prepared in mineral media with a magnetic stirrer and incubated with inoculum under aerobic conditions for 28 days. Under the conditions of this study, biodegradation of 8% was observed after 28 days.

RIFM, 1998: The inherent biodegradability of the test material was evaluated according to the OECD 302C guidelines. Under the conditions of the study, no biodegradation was observed.

11.2.2.2. Ecotoxicity. **RIFM, 1997a:** A fish (*Brachydanio rerio*) acute

toxicity study was conducted according to the OECD 202 method under semi-static conditions. Under the conditions of the study, the 96-h LC50 value based on mean measured concentration was reported to be 8.6 mg/L (95% CI: 5.4–13.5 mg/L).

RIFM, 1996g: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. Under the conditions of the study, the 48-h EC50 value based on mean measured concentration was reported to be 2.1 mg/L (95% CI: 1.7–2.6 mg/L).

RIFM, 1997b: An algal growth inhibition test was conducted according to the OECD 201 method under static conditions. Under the test conditions, the 72-h EC50 (algal biomass) and EC50 (growth rate) based on mean measured concentrations were reported to be 7.2 and 13.3 mg/L, respectively.

11.2.2.3. Other available data. 2,4,4,7-Tetramethyl-6-octen-3-one has been registered under REACH with no additional data at this time.

11.2.2.4. Risk assessment refinement. Since 2,4,4,7-tetramethyl-6-octen-3-one 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 (EU)	North America (NA)
Log K_{ow} used	4.5	4.5
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1934 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: 11/06/20

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/23/21.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.643			1,000,000	0.001643	
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	2.855	1.934	2.998	10,000	0.1934	Neutral Organics

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112611.

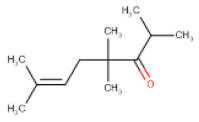
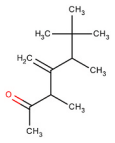
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow 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 substance 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material
Principal Name	2,4,4,7-Tetramethyl-6-octen-3-one	3,5,6,6-Tetramethyl-4-methyleneheptan-2-one
CAS No.	74,338-72-0	81,786-75-6
Structure		
Similarity (Tanimoto Score)		0.20
Endpoint		Skin Sensitization
Molecular Formula	$C_{12}H_{22}O$	$C_{12}H_{22}O$
Molecular Weight	182.31	182.31
Melting Point (°C, EPI Suite)	1.35	−21.02
Boiling Point (°C, EPI Suite)	224.71	193.77
Vapor Pressure (Pa @ 25°C, EPI Suite)	20.93	92.66
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	24.33	27.84
Log KOW	3.91	3.85
Jmax (μg/cm2/h, SAM)	2.81	3.08
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	66.77	56.54
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts 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

Summary

There are insufficient toxicity data on 2,4,4,7-tetramethyl-6-octen-3-one (CAS # 74,338-72-0). 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, 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81,786-75-6) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 3,5,6,6-Tetramethyl-4-methyleneheptan-2-one (CAS # 81,786-75-6) is used as a read-across analog for the target material 2,4,4,7-tetramethyl-6-octen-3-one (CAS # 74,338-72-0) for the skin senzitization endpoint.
  - o The target substance and the read-across analog belong to aliphatic unsaturated, branched ketones.
  - o The key difference between the target substance and the read-across analog is the length of the aliphatic side chain on either side of the ketone group. The target has a tetramethyl substituted C8 aliphatic chain, whereas the read-across analog has a tetramethyl-substituted C7 aliphatic chain. Moreover, the target has a vinylene bond at the sixth position, whereas the read-across analog has a vinyl bond at the fourth position. These structural differences render the read-across more reactive.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the ketone group. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o Data for the read-across analog is consistent with *in silico* alerts.
  - o The target substance 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.

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. 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 a detailed explanation) No
Q19. Open chain? Yes
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for a 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) Yes, Class II (Class Intermediate)

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