Food and Chemical Toxicology 130 (2019) 110637

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one, CAS Registry Number 13144-88-2

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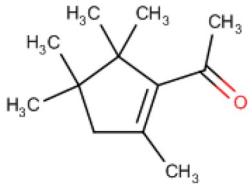
Version: 030619. This version replaces any previous versions.
Name: 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one
CAS Registry Number: 13144-88-2



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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

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https://doi.org/10.1016/j.fct.2019.110637
Received 21 March 2019; Received in revised form 30 May 2019; Accepted 19 June 2019
Available online 23 June 2019
0278-6915/

QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that this material is not genotoxic. Data provided a NESIL of 1000 μg/cm^2 for the skin sensitization endpoint. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively), and the exposure to 1-(2,4,4,5-,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is below the TTC. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. For the hazard assessment based on the screening data, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is not PBT as per the IFRA Environmental Standards. For the risk assessment, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2015a; RIFM, 2016)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 1000 μg/cm^2. (Gerberick et al., 2001; RIFM, 2010)
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: Screening-level: 2.35 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 213.9 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Not applicable
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: Not applicable; no volume of use in 2015 reported for Europe or North America

1. Identification

1. **Chemical Name:** 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl) ethan-1-one
2. **CAS Registry Number:** 13144-88-2
3. **Synonyms:** 2-Acetyl-1,3,3,4,4-pentamethyl-1-cyclopentene; Ethanone, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)-; 1-(2,4,4,5,5-Pentamethylcyclopent-1-en-1-yl)ethanone; Alpinone; 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one
4. **Molecular Formula:** $C_{12}H_{20}O$
5. **Molecular Weight:** 180.29
6. **RIFM Number:** 5397

2. Physical data

1. **Boiling Point:** 223.43 °C (EPI Suite)
2. **Flash Point:** 87 °C (GHS)
3. **Log K_{OW}:** 4.04 (EPI Suite)
4. **Melting Point**: 38.54 °C (EPI Suite)
5. **Water Solubility:** 19.61 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0711 mm Hg @ 20 °C (EPI Suite v4.0), 0.118 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor 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. **Volume of Use (worldwide band):** < 0.1 metric tons per year in 2011; 0 metric tons per year in 2015

(IFRA, 2011; IFRA, 2015).

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00012% (RIFM, 2015b)
2. **Inhalation Exposure*:** 0.0000015 mg/kg/day or 0.00010 mg/day (RIFM, 2015b)
3. **Total Systemic Exposure**:** 0.000019 mg/kg/day (RIFM, 2015b)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one is not reported to occur in food 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 which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Pre-registered for 2013, no dossier available as of 02/18/19.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one are detailed below.

IFRA Category[b]	Descript[a]on of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.077
2	Products applied to the axillae	0.023
3	Products applied to the face/body using fingertips	0.46
4	Products related to fine fragrances	0.43
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.11
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.11
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.11
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.25
7	Products applied to the hair with some hand contact	0.88
8	Products with significant ano-genital exposure (tampon)	0.045
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.84
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.0
10B	Aerosol air freshener	3.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.7
12	Other air care pro[a]ucts 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 endpoi[b]t evaluated in this safety assessment). For 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one, the basis was the skin sensitization NESIL of 1000 μg/cm^2.

[b] For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-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. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-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 dose in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one was not mutagenic in the Ames test.

The clastogenic activity of 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one 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 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one in DMSO at concentrations up to 240 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016). Under the conditions of the study, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/16/17.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one or on any read-across materials. The total systemic exposure to 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Table 1
Data summary for 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one.

LLNA Weighted Mean EC3 Value μg/cm[b] (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
3600 [1]	Weak	NA	NA	NA	1000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.
[c] WoE NESIL limited to 3 significant figures.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one (0.019 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 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: 01/25/18.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one or on any read-across materials. The total systemic exposure to 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one 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 insufficient reproductive toxicity data on 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one (0.019 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/25/18.

11.1.4. Skin sensitization

Based on the existing data, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is considered a weak skin sensitizer.

11.1.4.1. Risk assessment. Based on the existing data, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is considered a weak skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one was found to be sensitizing with an EC3 value of 14.4% (3600 μg/cm^2) (RIFM, 2010). In a guinea pig open epicutaneous test, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one was found to be negative (RIFM, 1980). Based on weight of evidence from structural analysis and animal and human studies, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 1000 μg/cm^2, which is a default value based on LLNA data (Gerberick et al., 2001) (Table 1). 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf).

Additional References: RIFM, 1980.

Literature Search and Risk Assessment Completed On: 02/25/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one 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 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/22/19.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one. Based on the Creme RIFM Model, the inhalation exposure is 0.00010 mg/day. This exposure is 14,000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/26/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 identified 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same criteria used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite models BIOWIN 2 or BIOWIN 6 < 0.5 and BIOWIN 3 < 2.2, then the material is considered as 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. Should additional assessment be required, based on these model outputs (Step 1), a weight of evidence based review is 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., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Not applicable.

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.3. Other available data

1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one has been pre-registered for REACH with no additional data at this time.

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

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 03/21/19.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

Gerberick, G.F., Robinson, M.K., Felter, S.P., White, I.R., Basketter, D.A., 2001. Understanding fragrance allergy using an exposure-based risk assessment approach. Contact Dermatitis 45 (6), 333–340.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental

toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Skin Irritation and Capacity of Allergenic Sensitization of 1-(2,4,4,5,5-Pentamethyl-1-Cyclopenten-1-Yl)ethan-1-One (Alpinone) Determined by the Open Epicutaneous Test (OET) on guinea Pigs. RIFM, Woodcliff Lake, NJ, USA Unpublished report from Givaudan. RIFM report number 56198.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM, Woodcliff Lake, NJ, USA RIFM report number 55663.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Local Lymph Node Assay: 1-(2,4,4,5,5-Pentamethyl-1-Cyclopenten-1-Yl)ethan-1-One. RIFM Report Number 61894. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 1-(2,4,4,5,5-Pentamethyl-1-Cyclopenten-1-Yl)ethan-1-One in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66123. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015a. 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM Report Number 70053. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015b. Exposure Survey 08, October 2015.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one: in Vitro Human Lymphocyte Micronucleus Assay. RIFM Report Number 69874. RIFM, Woodcliff Lake, NJ, USA.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.