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Short review

RIFM fragrance ingredient safety assessment, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one, CAS Registry Number 56973-85-4

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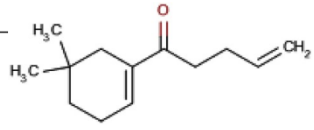
Version: 120919. This version replaces any previous versions.

Name: 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one
CAS Registry Number: 56973-85-4



Abbreviation/Definition List:

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

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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
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.

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-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (CAS # 56973-85-4) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analog 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one (CAS # 224031-70-3) show that 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one is not expected to be genotoxic. Data from 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one provided a No Expected Sensitization Induction Level (NESIL) of 2500 μg/cm^2 for the skin sensitization endpoint. Data on 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one provided a calculated margin of exposure (MOE) $>$ 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; 1-(5,5-dimethyl-1-cyclohexen-1-yl) pent-4-en-1-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-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.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2005a; RIFM, 2005b)
Repeated Dose Toxicity: NOAEL = 51 mg/kg/day.	(ECHA REACH Dossier: 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; ECHA, 2017)
Developmental and Reproductive Toxicity: NOAEL = 150 mg/kg/day.	(ECHA REACH Dossier: 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; ECHA, 2017)
Skin Sensitization: NESIL = 2500 μg/cm^2.	(RIFM, 1999c; RIFM, 2001a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV spectra; RIFM Database; RIFM, 1979)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 32.8% (OECD 310)	RIFM (2012)
Bioaccumulation: Critical Measured Value: 86	Groeber et al. (2016)
Ecotoxicity: Critical Measure Value: 48-h *Daphnia magna* EC50: 1.7 mg/L	(ECHA REACH Dossier: 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; ECHA, 2017)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) $>$ 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 1.7 mg/L	(ECHA REACH Dossier: 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; ECHA, 2017)
Revised RIFM PNEC is: 1.7 μg/L	

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

1. Identification

1. **Chemical Name:** 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one
2. **CAS Registry Number:** 56973-85-4
3. **Synonyms:**.α.-Dynascone; 4-Penten-1-one, 1-(5,5-dimethyl-1-cyclohexen-1-yl)-; Galbanone; Galbascone; 1-(5,5-ｼﾞﾒﾁﾙ-1-ｼｸﾛﾍｷｾﾆﾙ)-4-ﾍﾟﾝﾃﾝ-1-ｵﾝ; 1-(5,5-Dimethylcyclohex-1-en-1-yl)pent-4-en-1-one; Neobutenone; Neogalbenum; Neogal; Dynascone; 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one
4. **Molecular Formula:** $C_{13}H_{20}O$
5. **Molecular Weight:** 192.3
6. **RIFM Number:** 5745
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 257.9 °C (US EPA, 2012a)
2. **Flash Point:** 235.00 °F TCC (112.78 °C)*
3. **Log K_{OW}:** 3.64 (RIFM, 2009b), 4.45 (US EPA, 2012a)
4. **Melting Point**: 46.38 °C (US EPA, 2012a)
5. **Water Solubility:** 7.642 mg/L (US EPA, 2012a)
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** 0.0108 mm Hg @ 20 °C (US EPA, 2012a), 0.0187 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Pale yellow to yellow clear liquid with a high, fresh, green, galbanum, earthy, weedy, pineapple, and narcissus odor*

*http://www.thegoodscentscompany.com/data/rw1003151.html, retrieved 12/04/17.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.011% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000036 mg/kg/day or 0.0027 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00034 mg/kg/day (RIFM, 2016)

*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).

4. Derivation of systemic absorption

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

5. 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:** 1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one (CAS # 224031-70-3)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justifications: See Appendix below

6. Metabolism

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

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

1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-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.

8. REACH dossier

Available; accessed 12/04/17.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.19
2	Products applied to the axillae	0.057
3	Products applied to the face/body using fingertips	0.18
4	Products related to fine fragrances	1.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.27
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.27
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.27
5D	Baby cream, oil, talc	0.091
6	Products with oral and lip exposure	0.54
7	Products applied to the hair with some hand contact	0.54
8	Products with significant ano-genital exposure (tampon)	0.091

9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.4
10B	Aerosol air freshener	3.4
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.091
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 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one, the basis was the reference dose of 0.51 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2500 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (dynascone) does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2uvrA were treated with the test material in dimethyl sulfoxide (DMSO) at concentrations of 5, 15, 50, 150, 500, 1500, and 5000 μg/plate with and without metabolic activation (S9 mix). An increase in revertant colonies was not produced in any of the strains at any of the concentrations (RIFM, 2005a), and therefore the test material was considered not mutagenic.

There are no data assessing the clastogenic potential of 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (dynascone); however, read-across can be made to 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one (CAS # 224031-70-3; see Section V). The clastogenicity of 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-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 V79 cells were treated with analog in ethanol at concentrations ranging up to 25 μg/mL and 62.5 μg/mL in the absence and presence of metabolic activation, respectively. No relevant increases in the frequencies of polyploid metaphases were found after treatment with the analog as compared to the frequencies of the controls (RIFM, 2005b). Under the experimental conditions of the study, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one did not induce structural chromosomal aberrations as determined by the chromosome aberration test in V79 cells *in vitro* and this can be extended to 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (dynascone).

Based on the available data, 1-(5,5-dimethyl-1-cyclohexen-1-yl) pent-4-en-1-one (dynascone) does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/25/17.

10.1.2. Repeated Dose Toxicity

The MOE for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one to support the repeated dose toxicity endpoint. An OECD/GLP 422 dietary combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing the test material at concentrations of 0, 250, 700, or 2000 ppm. Males were dosed for 91 days (10 weeks prior to mating, during mating, and up to termination), while the females were dosed for 103–114 days (10 weeks prior to mating, during mating, post-coitum, and through lactation day 4). At 2000 ppm, there was a statistically significant decrease in body weight and food consumption for dams throughout the post-coitum and lactation periods and for body weight during the pre-mating period as well. The mean body weights were 10% lower than the controls, whereas the differences in food consumption were approximately 30–40% lower than the controls throughout the post-coitum and lactation periods. There was an increase in kidney weights among males treated at 2000 ppm (15% higher than the controls). Higher kidney weights were also observed in males at 700 ppm (13% higher than controls) and in females at 250, 700, and 2000 ppm (13%, 21%, and 16% higher, respectively). Microscopic examination revealed minimal to slight hypertrophy of the urothelium in the urinary bladder among females treated at 2000 ppm. This finding was considered to be adverse since this change was observed in 3/5 females, and it was not an effect which typically occurs as a background finding. It was not considered to be a secondary response to irritation by calculi, lower urinary tract obstruction, or in association with renal papillary necrosis, as these effects were not observed; therefore, these bladder effects were considered to be treatment-related. However, there were no indications that the kidney function in females was impaired based on the absence of any kidney-related findings. Furthermore, it was not seen in males. The only histopathological lesion observed was hyaline droplet accumulation, accompanied by indicators of renal tubular damage in the form of granular casts and increased tubular basophilia among males treated at 2000 ppm, which corresponded with the increased kidney weights. These kidney changes were consistent with documented changes of alpha-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 and Caudill, 1992; Lehman-McKeeman et al., 1990). Hepatocellular hypertrophy was observed in the livers of high-dose males and females. This microscopic finding was correlated with an increase in relative liver weight (13% higher than controls) and macroscopic liver enlargement observed in a few males treated with the highest dose (2000 ppm). In the absence of any other indicators of hepatocellular toxicity, these liver changes can be considered to be adaptive provided there is lack of histopathological evidence showing liver cell damage and clinical chemistry alterations (Hall et al., 2012). Thus, the NOAEL for systemic toxicity was considered to be 700 ppm (51 mg/kg/day for males and 59 mg/kg/day (pre-mating period), 87 mg/kg/day (post-coitum period), and 129 mg/kg/day (lactation period) for females), based on decreased food consumption of females throughout the post-coitum and lactation periods and hypertrophy of the urothelium of the urinary bladder among females of the high-dose group (ECHA, 2017). The most conservative NOAEL of 51 mg/kg/day from male animals was selected for the repeated dose toxicity endpoint.

Therefore, the MOE for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure, 51/0.00034 or 150000.

In addition, the total systemic exposure to 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (0.34 μg/kg/day) is below the TTC (30 μg/kg/day) for the repeated dose toxicity endpoint of a Cramer

Class I material at the current level of use.

10.1.2.1.1. Derivation of reference dose (RfD). Section IX 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) and a reference dose of 0.51 mg/kg/day.

The RfD for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 51 mg/kg/day by the uncertainty factor, 100 = 0.51 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/02/17.

10.1.3. Developmental and Reproductive Toxicity

The MOE for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient data to support the developmental and reproductive toxicity endpoints. An OECD/GLP 422 dietary combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing the test material at concentrations of 0, 250, 700, or 2000 ppm. Males were dosed for 91 days (10 weeks prior to mating, during mating, and up to termination), while the females were dosed for 103–114 days (10 weeks prior to mating, during mating, post-coitum, and through lactation day 4). In addition to systemic toxicity parameters, reproductive and developmental parameters were also evaluated. There were no treatment-related or toxicologically significant alterations observed in any of the reproductive parameters (i.e., mating, fertility, and conception indices, precoital time, numbers of corpora lutea and implantation sites, spermatogenic profiling, and histopathological examination of reproductive organs). No treatment-related or toxicologically significant changes in any of the developmental parameters were observed (i.e., gestation index and duration, parturition, maternal care, and early postnatal pup development consisting of mortality, clinical signs, body weight, and macroscopy). Thus, the NOAEL for reproductive and developmental toxicity was considered to be 2000 ppm (150 mg/kg/day for males and 168 mg/kg/day (pre-mating period), 184 mg/kg/day (post-coitum period), and 280 mg/kg/day (lactation period) for females) (ECHA, 2017). The most conservative NOAEL of 150 mg/kg/day from male animals was selected for the reproductive and developmental toxicity endpoints. Therefore, the 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one MOE can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure (150/0.00034 = 441176).

In addition, the total systemic exposure to 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (0.34 μg/kg/day) is below the TTC (30 μg/kg/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/25/17.

10.1.4. Skin Sensitization

Based on the available data, 1-(5,5-dimethyl-1-cyclohexen-1-yl) pent-4-en-1-one is considered to be a moderate skin sensitizer with a defined NESIL of 2500 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one is considered a skin sensitizer with a defined NESIL of 2500 μg/cm^2. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one was found to be positive in direct peptide reactivity assay and KeratinoSens (Natsch et al., 2007; RIFM, 2013). Additionally, in a murine local lymph node assay, 1-(5,5-dimethyl-1-cyclohexen-1-yl) pent-4-en-1-one was found to be sensitizing with an EC3 value of 3.0% or 747 μg/cm^2 (RIFM, 2001b). In a Buehler study, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one was not found to be sensitizing (RIFM, 1999b). However, in 2 separate guinea pig maximization tests, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one was considered a weak sensitizer (RIFM, 1999a; RIFM, 2003a). In a confirmatory human repeated insult patch test with 2500 μg/cm^2 of 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2001a).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one is a moderate sensitizer with a WoE NESIL of 2500 μg/cm^2 (Table 1). Section IX 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) and a reference dose of 0.51 mg/kg/day.

Additional References: RIFM, 1977; RIFM, 1979; RIFM, 1999a, RIFM, 2002; RIFM, 2003b; RIFM, 2000b; RIFM, 2000a.

Literature Search and Risk Assessment Completed On: 11/29/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra and data from a study conducted in humans, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In a study conducted in humans, no evidence for phototoxic or photoallergenic effects were observed following application of 1% 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one in white petrolatum (RIFM, 1979). Based on the human study data and the lack of absorbance, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/19/16.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one is below the Cramer Class I TTC value for inhalation exposure local effects.

Table 1
Data summary for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one.

LLNA Weighted Mean EC3 Value μg/cm^2 [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
747 [1]	Moderate	2500	NA	NA	2500

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 2 significant figures.

10.1.6.1. Risk assessment. There are insufficient inhalation data available on 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0027 mg/day. This exposure is 519 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: 03/19/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-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-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-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 v4.1 (US EPA, 2012a) identified 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-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 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 v4.1).

10.2.2. Risk assessment

Based on current VoU (2015), 1-(5,5-dimethyl-1-cyclohexen-1-yl) pent-4-en-1-one presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2009a: The CO_2 headspace test according to the OECD 310 method was conducted to evaluate the biodegradability of the test material under aerobic conditions. At 25 mg/L, the test material was biodegraded 4% and 12% at day 28 and day 56, respectively.

RIFM, 2012: The ready biodegradability of the test material was determined by a modified (2 parts) Headspace Test according to the OECD 310 method. The average cumulative percent biodegradation of the test material at the end of the 28-day initial test was 32.8%. At the end of the initial biodegradation test, the inoculated test medium for the second test was prepared by combining 200 mL of the pre-exposed inoculated test medium from the initial study per 800 mL of freshly prepared test medium, and incubated for its duration and aerated with CO_2-free air for approximately 30 min. The average cumulative percent biodegradation of the test material at the end of the 60-day second test was 29.9%.

RIFM, 2015a: Ready biodegradability of the test material was evaluated in a modified MITI test according to the OECD 301C method. Average biodegradation of 21% was observed after 28 days.

RIFM, 2015b: The bioaccumulation potential of the test material was evaluated in common carp following the Testing Methods for New Chemical Substances (Japan, March 21, 2011- No. 0331-7) under flow-through conditions. The BCF at a steady state was reported to be 86.

10.2.3.2. Ecotoxicity. RIFM, 2015b: As part of a fish bioaccumulation assay, a 96-h acute toxicity study was conducted with ricefish under semi–static conditions. The LC50 was reported to be greater than 5 mg/L.

10.2.4. Other available data

1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one has been registered under REACH and the following additional information is available:

Daphnia magna acute toxicity study was conducted according to the OECD 202 method. Based on the 0-h measured concentration, the 48-h EC50 was reported to be 1.7 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 0–72 h EC50 was reported to be 3.4 mg/L (ECHA, 2017).

10.2.5. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	10.05			1,000,000	0.0105	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.665	0.828	0.794			Vinyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.004	0.715	1.355	10,000	0.0715	Neutral Organics SAR (Baseline toxicity)
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	>5.0					
Daphnia		1.7		1000	1.7	
Algae		3.4				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.64	3.64
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–1000	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 1.7 μg/L. The revised PEC/PNECs for the EU and North America are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/13/19.

11. 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 05/30/19.

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.2020.111266.

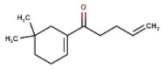
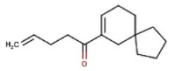
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-
CAS No.	56973-85-4	224031-70-3
Structure		
Similarity (Tanimoto Score)		0.76
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{13}H_{20}O$	$C_{15}H_{22}O$
Molecular Weight	192.3	218.34
Melting Point (°C, EPI Suite)	46.38	78.85
Boiling Point (°C, EPI Suite)	257.90	298.54
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.49	0.158
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.64[1]	5.32
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	7.642	1.014
J_{max} (μg/cm^2/h, SAM)	8.739	2.687
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.55E + 001	1.21E + 001
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition	• Michael addition
Carcinogenicity (ISS)	• Carcinogen (moderate reliability)	• Carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
In Vitro Mutagenicity (Ames, ISS)	• α,β-unsaturated carbonyls	• α,β-unsaturated carbonyls
In Vivo Mutagenicity (Micronucleus, ISS)	• α,β-unsaturated carbonyls	• α,β-unsaturated carbonyls
Oncologic Classification	• Not classified	• Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

1. RIFM, 2009b.

Summary

There are insufficient toxicity data on 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (CAS # 56973-85-4). 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-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- (CAS # 224031-70-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- (CAS # 224031-70-3) was used as a read-across analog for the target material 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (CAS # 56973-85-4) for the genotoxicity endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to the class of aliphatic ketones.

- The target material and the read-across analog share a common α,β-unsaturated and alkyl cyclic fragment.
- The key structural difference between the target material and the read-across analog is that the analog has a 4-carbon spiro substituent at C-5 of the cyclohexyl ring, whereas the target material has a dimethyl substitution at the same position. This structural difference is toxicologically insignificant.
- Structural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the common α,β-unsaturated and alkyl cyclic fragment. 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.
- According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and read-across analog have carcinogenicity alerts by the ISS model. In addition, they also have DNA binding alerts by OECD and *in vivo* and *in vitro* mutagenicity alerts. According to these predictions, the read-across analog has comparable reactivity to the target material. The data described in the genotoxicity section above shows that, based on the current existing data, the read-across analog does not pose a concern for genotoxicity. Therefore, the predictions are superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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