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Short review

RIFM fragrance ingredient safety assessment, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one, CAS Registry Number 56973-87-6

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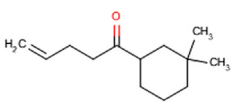

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
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
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines

(*continued on next page*)

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(*continued*)

PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits 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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic, provided a MOE >100 for the repeated dose toxicity endpoint and it does not have skin sensitization potential. The developmental and reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (RIFM, 1990a; RIFM, 1996a)
Repeated Dose Toxicity: (RIFM, 1996b)
NOAEL = 50 mg/kg/day
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not sensitizing (RIFM, 1983; RIFM, 1996c)
Phototoxicity/Photoallergenicity: (UV Spectra, RIFM DB)
Not phototoxic/photoallergenic
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 11% (OECD 301D) (RIFM, 1996d)
Bioaccumulation: Screening Level: 293 L/Kg (EpiSuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: *Daphnia Magna* 48 h LC50: 1.079 mg/L (EpiSuite ver 4.1)
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: (EpiSuite ver 4.1)
Daphnia Magna 48 h LC50: 1.079 mg/L
RIFM PNEC is: 0.1079 μg/L
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe <1

1. Identification

1 **Chemical Name:** 1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one
2 **CAS Registry Number:** 56973-87-6
3 **Synonyms:** 1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one; 4-Penten-1-one, 1-(3,3-dimethylcyclohexyl)-; Galbaniff
4 **Molecular Formula:** $C_{12}H_{22}O$
5 **Molecular Weight:** 194.32
6 **RIFM Number:** 6308

2. Physical data

1 **Boiling Point:** 243–260 °C at 1019 mbar [RIFM, 1996e], (calculated) 252.12 °C [EPI Suite]
2 **Flash Point:** 111.5 °C at 1016 mbar [RIFM, 1996e]
3 **Log K_{ow}:** Log P > 3.60 at 20 °C [RIFM, 1996e], 4.24 [EPI Suite]
4 **Melting Point:** 35.93 °C [EPI Suite]
5 **Water Solubility:** 3.23×10^2 g/L at 20 °C [RIFM, 1996e], (calculated) 11.13 mg/L [EPI Suite]
6 **Specific Gravity**: Not Available
7 **Vapor Pressure:** 1.25 Pa at 25 °C [RIFM, 1996e], (calculated) 0.0182 mm Hg @ 20 °C [EPI Suite 4.0], (calculated) 0.031 mm Hg @ 25 °C [EPI Suite]
8 **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} cm^{-1})
9 **Appearance/Organoleptic:** Not Available

3. Exposure

1 **Volume of Use (worldwide band):** 1–10 metric tons per year [IFRA, 2011]
2 **Average Maximum Concentration in Hydroalcoholics:** 0.002% [IFRA, 2008]
3 **97.5**th **Percentile:** 0.011% [IFRA, 2008]
4 **Dermal Exposure*:** 0.0003 mg/kg/day [IFRA, 2008]
5 **Oral Exposure:** Not available
6 **Inhalation Exposures**:** 0.000017 mg/kg/day or 0.0010 mg/day [IFRA, 2008]
7 **Total Systemic Exposure (Dermal + Inhalation):** 0.00032 mg/kg/day

* Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap). (Cadby et al., 2002; Ford et al., 2000)

** Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1 **Dermal:** Assumed 100%
2 **Oral:** Data not available – not considered.
3 **Inhalation:** Assumed 100%
4 **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.00032 mg/kg/day

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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 **Analogues Selected:**
- a. **Genotoxicity:** None
- 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: None**

6. Metabolism

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

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

1-(3,3-Dimethylcyclohexyl)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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. Reach dossier

Available, accessed 8/24/2015.

10. Summary

1 Human Health Endpoint Summaries:

10.1. Genotoxicity

Based on the current existing data and use levels, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one does not present a concern for genetic toxicity.

10.1.1. Risk assessment

1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). The mutagenic activity of 1-(3,3-dimethylcyclohexyl)pent-4-en-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 method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 and *Escherichia coli* strain WP2uvrA were treated with 1-(3,3-dimethylcyclohexyl) pent-4-en-1-one in DMSO (dimethyl sulfoxide) 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, 1990a). Under the conditions of the study, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one was not mutagenic in the Ames test.

The clastogenic activity of 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one was assessed in an *in vitro* chromosome abberation assay conducted in compliance with GLP regulations and in accordance with OECD guidelines. Human peripheral blood lymphocytes were treated with 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one in DMSO (dimethyl sulfoxide) at concentrations up to 125 μg/ml in the presence and absence of exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations were observed with any dose of the test item, in either the presence or absence of S9 metabolic activation (RIFM, 1996f). Under the conditions of the study, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one was considered to be non-clastogenic. These *in vitro* results were further confirmed in a GLP, OECD 474 *in vivo* micronucleus study on male and female CD-1 Swiss mice administered up to 5000 mg/kg bodyweight of 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one in 1% methylcellulose. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes (RIFM, 1990b) and was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/07/14.

10.2. Repeated dose toxicity

The margin of exposure for 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one is adequate for the repeated dose toxicity endpoint at the current level of use.

10.2.1. Risk assessment

The repeated dose toxicity data on 1-(3,3-dimethylcyclohexyl) pent-4-en-1-one are sufficient for the repeated dose toxicity endpoint. An OECD 407 gavage 28-day subchronic toxicity study conducted in rats determined the NOAEL to be 150 mg/kg/day (RIFM, 1996g).

A default safety factor of 3 was used when deriving a NOAEL from the 28 day or OECD 422/421/407 studies. The safety factor has been approved by RIFM's Independent Expert Panel*.

Thus the derived NOAEL for the repeated dose toxicity data is 150/3 or 50 mg/kg/day.

Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.00032 or 156250.

In addition, the total systemic exposure for 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one (0.32 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: Scognamiglio et al., 2013a, 2013b, 2013c; Belsito et al., 2013; RIFM, 2004; Lalko et al., 2007; Belsito et al., 2007.

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Literature Search and Risk Assessment Completed on: 03/03/14.

10.3. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.3.1. Risk assessment

There are no developmental or reproductive toxicity data. The total systemic exposure (0.32 μg/kg/day) is below the TTC for 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one (30 μg/kg bw/day).

Key Studies: None.

Additional References: Scognamiglio et al., 2013a, 2013b, 2013c; Belsito et al., 2013; RIFM, 2004; Lalko et al., 2007; Belsito et al., 2007.

Literature Search and Risk Assessment Completed on: 03/03/14.

10.4. Skin sensitization

Based on the available data, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one does not present a concern for skin sensitization.

10.4.1. Risk assessment

The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; OECD toolbox v3.1). In a guinea pig maximization test, no results indicative of sensitization were observed (RIFM, 1996h). Additionally, no reactions indicative of skin sensitization were observed in the human repeated insult patch test (RIFM, 1983).

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/14/14.

10.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one would not be expected to present a concern for phototoxicity or photoallergenicity.

10.5.1. Risk assessment

There are no phototoxicity studies available for 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.6.1. Risk assessment

There are no inhalation data available on 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.011%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.0010 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value.

This value is 1400 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: 07/20/16.

2 Environmental Endpoint Summary:

10.7. Screening-level assessment

A screening level risk assessment of 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 1-(3,3-dimethylcyclohexyl)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 EPISUITE ver 4.1 did identify 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one as possibly persistent but not bio-accumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver. 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.7.1. Risk assessment

Based on current Volume of Use (2011), 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one presents a risk to the aquatic compartment in the screening level assessment.

Key Studies:

10.8. Biodegradation

RIFM, 1996f: A sealed test according to the OECD 301D method was conducted to determine the biodegradability of 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one. After 28 days, a biodegradation of 11% was observed.

10.9. Ecotoxicity

RIFM, 1996c: A 48 h *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method. Under the conditions of the study, the 48-h EC50s was 2.7.

RIFM, 1996d: A 96 h fish (Rainbow trout) acute toxicity test was conducted according to the OECD 203 method. Under the conditions of this study, the 96-h LC50 value of the test substance in rainbow trout was 5.7 mg/L.

RIFM, 1996e: An algae inhibition test was conducted according to the OECD 201 method. The 72 h EC50 was greater than 9.0 mg/L.

Other available data: Not available.

10.9.1. Risk assessment refinement

Since 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one passed the screening criteria, measured data is included in the document for completeness only and has not been used for PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

Literature Search and Risk Assessment Completed on: 03/14/14.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

* Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.92 mg/l			1,000,000	0.00292 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.545 mg/l	1.079 mg/l	1.893 mg/l	10,000	0.1079 μg/l	Neutral organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.24	4.24
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is < 1. Additional assessment is necessary.

The RIFM PNEC is 0.1079 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.10.007.

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