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Short Review

RIFM fragrance ingredient safety assessment, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone, CAS Registry Number 33704-61-9

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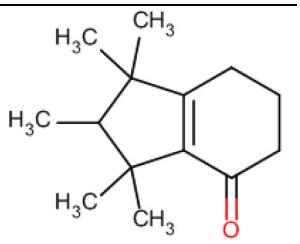

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data show that 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is not genotoxic. Data on 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone provide a calculated MOE >100 for the repeated dose and reproductive toxicity endpoints. Data provided a NESIL of 12,000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material, and the exposure to 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2005a; Kevekordes, 1997; RIFM, 2014; RIFM, 2020)

Repeated Dose Toxicity: NOAEL = 10 mg/kg/day. (ECHA REACH Dossier: 1,2,3,5,6,7-Hexahydro-1,1,2,3,3-pentamethyl-4H-inden-4-one; ECHA, 2013)

Developmental and Reproductive Toxicity: NOAEL = 115.24 mg/kg/day (RIFM, 2012b)

Skin Sensitization: NESIL = 12,000 μg/cm^2 (RIFM, 2012a; RIFM, 2013a)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 0% (OECD 302C) (RIFM, 1998)

Bioaccumulation: Critical Measured Value: BCF: 82–140 (OECD 305) (RIFM, 2006)

Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h *Daphnia Magna* EC50: 1.5 mg/L (RIFM, 2011a)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)

Critical Ecotoxicity Endpoint: 48-h *Daphnia Magna* EC50: 1.5 mg/L (RIFM, 2011a)

RIFM PNEC is: 1.4 μg/L

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

1. Identification

1. **Chemical Name:** 6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone
2. **CAS Registry Number:** 33704-61-9
3. **Synonyms:** Cashmeran; DPMI; 1,2,3,5,6,7-Hexahydro-1,1,2,3,3-pentamethyl-4H-inden-4-one; 4H-Inden-4-one, 1,2,3,5,6,7-hexahydro-1,1,2,3,3-pentamethyl-; 1,1,2,3,3-Pentamethyl-1,2,3,5,6,7-hexahydro-4H-inden-4-one; 6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone
4. **Molecular Formula:** $C_{14}H_{22}O$
5. **Molecular Weight:** 206.32
6. **RIFM Number:** 1269

2. Physical data

1. **Boiling Point:** 277.89 °C (EPI Suite)
2. **Flash Point:** 200 °F (IFF Specification Sheet, 1992)
3. **Log K_{OW}:** log Pow = 4.5 (RIFM, 1997a), 4.49 (EPI Suite)
4. **Melting Point**: 70.77 °C (EPI Suite)

5. **Water Solubility:** 5.937 mg/L (EPI Suite)
6. **Specific Gravity:** 0.95400 to 0.96200 @ 25.00 °C*
7. **Vapor Pressure:** 0.00224 mm Hg @ 20 °C (EPI Suite v4.0), 0.004 mm Hg 20 °C (FMA), 0.00403 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorption in the region of 290–700 nm; the 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. 100–1000 metric tons per year (IFRA, 2015a)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.6% (RIFM, 2018a)
2. **Inhalation Exposure*:** 0.00036 mg/kg/day or 0.026 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure**:** 0.0062 mg/kg/day (RIFM, 2018a)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II*	III	II

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.

2. Analogs 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

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)

6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone 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 that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 07/10/20 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.0063
2	Products applied to the axillae	0.26
3	Products applied to the face/body using fingertips	0.019
4	Products related to fine fragrances	3.8
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.31
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.025
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.038
5D	Baby cream, oil, talc	0.0084
6	Products with oral and lip exposure	0.0063
7	Products applied to the hair with some hand contact	0.031
8	Products with significant ano-genital exposure (tampon)	0.0084
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.13
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.13
10B	Aerosol air freshener	0.28
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0084
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	9.4

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 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone, the basis was the reference dose of 0.1 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 12,000 μg/cm^2. [b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, 6,7-dihydro-

1,1,2,3,3-pentamethyl-4(5H)-indanone does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the modified preincubation method. *Salmonella typhimurium* strains TA100, TA1535, TA98, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone in dimethyl sulfoxide (DMSO) at concentrations of 9.77, 19.5, 39.1, 78.1, 156, and 313 μg/plate in the presence of exogenous metabolic mix (S9) and at 2.44, 4.88, 9.77, 19.5, 39.1, and 78.1 μg/plate in the absence of S9. No increase in the number of revertant colonies was observed in any of the tester strains at any of the concentrations assessed (RIFM, 2005a). Under the conditions of the study, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was considered not mutagenic in the Ames test.

The clastogenic potential of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was assessed in an *in vitro* micronucleus test conducted equivalent to OECD TG 487. Human peripheral blood lymphocytes (HPBL) were exposed to 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone in DMSO at concentrations 0.06, 0.61, 6.1, 61, 122, and 242.5 μM with and without metabolic activation mix (S9). No significant increase was observed in the frequency of micronuclei in both human lymphocytes (Kevekordes, 1997). Under the conditions of the study, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was considered negative in the *in vitro* micronucleus assay.

The clastogenicity of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and equivalent to OECD TG 473. Chinese hamster lung cells were treated with 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone in DMSO at concentrations up to 2060 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (RIFM, 2014). Under the conditions of the study, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was considered to be clastogenic for structural aberrations in the *in vitro* chromosome aberration assay. Considering the cells have wild type p53 DNA sequence, but an expression of p53 is not normally regulated, it may generate a higher number of false positives (Kirkland, 2007). In order to verify the biological relevance of the clastogenic potential, a follow-up *in vitro* micronucleus study was conducted using HPBL. The clastogenic activity of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. HPBL were treated with 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone in dimethyl sulfoxide (DMSO) at concentrations up to 1910 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 100 μg/mL in the presence and absence of metabolic activation. 6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone did not induce binucleated cells with micronuclei when tested up to cytotoxic levels concentration in either the presence or absence of an S9 activation system (RIFM, 2020). Under the conditions of the study, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was considered to be non-clastogenic in the *in vitro* micronucleus test. Taken together, with negative data on a more biologically relevant cell line study along with negative results on one more *in vitro* micronucleus study using HepG2 cells, it can be concluded that 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone may not be a concern for genotoxicity.

Based on the available data, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone does not present a concern for genotoxic potential.

Additional References: Mersch-Sundermann, 2001; Mersch-Sundermann, 1998a; Mersch-Sundermann, 1998b.

Literature Search and Risk Assessment Completed On: 07/10/20.

11.1.2. Repeated dose toxicity

The margin of exposure for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. The repeated dose toxicity data on 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone are sufficient for the repeated dose toxicity endpoint. An OECD 408 gavage 90-day sub-chronic toxicity study conducted in rats determined the NOAEL to be 10 mg/kg/day, based on clinical signs, increased kidney and liver weights, changes in urine, and kidney histological changes (ECHA, 2013).

Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 10/0.0062, or 1613.

In addition, the total systemic exposure to 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone (6.2 μg/kg/day) is below the TTC (9 μg/kg bw/day) at the current level of use for the repeated dose toxicity endpoint.

The RIFM Criteria Document (Api, 2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10x) and intraspecies (10x) differences. These factors can be refined based on the availability of data. Due to insufficient intraspecies susceptibility data for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone, the factor of 10 remains unchanged. For interspecies variability, the factor of 10 can be further sub-divided into 4 and 2.5 based on toxicokinetic and toxicodynamic differences, respectively (Renwick, 1993).

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, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.1 mg/kg/day.

11.1.2.2. Derivation of reference dose (RfD). The reference dose for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 10 mg/kg/day by the uncertainty factor, 100 = 0.1 mg/kg/day.

Additional References: Mori, 2007; Casellas, 2002; Gomez, 2005.

Literature Search and Risk Assessment Completed On: 08/13/20.

11.1.3. Reproductive toxicity

The margin of exposure for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. The reproductive toxicity data on 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone are sufficient for the developmental and fertility endpoints. The NOAEL for fertility and developmental toxicity was determined to be 1875 mg/kg when tested in an OECD 421 dietary reproduction/developmental toxicity screening test in rats. A NOAEL of 1875 mg/kg in the diet is equivalent to an overall intake of 115.24 mg/kg/day and 121.83 mg/kg/day for males and females, respectively, which was the highest dosage tested (RIFM, 2012b).

Therefore, the MOE for developmental toxicity and fertility is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 115.24/0.0062, or 18587.

In addition, the total systemic exposure to 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone (6.2 μg/kg/day) is below the TTC (9 μg/

kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Mori, 2007; Casellas, 2002; Gomez, 2005.

Literature Search and Risk Assessment Completed On: 08/19/20.

11.1.4. Skin sensitization

Based on the available data, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is considered a skin sensitizer with a defined NESIL of 12,000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts, 2007; Toxtree 3.1.0; OECD toolbox v 4.2). 6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was found to be negative in the direct peptide reactivity assay (DPRA) and KeratinoSens but positive in an *in vitro* human Cell Line Activation Test (h-CLAT) (RIFM, 2016a; RIFM, 2018b; RIFM, 2016b). In a murine local lymph node assay (LLNA), 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was found to be sensitizing with an EC3 of 33% (8250 μg/cm2) (ECHA, 2013; RIFM, 2012a). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 22% or 12121 μg/cm2 of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone in 1:3 ethanol: diethyl phthalate (1:3 EtOH:DEP) no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2013a).

Based on weight of evidence from structural analysis as well as animal and human studies, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 12000 μg/cm^2 (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, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.1 mg/kg/day.

Additional References: Larsen, 1996; RIFM, 1981a; RIFM, 1981b; RIFM, 2017; IFRA, 2015b.

Literature Search and Risk Assessment Completed On: 08/18/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis spectra, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1
Data summary for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone.

LLNA weighted mean EC3 value (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]
8250 (1)	Weak	12,121	NA	NA	12,000

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.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/07/20.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone. Based on the Creme RIFM Model, the inhalation exposure is 0.026 mg/day. This exposure is 18.1 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew, 2009, Cramer Class II materials default to Cramer Class III.

Additional References: Peck, 2004.

Literature Search and Risk Assessment Completed On: 07/29/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 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 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was identified as a fragrance material with the potential to present possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 26,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on current VoU (2015), 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1997b: To determine the inherent biodegradability of the test substance, the sealed vessel test was conducted using an acclimatized inoculum from a modified Semi-Continuous Activated Sludge (SCAS) test following the OECD 302A guidelines, "Inherent Biodegradability: Modified SCAS Test," 1981; OECD Guideline 301B. The average extent of mineralization of the test material in the sealed vessel test using acclimatized inoculum was 0.8%.

Givaudan, 1997m, #39276: The ready biodegradability of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was determined by the manometric respirometry test, which was conducted according to OECD Guideline 301 F. The test material underwent no biodegradation after 28 days in the test conditions.

RIFM, 1998: Inherent biodegradability of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was determined by the manometric respirometry test, which was conducted according to OECD Guideline 302 C. Inoculated mineral medium containing 30 mg/L test material was stirred in a closed flask for 28 days. No biodegradation after 28 days was observed.

RIFM, 2005b: A biodegradation study of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone by microorganisms was conducted. Activated sludge was added to the test vessels so that the concentration of the suspended solid reached 30 mg/L. A closed system oxygen consumption measuring apparatus was used to measure the biochemical oxygen demand. The average percentage biodegradation of 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone was 1% after 28 days.

RIFM, 1994: The biodegradation potential of the test material was measured using a manometric respirometer. The test material (100 mg/L) was combined with a mineral medium and inoculated with a mixed aquatic population of microorganisms (activated sludge). The test material/sludge mixture was incubated in the dark at 20 ± 1 °C under aerobic conditions for 28 days. Biodegradation of 3% was observed after 28 days.

RIFM, 2006: A bioconcentration study was conducted in Carp (*Cyprinus carpio*) according to OECD 305 guidelines. Bioconcentration factors at a steady-state ranged from 81 to 140 after exposure to 10 μg/L test material and 82–140 after exposure to 1 μg/L.

11.2.2.1.2. Ecotoxicity. RIFM, 2006: An acute toxicity test was conducted with 10 orange-red killifish (*Oryzias latipes*) per dose level following the Japanese Industrial Standard (JIS K 0102-1998-71) method. The acute 96-h LC50 value of the test material was reported to be 2.12 mg/L.

RIFM, 2011a: The acute toxicity of the test material towards *Daphnia magna* was investigated according to OECD 202 guidelines under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 1.5 mg/L (95% CI: 1.2–1.7 mg/L).

RIFM, 2011b: The algae acute toxicity test was conducted according to OECD 201 guidelines. Because test concentrations decreased during the test 10%–24% of the nominal concentrations, the 72-h EC50s were based on the geometric mean concentrations and were 6.6 and 10 mg/L for yield and growth rate, respectively.

RIFM, 2013b: The acute fish (*Oryzias latipes*) study was conducted according to the OECD 203 method under static conditions. The 96-h LC50 value based on mean measured concentration was reported to be 1.7 mg/L.

11.2.2.1.3. Other available data. 6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone has been registered under REACH, and the following data is available (ECHA, 2013):

The acute toxicity towards *Cyprinus carpio* was investigated according to OECD 203 guidelines under static conditions. Fish were exposed to a WAF with a loading rate of 10 mg/L and observed for 96 h. All fish were dead after 3.5 h.

11.2.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.5	4.5
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 1.5 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 08/21/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery Results&EndPointRpt=Y#submission

RIFM Framework Screening-level **(Tier 1)**	1.86			1,000,000	0.00186	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.983	0.702	1.354	10,000	0.0702	Vinyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.644	0.810	0.784			Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.7					
Daphnia		1.5		1000	1.5	
Algae		6.6				

- **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 07/14/20.

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

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane, cyclobutane with substituents from Q.24 or a mono- or bicyclic sulfide or mercaptan? No
Q26. Monocycloalkanone or a bicycle compound? Yes, Class II

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