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RIFM fragrance ingredient safety assessment, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one, CAS registry number 41724-19-0

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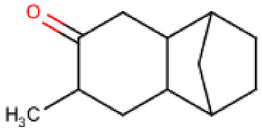


Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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 Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

(*continued on next column*)

(*continued*)

*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.

Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one and the read-across analog 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one (CAS # 51519-65-4) show that octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). Data on octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one provided a No Expected Sensitization Induction Level (NESIL) of 5300 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-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, 2016c)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 5300 μg/cm^2. RIFM (2017)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 2.78 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 19.32 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 97.6 mg/L (RIFM Framework; Salvito, 2002)
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: Fish LC50: 97.6 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.0976 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one
2. **CAS Registry Number:** 41724-19-0
3. **Synonyms:** 1,4-Methanonaphthalen-6(2H)-one, octahydro-7-methyl-; 5-Methyl-4-oxotricyclo[6.2.1.02,7]undecane; 5-ﾒﾁﾙﾄﾘｼｸﾛ[6.2.1.02,7]ｳﾝﾃﾞｶﾝ-4-ｵﾝ; 7-Methyloctahydro-1,4-methanonaphthalen-6(2H)-one; Plicatone; Reaction mass of rel-(1R,2S,5S,7R,8S)-5-methyltricyclo[6.2.1.02,7]undecan-4-one and (1RS,2SR,5RS,7RS,8SR)-5-methyltricyclo[6.2.1.02,7]undecan-4-one; Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one
4. **Molecular Formula:** $C_{12}H_{18}O$
5. **Molecular Weight:** 178.27
6. **RIFM Number:** 5703

7. **Stereochemistry:** Isomer not specified. Five chiral centers and a total of 32 enantiomers possible.

2. Physical data

1. **Boiling Point:** 259.49 °C (EPI Suite), 271 ± 2 °C (544 ± 2 K) at 97.9 kPa (RIFM, 2005b)
2. **Flash Point:** >100 °C (Globally Harmonized System), 121 ± 2 °C (RIFM, 2005b)
3. **Log K_{OW}:** 2.45 (EPI Suite)
4. **Melting Point**: 48.11 °C (EPI Suite)
5. **Water Solubility:** 450.4 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00959 mm Hg at 20 °C (EPI Suite v4.0), 0.0166 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.089% (RIFM, 2016a)
2. **Inhalation Exposure*:** 0.00016 mg/kg/day or 0.012 mg/day (RIFM, 2016a)
3. **Total Systemic Exposure**:** 0.00098 mg/kg/day (RIFM, 2016a)

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

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

5. Derivation of systemic absorption

1. **Dermal:** Data from RIFM's *in silico* skin absorption model (Shen et al., 2014) were used to predict the dermal penetration of 40% for octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one as shown below.

	Chemical Name
Name	Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one
J_{max} (mg/cm^2/h)	0.006[1]
Skin Absorption Class	40%

[1] J_{max} was calculated based on measured log K_{ow} = 2.67 (EPI Suite) and water solubility = 2.92 mg/L (RIFM, 2000b).

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III*, High (Expert Judgment)

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

*See the Appendix below for further details.

2. **Analogs Selected:**
   a. **Genotoxicity:** 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one (CAS # 51519-65-4)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

Additional References: None.

8. Natural occurrence

Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one has been pre-registered for 2010; no dossier available as of 04/14/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-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)	0.41
2	Products applied to the axillae	0.12
3	Products applied to the face/body using fingertips	2.4
4	Products related to fine fragrances	2.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.58
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.58
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.58
5D	Baby cream, oil, talc	0.58
6	Products with oral and lip exposure	1.3
7	Products applied to the hair with some hand contact	4.6
8	Products with significant ano-genital exposure (tampon)	0.24
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.4
10A		16

(continued on next page)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
	Household care products with mostly hand contact (hand dishwashing detergent)	
10B	Aerosol air freshener	16
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	8.8
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 octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one, the basis was a skin sensitization NESIL of 5300 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, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2005a). Under the conditions of the study, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one read-across can be made to 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one (CAS # 51519-65-4; see Section VI). The clastogenic activity of 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one in DMSO at concentrations up to 1622.3 μg/mL in the presence and absence of S9 for 4 and 24 h 4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in the 4-h exposure group in the absence of S9. A small but statistically significant increase was observed in the 4-h group in the presence of S9. However, this increase was observed at a middle concentration and was within the historical control range and was considered to be biologically not relevant. All concentrations in the 24-h test group in the absence of S9 demonstrated small but statistically significant increases in micronuclei. The vehicle control value of this treatment group was abnormally low, and the increases were within or marginally above the historical control range for the vehicle. Additionally, a dose-related response was not observed, and these results were not considered as biologically relevant (RIFM, 2016c). Under the conditions of the study, 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one.

Based on the data available, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one does not present a concern for genotoxic potential.

Additional References: RIFM, 2016b.

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

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one or any read-across materials. The total systemic exposure to octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one or any read-across materials that can be used to support the repeated dose toxicity endpoint. When correcting for skin absorption (see Section V), the total systemic exposure to octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one (0.98 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/06/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one or any read-across materials. The total systemic exposure to octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one or any read-across materials that can be used to support the reproductive toxicity endpoint. When correcting for skin absorption (see Section V), the total systemic exposure to octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one (0.98 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/31/20.

11.1.4. Skin sensitization

Based on the existing data, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is considered a skin sensitizer with a defined NESIL of 5300 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is considered a skin sensitizer with a defined NESIL of 5300 μg/cm^2. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one was found to be sensitizing with an EC3 value of 22.16% (5540 μg/cm^2) (RIFM, 2015). In a Confirmation of No Induction in Humans (CNIH) test with 0.5% octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one in petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1978). In an additional CNIH test with 5315 μg/cm^2 of octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2017).

Based on the weight of evidence (WoE) from structural analysis and animal and human data, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one is considered a weak skin sensitizer with a defined WoE NESIL of 5300 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, 2020b).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/26/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one would not be expected to present a concern for phototoxicity or photoallergenicity.

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

11.1.5.2. 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, 2009).

Additional References: None.

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

Table 1
Data Summary for octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one.

LLNA EC3 value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
5540 [1]	Weak	5315	NA	NA	5300

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH test or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one 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 octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 39.2 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.

Additional References: None.

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one as possibly persistent or 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).

11.2.2. Risk assessment. Based on the current Volume of Use (2015), octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

Biodegradation

No data available.

Ecotoxicity

RIFM, 2000a: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on mean measured concentration was reported to be 20.3 mg/L (95% CI: 16–25.6 mg/L).

Other available data

Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one has been pre-registered for REACH with no additional data at this time.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	97.6			1000000	0.0976	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.45	2.45
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0976 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

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

12. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/14/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix G. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112429.

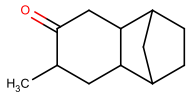
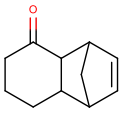
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one	4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one
CAS No.	41724-19-0	51519-65-4
Structure		
Similarity (Tanimoto Score)		0.50
Endpoint		• Genotoxicity
Molecular Formula	$C_{12}H_{18}O$	$C_{11}H_{14}O$
Molecular Weight	178.275	162.232
Melting Point (°C, EPI Suite)	48.11	42.05
Boiling Point (°C, EPI Suite)	259.49	249.49
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.21E+00	4.13E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.50E+02	1.86E+03
Log KOW	2.45	1.82
J_{max} (μg/cm^2/h, SAM)	10.02	22.60
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.51E+00	3.65E+00
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one (CAS # 41724-19-0). 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, 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one (CAS # 51519-65-4) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one (CAS # 51519-65-4) was used as a read-across analog for the target material octahydro-7-methyl-1,4-methanonaphtalen-6(2H)-one (CAS # 41724-19-0) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of cyclic ketones.
  - o The target material and the read-across analog share a fused cyclic structure with ketone moiety.
  - o The key difference between the target material and the read-across analog is that the read-across analog has unsaturation in the ring structure distant to the ketone moiety, whereas the target material is saturated. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the fused cyclic structure with ketone moiety. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? No
Q22. A common component of food? No
Q33. Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No, Class III (High Class)

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