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Short Review

# RIFM fragrance ingredient safety assessment, 3,4-dihydro-5-methylnaphthalen-1(2H)-one, CAS Registry Number 6939-35-1

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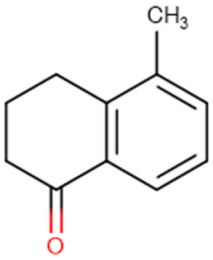


Name: 3,4-Dihydro-5-methylnaphthalen-1(2H)-one CAS Registry Number: 6939-35-1

**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., 2021)
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 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 et al., 2015), which should be referred to for clarifications.

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

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

**Summary: The existing information supports the use of this material as described in this safety assessment.**

3,4-Dihydro-5-methylnaphthalen-1(2H)-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 3,4-dihydro-5-methylnaphthalen-1(2H)-one is not genotoxic. Data on read-across analog 2,3,3-trimethylindanone (CAS # 54440-17-4) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 3,4-dihydro-5-methylnaphthalen-1(2H)-one is

(*continued on next page*)

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| | |
|---|---|
| below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data from read-across analog 2,3,3-trimethylindanone (CAS # 54440-17-4) show that there are no safety concerns for 3,4-dihydro-5-methylnaphthalen-1(2H)-one for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 3,4-dihydro-5-methylnaphthalen-1(2H)-one is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; for the hazard assessment based on the screening data, 3,4-dihydro-5-methylnaphthalen-1(2H)-one is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, 3,4-dihydro-5-methylnaphthalen-1(2H)-one was not able to be risk screened as there were no reported volumes of use (VoU) for either North America or Europe in the 2019 IFRA Survey. | |
| **Human Health Safety Assessment** | |
| **Genotoxicity:** Not genotoxic. | (RIFM, 2016b; RIFM, 2016a) |
| **Repeated Dose Toxicity:** NOAEL = 150 mg/kg/day. | RIFM (2007) |
| **Reproductive Toxicity:** No NOAEL available. Exposure is below TTC. | |
| **Skin Sensitization:** No concern for skin sensitization under the current declared levels of use. | RIFM (2004) |
| **Photoirritation/Photoallergenicity:** Not photoirritating/photoallergenic. | (UV/Vis spectra; RIFM Database; RIFM, 2016c) |
| **Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC. | |
| **Environmental Safety Assessment** | |
| **Hazard Assessment:** | |
| **Persistence:** | |
| Screening-level: 2.7 (BIOWIN 3) | (EPI Suite v4.11; US EPA, 2012a) |
| **Bioaccumulation:** | |
| Screening-level: 3.9 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Screening-level: Fish LC50: 21.58 mg/L | (RIFM Framework; Salvito et al., 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 et al., 2002) |
| **Critical Ecotoxicity Endpoint:** LC50: 21.58 mg/L | (RIFM Framework; Salvito et al., 2002) |
| **RIFM PNEC is:** 0.02158 μg/L | |
| • **Revised PEC/PNECs (2019 IFRA VoU):** Not applicable; cleared at screening-level | |

## 1. Identification

1. **Chemical Name:** 3,4-Dihydro-5-methylnaphthalen-1(2H)-one
2. **CAS Registry Number:** 6939-35-1
3. **Synonyms:** 5-Methyl-1-tetralone; 1(2H)-Naphthalenone, 3,4-dihydro-5-methyl-; 5-Methyl-3,4-dihydronaphthalen-1(2H)-one; Jasmutone; 3,4-Dihydro-5-methylnaphthalen-1(2H)-one
4. **Molecular Formula:** $C_{11}H_{12}O$
5. **Molecular Weight:** 160.21 g/mol
6. **RIFM Number:** 5355
7. **Stereochemistry:** No stereocenter is present, and no stereoisomers are possible.

## 2. Physical data

1. **Boiling Point:** 270.98 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log $K_{OW}$:** 3.15 (EPI Suite)
4. **Melting Point**: 61.74 °C (EPI Suite)
5. **Water Solubility:** 140.2 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00225 mm Hg at 20 °C (EPI Suite v4.0), 0.00408 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm under the biologically relevant neutral condition and basic condition. The corresponding molar absorption coefficients (862 and 853 L $mol^{-1}$ • $cm^{-1}$, under neutral and basic conditions, respectively) are below the benchmark. Under the acidic condition, there was significant absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline by 330 nm. The molar absorption coefficients (1042 L $mol^{-1}$ • $cm^{-1}$, under acidic condition) is above the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

## 3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.000004% (RIFM, 2020)
2. **Inhalation Exposure*:** 0.0000001 mg/kg/day or 0.0000041 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.000025 mg/kg/day (RIFM, 2020)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey, 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 et al., 2015; Safford et al., 2015; Safford et al., 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 v3.1 | OECD QSAR Toolbox v4.5 |
|---|---|---|
| II* | I | II |

*See the Appendix below for details.

2. Analogs Selected:
   a. Genotoxicity: None
   b. **Repeated Dose Toxicity:** 2,3,3-Trimethylindanone (CAS # 54440-17-4)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2,3,3-Trimethylindanone (CAS # 54440-17-4)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 7. Metabolism

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

## 8. Natural occurrence

3,4-Dihydro-5-methylnaphthalen-1(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

3,4-Dihydro-5-methylnaphthalen-1(2H)-one has been pre-registered for 2010; no dossier available as of 03/03/23.

## 10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

## 11. Summary

### *11.1. Human health endpoint summaries*

#### *11.1.1. Genotoxicity*

Based on the current existing data, 3,4-dihydro-5-methylnaphthalen-1(2H)-one does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* 3,4-Dihydro-5-methylnaphthalen-1(2H)-one was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 3,4-dihydro-5-methylnaphthalen-1(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 3,4-dihydro-5-methylnaphthalen-1(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 concentration in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, 3,4-dihydro-5-methylnaphthalen-1(2H)-one was not mutagenic in the Ames test.

The clastogenic activity of 3,4-dihydro-5-methylnaphthalen-1(2H)-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 3,4-dihydro-5-methylnaphthalen-1(2H)-one in DMSO at concentrations up to 1600 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 400 μg/mL in the presence and absence of metabolic activation. 3,4-Dihydro-5-methylnaphthalen-1(2H)-one did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2016a). Under the conditions of the study, 3,4-dihydro-5-methylnaphthalen-1(2H)-one was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/14/22.

#### *11.1.2. Repeated dose toxicity*

The MOE for 3,4-dihydro-5-methylnaphthalen-1(2H)-one is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on 3,4-Dihydro-5-methylnaphthalen-1(2H)-one. Read-across material 2,3,3-trimethylindanone (CAS # 54440-17-4; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a GLP and OECD 407-compliant study, groups of 5 SPF Wistar rats/sex/dose were administered 2,3,3-Trimethylindanone via gavage at doses of 0, 50, 150, and 450 mg/kg/day for 28 days. No mortality occurred throughout the study period. No treatment-related adverse effects were observed in clinical signs, food consumption, body weights, hematology, clinical chemistry, urinalysis, organ weights, or macroscopic or microscopic pathology. Based on no treatment-related adverse effects seen up to the highest dose, the repeated dose NOAEL for this study was considered to be 450 mg/kg/day (RIFM, 2007).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 407 study (ECHA, 2012). The safety factor has been approved by The Expert Panel for Fragrance Safety*.

### *11.2. Thus, the derived NOAEL for the repeated dose toxicity data is 450/3 or 150 mg/kg/day*

Therefore, the MOE for 3,4-dihydro-5-methylnaphthalen-1(2H)-one is equal to the 2,3,3-trimethylindanone NOAEL in mg/kg/day divided by the total systemic exposure for 3,4-dihydro-5-methylnaphthalen-1(2H)-one, 150/0.000025 or 6000000.

In addition, the total systemic exposure to 3,4-dihydro-5-methylnaphthalen-1(2H)-one (0.025 μg/kg/day) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material (9 μg/kg/day; Kroes et al., 2007) at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

**Additional References:** None.

**Table 1**
Summary of existing data on 2,3,3-trimethylindanone as a read-across for 3,4-dihydro-5-methylnaphthalen-1(2H)-one.

| Sensitization Potency Category[1] | NOEL-CNIH (induction) µg/cm² | NOEL-HMT (induction) µg/cm² | LOEL[2] (induction) µg/cm² | WoE NESIL[3] µg/cm² | LLNA[4] Weighted Mean EC3 Value µg/cm² | GPMT[5] | Buehler[5] |
|---|---|---|---|---|---|---|---|
| No evidence of sensitization[7] | 5000 | N/A | N/A | N/A | Negative up to 25000 (100%) | N/A | N/A |
| | ***In vitro* Data[6]** | | | | ***In silico* protein binding alerts (OECD Toolbox v4.5)** | | |
| | **KE 1** | **KE 2** | **KE 3** | | **Target Material** | **Autoxidation simulator** | **Metabolism simulator** |
| | N/A | N/A | N/A | | No alert found | No alert found | No alert found |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[5]Studies conducted according to the OECD TG 406 are included in the table.
[6]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.
[7]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

**Literature Search and Risk Assessment Completed On:** 07/13/22.

*11.2.1. Reproductive toxicity*

There are insufficient reproductive toxicity data on 3,4-dihydro-5-methylnaphthalen-1(2H)-one or any read-across materials. The total systemic exposure to 3,4-dihydro-5-methylnaphthalen-1(2H)-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

*11.2.1.1. Risk assessment.* There are no reproductive toxicity data on 3,4-dihydro-5-methylnaphthalen-1(2H)-one or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3,4-dihydro-5-methylnaphthalen-1(2H)-one (0.025 µg/kg/day) is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material (9 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 07/13/22.

*11.2.2. Skin sensitization*

Based on the existing data on the target material and read-across material 2,3,3-trimethylindanone (CAS # 54440-17-4; see Section VI), 3,4-dihydro-5-methylnaphthalen-1(2H)-one does not present a safety concern for skin sensitization under the current declared levels of use.

*11.2.2.1. Risk assessment.* No skin sensitization data are available for 3,4-dihydro-5-methylnaphthalen-1(2H)-one. Therefore, 2,3,3-trimethylindanone (CAS # 54440-17-4; see Section VI) was used for the risk assessment of 3,4-dihydro-5-methylnaphthalen-1(2H)-one. The data on the read-across material are summarized in Table 1. In a murine local lymph node assay (LLNA), read-across material 2,3,3-trimethylindanone was not found to be sensitizing when tested up to 100% (RIFM, 2004). Additionally, in a CNIH with 10% or 5000 µg/cm$^2$ of read-across material 2,3,3-trimethylindanone in 1:3 ethyl alcohol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 97 volunteers (RIFM, 2006). Based on the existing data on the read-across material, 3,4-dihydro-5-methylnaphthalen-1(2H)-one is not considered

a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5).

Based on the weight of evidence (WoE) from structural analysis, animal studies, and human studies on the read-across material, 3,4-dihydro-5-methylnaphthalen-1(2H)-one does not present a concern for skin sensitization.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/09/22.

*11.2.3. Photoirritation/photoallergenicity*

Based on the available UV/Vis absorption spectra and *in vitro* study data, 3,4-dihydro-5-methylnaphthalen-1(2H)-one would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, 3,4-dihydro-5-methylnaphthalen-1(2H)-one would not be expected to present a concern for photoallergenicity.

*11.2.3.1. Risk assessment.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the critical range of 290–700 nm under neutral and basic conditions and significant absorbance under acidic conditions. Under neutral and basic conditions, the molar absorption coefficients are below the benchmark of concern for photoirritation/photoallergenicity. Under acidic conditions, the corresponding molar absorption coefficient is above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). However, the acidic and basic conditions in this assay are defined as pH 2 or less and pH 10 or greater, respectively, and are not biologically relevant for our purposes, where the route of exposure is topical. In a 3T3-Neutral Red Uptake phototoxicity test, 3,4-dihydro-5-methylnaphthalen-1(2H)-one was not predicted to have photoirritating potential (RIFM, 2016c). Based on the available UV/Vis absorption spectra and *in vitro* study data, 3,4-dihydro-5-methylnaphthalen-1(2H)-one would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, 3,4-dihydro-5-methylnaphthalen-1(2H)-one would not be expected to present a concern for photoallergenicity.

*11.2.4. UV spectra analysis*

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance between 290 and 700 nm under the biologically relevant neutral condition and basic condition. The corresponding molar absorption coefficients (862 and 853 L $mol^{-1}$ • $cm^{-1}$, under neutral and basic conditions, respectively) are below the benchmark. Under acidic conditions, there was significant absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline by 330 nm. The molar absorption coefficient (1042 L $mol^{-1}$ • $cm^{-1}$, under acidic conditions) is above the benchmark of concern for photoirritating effects, 1000 L $mol^{-1}$ • $cm^{-1}$ (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/11/22.

*11.2.5. Local respiratory toxicity*

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

*11.2.5.1. Risk assessment.* There are no inhalation data available on 3,4-Dihydro-5-methylnaphthalen-1(2H)-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0000041 mg/day. This exposure is 114634 times lower than the Cramer Class III* TTC value of 0.47 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/12/22.

*11.3. Environmental endpoint summary*

*11.3.1. Screening-level assessment*

A screening-level risk assessment of 3,4-dihydro-5-methylnaphthalen-1(2H)-one was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log $K_{OW}$, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio of 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3,4-dihydro-5-methylnaphthalen-1(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 3,4-dihydro-5-methylnaphthalen-1(2H)-one as possibly being 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). 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).

*11.3.1.1. Risk assessment.* Based on the current VoU (2019), 3,4-dihydro-5-methylnaphthalen-1(2H)-one does not present a risk to the aquatic compartment in the screening-level assessment.

*11.3.1.2. Key studies.* ***Biodegradation***:

No data available.

***Ecotoxicity***:

No data available.

*11.3.1.3. Other available data.* 3,4-Dihydro-5-methylnaphthalen-1(2H)-one has been pre-registered for REACH with no additional data at this time.

*11.3.2. 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)** | 21.58 | | | 1000000 | 0.02158 | |

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

| Exposure | Europe | North America |
|---|---|---|
| Log $K_{ow}$ Used | 3.14 | 3.14 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional VoU Tonnage Band | <1 | <1 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

**The RIFM PNEC is 0.02158 μg/L.** The revised PEC/PNECs for the EU and North America are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 10/03/22.

## 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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 03/03/23.

## Declaration of competing interest

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

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114208.

## Appendix

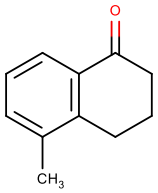
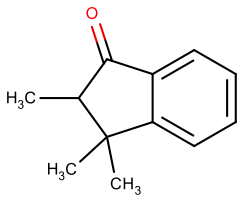
*Read-across Justification*

*Methods*

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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 Chemicals Agency read-across assessment framework (ECHA, 2017b).

- 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 (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

| | Target Material | Read-across Material |
|---|---|---|
| **Principal Name** | 3,4-Dihydro-5-methylnaphthalen-1(2H)-one | 2,3,3-Trimethylindanone |
| **CAS No.** | 6939-35-1 | 54440-17-4 |
| **Structure** |  |  |
| **Similarity (Tanimoto Score)** | | 0.56 |
| **SMILES** | Cc1cccc2C (=O)CCCc12 | CC1C(=O)c2ccccc2C1(C)C |
| **Endpoint** | | Skin sensitization<br>Repeated dose toxicity |
| **Molecular Formula** | $C_{11}H_{12}O$ | $C_{12}H_{14}O$ |
| **Molecular Weight (g/mol)** | 160.216 | 174.243 |
| **Melting Point (°C, EPI Suite)** | 61.74 | 60.64 |
| **Boiling Point (°C, EPI Suite)** | 270.98 | 267.71 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 5.44E-01 | 6.61E-01 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 1.40E+02 | 7.37E+01 |
| **Log KOW** | 3.15 | 3.4 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 11.64 | 6.21 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 7.08E-01 | 1.13E+00 |
| ***Repeated Dose Toxicity*** | | |
| **Repeated Dose (HESS)** | Not categorized | Not categorized |
| ***Skin Sensitization*** | | |
| **Protein Binding (OASIS v1.1)** | No alert found | No alert found |
| **Protein Binding (OECD)** | No alert found | No alert found |
| **Protein Binding Potency** | Not possible to classify according to these rules (GSH) | Not possible to classify according to these rules (GSH) |
| **Protein Binding Alerts for Skin Sensitization (OASIS v1.1)** | No alert found | No alert found |
| **Skin Sensitization Reactivity Domains (Toxtree v2.6.13)** | No skin sensitization reactivity domain alerts were identified | No skin sensitization reactivity domain alerts were identified |
| ***Metabolism*** | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)** | See Supplemental Data 1 | See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on 3,4-dihydro-5-methylnaphthalen-1(2H)-one (CAS # 6939-35-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2,3,3-trimethylindanone (CAS # 54440-17-4) was identified as a read-across analog with sufficient data for toxicological evaluation.

*Conclusions*

- 2,3,3-Trimethylindanone (CAS # 54440-17-4) was used as a read-across analog for the target material 3,4-dihydro-5-methylnaphthalen-1(2H)-one (CAS # 6939-35-1) for the repeated dose toxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the cyclic alkyl aryl ketone group.
  - o The key difference between the target material and the read-across analog is the target material has a methyl group on the benzene ring, and the ketone is on a cyclohexane ring, whereas in the read-across analog, the ketone is on a cyclopentane ring and there are 3 methyl groups on the cyclopentane ring. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. 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 Differences are predicted for $J_{max}$, which estimates skin absorption. $J_{max}$ for the target material corresponds to skin absorption $\leq$80%, and $J_{max}$ for the read-across analog corresponds to skin absorption $\leq$40%. While the percentage of skin absorption estimated from $J_{max}$ indicates exposure

to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.

- o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o There are no alerts for skin sensitization or repeated dose toxicity for the target material or the read-across analog. The data on the read-across analog confirms that the material does not pose a concern for skin sensitization or repeated dose toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
- 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*

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, 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 a detailed explanation). No. |
| Q17. | Readily hydrolyzed to a common terpene? No. |
| Q19. | Open chain? No. |
| Q23. | Aromatic? Yes. |
| Q27. | Rings with substituents? Yes. |
| Q28. | More than one aromatic ring? No. |
| Q30. | Aromatic ring with complex substituents? Yes. |
| Q31. | Is the substance an acyclic acetal or ester of substances defined in Q30? No. |
| Q32. | It contains only the functional groups listed in Q30 or Q31 and either: a) a single fused non-aromatic carbocyclic ring; b) aliphatic substituent chains longer than 5 carbon atoms; or c) a polyoxyethylene ($n \geq 4$) on the aromatic or aliphatic side chain? Yes. Class Intermediate (Class II). |

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