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RIFM fragrance ingredient safety assessment, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone, CAS Registry Number 774-55-0

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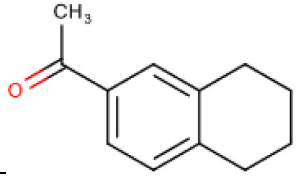
Name: 1-(5,6,7,8-Tetrahydro-2-naphthalenyl)ethanone
CAS Registry Number: 774-55-0



Abbreviation/Definition List:

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

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MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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.

1-(5,6,7,8-Tetrahydro-2-naphthalenyl)ethanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 4′-methylacetophenone (CAS # 122-00-9) show that 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone is not expected to be genotoxic. Data on read-across analog acetophenone (CAS # 98-86-2) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone is not expected to be phototoxic/photoallergenic. Local respiratory toxicity was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class II material, and the exposure to 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone 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, 1987; RIFM, 2013)

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Repeated Dose Toxicity: NOAEL = 250 mg/kg/day.	(ECHA REACH Dossier: Acetophenone; ECHA, 2011)
Reproductive Toxicity: Developmental toxicity: NOAEL = 125 mg/kg/day. Fertility: NOAEL = 750 mg/kg/day.	(ECHA REACH Dossier: Acetophenone; ECHA, 2011)
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST	RIFM (1998)
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: 6% (OECD 301D)	RIFM (2018)
Bioaccumulation: Screening-level: 30.36 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 8.80 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: Fish LC50: 8.80 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.0088 μg/L

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

1. Identification

1. **Chemical Name:** 1-(5,6,7,8-Tetrahydro-2-naphthalenyl)ethanone
2. **CAS Registry Number:** 774-55-0
3. **Synonyms:** 1-(5,6,7,8-Tetrahydro-2-naphthyl)ethan-1-one; 2′-Acetonaphthone, 5′,6′,7′,8′-tetrahydro-; 5,6,7,8-Tetrahydronaphth-2-yl methyl ketone; 5,6,7,8-Tetrahydronaphth-2-yl methyl ketone 5; 6-Acetyltetralin; Ethanone, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)-; 1-(5,6,7,8-Tetrahydronaphthalen-2-yl)ethanone; Florantone T; Acetyl Tetralin; 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone
4. **Molecular Formula:** $C_{12}H_{14}O$
5. **Molecular Weight:** 174.24
6. **RIFM Number:** 6427
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 273.15 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.64 (EPI Suite)
4. **Melting Point**: 58.86 °C (EPI Suite)
5. **Water Solubility:** 45.9 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00215 mm Hg @ 20 °C (EPI Suite v4.0), 0.00389 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor 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. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)

2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0099% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000024 mg/kg/day or 0.0017 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00017 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

*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 the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** 4′-Methylacetophenone (CAS # 122-00-9)
   b. **Repeated Dose Toxicity:** Acetophenone (CAS # 98-86-2)
   c. **Reproductive Toxicity:** Acetophenone (CAS # 98-86-2)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

6.1. Additional References

None.

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

1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone 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.

8. Reach dossier

Available; accessed 04/02/19.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone in dimethyl sulfoxide (DMSO) at concentrations up to 500 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, 1987). Under the conditions of the study, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone; however, read-across can be made to 4′-methylacetophenone (CAS # 122-00-9); see Section 5). The clastogenic activity of 4′-methylacetophenone 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′-methylacetophenone in DMSO at concentrations up to 1400 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 20 h 4′-Methylacetophenone did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2013). Under the conditions of the study, 4′-methylacetophenone was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone.

Based on the available data, 1-(5,6,7,8-tetrahydro-2-naphthalenyl) ethanone and read-across material 4′-methylacetophenone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/18/19.

10.1.2. Repeated dose toxicity

The MOE for 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone is adequate for repeated dose toxicity at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethenone. Read-across material acetophenone (CAS # 98-86-2; see Section 5) has sufficient repeated dose toxicity data that can be used to support the repeated dose toxicity endpoint.

Groups of 10 male and 10 female weanling Osborne-Mendel rats were administered via the diet containing test material acetophenone for 17 weeks in nominal concentrations of 0, 1000, 2500, or 10000 ppm (equivalent to doses of 0, 75, 188, or 750 mg/kg/day, neglecting 31% loss within 1 week due to evaporation). Body weight, food intake, and

general conditions were recorded weekly. Hematology, gross pathology, and microscopic examination were conducted at the end of the study. There were no effects on growth, hematology, or macroscopic or microscopic changes in tissue. The NOEL was reported to be 10000 ppm or 750 mg/kg/day. The US EPA IRIS online summary has derived a NOAEL of 423 mg/kg/day, taking into account the loss by evaporation from food (Hagan et al., 1967). In an OECD 422 gavage study, groups of 10 male and 5 female (additional 10 females for the reproductive toxicity part of the study) Sprague Dawley rats/dose were administered acetophenone at doses of 0, 75, 225, or 750 mg/kg/day daily for a minimum of 14 days before mating and throughout the mating and gestation periods up to lactation day 3. There was no parental mortality. At 750 mg/kg/day, reductions in body weight and food consumption, as well as wobbly gait and urine staining, appeared in both males and females, while hair loss was limited to 3/5 females. Mean forelimb grip strength and mean motor activity of males were statistically lower than the controls. The NOAEL for the repeated dose toxicity endpoint was considered to be 225 mg/kg/day, based on clinical and neurobehavioral findings among high-dose animals (ECHA, 2011; data also available in Kapp et al., 2003). In another study, acetophenone was administered to groups of 10 Wistar rats/sex/dose at doses of 0, 125, 250, and 500 mg/kg/day in a corn oil vehicle. The study was conducted according to the OECD 408 and GLP guidelines. At 500 mg/kg/day, the mean bodyweight gain was significantly lower among the males, while no toxicologically relevant effect for body weight was observed for females. Clinical signs related to the known hypnotic effect of acetophenone (decreased spontaneous activity) were observed mainly in the male and female groups treated with 500 mg/kg/day. A significantly higher mean percent reticulocyte count was observed for males and females of the highest-dose group, which was considered as an adverse effect due to the administration of the test material. Furthermore, a statistically significantly lower red blood cell count and hemoglobin were also observed in the female animals at 500 mg/kg/day. The NOAEL was considered to be 250 mg/kg/day, based on decreased bodyweight gains, reduced activity, and increased reticulocyte levels (ECHA, 2011). The NOAEL of 250 mg/kg/day from the OECD 408 gavage study was considered for this safety assessment.

Therefore, the 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethenone MOE for the repeated dose toxicity endpoint can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethenone, 250/0.00017, or 1470588.

In addition, the total systemic exposure to 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethenone (0.17 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/09/19.

10.1.3. Reproductive toxicity

The MOE for 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone. Read-across material acetophenone (CAS # 98-86-2; see Section 5) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint.

An OECD 414 prenatal developmental toxicity study was conducted in pregnant female Wistar rats. Acetophenone was administered via oral gavage to groups of 25 rats/dose at 0, 125, 300, or 750 mg/kg/day in corn oil. Additional groups of 10 female rats were added to the control and high-dose groups. Females were treated daily from gestation days (GD) 5–19. At 300 and 750 mg/kg/day, treatment-related clinical signs of reduced activity, ataxia, and salivation (known hypnotic effect of acetophenone) along with statistically significantly reduced body weight and food consumption were observed. At the same dose levels, a dose-dependent, statistically significantly lower uterus weight and adjusted maternal weights (maternal weight minus gravid uterus weight) were observed. The mean fetus and litter weight among the mid- and high-dose groups were dose-dependently and statistically significantly lower when compared to the controls. Furthermore, skeletal examination showed a moderately, statistically significantly higher incidence of bilateral pelvic girdle caudal shift when compared to concurrent controls for pups in the highest-dose group. This change of position of pelvic girdle relative to the number of pre-pelvic vertebrae was associated with a moderately higher litter incidence of supernumerary bilateral full fourteenth thoracolumbal rib but without achieving statistical significance. Both findings were observed in greater incidences at 750 mg/kg/day when compared to the maximum litter and fetal incidence of historical data. Under the conditions of the study, the NOAEL for maternal and developmental toxicity was considered to be 125 mg/kg/day (ECHA, 2011).

In an OECD 422 combined repeated dose toxicity and reproduction/developmental screening study, groups of 10 Sprague Dawley rats/sex/dose were administered via oral gavage acetophenone at doses of 0, 75, 225, or 750 mg/kg/day daily for a minimum of 14 days before mating, throughout mating and gestation, and up to lactation day 3. In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. There was a significant increase in the number of stillborn offspring among the high-dose group as compared to controls. There was a significant increase in the number of offspring dying, missing and/or cannibalized, along with an increase in the number of litters with total litter loss among the high-dose group during lactation days 1–4. There was a significant decrease in the total number of liveborn pups, viability index, and mean number of live pups per litter on lactation days 1–4. The number of mean live pups per litter was significantly lower on lactation days 1–4, and the live birth index was also reported to be out of the historical control range. Clinical signs among the high-dose group offspring included increased incidences of desquamation, cool to the touch, skin with a shiny appearance, skin appearing tight with restricting movement, and a slightly increased incidence of gasping and pale skin color. There was a significant decrease in the pup weight per litter among the high-dose group on lactation days 1 and 4, and this was reported to be out of the historical control ranges. During the gross pathological examination of the offspring, high-dose group pups were reported with incidences of cleft palate and edema, atelectasis, dermal hypoplasia, scabbing, and desquamation; 22 dead pups were observed with autolysis. The NOAEL for developmental toxicity was considered to be 225 mg/kg/day, based on the effects of treatment on the viability of the offspring, alterations in clinical signs, body weight, and gross pathological alterations among the high-dose group offspring. There were no effects of treatment on the reproductive performance of parental animals up to the highest dose tested. The NOAEL for fertility effects was considered to be 750 mg/kg/day, the highest dose tested (ECHA, 2011).

Therefore, the 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone MOE for the fertility endpoint can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone, 750/0.00017 or 4411765.

The most conservative NOAEL of 125 mg/kg/day from the OECD 414 study was selected for the developmental toxicity endpoint. Therefore, the 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone MOE for the developmental toxicity endpoint can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone, 125/0.00017 or 735294.

In addition, the total systemic exposure to 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone (0.17 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive

toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/19.

10.1.4. Skin sensitization

Based on existing data and the application of DST, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) but positive in the KeratinoSens assay (ECHA, 2018b; 001 key experimental result, 002 key experimental result). In a guinea pig maximization test with the target material, no reactions indicative of skin sensitization were observed (RIFM, 1989). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/17/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone does not present a concern for phototoxicity or photoallergenicity.

Key studies

There are no studies available on 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone in experimental models.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/03/19.

10.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

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

Table 1
Maximum acceptable concentrations for 1-(5,6,7,8-tetrahydro-2-naphthalenyl) ethanone that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	0.0010%
3	Products applied to the face using fingertips	0.41%	1.2×10^{-4}%
4	Fine fragrance products	0.39%	0.0071%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0012%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	3.9×10^{-4}%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	8.6×10^{-4}%
10	Household care products with mostly hand contact	2.7%	0.0012%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.065%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

10.1.6.1. Risk assessment. There are no inhalation data available on 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone. Based on the Creme RIFM Model, the inhalation exposure is 0.0017 mg/day. This exposure is 276.5 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/04/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of

screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone 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) identified 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone as possibly persistent and not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. RIFM, 2018: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guidelines. Biodegradation of 5% and 6% was observed at 1 mg/L and 3 mg/L test concentrations, respectively, after 28 days.

10.2.2.1.2. Ecotoxicity. No data available.

10.2.2.1.3. Other available data. 1-(5,6,7,8-Tetrahydro-2-naphthalenyl)ethanone has been registered for REACH with following additional data available:

A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. Based on initial concentrations, the 48-h EC50 value was reported to be 12 mg/L.

An algae growth inhibition test was conducted according to OECD 201 method under static conditions. The 72-h EC50 and NOEC values based on growth rate were reported to be 5.3 mg/L (95% CI: 5.2–5.4 mg/L) and 0.22 mg/L, respectively (ECHA, 2018b).

10.2.3. Risk assessment refinement

Since 1-(5,6,7,8-Tetrahydro-2-naphthalenyl)ethanone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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 et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.64	3.64
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0088 μg/L. The revised PEC/PNECs for 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 volumes of use.

Literature Search and Risk Assessment Completed On: 03/11/19.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/30/19.

Declaration of competing interest

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	8.80			1000000	0.0088	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111629.

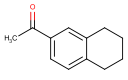
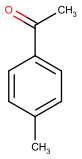
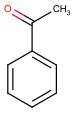
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization 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).

	Target Material	Read-across Material	Read-across Material
Principal Name	1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone	4′-Methylacetophenone	Acetophenone
CAS No.	774-55-0	122-00-9	98-86-2
Structure			
Similarity (Tanimoto Score)		0.52	0.44
Read-across Endpoint		• Genotoxicity	• Reproductive Toxicity • Repeated Dose Toxicity
Molecular Formula	$C_{12}H_{14}O$	$C_9H_{10}O$	C_8H_8O
Molecular Weight	174.24	134.17	120.15
Melting Point (°C, EPI Suite)	58.86	28	20
Boiling Point (°C, EPI Suite)	273.15	226	202
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.519	11.3	5.29E+001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.64	2.10	1.58
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	45.9	1424	6130
J_{max} (μg/cm^2/h, SAM)	16.841	13.981	146.789
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.41E-001	1.10E+000	1.05E+000

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
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	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized		• Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert • Carbamazepine (Hepatotoxicity) Alert • Carbamazepine (Renal Toxicity) Alert • Coumarin (Hepatotoxicity) Alert • Mefenamic Acid (Hepatotoxicity) Alert • Menadione (Hepatotoxicity) Alert • Styrene (Renal Toxicity) Alert • Toluene (Renal toxicity) Alert
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group		• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (moderate reliability)		• Toxicant (low reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone (CAS # 774-55-0). 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, 4′-methylacetophenone (CAS # 122-00-9) and acetophenone (CAS # 98-86-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 4′-Methylacetophenone (CAS # 122-00-9) was used as a read-across analog for the target material 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone (CAS # 774-55-0) for the genotoxicity endpoint.

  - o The target material and the read-across analog are structurally similar and belong to a class of acetophenones.
  - o The target material and the read-across analog share an acetophenone structure.
  - o The key difference between the target material and the read-across analog is that the target material has a tetralin structure (2 fused rings), whereas the read-across analog has a p-methyl substitution. This structural difference is toxicologically insignificant.
  - o 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 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.

- Acetophenone (CAS # 98-86-2) was used as a read-across analog for the target material 1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone (CAS # 774-55-0) for the reproductive toxicity and repeated dose toxicity endpoints.

  - o The target material and the read-across analog are structurally similar and belong to a class of acetophenones.
  - o The target material and the read-across analog share an acetophenone structure.
  - o The key difference between the target material and the read-across analog is that the target material has a tetralin structure (2 fused rings), whereas the read-across analog contains a single aromatic ring. This structural difference is toxicologically insignificant.
  - o 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 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 read-across analog presents several alerts for repeated dose toxicity by the HESS categorization scheme. Those alerts are due to structural similarity between the read-across analog and several toxicants. However, the read-across does not match any active structural fragments reported for these alerts. Therefore, predictions can be ignored.

- o The target material has a toxicant alert for developmental toxicity (CAESAR v2.1.6). The data described in the reproductive toxicity section shows that the MOE is adequate at the current level of use. The predictions are superseded by 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 between 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.

Q1 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? 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 Contains only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms or c) a polyoxyethylene (n>=4) on the aromatic or aliphatic side chain? Yes, Intermediate (Class II)

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