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Short review

RIFM fragrance ingredient safety assessment, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one, CAS Registry Number 74499-60-8

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ABSTRACT

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and the suitable read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7) show that this material is not genotoxic. Data from the suitable read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7) provided a MOE > 100 for the repeat dose and developmental toxicity endpoints. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). Data on the target material showed that this material is below the non-reactive DST for skin sensitization and did not have the potential for phototoxicity or photoallergenicity. The environmental endpoint was completed as described in the RIFM Framework.

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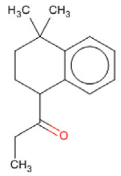
CAS Registry Number: 74499-60-8



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD – Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel[a] concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and the suitable read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7) show that this material is not genotoxic. Data from the suitable read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7) provided a MOE > 100 for the repeat dose and developmental toxicity endpoints. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). Data on the target material showed that this material is below the non-reactive DST for skin sensitization and did not have the potential for phototoxicity or photoallergenicity. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (RIFM, 1981; Api and San, 1999b)
Repeated Dose Toxicity: NOAEL = 1.5 mg/kg/day (Api et al., 2004)
Developmental and Reproductive Toxicity: Developmental NOAEL = 50 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC. (Christian et al., 1999)
Skin Sensitization: Not a sensitization concern. Exposure is below the DST
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (RIFM, 1983a; RIFM, 1983b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 40% (OECD 301D) (RIFM, 1983c)
Bioaccumulation: Screening Level: 266 L/Kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 3.701 (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-Level: PEC/PNEC (North America (Not Reported) and Europe): <1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 3.701 mg/L
RIFM PNEC is: 0.0037 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America (Not Reported) and Europe: Not Applicable; Cleared at the Screening Level

[a] RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

1. Identification

1. **Chemical Name:** 1-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one
2. **CAS Registry Number:** 74499-60-8
3. **Synonyms:** 1-Propanone, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthalenyl)-, 1-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-naphthyl) propan-1-one, Tetrascone
4. **Molecular Formula:** $C_{15}H_{20}O$
5. **Molecular Weight:** 216.24
6. **RIFM Number:** 5987

2. Physical data

1. **Boiling Point:** 302.3 °C [EPI Suite]
2. **Flash Point:** 271.00°FTCC (132.90 °C)*
3. **Log K_{OW}:** 4.18 [EPI Suite]
4. **Melting Point**: 78.1 °C [EPI Suite]
5. **Water Solubility:** 9.721 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00054 mm Hg @ 25 °C [EPI Suite], 0.000285 mm Hg @ 20 °C [EPI Suite 4.0]
8. **UV Spectra:** Not available
9. **Appearance/Organoleptic:** Not Available

* http://www.thegoodscentscompany.com/data/rw1467581.html, retrieved 5/2/14.

3. Exposure

1. **Volume of Use (worldwide band):** <0.1 metric tons per year [IFRA, 2011]
2. **Average Maximum Concentration in Hydroalcoholics:** 0.03% [IFRA, 2008]
3. **97.5th Percentile:** 0.45% [IFRA, 2008]
4. **Dermal Exposure[a]:** 0.0115 mg/kg/day [IFRA, 2008]
5. **Oral Exposure:** Not available
6. **Inhalation Exposures[b]:** 0.00070 mg/kg/day or 0.042 mg/day [IFRA, 2008]
7. **Total Systemic Exposure (Dermal + Inhalation):** (0.0115 mg/kg/day × 40%) + 0.00070 mg/kg/day = 0.0053 mg/kg/day

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

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

4. Derivation of systemic absorption

1. **Dermal:** 40% (predicted)

Using RIFM's *in silico* skin absorption model that was approved by RIFM's Independent Expert Panel (Meeting, Miami, FL, Jan 13–14, 2014) the prediction results are:

	Parent
Name	1-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one
J_{max} (mg/cm^2/h)[a]	2.46
Skin Absorption Class	40%

[a] J_{max} was calculated based on estimated log K_{ow} = 4.11 (Consensus model) and estimated Solubility = 29 mg/L (Consensus model).

2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Dermal (40%) + Inhalation (100%) = (0.0115 mg/kg/day × 40%) + 0.00070 mg/kg/day = 0.0053 mg/kg/day

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[a]	II	I

[a] See Appendix below for explanation.

2. **Analogues Selected:**
   a. **Genotoxicity:** 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7)
   b. **Repeated Dose Toxicity:** 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7)
   c. **Developmental and Reproductive Toxicity:** 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justifications:** See Appendix below

6. Metabolism

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

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

1-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one

is not reported to occur in food by the VCF.*

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

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 05/24/2016.

10. Summary

1. Human Health Endpoint Summaries:

10.1. Genotoxicity

Based on the current existing data and use levels, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one does not present a concern for genetic toxicity.

10.1.1. Risk assessment

The mutagenic potential of 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one was assessed in an Ames study conducted in compliance to GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method (RIFM, 1981). Under the conditions of the study, it was determined to be not mutagenic.

There are no data assessing the clastogenic activity of 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one. Read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7; see Section 5) was assessed for clastogenicity in an in vivo micronucleus assay administered to groups of male and female ICR mice. No significant increase in micronucleated polychromatic erythrocytes was observed in any of the treatment groups (Api and San, 1999b). Under the conditions of the study, the read across material was considered negative and this can be extended to 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one.

Taken together, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl) propan-1-one does not present a concern for genotoxic potential.

Additional References: RIFM, 1993a,b; Mersch-Sundermann et al., 1998a; Steinberg et al., 1999; Kevekordes et al., 1998; Mersch-Sundermann et al., 1998b; RIFM, 1994; RIFM, 1995a; Kevekordes et al., 1997; RIFM, 1997b; Janzowski et al., 2000; Mersch-Sundermann et al., 2001.

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

10.2. Repeated dose toxicity

The margin of exposure for the repeated dose toxicity endpoint is 283.

10.2.1. Risk assessment

There are no repeated dose toxicity data on 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one. Read across material 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS # 21145-77-7; see Section 5) has an OECD 408 dietary 90-day subchronic toxicity study in rats which concluded a NOAEL of 1.5 mg/kg/day, based on altered hematology and green lachrymal glands (Api et al., 2004; data also available in RIFM, 1996a). **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 1.5/0.0053 or 283.**

Additional References: RIFM, 2001; Api and Isola, 2002; Ford, 1998; Guy, 2010; RIFM, 1976a; RIFM, 1976b; RIFM, 1978a; Ford et al., 1999a, 1999b; RIFM, 1996c; Ashcroft and Hotchkiss, 1996; RIFM, 1983a,b,c,d; RIFM, 1995b; RIFM, 1997c; RIFM, 1996b; RIFM, 1997d; RIFM, 1998; Api et al., 2013; RIFM, 2002; Pipino et al., 2004a; Rimkus and Wolf, 1996; Muller et al., 1996a, 1996b; Pipino et al., 2004b; Api and Ford, 1999a; RIFM, 1983a,b,c,d; Steinberg et al., 2001; Gressel et al., 1980a, 1980b; RIFM, 1978b; Eschke et al., 1995; Duedahl-Olesen et al., 2005; Reiner et al., 2007; Hawkins and Ford, 1996; Zehringerand Hermann, 2001; Liebl et al., 2000; RIFM, 1999; Seinen et al., 1999; Schreurs et al., 2001a; RIFM, 1997e; Li et al., 2013; Schreurs et al., 2005; Mori et al., 2007; Schreurs et al., 2004; Bitsch et al., 2002; Schreurs et al., 2002; Schreurs et al., 2001b; Van Meeuwen et al., 2008; Spencer, 2000; Spencer et al., 1980.

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

10.3. Developmental and Reproductive Toxicity

The margin of exposure for the developmental toxicity endpoints is 9434. The exposure is below the TTC for the repeated dose toxicity endpoint.

10.3.1. Risk Assessment

There are no developmental toxicity data on 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one. Read across material 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS # 21145-77-7; see Section 5) has a developmental toxicity study in rats which concluded a NOAEL of 50 mg/kg/day for developmental toxicity, the highest dosage tested (Christian, 1999; data also available in RIFM, 1997a). **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.0053 or 9434.**

There are no reproductive toxicity data on 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one. Read across material 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS # 21145-77-7) has a study conducted to examine the effects of peri- and post-natal development including maternal function in the rat (RIFM, 1996d; data also available in Ford and Bottomley, 1997). There were no effects on the development of the fetus during the peri-natal phase or on post-natal growth, development, and performance in specific behavioral tests and reproductive capacity of the offspring. Exposure of the offspring was limited to possible in utero transfer across the placenta during late pregnancy or via indirect transfer via mother's milk. Treatment of the pregnant rat during the peri- and post-natal period at dosages of AHTN up to 20 mg/kg/day was without adverse toxic effect. The NOAEL based on pregnant and lactating rats and peri- and post-natal development of the offspring, was determined to be 20 mg/kg/day, the highest dosage tested. Additionally, a repeated dose toxicity OECD 408 dietary 90-day subchronic study in rats with AHTN evaluated reproductive organ weights and histopathology and observed no effects on any reproductive parameter up to dosages of 50 mg/kg/day (Api et al., 2004; data also available in RIFM, 1996a). This study concluded a NOAEL of 5 mg/kg/day for maternal toxicity based on maternal weight gain and food intake (Christian et al., 1999). While the data indicate no specific male reproductive concern, there are insufficient data to determine a NOAEL for male reproductive toxicity. However, the total systemic exposure (5.3 μg/kg/day) is below the TTC for 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-

one (9 μg/kg bw/day), when correcting for skin absorption.

Additional References: RIFM, 2001; Api and Isla, 2002; Ford, 1998; Guy, 2010; RIFM, 1976a; RIFM, 1976b; RIFM, 1978a; Ford et al., 1999a, 1999b; RIFM, 1996c; Ashcroft and Hotchkiss, 1996; RIFM, 1983a,b,c,d; RIFM, 1995b; RIFM, 1997c; RIFM, 1996b; RIFM, 1997d; RIFM, 1998; Api et al., 2013; RIFM, 2002; Pipino et al., 2004a; Rimkus and Wolf, 1996; Muller et al., 1996a, 1996b; Pipino et al., 2004b; Api and San, 1999b; RIFM, 1993a,b; Steinberg et al., 2001; Gressel et al., 1980a, 1980b; RIFM, 1978b; Eschke et al., 1995; Duedahl-Olesen et al., 2005; Reiner et al., 2007; Hawkins and Ford, 1996; Zehringer and Herrmann, 2001; Liebl et al., 2000; RIFM, 1999; Seinen et al., 1999; Schreurs et al., 2001a, 2005; RIFM, 1997e; Li et al., 2013; Mori et al., 2007; Schreurs, 2001b, 2002, 2004; Bitsch et al., 2002; Schreurs et al., 2002; Schreurs et al., 2001b; van Meeuwen et al., 2008; Spencer, 2000; Spencer et al., 1980.

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

10.4. Skin sensitization

Based on the application of the DST, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one does not present a concern for skin sensitization.

10.4.1. Risk assessment

Based on the available data and application of the DST, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig test methods, no reactions indicative of sensitization were observed (RIFM, 1980). However, in a human repeated insult patch test an equivocal result was reported (RIFM, 1982a; RIFM, 1982b). The reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST). The current dermal exposure from hydroalcoholic products, 0.009%, is below the DST for non-reactive materials when evaluated in QRA categories 3 and 4 (DST levels of 0.14% and 0.41%, respectively).

Additional References: None.

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

10.5. Phototoxicity/photoallergenicity

Based on the existing data, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one does not present a concern for phototoxicity or photoallergenicity.

10.5.1. Risk assessment

UV spectra are not available for 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one. In guinea pig studies there were no reactions indicative of phototoxic or photoallergenic responses following applications of up to 10% 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one (RIFM, 1983a; RIFM, 1983b). Based on the existing in vivo data, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/21/15.

10.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.6.1. Risk assessment

There are no inhalation data available on 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.45%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.042 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value.

This value is 11.2 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.

Additional References: None.

Literature Search and Risk Assessment Completed on: 5/27/2016.

2. Environmental Endpoint Summary:

10.7. Screening-level assessment

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

10.8. Risk assessment

Based on the current Volume of Use (2011), 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one does not present a risk to the aquatic compartment in the screening level assessment.

10.9. Key studies

10.9.1. Biodegradation

RIFM, 1983a,b,c,d: Biodegradation of 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one was evaluated in a closed bottle test according to the OECD 301D method. 10, 50 and 100 mg/L of the test material were incubated for 28 days. No biodegradation was observed at 10 mg/L, 16% biodegradation was observed at 50 mg/L and 40% at 100 mg/L.

10.9.2. Ecotoxicity

RIFM, 1983a,b,c,d: A 48 h fish (Rainbow trout) acute toxicity test was conducted and a LC100 of 30 mg/L was reported.

10.10. Other available data

1-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one has been pre-registered for REACH with no additional data at this time.

10.11. Risk assessment refinement

Since 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one has passed the screening level, measured data is included for completeness only and was not 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.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	3.701 mg/l			1,000,000	0.0037 μg/l	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.18	4.18
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	Not Reported
Risk Characterization: PEC/PNEC	**<1**	**N/A**

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

The RIFM PNEC is 0.0037 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable. Cleared at the Screening Level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

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

11. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

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

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.07.031.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.07.031.

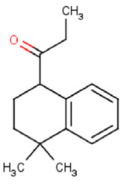
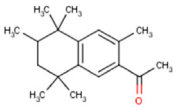
Appendix

Summary:

There are insufficient toxicity data on 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one (RIFM # 5987, CAS # 74499-60-8). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods:

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)

	Target material	Read across material
Principal Name	1-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline
CAS No.	74499-60-8	21145-77-7
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/74499-60-8.html	http://www.thegoodscentscompany.com/opl/21145-77-7.html
Read-across endpoint		• Genotoxicity • Repeated Dose • Devel/Repro
Molecular Formula	C15H20O	C18H26O
Molecular Weight	216.33	258.41
Melting Point (°C, EPISUITE)	78.10	106.87
Boiling Point (°C, EPISUITE)	302.30	331.88
Vapor Pressure(Pa @ 25°C, EPISUITE)	0.07199	0.0252
Log Kow (KOWWIN v1.68 in EPISUITE)	4.18	6.35
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	9.721	0.2879
J_{max} (mg/cm^2/h, SAM)	2.460432219	0.225628245
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	0.813234	4.280981
Similarity (Tanimoto score)[a]		61%
Genotoxicity		
DNA binding (OASIS v1.1)	•No alert found	•No alert found
DNA binding (OECD)	• Michael addition • Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals • Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	•No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	•No alert found	•No alert found
DNA alerts for Ames, MN, CA (OASIS v1.1)	•No alert found	•No alert found
In vitro mutagenicity (Ames test) alerts (ISS)	•No alert found	•No alert found
In vivo mutagenicity (Micronucleus) alerts (ISS)	•No alert found	•No alert found
Oncologic classification (OECD)	•Not classified	•Not classified
Repeated Dose Toxicity		
Repeated dose (HESS)	Not categorized	Not categorized
Developmental and Reproductive Toxicity		
ER binding (OECD)	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (good reliability)	Toxicant (good reliability)
Metabolism		
Rat liver S9 metabolism simulator (OECD)	See Supplemental Data 1	See Supplemental Data 2

[a] Values calculated using JChem with FCFP4 1024 bits fingerprint. J. Chem. Inf. Model. 2010, 50: 742 (Rogers and Hahn, 2010).

- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale:

- 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (analog) was used as a read-across for 1-(1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthyl) propan-1-one (target) based on:
  - o The target and analog belong to the generic class of aromatic ketones.
  - o They have the same core structure of tetralin.
  - o The key difference is in the position of the ketone group. The target has an ethyl ketone group attached to the hydrogenated ring, while the analog has a methyl ketone group attached to the benzene ring. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - o The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of Cramer class:

Due to potential discrepancies with the current *in silico* tools

(Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1976).

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,divalent S? **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene? **No**
Q17. Readily hydrolysed 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 those listed below? **Yes** Class Intermediate (Class II)

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