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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline, CAS Registry Number 21145-77-7

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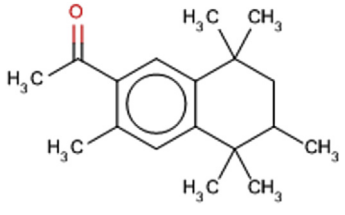

Additional CAS Numbers*:
1506-02-1 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (Fixolid)
*This material in included in this assessment because they are a mixture of isomers.

(*continued on next page*)

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(*continued*)

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

Summary: The use of this material under current conditions is supported by 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 show that this material is not genotoxic, it does not have skin sensitization potential, and provided a MOE >100 for the repeated 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). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra and data on the target material. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 1993a; Api et al., 1996; Api and San, 1999)
Repeated Dose Toxicity: NOAEL = 1.5 mg/kg/day (Api et al., 2004)
Developmental and Reproductive Toxicity: Developmental toxicity NOAEL = 50 mg/kg/day. No reproductive toxicity data available. Exposure is below TTC. (Christian et al., 1999)
Skin Sensitization: Not a sensitization concern. (RIFM, 1998)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB; RIFM, 1987a; RIFM, 1987b; RIFM, 1989a; RIFM, 1983a; RIFM, 1997b; RIFM, 1997c)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: Multiple biotransformation studies; Inherently biodegradable (EU RAR, 2008)
Bioaccumulation: Critical Measured Value: BCF: 597 (OECD 305E) (RIFM, 1996c)
Ecotoxicity: Critical Ecotoxicity Endpoint: 6 days *Acartia tonsa* EC10: 0.028 mg/l (EU RAR, 2008)
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: 6 days *Acartia tonsa* EC10: 0.028 mg/l (EU RAR, 2008)
RIFM PNEC is: 2.8 μg/l
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe <1

1. Identification

Chemical Name: 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	**Chemical Name:** 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (Fixolid)
CAS Registry Number: 21145-77-7	**CAS Registry Number:** 1506-02-1
Synonyms: 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline; 7-Acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene; AHTN; Fixolide; 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (Tonalid); Tetralide; Tonalid; 7-Aceto-1,1,3,4,4,6-hexamethyltetralin; 7-Aceto-1,2,3,4-tetrahydro-1,1,3,4,4,6-hexamethylnaphthalene; Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)-; Tentarome; 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (Fixolid); 2′-Acetonaphthone, 5′,6′,7′,8′-tetrahydro-3′,5′,5′,6′,8′,8'-hexamethyl; 6-Acetyl-1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydronaphthalene; AHMT; Ganolid; Acetyl hexamethyl tetralin; 7-Acetyl-1,1,3,4,4,6-hexamethyltetrahydronaphthalene; 7-ｱｾﾁﾙ-1, 1, 3, 4, 4, 6-ﾍｷｻﾒﾁﾙﾃﾄﾗﾋﾄﾞﾛﾅﾌﾀﾚﾝ(第一品名と同じ); 1-(3,5,5,6,8,8-Hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone	**Synonyms:** 7-Aceto-1,1,3,4,4,6-hexamethyltetralin; 7-Aceto-1,2,3,4-tetrahydro-1,1,3,4,4,6-hexamethylnaphthalene; Acetyl hexamethyl tetralin; Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)-; 1-(3,5,5,6,8,8-Hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone; Tentarome; 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (Fixolid); 7-ｱｾﾁﾙ-1, 1, 3, 4, 4, 6-ﾍｷｻﾒﾁﾙﾃﾄﾗﾋﾄﾞﾛﾅﾌﾀﾚﾝ
Molecular Formula: $C_{18}H_{26}O$	**Molecular Formula:** $C_{18}H_{26}O$
Molecular Weight: 258.41	**Molecular Weight:** 258.05
RIFM Number: 611	**RIFM Number:** N/A

2. Physical data*

1. **Boiling Point:** 331.88 °C [EPI Suite]
2. **Flash Point:** >100 °C [GHS, 2011], >200 °F; CC [FMA database]
3. **Log K_{OW}:** Log Pow = 5.7 [RIFM, 1993c], 6.35 [EPI Suite]
4. **Melting Point**: 55~C [RIFM, 1993b], 55.7~C [RIFM, 1993c], 55.2~C [RIFM, 1989b], about 50~C [RIFM, 1991], 52 °C [FMA database], 106.87 °C [EPI Suite]
5. **Water Solubility:** 0.2879 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000977 mmHg @ 20 °C [EPI Suite 4.0], 0.000189 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless or white crystalline mass or fused opaque mass with a sweet woody-musky odor of considerable tenacity (Arctander, 1969).

*All physical data are identical for both materials covered in this document.

3. Exposure***

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 1.0% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0017 mg/kg/day or 0.12 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0027 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015).

**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., 2015).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics, inhalation exposure and total exposure.

4. Derivation of systemic absorption

1. Dermal: 4.1%

RIFM, 2001 **(data also available in** Api and Isola, 2002): *In vitro* human skin permeation rate and distribution of a radiolabelled polycyclic musk, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS # 21145-77-7; see Section 5), following application under non-occlusive conditions was determined. The studies followed the European Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) guidelines and used human cosmetic reduction skin from surgery. Screening studies were conducted to identify the most appropriate receptor fluid, which for these studies was 6% of the surfactant VolpoN2O in physiologically balanced saline. The skin samples were heat separated and the epidermal membranes comprising both the stratum corneum and the epidermis were used. Because the system was static, the dermis was stripped away. The integrity of the membranes was determined prior to dosing using tritiated water. A 1% solution of radiolabelled ($^{(14)}$C-AHTN) test material in ethanol was applied to the membrane (20 μL/cm^2). After 24 h, radiolabel in aliqouts of the receptor fluid were determined by scintillation counting the results of which were used to calculate the % of applied material that was absorbed. Mass balance was determined and included test material collected from the surface wipes, 10 skin strippings, remaining epidermis, receptor phase, donor chamber, and filter paper supports. After 24 h, 0.38% of the applied AHTN dose permeated the epidermal membranes into the receptor phase. The total absorbed dose for AHTN, determined by adding the amounts of test material in the remaining epidermis, the receptor phase and the filter paper was 4.1% of the applied dose. The evaporative loss was 2.9%. Overall recovery of applied AHTN was high at 92.5% or 95.4% when loss due to evaporation is included. The results show that the percutaneous absorption was 4.1% for AHTN.

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(OECD, 2013)
II*	II	I

*See Appendix below for explanation.

2. Analogues Selected:
a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Developmental and Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

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)

6-Acetyl-1,1,2,4,4,7-hexamethyltetraline and 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (Fixolid) are 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

Dossiers for both materials available.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline does not present a concern for genetic toxicity.

10.1.2. Risk assessment

The mutagenic potential of 6-acetyl-1,1,2,4,4,7-hexamethyltetraline 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. *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, TA100, TA102 and *Escherichia coli* strain WP2uvrA were treated with 6-acetyl-1,1,2,4,4,7-hexamethyltetraline in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of a liver microsome activation system. No increase in the number of revertant colonies was observed in any of strains at the concentrations tested (RIFM, 1993a). Under the conditions of the study, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline was not considered mutagenic in the Ames test.

The clastogenic activity of 6-acetyl-1,1,2,4,4,7-hexamethyltetraline was assessed using several methods. In an *in vitro* sister chromatid exchange test using human peripheral blood lymphocytes, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline did not induce chromosome damage up to lethal concentrations (25–40 μg/ml) and was not considered clastogenic (Steinberg et al., 1999). These results were confirmed in an *in vitro* MNT assay testing concentrations of 6-acetyl-1,1,2,4,4,7-hexamethyltetraline up to 194 μM (Kevekordes et al., 1997). 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline in acetone did not induce chromosomal aberrations in an *in vitro* chromosome aberration assay using Chinese hamster ovary cells at concentrations of 0.008, 0.023, 0.078, 0.234, 0.78, 2.34, 7.8, 23.4, and 78 μg/mL (Api et al., 1996). Additionally, in an *in vivo* micronucleus assay, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline was administered to groups of male and female ICR mice at doses 400, 800 and 1600 mg/kg boy weight in corn oil via intraperitoneal injection. Bone marrow was collected at 24, 48 and 78 h after dose administration and slides were prepared. No significant increase in micronucleated polychromatic erythrocytes was observed in any of the treatment groups (Api and San, 1999). Under the conditions of the study, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline was considered negative in the *in vivo* micronucleus test.

Based on the available data, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline does not present a concern for genotoxic potential.

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

Literature Search and Risk Assessment Completed on: 02/01/2016.

10.1.3. Repeated dose toxicity

The margin of exposure for 6-acetyl-1,1,2,4,4,7-hexamethyltetraline is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are sufficient repeated dose toxicity data on 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS # 21145-77-7). An OECD 408 dietary 90-day subchronic toxicity study was conducted in rats. AHTN was added to the diet of rats at levels calculated to result in mean daily doses of 1.5, 5, 15 or 50 mg AHTN/kg body weight/day. On completion of the treatment period, 3 males and 3 females from each of the high dose groups and controls were maintained for a treatment-free period of 4 weeks. The NOAEL was concluded to be 1.5 mg/kg/day, based on altered hematology and the presence of green lachrymal glands at higher tested doses (Api et al., 2004). The results obtained from a percutaneous skin absorption of AHTN under non-occluded conditions show that the percutaneous absorption was 4.1% for AHTN (RIFM, 2001; see section 4). **Therefore, the AHTN MOE is equal to the AHTN NOAEL in mg/kg/day divided by the total systemic exposure of AHTN, 1.5/0.0027 or 556.**

In addition, the total systemic exposure for 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (2.7 μg/kg bw/day) is below the TTC (9 μg/

kg bw/day) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/11/2016.

10.1.5. Developmental and Reproductive Toxicity

The margin of exposure for 6-acetyl-1,1,2,4,4,7-hexamethyltetraline is adequate for the developmental toxicity endpoint at the current level of use. There are insufficient reproductive data on 6-acetyl-1,1,2,4,4,7-hexamethyltetraline or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.6. Risk assessment

There are sufficient developmental toxicity data on 6-acetyl-1,1,2,4,4,7-hexamethyltetraline. The test material 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS # 21145-77-7) has a developmental toxicity study in rats which concluded a NOAEL of 50 mg/kg/day for developmental toxicity, the highest dosage tested (Christian et al., 1999). The results obtained from a percutaneous skin absorption of AHTN under non-occluded conditions show that the percutaneous absorption was 4.1% for AHTN (RIFM, 2001; see section 4). **Therefore, the AHTN MOE for developmental toxicity is equal to the AHTN NOAEL in mg/kg/day divided by the total systemic exposure for AHTN, 50/0.0027 or 18519.**

In addition, the total systemic exposure for 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (2.7 μg/kg bw/day) is below the TTC (9 μg/kg bw/day) at the current level of use.

There are no reproductive toxicity data on 6-acetyl-1,1,2,4,4,7-hexamethyltetraline. The test 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). There were no effects on the development of the pup during the peri-natal phase or on post-natal growth, 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 the 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 for the 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, the OECD 408 dietary 90-day subchronic toxicity study in rats with AHTN, in addition to the repeated dose toxicity endpoint, also evaluated reproductive organ weights and histopathology. There were no effects observed on any reproductive parameter up to dosages of 50 mg/kg/day (Api et al., 2004). The developmental toxicity study on AHTN 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 on AHTN to determine a NOAEL for male reproductive toxicity. There are no male reproductive data on any other read across material. The results obtained from a percutaneous skin absorption of AHTN under non-occluded conditions show that the percutaneous absorption was 4.1% for AHTN (RIFM, 2001; see section 4). The total systemic exposure for 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (2.7 μg/kg bw/day) is below the TTC (9 μg/kg bw/day) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/11/2016.

10.1.7. Skin sensitization

Based on the existing data, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available animal and human data, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline does not present a concern for skin sensitization. The chemical structures of 6-acetyl-1,1,2,4,4,7-hexamethyltetraline indicate that it would not be expected to be reactive to skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD Toolbox v3.3). In guinea pig sensitization methods, both positive and negative results have been observed (RIFM, 1978d; RIFM, 1978c; Klecak, 1985). However, a human maximization study showed no sensitization reactions at 1380 μg/cm^2 (RIFM, 1975). Moreover, in a confirmatory human repeated insult patch test (HRIPT) conducted according to (Politano and Api, 2008) with 11811 μg/cm^2 6-acetyl-1,1,2,4,4,7-hexamethyltetraline in 3:1 ethanol:diethylphthalate on 111 human volunteers, no reactions indicative of sensitization have been observed in any of the subjects tested (RIFM, 1998). Based on the weight of evidence from structural analysis, animal and human data, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline does not present a concern for skin sensitization.

Additional References: RIFM, 1964.

Literature Search and Risk Assessment Completed on: 08/31/2015.

10.1.9. Phototoxicity/photoallergenicity

Based on human study data, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN) would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

UV/Vis absorption spectra (OECD 101) were obtained on market-quality AHTN in 2016. The spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern (1000 L · mol-1 · cm-1) for phototoxicity and photoallergenicity (Henry et al., 2009). An *in vitro* 3T3 Neutral Red Uptake phototoxicity assay was conducted and AHTN was not considered phototoxic or cytotoxic based both on photo-irritancy factor (PIF) and mean photo-effect (MEP) (RIFM, 2002). Historically, numerous *in vivo* and human phototoxicity and photoallergenicity studies have been conducted to evaluate the potential for AHTN to induce reactions. Phototoxicity was observed in guinea pigs and rabbits (RIFM, 1985a; RIFM, 1985b; Ogoshi et al., 1980; Ohkoshi et al., 1981; Guillot et al., 1985; RIFM, 1978b; RIFM, 1982; RIFM, 1983b), but not in hairless mice (RIFM, 1978a). In separate studies, a 10% solution of AHTN did not produce phototoxic effects in humans (RIFM, 1987b; RIFM, 1987a; RIFM, 1987c; RIFM, 1983a,b). Guinea pigs showed well-defined positive results in several photoallergenicity tests (RIFM, 1994a; RIFM, 1984a; RIFM, 1984b; RIFM, 1990) but results were negative in one test at 2% in ethanol (RIFM, 1985c; RIFM, 1985d). It has been demonstrated that the response in guinea pigs was due to photodegradation to a cyclic peroxide and to a keto-aldehyde, both of which were contact sensitizers in their own right (RIFM, 1985e; RIFM, 1984c). Humans were not considered to show evidence of photoallergenicity when tested with a 5% solution of AHTN in ethanol, or a 10% solution of AHTN in acetone/

ethanol (RIFM, 1989a). However, when photodegradation products were artificially produced *in vitro* by irradiating a 3% solution of AHTN with 10 J of UVA, the resulting solution of photodegradation products was shown to be a contact sensitizer to humans (RIFM, 1984d). Thus, while humans can be sensitized by photodegradation products of AHTN, there were not sufficient degradation products formed on irradiated human skin for a reaction and AHTN was not considered a photoallergen in humans under these standard test conditions. Due to the presence of some equivocal reactions in a few of the human subjects another photoallergy study was conducted and it confirmed these conclusions (RIFM, 1997b; RIFM, 1997c). Under the conditions used, AHTN showed neither allergenic nor photoallergenic potential. Neither challenge with a 10% solution of AHTN in ethanol and diethyl phthalate, nor challenge with any of the three photo-preparations (4001, 4002, photo AHTN-3%) resulted in any observations of skin contact sensitization reactions in humans. It was concluded that under conditions of this study, the ultraviolet irradiation of AHTN-10% on human skin did not result in any potentially allergenic photoproducts as observable by human skin contact sensitization. Based on the human studies, AHTN does not present a concern for phototoxicity or photoallergenicity.

Additional References: RIFM, 1984a,b,c,d; RIFM, 1996e; RIFM, 1980.

Literature Search and Risk Assessment Completed on: 08/30/2016.

10.1.11. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There is limited inhalation data available on 6-acetyl-1,1,2,4,4,7-hexamethyltetraline. Based on the Creme RIFM model, the inhalation exposure is 0.12 mg/day. This exposure is 3.9 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: RIFM, 1997e; Gilbert and Kemp, 1996; Peck and Hornbuckle, 2004.

Literature Search and Risk Assessment Completed on: 6/17/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN) has been identified as a high priority material by the fragrance industry and regulatory authorities for many years. As such, it has an extensive database of information available, including monitoring data, regarding its environmental safety. A brief summary of the information is provided below. For more details, the European Union Risk assessment Report (EU RAR) is available for download.

http://www.echa.europa.eu/documents/10162/6434698/orats_final_rar_1–5_6_7_8-tetrahydro-3_5_5_6_8_en.pdf.

10.2.2. Risk assessment

Based on current the Volume of Use (2011), 6-acetyl-1,1,2,4,4,7-hexamethyltetraline does not presents a risk to the aquatic compartment in the screening level assessment.

10.3. Key studies

10.3.1. Biodegradation

While AHTN does not pass standard ready biodegradation studies (e.g. OECD Test Guidelines 301) there are several studies that demonstrate rapid transformation in wastewater treatment to a more polar metabolite (i.e less toxic than the parent molecule and less likely to bioaccumulate). In batch experiments with activated sludge spiked with radio-labelled AHTN, the half-life of the parent compound was less than 1 day and within 20 days AHTN was largely transformed to its metabolite. In the river water die-away test, the overall half-life was around 9 days and the biological degradation after 28 days was 42%. For the environmental risk assessment, AHTN may be considered as inherently biodegradable, "not fulfilling criteria" (EU RAR).

Monitoring data from several years show decreasing trend of concentrations in sludge, water, suspended matter, biota and sediment and provide hence additional evidence on that AHTN degrades in aquatic environment.

10.3.2. Ecotoxicity

From the EU RAR, the following summary table is provided:

Test Organisms	Test	Results (mg/l)	Reference
Pseudokirchneriella subcapitata	72 h Static	NOEC(biomass) = 0.204 mg/l	RIFM, 1997d
Daphnia magna	21 day semi-static	NOEC (reproduction) = 0.196 mg/l	RIFM, 1996a
Bluegill sunfish	21 day flow-through	NOEC (growth) = 0.089 mg/l	RIFM, 1996b
Fathead minnow	36d Flow-through	NOEC (development) = 0.035 mg/l	RIFM, 1997a
Brachydanio rerio	34d Intermittent flow-through	NOEC (growth) = 0.035 mg/l	RIFM, 1999
Acartia tonsa	6d static	EC10 (development) = 0.028 mg/l	Bjornestad, 2007

Bioaccumulation:

(**RIFM, 1996c**; **EU RAR)**: The bioconcentration of AHTN was evaluated in bluegill sunfish according to the OECD 305E method under flow-through conditions. The elimination period was 28 days, and the concentration of AHTN in the fish reached plateau levels after 3–7 days of exposure. Based on concentrations of parent material, the BCF for the whole fish was 597.

10.3.3. Other available data

6-Acetyl-1,1,2,4,4,7-hexamethyltetraline has been registered under REACH. See also RAR.

10.3.4. Risk assessment refinement

The calculated PNEC for both Europe (RAR) and North America (RIFM Framework, Salvito et al., 2002) is 2.8 μg/l using an Assessment Factor of 10.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.7	5.7
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1 (Based on RAR)**	**<1**

Based on available data, the RQ for this material is <1. Additional assessment is necessary.

The RIFM PNEC is 2.8 μg/L. The revised PEC/PNECs for EU (RAR) and NA are <1 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: 9/28/15.

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.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.019.

Appendix

Explanation of Cramer Class:

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