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Short review

RIFM fragrance ingredient safety assessment, 5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane, CAS Registry Number 68140-48-7

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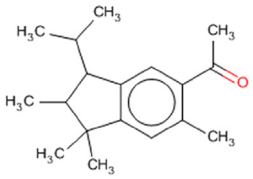


Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data 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 on the target material and suitable read across analog 5-acetyl-1,1,2,3,3,6-hexamethylindan show that this material is not genotoxic. Data on the target material show that this material does not have skin sensitization potential. 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 repeated dose and developmental toxicity endpoints were completed using 6-acetyl-1,1,2,4,4,7-hexamethyltetraline as a suitable read across analog, which provided a MOE >100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra along with data on the target material. The environmental endpoint was completed as described in the RIFM Framework along with data on the suitable read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2007a; RIFM, 1998c)
Repeated Dose Toxicity: NOAEL = 1 mg/kg/day (RIFM, 1978a)
Developmental and Reproductive Toxicity: Developmental toxicity NOAEL = 50 mg/kg/day. No data available for reproductive toxicity. Exposure is below the TTC. (Christian et al., 1999)
Skin Sensitization: Not sensitizing. (RIFM, 1979a; RIFM, 1978d; RIFM, 1980a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB; RIFM, 1980b; RIFM, 1980c;

(*continued on next page*)

(*continued*)

RIFM, 1987a; RIFM, 1987b; RIFM, 1987c)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: −0.8% OECD 302A (RIFM, 1994)
Bioaccumulation: Critical Ecotoxicity Endpoint: BCF: 597 (OECD 305E) Read across to 6-acetyl-1,1,2,4,4,7-hexamethyltetraline CAS# 21145-77-7 (RIFM, 1996c)
Ecotoxicity: Critical Ecotoxicity Endpoint: 6 days *Acartia tonsa* EC10: 0.028 mg/L; Read across to 6-acetyl-1,1,2,4,4,7-hexamethyltetraline CAS# 21145-77-7 (EU RAR, 2006)
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; Read across to 6-acetyl-1,1,2,4,4,7-hexamethyltetraline CAS# 21145-77-7 (EU RAR, 2006)
RIFM PNEC is: 2.8 μg/L
•**Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe <1

1. Identification

1. **Chemical Name:** 5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane
2. **CAS Registry Number:** 68140-48-7
3. **Synonyms:** 5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane; 5-Acetyl-1,1,2,6-tetramethyl-3-isopropylindane; AITI; ATII; 1-(2,3-Dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1H-inden-5-yl)ethan-1-one; Ethanone, 1-[2,3-dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1H-inden-5-yl]-; Traseolide; 1-(3-Isopropyl-1,1,2,6-tetramethyl-2,3-dihydro-1H-inden-5-yl) ethanone
4. **Molecular Formula:** $C_{18}H_{26}O$
5. **Molecular Weight:** 258.41
6. **RIFM Number:** 1042

2. Physical data

1. **Boiling Point:** 329.77 °C [EPI Suite]
2. **Flash Point:** > 133C [RIFM database], >133 °C [GHS]
3. **Log K_{OW}:** 6.31 [EPI Suite]
4. **Melting Point**: 103.17 °C [EPI Suite]
5. **Water Solubility:** 0.0869 mg/L [EPI Suite]
6. **Specific Gravity:** 0.97390 to 0.98400 @ 25.00 °C*
7. **Vapor Pressure:** 0.0000344 mmHg @ 20 °C [EPI Suite 4.0], 6.83e−005 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:** A clear, colorless to yellowish viscous liquid with a medium dry, sweet, amber, musk, herbal, creamy odor while at 10% or less in dipropylene glycol.*

* http://www.thegoodscentscompany.com/data/rw1023772.html#toorgano, retrieved 5/28/2015.

3. Exposure

1. Volume of Use (worldwide band): 10−100 metric tons per year (IFRA , 2011)
2. 95th Percentile Concentration in Hydroalcoholics: 1.01% (RIFM, 2014)
3. Inhalation Exposure*: 0.0011 mg/kg/day or 0.078 mg/day (RIFM, 2014)
4. Total Systemic Exposure**: 0.0016 mg/kg/day (RIFM, 2014)

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

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

4. Derivation of systemic absorption

1. **Dermal:** Assumed 4.06%

RIFM, 2001; **(data also available in** RIFM, 2002a**):** *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 V), 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 Volpo N2O in physiologically balanced saline. The skin samples were heat separated and the epidermal membranes comprising both the stratum corneum and the epidermis were used. Due to the static nature of the system, 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) test material in ethanol was applied to the membrane (20 μL/cm^2). After 24 h, the amount of radiolabel present in the receptor fluid was determined by scintillation counting and expressed as % of applied radiolabel. 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 4.06% 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 of show that the percutaneous absorption was 4.06% 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
II*	II	I

*See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** 5-Acetyl-1,1,2,3,3,6-hexamethylindan (CAS# 15323-35-0)
   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:** 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS# 21145-77-7)
3. Read-across Justification: 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)

5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane 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 01/27/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *E. coli* strain WP2uvrA were treated with 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains with any dose of the test material (RIFM, 2007a). Under the conditions of the study, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane was not considered mutagenic in bacteria.

There are no studies assessing the clastogenic activity of 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane. The clastogenicity of read across material, 5-acetyl-1,1,2,3,3,6-hexamethylindan (CAS# 15323-35-0; see Section V) was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung cells were exposed to 5-acetyl-1,1,2,3,3,6-hexamethylindan in DMSO at concentrations ranging from 10 to 100μg/ml in the presence and absence of S9 mix. In the presence of S9 mix, a statistically significant increase in the number of cells with chromosome aberrations was observed at the concentration of 33 μg/ml at the 3 h treatment time in the first experiment and at concentrations of 18 and 33 μg/mL without S9 metabolic activation. Since the types of aberrations observed were mainly breaks and gaps, the increase was not dose-related; the second experiment did not confirm this result and the number of cells with chromosome aberrations were still within the historical control data range; the authors concluded that this increase was not considered biologically relevant. Under the conditions of the study, the test material is not clastogenic (RIFM, 1998c). 5-Acetyl-1,1,2,3,3,6-hexamethylindan was not considered clastogenic in the *in vitro* chromosome aberration test and this can be applied to 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane.

Based on the available data, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane does not present a concern for genotoxic potential.

Additional References: RIFM, 1978b; Kevekordes et al., 1997; Kevekordes et al., 1998; Mersch-Sundermann et al., 1998a, 2001a; Mersch- Sundermann et al., 1998b; RIFM, 1998c; Mersch-Sundermann et al., 1998c, 2001b; Literature Search and Risk Assessment Completed on: 06/14/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane. A 14-week dermal toxicity study was conducted with the test material, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane, which was applied topically to a group of 15 female albino rats/dose/group at dose levels of 0, 1, 10 or 100 mg/kg/day. An additional group of 5 female animals were maintained treatment free for a period of 6 weeks from the control and high dose treatment groups. Following 8 days of treatment, the dose was reduced from 100 mg/kg/day to 10 mg/kg/day since there were incidences of severe erythema accompanied by inflammation. The NOEL was determined to be 1 mg/kg/day based on incidences of inflammation of treated skin, decreased body weight and food intake, alterations in hematology, urinalysis and clinical chemistry parameters. Alteration in

histopathological evaluation of the liver related to test material administration was reported only in the high dose animals; these hepatic alterations were not reported among the recovery group animals (RIFM, 1978a). Due to the lack of toxicity data on the males treated with 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane, a NOAEL cannot be determined. Read across material, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS# 21145-77-7; see section V) 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 (RIFM, 2004). The results obtained from a percutaneous skin absorption of AHTN under non-occluded conditions show that the percutaneous absorption was 4.06% for AHTN (RIFM, 2001; see section IV). The most conservative NOAEL of 1 mg/kg/day for 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane was selected for the repeated dose toxicity studies. **Therefore, the 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane MOE for the repeated dose toxicity endpoint can be calculated by dividing the 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane NOAEL in mg/kg/day by the total systemic exposure to 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane, 1/0.0016 or 625.**

In addition, the total systemic exposure to 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane (1.6 μg/kg/day) is below the TTC (9 μg/kg bw/day) at the current level of use for the repeated dose toxicity endpoint.

Additional References: Ford, 1998; Guy, 2010; RIFM, 1976a; RIFM, 1976b; RIFM, 1978e; Ford et al., 1999a, 1999b; RIFM, 1996f; Ashcroft and Hotchkiss, 1996; RIFM, 1983; RIFM, 1995; RIFM, 1997a; RIFM, 1996e; RIFM, 1997c; RIFM, 1998b; Api et al., 2013; RIFM, 2002b; Pipino et al., 2004a; Rimkus and Wolf, 1996; Muller et al., 1996a, 1996b; Pipino et al., 2004b; RIFM, 1999a; RIFM, 1993a; Steinberg et al., 2001; Gressel et al., 1980a, 1980b; RIFM, 1978a; 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, 1999c; Seinen et al., 1999; Schreurs et al., 2001a, 2005; RIFM, 1997d; Li et al., 2013; Mori et al., 2007; Schreurs et al., 2001b, 2002, 2004; Bitsch et al., 2002; Schreurs et al., 2002; Schreurs et al., 2001b; van Meeuwen et al., 2008; Christian et al., 1999; (data also available in RIFM, 1997e; and in the OECD SIDS, accessed on 2/11/2016).

Literature Search and Risk Assessment Completed on: 02/16/2016.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.4. Risk assessment

There are insufficient developmental toxicity data on 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane traline. Read across material, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS# 21145-77-7; see section V) 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 4.06% for AHTN (RIFM, 2001; see section IV). Therefore, the 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane MOE for the developmental toxicity endpoint can be calculated by dividing the AHTN NOAEL in mg/kg/day by the total systemic exposure to 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane, 50/0.0016 or 31250.

In addition, the total systemic exposure to 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane (1.6 μg/kg/day) is below the TTC (9 μg/kg bw/day) at the current level of use for the developmental toxicity endpoint.

There are no reproductive data on 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane. A study was conducted on test material, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN; CAS# 21145-77-7; see section V) to examine the effects of peri- and post-natal development including maternal function in rats (RIFM, 1996d). There were no effects on the development of the pup during the peri-natal phase or on post-natal growth, development, 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 did not result in an 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 (RIFM, 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 4.06% for AHTN (RIFM, 2001; see section IV). The total systemic exposure to 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane (1.6 μg/kg/day) is below the TTC (9 μg/kg bw/day) at the current level of use for the reproductive toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/16/2016.

10.1.5. Skin sensitization

Based on the existing data, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane does not present a concern for skin sensitization.

10.1.5.1. Risk assessment. The chemical structure of 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane indicates 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, no reaction indicative of sensitization was observed (RIFM, 1979a; RIFM, 1978d; RIFM, 1977). Moreover, a human maximization study showed no sensitization reactions at 3450 μg/cm^2 (RIFM, 1980a). Based on the weight of evidence from structural analysis, animal and human data, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane does not present a concern for skin sensitization.

10.2. Additional references

None.

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

10.2.1. Phototoxicity/photoallergenicity

	Phototoxicity	Photoallergenicity
Step 1: UV Benchmark (1000 L mol^{-1} … cm^{-1})	Below	
Step 2: Study data	Sufficient	Sufficient
Step 3: Exposure Benchmark		
Step 4: Read Across		
Step 5: Generate Data		

Based on the available UV/Vis spectra along with existing human data, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane would not be expected to present a concern for phototoxicity or photoallergenicity.

10.2.1.1. Risk assessment. UV/Vis absorption spectra were obtained on market-quality 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane in 2014. The spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L … mol-1 … cm-1 (Henry et al., 2009). Numerous in vivo phototoxicity tests and one photoallergenicity test were conducted with 1%–10% 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane in rabbits and guinea pigs. In most of the studies, slight skin reactions were observed even in non-irradiated controls topically treated with >1% 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane. However, the reactions following topical application of >1% 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane were always more severe at the irradiated test sites, and tend to be concentration dependent (Ogoshi et al., 1980; Ohkoshi et al., 1981; RIFM, 1978c; RIFM, 1980d; RIFM, 1979b; RIFM, 1980e; RIFM, 1985; RIFM, 1986; RIFM, 1980f). In human volunteers, topical application of up to 100% 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane did not result in skin reaction indicative of either phototoxicity or photoallergenicity (RIFM, 1980b; RIFM, 1980c; RIFM, 1987a; RIFM, 1987b; RIFM, 1987c). Based on the lack of significant absorbance in the critical range and human study data, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane does not present a concern for phototoxicity or photoallergenicity under the current levels of use.

10.2.1.2. UV spectra analysis. UV/Vis absorption spectra (OECD test guideline 101) for 5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L … mol-1 … cm-1, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/21/2016.

10.2.2. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.2.2.1. Risk assessment. There is limited inhalation data available on 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane. Based on the Creme RIFM model, the inhalation exposure is 0.078 mg/day. This exposure is 6.0 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.

Additional References: Peck and Hornbuckle, 2004.

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

10.3. Environmental endpoint summary

10.3.1. Screening-level assessment

A screening level risk assessment of 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane 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, 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane was identified as a fragrance material with the 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 did not identify 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane as either being possibly persistent nor bioaccumulative 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 I.

10.3.2. Risk assessment

Based on the current Volume of Use (2011), 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane presents a risk to the aquatic compartment in the screening level assessment.

10.3.2.1. Biodegradation. RIFM, 1994: The inherent biodegradability of the test material was determined in a sealed vessel CO2 production test using an acclimatized inoculum from a modified semi-continuous activated sludge test (SCAS) according to the OECD 302A. 10.6 mg/L of 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane was incubated with filtered activated sludge on a rotary shaker for 28 days. The rate of degradation after 28 days was −0.8%.

RIFM, 1993b: A study was conducted to determine the inherent biodegradability of the test material using a modified sealed vessel test following the OECD 301B method. 10 mg/L of 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane was incubated with filtered activated sludge on a rotary shaker for 56 days. Degradation rate after 28 days was −1.4%.

RIFM, 1996g: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed

vessel test following the OECD 301B method. 10 mg/L of 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane was incubated with filtered activated sludge on a rotary shaker for 28 days. The rate of degradation after 28 days was −6.6%.

10.3.2.2. Ecotoxicity. No data available.

10.3.2.3. Other available data.
5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane has been pre-registered for REACH with no additional data at this time.

Read across material, 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN) has been registered under REACH and 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

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

Test Organisms	Test	Results	Reference
Pseudokirchneriella subcapitata	72 h Static	NOEC (biomass) = 0.204 mg/L	(RIFM, 1998a)
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, 1997b)
Brachydanio rerio	34d Intermittent flow-through	NOEC (growth) = 0.035 mg/L	(RIFM, 1999b)
Acartia tonsa	6d static	EC10 (development) = 0.028 mg/L	(RIFM, 2007b)

10.3.2.4. 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.

11. Risk assessment refinement

For the read across material AHTN, EC10 of 0.028 mg/L for Acartia tonsa was selected as the most sensitive endpoint, and it has been used for PNEC derivation. Therefore, this is also used as the lowest, most sensitive endpoint for this material.

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 Environmental Framework: Salvito et al., 2002; #40315).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	6.31	6.31
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1−10	1−10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 2.8 μg/L. The revised PEC/PNECs for EU 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: 09/29/2015.

12. 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

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.06328 mg/L			1,000,000	6.328E-05 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.029 mg/L	0.024 mg/L	0.093 mg/L	10,000	0.0024 μg/L	Neutral Organics
Tier 3: Measured Data (including read-across data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish			0.035 mg/L			
Daphnia			0.196 mg/L			
Algae			0.204 mg/L			

- 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.2017.05.015.

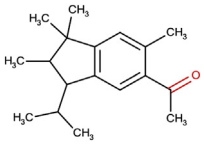
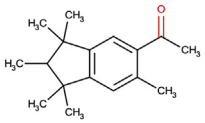
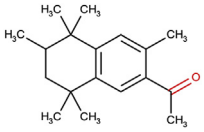
Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.05.015.

Appendix

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

Principal Name	Target material	Read across material	
	5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane	5-Acetyl-1,1,2,3,3,6-hexamethylindan	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline
CAS No.	68140-48-7	15323-35-0	21145-77-7
Structure			
Similarity (Tanimoto score)	1	0.90110	0.91135
Read across endpoint		•Genotoxicity	•Repeated dose, Developmental, Reproductive, •Environmental
Molecular Formula	$C_{18}H_{26}O$	$C_{17}H_{24}O$	$C_{18}H_{26}O$
Molecular Weight	258.41	244.38	258.41
Melting Point (°C, EPISUITE)	103.17	98.68	106.87
Boiling Point (°C, EPISUITE)	329.77	317.61	331.88
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.00911	0.0195	0.0252
Log Kow (KOWWIN v1.68 in EPISUITE)	6.31	5.85	5.70
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	0.0869	0.2545	0.2879
J_{max} (mg/cm^2/h, SAM)	0.013175	0.038312	0.039
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.28E+000	3.22E+000	4.28E+000
Genotoxicity			
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	•No alert found	No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	•No alert found	•No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	•No alert found	•No alert found	
DNA alerts for Ames, MN, CA by OASIS v 1.1	•No alert found	•No alert found	
In-vitro Mutagenicity (Ames test) alerts by ISS	•No alert found	•No alert found	
In-vivo mutagenicity (Micronucleus) alerts by ISS	•No alert found	•No alert found	
Oncologic Classification	•Not classified	•Not classified	
	Repeated dose toxicity		
Repeated Dose (HESS)	•Not categorized		•Not categorized
	Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	•Non binder, without OH or NH_2 group		•Non binder, without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	•Toxicant (good reliability)		•Toxicant (good reliability)

(continued on next page)

(*continued*)

Principal Name	Target material	Read across material	
	5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane	5-Acetyl-1,1,2,3,3,6-hexamethylindan	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane (CAS# 68140-48-7). Hence *in-silico* evaluation was conducted to determine suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs 5-acetyl-1,1,2,3,3,6-hexamethylindan (CAS# 15323-35-0) and 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS# 21145-77-7) were identified as read across materials with data for their respective toxicity endpoints.

Conclusion/Rationale

- 5-Acetyl-1,1,2,3,3,6-hexamethylindan (CAS# 15323-35-0) is used as a structurally similar read across analog for 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane (CAS# 68140-48-7) for the genotoxicity toxicological endpoint.
  - o The target substance and the read across analog are structurally similar and belong to a class of ketones.
  - o The key difference between the target material and the read across is size of aliphatic groups on the molecule. The target has slightly larger aliphatic groups on it compared to read across.
  - o The target and read across analog have a Tanimoto score of 0.90110 which is mainly driven by 2,3-dihydro-1H-indene fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - o The physical chemical properties of the target and the read across analog are very similar.
  - o The structural alerts for the toxicological endpoints are consistent between the target as well as the read across material.
  - o The structural alerts show that the read across material is similarly reactive for the genotoxicity endpoint as compared to the target material.
  - o The structural alerts show that the predicted metabolites of read across material are similarly reactive as compared to the target material or its predicted metabolites.
  - o The target and analog are expected to be metabolized similarly as shown by the metabolism simulator. All of the read across metabolites show no structural alerts for genotoxicity
  - o The structural differences between target and the read across analog appear to be toxicologically insignificant.
- 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS# 21145-77-7) is used as a structurally similar read across analog for 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane (CAS# 68140-48-7) for the repeated dose, developmental and reproductive, and environmental toxicity endpoints.
  - o The target and analog are structurally similar and belong to a class of ketones.
  - o The key difference between the target material and the read across is size of aliphatic groups on the molecule. The target have slightly shorter aliphatic groups on it compared to read across.
  - o The target and read across analog have a Tanimoto score of 0.91135 which is mainly driven by 2,3-dihydro-1H-indene fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - o The physical chemical properties of the target and the read across analog are very similar.
  - o The structural alerts for the toxicological endpoints are consistent between the target as well as the read across material.
  - o The structural alerts show that the read across material is similarly reactive for the repeated dose, developmental and reproductive, and enviornmental toxicity endpoint as compared to the target material.
  - o The structural alerts show that the predicted metabolites of read across material are similarly reactive as compared to the target material or its predicted metabolites.
  - o The target and analog are expected to be metabolized similarly as shown by the metabolism simulator. All of the read across metabolites show no structural alerts for repeated dose, developmental and reproductive, and enviornmental toxicity endpoint toxicity.
  - o The structural differences between target and the read across analog appear to be toxicologically insignificant.

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., 1978).

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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