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Short review

RIFM fragrance ingredient safety assessment, Isolongifolene ketone, CAS registry number 23787-90-8

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1. Identification

2. Physical data**

1 **Boiling Point:** 282.66 °C [EPI Suite]
2 .**Flash Point**: >212 °F [Dragoco], >200 °F; CC [FMA]
3 **Log K_{OW}**: 3.81 [EPI Suite]
4 **Melting Point**: 79.51 °C [EPI Suite]
5 **Water Solubility:** 18.94 mg/L [EPI Suite]
6. **Specific Gravity**: 0.9977–1.0987 (25 °C) [Dragoco], 0.999–1.099 (20/4 °C) [Dragoco], 1.003 [FMA]
7. **Vapor Pressure**: 0.00143 mm Hg @ 20 °C [EPI Suite 4.0], 0.001 mm Hg 20 °C [FMA], 0.00259 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 pale yellow liquid with a dry, woody, patchouli, cedar, earthy, tobacco, and incense like medium strength odor (Luebke, William tgsc, 1984).* *http://www.thegoodscentscompany.com/data/rw1007011.htmlretrieved 07/27/14

**Physical data for all 3 material included in this safety assessment are the same.

3. Exposure***

4. Derivation of systemic absorption

1 **Dermal**: 16%

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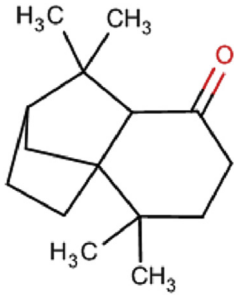
Version: 112216. This version replaces any previous versions.
Name: Isolongifolene ketone
CAS Registry Number: 23787-90-8
Additional CAS Numbers*:
29461-13-0 (2.alpha.,4a.alpha.,8.beta.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalene-8(5H)-one
29461-14-1 (2.alpha.,4a.alpha.,8.alpha.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one (no reported use)
*These materials are included in this assessment because they are a mixture of conformational isomers.



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, 2016: The *in vitro* human skin permeation rate and distribution of test material, isolongifolene ketone (ILFK, CAS No. 23787-90-8). The application (finite dose of 48.7 μg/cm^2 prepared in 5 μl/cm^2) was in 70/30 (v/v) ethanol/water under both unoccluded and occluded conditions, at a target concentration of 1% (measured concentration 0.974% (w/v), 0.50% RSD, n = 3). For this skin penetration study, twelve active dosed diffusion cells were prepared for both unoccluded and occluded conditions plus four control cells (one per donor, unoccluded conditions). Epidermal membranes (four donors, female abdominal skin) were used and integrity assessed by measuring electrical resistance. Permeation of ILFK, from a 5 μl/cm^2 dose of the 1% (w/v) donor solution, was measured at twelve time-points over 24 h, using a 30/70 (v/v) ethanol/water receptor phase (which provided sink conditions). The ILFK dose for all active cells was 48.7 μg/cm^2. For the occluded group, donor chambers were occluded using greased glass coverslips applied immediately following application of the dose. At 24 h, the epidermal membranes were wiped, tape stripped 10 times and the ILFK content of the wipes, strips and remaining epidermis was determined. The filter paper skin supports were extracted and the diffusion cell donor chambers (and the glass coverslip for occluded cells) wiped to remove sealing grease then washed. Analysis of these samples allowed mass balance to be performed. Aliquots of donor solution (6 μl, n = 3) were diluted following cell dosing and stored frozen with the study samples pending analysis. Evaporative loss of ILFK was estimated by measuring the loss from polytetrafluoroethylene sheets under the same experimental conditions. Under both application conditions initial permeation was reasonably rapid, but the rate of permeation gradually reduced (probably due to donor phase depletion, via both evaporative loss and, to a much lesser extent, permeation). Data from two cells were excluded due to evidence of atypical and very rapid/high initial permeation indicating compromised skin barrier function. Average data for each test group are from the remaining eleven cells. At 24 h, 2.85 ± 0.64 and 6.10 ± 0.65 μg/cm^2 ILFK had permeated under unoccluded and occluded conditions respectively, corresponding to 5.86 ± 1.31 and 12.5 ± 1.3% of the applied dose. Occluded conditions not only reduce loss of volatile application vehicles and test compounds but also increase skin hydration, and these factors caused an increase in the permeation of ILFK compared to unoccluded conditions. The amount of absorbed dose, corresponding to the amounts in the epidermis, filter paper support and receptor phase for both conditions, occluded and unoccluded corresponded to 7.79 μg/cm^2 (16 ± 1.3% of applied dose) 0.65 and 4.22 ± 0.71 μg/cm^2

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, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.0015, 0.0015 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: Not sensitizing	(RIFM, 1976; RIFM, 1989a; RIFM, 1989b; RIFM, 1973a; RIFM, 1973b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 5.1% (OECD 310)	(RIFM, 2011a)
Bioaccumulation: Critical Measured Value: 381 (BCFK)	(RIFM, 2011b)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48 h *Daphnia magna* LC50: 2.852 mg/L	(EpiSuite ver 4.1)
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: 48 h *Daphnia magna* LC50: 2.852 mg/L	(EpiSuite ver 4.1)
RIFM PNEC is: 0.2852 μg/L	
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1	

Chemical Name: Isolongifolene ketone	**Chemical Name**: (2.alpha.,4a.alpha.,8.beta.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalene-8(5H)-one	**Chemical Name**: (2.alpha.,4a.alpha.,8.alpha.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one
CAS Registry Number: 23787-90-8	**CAS Registry Number:** 29461-13-0	**CAS Registry Number:** 29461-14-1
Synonyms: Isolongifolene ketone; 2H-2,4a-Methanonaphthalene-8(5H)-one, 1,3,4,6,7,8a-hexahydro-1,1,5,5-tetramethyl-; 1,5,5-ﾃﾄﾗﾒﾁﾙｵｸﾀﾊｲﾄﾞﾛ-2,4a-ﾒﾀﾉﾅﾌﾀﾚﾝ-8-ｵﾝ; 1,1,5,5-ﾃﾄﾗﾒﾁﾙｵｸﾀﾊｲﾄﾞﾛ-2,4a-ﾒﾀﾉﾅﾌﾀﾚﾝ-8-ｵﾝ; 1,1,5,5-Tetramethylhexahydro-2H-2,4a-methanonaphthalen-8(5H)-one; Picomate; Paxamber; Piconia; Isolongifolanone; Isolongifolanon coeur; Timberone; Tetramethyl tricyclo undecane; 1,3,4,6,7,8a-hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one	**Synonyms: 2H-2,4a-**Methanonaphthalen-8(5H)-one, hexahydro-1,1,5,5-tetramethyl-, (2.α.,4a.α.,8.β.)-; 2H-2,4a-Methanonaphthalen-8(5H)-one, hexahydro-1,1,5,5-tetramethyl-, (2R,4aR,8aS)-rel-; 1,1,5,5-Tetramethylhexahydro-2H-2,4a-methanonaphthalen-8(5H)-one	**Synonyms:** Isolongifolene ketone exo; 2H-2,4a-Methanonaphthalen-8(5H)-one, hexahydro-1,1,5,5-tetramethyl-, (2.α.,4a.α.,8.α.); 2H-2.α.,4a.α.-Methanonaphthalen-8(5H)-one, 1,3,4,6,7,8a.α.-hexahydro-1,1,5,5-tetramethyl-; 2H-2,4a-Methanonaphthalen-8(5H)-one, hexahydro-1,1,5,5-tetramethyl-, (2R,4aR,8aR)-rel-; 3-β-H-4-Oxo-2,3,7,7-tetramethyltricyclo[6,2,1,0]undecane; 1,1,5,5-Tetramethylhexahydro-2H-2,4a-methanonaphthalen-8(5H)-one; Valanone B
Molecular Formula: $C_{15}H_{24}O$	**Molecular Formula:** $C_{15}H_{24}O$	**Molecular Formula:** $C_{15}H_{24}O$
Molecular Weight: 220.36	**Molecular Weight:** 220.56	**Molecular Weight:** 220.36
RIFM Number: 1131	**RIFM Number:** 5649	**RIFM Number:** N/A

1	**Volume of Use (worldwide band)**: 10–100 metric tons per year	(IFRA, 2011)
2	**95th Percentile Concentration in Hydroalcoholics**: 0.13%	(RIFM, 2015)
3	**Inhalation Exposure***: 0.000068 mg/kg/day or 0.0049 mg/day	(RIFM, 2015)
4	**Total Systemic Exposure****: 0.00024 mg/kg/day	(RIFM, 2015)

*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 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; 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.

(8.67 ± 1.47% of applied dose), respectively. Overall recoveries of the applied ILFK were low under unoccluded conditions at 29.2 ± 2.7, but good under occluded conditions at 89.7 ± 1.0% of the applied dose. The investigation of evaporative loss from PTFE sheet mounted in diffusion cells showed that evaporation was gradual but virtually complete (95% recovered at 1 h, 87% at 2 h, 55% at 6 h, 22% at 12 h, 1% at 24 h). Evaporative loss would fully account for reduced recovery for the unoccluded group. It is probable that evaporation from the skin surface and subsequent loss through the donor chamber sealing grease for the occlusive cover was the reason for less than complete recovery for the occluded group. The most conservative skin absorption value of 16% obtained under occluded conditions was used for the safety assessment.

2 **Oral:** Data not available – not considered.
3 **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification**: Class III, High (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
III*	III	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 Justifications**: 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)

Isolongifolanone (isolongifolene ketone), (2.alpha.,4a.alpha.,8.-beta.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalene-8(5H)-one and (2.alpha.,4a.alpha.,8.alpha.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one have not been 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

Isolongifolene ketone has been pre-Registered for 2010; No dossier available as of 11/22/2016. (2.alpha.,4a.alpha.,8.beta.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalene-8(5H)-one has been pre-registered for 2013, no dossier available as of 11/22/2016. (2.alpha.,4a.alpha.,8.alpha.)-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one has been pre-Registered for 2010; No dossier available as of 11/22/2016.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels isolongifolene ketone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Isolongifolene ketone was found to be negative for both cytotoxicity and genotoxicity when tested in the BlueScreen assay indicating a lack for genotoxic potential (RIFM, 2013). The mutagenic activity of isolongifolene ketone was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2uvrA were treated with isolongifolene ketone in DMSO (dimethyl sulfoxide) at dose levels of 5.00, 16.0, 50.0, 160, 500, 1600, and 5000 μg/plate in the presence of S9 and at dose levels of 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, and 5000 μg/plate in the absence of S9. No increase in the mean number of revertant colonies was observed at any tested dose level in any tester strain in the presence or absence of S9 in the initial or the confirmatory assays (RIFM, 2014a). Under the conditions of the study, isolongifolene ketone was considered not mutagenic.

The clastogenic activity of isolongifolene ketone was assessed for clastogenic/aneugenic potential in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD 487. Human peripheral blood lymphocytes (HPBL) were treated with isolongifolene ketone in DMSO at concentrations ranging from 8.70 to 176 μg/mL in the 24 h treatment and at 16.6–220 μg/mL in the 3 h treatment, both in the absence of S9. The test article was also evaluated at concentrations ranging from 29.6 to 275 μg/mL in the 3 h treatment in the presence of S9. No statistically significant increase in the frequency of BNMN was observed at any tested dose level in approximately 24 h treatment in the absence of S9 and in the 3 h treatment in the presence of S9 (RIFM, 2014b). Under the conditions of the study, isolongifolene ketone was considered negative for clastogenicity in the *in vitro* micronucleus test.

Based on the available data, isolongifolene ketone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on isolongifolene ketone or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on isolongifolene ketone or any read across materials that can be used to support the repeated dose toxicity endpoint. After correcting for skin absorption value of 16% obtained from an *in vitro*

skin absorption study (RIFM, 2016; see section IV), the refined total systemic exposure for isolongifolene ketone (0.24 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 6/15/2016.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on isolongifolene ketone or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on isolongifolene ketone or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. After correcting for skin absorption value of 16% obtained from an *in vitro* skin absorption study (RIFM, 2016; see section IV), the refined total systemic exposure for isolongifolene ketone (0.24 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 6/15/2016.

10.1.4. Skin sensitization

Based on the available data, isolongifolene ketone does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available material specific data, isolongifolene ketone does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig maximization test no results indicative of sensitization were observed with (2.alpha.,4a.alpha.,8.alpha.)-hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one (RIFM, 1976). Additionally, no reactions indicative of skin sensitization were observed in the human repeated insult patch test up to 6.25% (4845 μg/cm^2) isolongifolene ketone in alcohol SDA 39C (RIFM, 1989a; RIFM, 1989b; RIFM, 1973a; RIFM, 1973b). Similarly no reactions indicative of sensitization were observed in human maximization tests up to 10% (6900 μg/cm^2) isolongifolene ketone in petrolatum (RIFM, 1982; RIFM, 1980; RIFM, 1977b; RIFM, 1977a).

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, isolongifolene ketone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for isolongifolene ketone in experimental models. UV/Vis absorption 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). Based on lack of significant absorbance in the critical range, isolongifolene ketone does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/20/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, isolongifolanone (isolongifolene ketone), exposure level is below the inhalation TTC Cramer Class III limit for local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on isolongifolanone (isolongifolene ketone). Based on the Creme RIFM model, the inhalation exposure is 0.0049 mg/day. This exposure is 95.9 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.

Additional References: None.

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

10.2. Environmental endpoint summary

10.2.1. Analogues identified/justification

10.2.1.1. Screening-level assessment. A screening level risk assessment of isolongifolanone (isolongifolene ketone) was performed following the RIFM Environmental Framework (Salvito et al., 2002) that 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, isolongifolanone (isolongifolene ketone) was identified as a fragrance material with 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 isolongifolanone (isolongifolene ketone) as possibly persistent but not 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.

10.2.2. Risk assessment

Based on current Volume of Use (2011), isolongifolanone (isolongifolene ketone) presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2011a: The ready biodegradability of isolongifolanone (isolongifolene ketone) was determined by the Headspace test according to the OECD 310 methods. 20 mg of the test material was incubated for 28 days in the initial test and 100

days for the second test. The average cumulative percent biodegradation for the test material was −2.0% in the initial test and 5.1% in the second test.

10.2.3.2. Bioaccumulation. RIFM, 2011b: A modified fish (rainbow trout) bioaccumulation study was conducted according to the OECD 305 method. The Kinetic BCF value for the test material in rainbow trout was calculated for the 44.5 μg a.i./L treatment group (mean measured concentration). The kinetic BCF (BCFK) value for the test material in whole fish tissue was 381. The estimated time to reach 90% of steady state during the uptake phase was 9.14 days. The Day 14 depuration tissue concentration was approximately 3% of the Day 28 uptake mean tissue concentration. The estimated time to reach 50% clearance for whole fish tissue concentrations was 2.75 days.

10.2.3.3. Ecotoxicity. No data available.

10.2.3.4. Other available data. Isolongifolanone (isolongifolene ketone) has been pre-registered for REACH with no additional data at this time.

11. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L.

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	7.914 mg/L			1,000,000	0.00791 μg/L	
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	4.248 mg/L	2.852 mg/L	4.247 mg/L	10000	0.2852 μg/L	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.81	3.81
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10-100*	1-10*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined volume for CAS# 23787-90-8, CAS# 29461-13-0 and CAS# 29461-14-1.

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

The RIFM PNEC is 0.2852 **μg/L. The revised PEC/PNECs for EU and NA < 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: 3/16/16.

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
- **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%3dww%26ei%3dKMSoUpiQK-arsQS324GwBg%26ved%3d0CBQQ1S4

*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.2017.02.034.

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., 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? **No**.

Q24.Monocarbocyclic with simple substituents? **No**.

Q25. Cyclopropane, cyclobutane with substituents in Q24 or a mono or bicyclic sulphide or mercaptan? **No**.

Q26.Monocycloalkanone or a bicyclocompound? **No**.

Q22.Common component of food? **No**.

Q33.Has sufficient number of sulphonate or sulphamate groups? **No** Class High (Class III).

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renkers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between Toxtree, the OECD QSAR toolbox and expert judgment. Regul. Toxicol. Pharmacol. 73 (3), 71(1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.

Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software]. (Copyright 2000-2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Retrieved from http://www.epa.gov/opptintr/exposure/pubs/episuite.htm Research, 20(6), 482–487.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973a. Repeated Insult Patch Test with Isolongifolanone (Isolongifolene Ketone) (Picomate). Unpublished report from International Flavors and Fragrances. RIFM report number 54565. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973b. Repeated Insult Patch Test with Isolongifolanone (Isolongifolene Ketone) (Piconia) in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 54736. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1976. Screening Test for Delayed Contact Hypersensitivity with Cytenol, Isolongifolene Ketone (Valanone B), C10 Methoxylated Hydrocarbons, Myrtenyl Acetate, and Pinocarvyl Acetate in the Albino Guinea-pig. Unpublished report from Bush Boake Allen Ltd. RIFM report number 1762. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1977a. Human Maximization Test on Isolongifolene Ketone. Unpublished report from PFW, a Division of Hercules Inc. RIFM report number 7835. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1977b. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1691. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1790. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1643. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. Repeated Insult Patch Test with Isolongifolanone (Isolongifolene Ketone) (Paxamber) in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 54714. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Repeated Insult Patch Test with Isolongifolanone (Isolongifolene Ketone) (Paxamber) in Humans. Unpublished Report from International Flavors and Fragrances. RIFM report number 54715. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011a. Piconia: Enhanced Ready Biodegradability Test CO2 in Sealed Vessels Low Level Pre-adaptation. RIFM report number 62813. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011b. Isolongifolene Ketone (Piconia): a Flow-through Bioconcentration Screening Test with the Rainbow Trout (Oncorhynchus mykiss). RIFM report number 61071. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Isolongifolanone (Isolongifolene Ketone) in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65550. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Isolongifolanone (Isolongifolene Ketone): Bacterial Reverse Mutation Assay. RIFM report number 67348. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. Isolongifolene Ketone (Isolongifolanone): in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 67610. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials), 2015. Use Level Survey, May 2015.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Isolongifolene Ketone: in Vitro Human Skin Penetration under Unoccluded and Occluded Conditions. RIFM report number 70628. RIFM, Woodcliff Lake, NJ, USA.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., et al., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Contact Dermat. 21 (6), 1301–1308.