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Short Review

RIFM fragrance ingredient safety assessment, 6-isopropyl-2(1H)-octahydronaphthalenone, CAS Registry Number 34131-98-1

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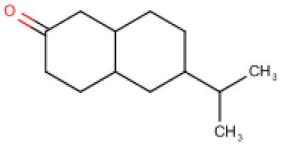

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015; Safford et al., 2017) 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
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

6-Isopropyl-2(1H)-octahydronaphthalenone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 6-isopropyl-2(1H)-octahydronaphthalenone is not genotoxic. Data on read-across analog 2,5,6-trimethylcyclohex-2-en-1-one (CAS # 20030-30-2) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to 6-isopropyl-2(1H)-octahydronaphthalenone is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data from read-across analog tetrahydronootkatone (CAS # 38427-80-4) show that there are no safety concerns for 6-isopropyl-2(1H)-octahydronaphthalenone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 6-isopropyl-2(1H)-octahydronaphthalenone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 6-isopropyl-2(1H)-octahydronaphthalenone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2003; RIFM, 2018)

Repeated Dose Toxicity: NOAEL = 20 mg/kg/day.

ECHA REACH Dossier: 2,5,6-Trimethylcyclohex-2-en-1-one; ECHA (2016b)

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: No evidence of skin sensitization under the current, declared level of use. RIFM (2005)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Screening-level: 2.7 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:

Screening-level: 152.8 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 6.840 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 6.840 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00684 μg/L

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

1. Identification

1. **Chemical Name:** 6-Isopropyl-2(1H)-octahydronaphthalenone
2. **CAS Registry Number:** 34131-98-1
3. **Synonyms:** Decatone; 6-Isopropyldecalone; 2(1H)-Naphthalenone, octahydro-6-(1-methylethyl)-; 3,4,4a,5,6,7,8,8a-Octahydro-6-isopropyl-2(1H)naphthalenone; 6-ｲｿﾌﾟﾛﾋﾟﾙ-3,4,4a,5,6,7,8,8a-ｵｸﾀﾋﾄﾞﾛﾅﾌﾀﾚﾝ-2(H)-ｵﾝ; 6-Isopropyloctahydronaphthalen-2(1H)-one; 6-Isopropyl-2(1H)-octahydronaphthalenone
4. **Molecular Formula:** $C_{13}H_{22}O$
5. **Molecular Weight:** 194.31
6. **RIFM Number:** 57
7. **Stererochemistry:** Isomer not specified. Three chiral centers present and 8 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 271.17 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 3.82 (EPI Suite)
4. **Melting Point**: 39.28 °C (EPI Suite)
5. **Water Solubility:** 25.81 mg/L (EPI Suite)
6. **Specific Gravity:** 0.960 (FMA Database), 0.9586 (RIFM Database)
7. **Vapor Pressure:** 0.00646 mm Hg @ 20 °C (EPI Suite v4.0), 0.0113 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not available

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.11% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000077 mg/kg/day or 0.0055 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0014 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** 2,5,6-Trimethylcyclohex-2-en-1-one (CAS # 20030-30-2)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Tetrahydronootkatone (CAS # 38427-80-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
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)

6-Isopropyl-2(1H)-octahydronaphthalenone is not reported to occur in foods by the VCF*.

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

8. IFRA standard

None.

9. REACH dossier

Pre-registered; no dossier available as of 10/09/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 6-isopropyl-2(1H)-octahydronaphthalenone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 6-isopropyl-2(1H)-octahydronaphthalenone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 6-isopropyl-2(1H)-octahydronaphthalenone in dimethyl sulfoxide (DMSO) at

concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2003). Under the conditions of the study, 6-isopropyl-2(1H)-octahydronaphthalenone was not mutagenic in the Ames test.

The clastogenic activity of 6-isopropyl-2(1H)-octahydronaphthalenone was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 6-isopropyl-2(1H)-octahydronaphthalenone in DMSO at concentrations up to 1940 μg/mL in dose range finding (DRF) study. Micronucleus analysis was conducted at 100 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h 6-Isopropyl-2(1H)-octahydronaphthalenone did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2018). Under the conditions of the study, 6-isopropyl-2(1H)-octahydronaphthalenone was considered to be non-clastogenic in the *in vitro* micronucleus test.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/21/18.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for 6-isopropyl-2(1H)-octahydronaphthalenone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data for 6-isopropyl-2(1H)-octahydronaphthalenone. Read-across material 2,5,6-trimethylcyclohex-2-en-1-one (CAS, 20030-30-2; see section 5) has sufficient repeated dose toxicity data. In an OECD 407 and GLP-compliant subacute study, 5 Chbb:THOM (SPF) rats/sex/dose were orally administered 2,5,6-trimethylcyclohex-2-en-1-one at the doses (actual) of 0, 15, 60, and 300 mg/kg/day for 5 days/week. During the study, no mortality was reported at any tested dose in either sex. During the first week of the study, animals of both sexes in the 300 mg/kg/day group demonstrated reduced activity for 1 h following treatment. Following the second dose (and onwards), all animals in the highest-dose group were reported to have excessive salivation for 30 min following treatment application. With the exception of 1 male animal from the 15 mg/kg/day that had an incidental tail injury, no gross changes in behavior, function, and/or health were observed in animals receiving 15 and 60 mg/kg/day doses. No bodyweight differences were reported in all groups, except for a statistical decrease in males of the highest-dose group during the first 2 weeks. Food consumption in animals receiving 15 and 60 mg/kg/day was not altered; however, food consumption was lower in both sexes on study day 7 at the highest dose. The decrease in food consumption in both sexes combined with bodyweight alterations in males at the highest dose is a treatment-related effect. During organ weight analysis, increases in absolute and relative liver weight were reported in females from the highest-dose group. Upon histological examination, the only observed effect in evaluated organs was α-2u-microglobulin nephropathy in the kidneys of male rats at the highest dose of 300 mg/kg/day. This finding is specific to male rats and is not relevant to humans. Urinalysis revealed increased sediment concentration (2/5 males) as well as increased presence of transitional epithelium and tubular cells (1/5 males) in the urine, potentially due to underlying treatment-related mild kidney damage. Based on the observed alterations of food consumption, bodyweight change, liver weight, and mild kidney damage, a conservative NOAEL for repeated dose toxicity was determined to be 60 mg/kg/day (ECHA, 2016b).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day OECD 407 studies. The safety factor has been approved by the independent Expert Panel for Fragrance Safety*.

Thus the derived NOAEL for the repeated dose toxicity data is 60/3 or 20 mg/kg/day.

Therefore, the 6-isopropyl-2(1H)-octahydronaphthalenone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,5,6-trimethylcyclohex-2-en-1-one NOAEL in mg/kg/day by the total systemic exposure to 6-isopropyl-2(1H)-octahydronaphthalenone, 20/0.0014 or 14286.

In addition, the total systemic to 6-isopropyl-2(1H)-octahydronaphthalenone (1.4 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

* The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/15/18.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on 6-isopropyl-2(1H)-octahydronaphthalenone or on any read-across materials. The total systemic exposure to 6-isopropyl-2(1H)-octahydronaphthalenone is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment

There are no reproductive toxicity data on 6-isopropyl-2(1H)-octahydronaphthalenone or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 6-isopropyl-2(1H)-octahydronaphthalenone (1.4 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/07/18.

10.1.4. Skin sensitization

Based on the read-across material tetrahydronootkatone (CAS # 38427-80-4), 6-isopropyl-2(1H)-octahydronaphthalenone presents no evidence of sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment

The chemical structure of the target material indicates that it would not be expected to react with skin proteins, while the read-across material would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for the target material 6-isopropyl-2(1H)-octahydronaphthalenone and the read-across material tetrahydronootkatone. However, in a confirmatory human repeat insult patch test with 1000 μg/cm^2 of read-across material tetrahydronootkatone, no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2005).

Based on weight of evidence (WoE) from structural analysis and read-across material tetrahydronootkatone, 6-isopropyl-2(1H)-

octahydronaphthalenone presents no evidence of sensitization under the current, declared levels of use.

Additional References: RIFM, 1972.

Literature Search and Risk Assessment Completed On: 11/15/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 6-isopropyl-2(1H)-octahydronaphthalenone 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 6-isopropyl-2(1H)-octahydronaphthalenone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 6-isopropyl-2(1H)-octahydronaphthalenone does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/14/18.

10.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 6-isopropyl-2(1H)-octahydronaphthalenone is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment

There are no inhalation data available on 6-isopropyl-2(1H)-octahydronaphthalenone. Based on the Creme RIFM Model, the inhalation exposure is 0.0055 mg/day. This exposure is 85.5 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/13/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 6-isopropyl-2(1H)-octahydronaphthalenone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 6-isopropyl-2(1H)-octahydronaphthalenone was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 6-isopropyl-2(1H)-octahydronaphthalenone as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value $<$ 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value $<$ 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current VoU (IFRA, 2015), 6-isopropyl-2(1H)-octahydronaphthalenone presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. RIFM, 2001: The inherent biodegradability of the test material was determined by the manometric respirometry test according to the OECD 302C method. Under the conditions of this study, no biodegradation was observed after 31 days.

RIFM, 1999: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Under the conditions of this study, no biodegradation was observed after 28 days.

10.2.2.1.2. Ecotoxicity. No data available.

10.2.2.1.3. Other available data. 6-isopropyl-2(1H)-octahydronaphthalenone has been registered under REACH with no additional data available at this time.

10.2.3. 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	6.840			1000000	0.00684	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.82	3.82
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.00684 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/14/18.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.111005.

Appendix

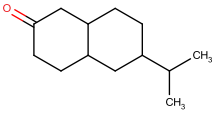
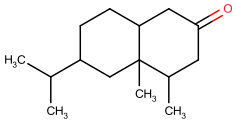
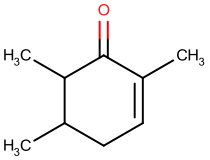
Read-across Justification

Methods

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

- First, the materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US ECHA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	6-Isopropyl-2(1H)-octahydronaphthalenone	Tetrahydronootkatone	2,5,6-Trimethylcyclohex-2-en-1-one
CAS No.	34131-98-1	38427-80-4	20030-30-2
Structure			
Similarity (Tanimoto Score)		0.92	0.34
Read-across Endpoint		• Skin sensitization	• Repeated dose toxicity
Molecular Formula	$C_{13}H_{22}O$	$C_{15}H_{26}O$	$C_9H_{14}O$
Molecular Weight	194.31	222.37	138.21
Melting Point (°C, EPI Suite)	39.28	65.85	4.68
Boiling Point (°C, EPI Suite)	271.17	289.88	206.13
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.51	0.329	51.5
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.82	4.69	2.58
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	25.81	3.328	531.3
J_{max} (μg/cm^2/h, SAM)	13.89	633.76	224.93
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.66E+001	2.92E+001	6.71
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized		• Not categorized
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein Binding (OECD)	• No alert found	• No alert found	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on 6-isopropyl-2(1H)-octahydronaphthalenone (CAS # 34131-98-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, tetrahydronootkatone (CAS # 38427-80-4) and 2,5,6-trimethylcyclohex-2-en-1-one (CAS # 20030-30-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Tetrahydronootkatone (CAS # 38427-80-4) was used as a read-across analog for the target material 6-isopropyl-2(1H)-octahydronaphthalenone (CAS # 34131-98-1) for the skin sensitization endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of cyclic, fused saturated ketones.
  - ○ The target material and the read-across analog share an octahydronaphthalenone structure with an isopropyl group in position 6.
  - ○ The key difference between the target material and the read-across analog is that the read-across analog contains 2 additional methyl substituents on the ring. This structural difference is toxicologically insignificant.
  - ○ The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2,5,6-Trimethylcyclohex-2-en-1-one (CAS # 20030-30-2) was used as a read-across analog for the target material 6-Isopropyl-2(1H)-octahydronaphthalenone (CAS # 34131-98-1) for the repeated dose toxicity endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of cyclic ketones.
  - ○ The target material and the read-across analog share 6-membered cyclic ketone structures.

- ○ The key difference between the target material and the read-across analog is that the target material consists of a saturated octahydronaphthalenone ring, whereas the read-across analog has a cyclohexene ring with an α,β-unsaturated ketone and an α-methyl substitution. These structural differences are toxicologically insignificant.
- ○ The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

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

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for a detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? Yes, Class II (Class intermediate)

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