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RIFM fragrance ingredient safety assessment, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl, CAS Registry Number 476332-65-7

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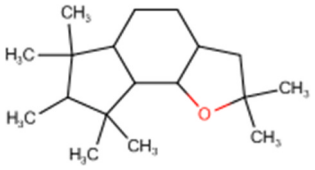

Name: 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl
CAS Registry Number: 476332-65-7
Additional CAS*
647828-16-8
Indeno[4,3a-b]furan,decahydro-2,2,7,7,8,9,9-heptamethyl-*Included because the materials are homologues

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
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.

(*continued on next column*)

(*continued*)

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.

2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is not genotoxic and provide a No Expected Sensitization Induction Level (NESIL) of 2200 μg/cm^2 for the skin sensitization endpoint. Data on 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2003c; RIFM, 2003b)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day.	RIFM (2004a)
Reproductive Toxicity: NOAEL = 85 mg/kg/day.	RIFM (2012)
Skin Sensitization: NESIL = 2200 μg/cm^2.	(RIFM, 2003i)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 2% (OCD 301B)	RIFM (2003e)
Bioaccumulation:	
Screening-level: 371 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: *Daphnia magna* 21-day NOEC: 0.034 mg/L	RIFM (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: *Daphnia magna* 21-day NOEC: 0.034 mg/L	RIFM (2006)

RIFM PNEC is: 0.68 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

Chemical Name: 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl	Chemical Name: Indeno[4,3a-b]furan, decahydro-2,2,7,7,8,9,9-heptamethyl-
CAS Registry Number: 476332-65-7	**CAS Registry Number:** 647828-16-8
Synonyms: Amber Xtreme; Amber Extreme; 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl	**Synonyms:** Amber Xtreme; Amber Extreme; Indeno[4,3a-b]furan, decahydro-2,2,7,7,8,9,9-heptamethyl-
Molecular Formula: $C_{18}H_{32}O$	**Molecular Formula:** $C_{18}H_{32}O$
Molecular Weight: 264.45	**Molecular Weight:** 264.45
RIFM Number: 6975	**RIFM Number:** 6493
Stereochemistry: Isomer not specified. Five stereocenters and a total of 32 stereoisomers possible.	**Stereochemistry:** Isomer not specified. Five stereocenters and a total of 32 stereoisomers possible.

2. Physical data*

1. **Boiling Point:** Approx. 528 K at 101.43–102.15 kPa (RIFM, 2003h)
2. **Flash Point:** 128±2 °C (RIFM, 2003d)
3. **Log K_{OW}:** 4.42 (RIFM, 2003h)
4. **Melting Point**: <253±0.5 K (RIFM, 2003h)
5. **Water Solubility:** $<2.02 \times 10^{(-4)}$ g/L of sol at 20.0±0.5 °C (RIFM, 2003h)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** $3.8 \times 10^{(-1)}$ Pa at 25 °C (RIFM, 2003f)
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:** Not Available

*Physical data same for both materials.

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient***

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.090% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.000064 mg/kg/day or 0.0047 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.00097 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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, 2017; Safford, 2015, 2017).

***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 or 97.5th percentile, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

6.2. Analogs Selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across Justification

None

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl and the additional CAS are 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.

9. REACH dossier

Available for both materials in a single dossier; accessed 09/28/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.17
2	Products applied to the axillae	0.050
3	Products applied to the face/body using fingertips	1.0
4	Products related to fine fragrances	0.94
5A		0.24

(continued on next page)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.24
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.24
5D	Baby cream, oil, talc	0.080
6	Products with oral and lip exposure	0.50
7	Products applied to the hair with some hand contact	0.50
8	Products with significant ano-genital exposure (tampon)	0.080
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.0
10B	Aerosol air freshener	5.6
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.080
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl, the basis was the reference dose of 0.50 mg/kg/day, a predicted skin absorption value of 10%, and a skin sensitization NESIL of 2200 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl 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 dose in the presence or absence of S9 (RIFM, 2003c). Under the conditions of the study, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was not mutagenic in the Ames test.

The clastogenic activity 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in Arachis oil via a single intraperitoneal dose to groups of male mice. Doses up to 2000 mg/kg were administered. Mice were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2003b). Under the conditions of the study, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl does not present a concern for genotoxic potential.

Additional References: RIFM, 2003g.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

The MOE for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl. An OECD 407/GLP study was conducted on groups of 5 Sprague Dawley Crl:CD (SD) IGS BR rats/sex/group that were administered the test material 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl via oral gavage at doses of 0, 15, 150, or 1000 mg/kg/day. Additional high dose and vehicle control recovery-group animals (5/sex/dose) received 1000 mg/kg/day or vehicle Arachis oil BP for 28 days followed by a 14-day recovery period. Post-dose salivation was reported among mid- and high-dose group animals. A statistically significant increase in prothrombin time was reported among high-dose males. Organ weight analysis revealed a statistically significant increase in the relative liver weights among high- and mid-dose group animals as well as high-dose recovery-group animals. Absolute liver weights were statistically significantly higher among high-dose treatment and recovery-group females. Microscopic examination showed the presence of centrilobular hepatocyte enlargement among high- and mid-dose group animals. Treatment-related thyroid follicular cell hypertrophy was also observed among high-dose animals and mid-dose males. Microscopic alterations in the thyroid and liver were not reported among recovery-group animals, indicative of a reversible event. The report concluded a NOAEL of 150 mg/kg/day, based on alterations in the liver among high-dose group animals (RIFM, 2004a).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for fragrance safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 150/3 or 50 mg/kg/day.

Therefore, the 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl MOE for the repeated dose toxicity endpoint can be

calculated by dividing the 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl NOAEL in mg/kg/day by the total systemic exposure to 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl, 50/0.00097, or 51546.

In addition, the total systemic exposure for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (0.97 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.50 mg/kg/day.

Derivation of RfD

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The reference dose for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.50 mg/kg/day.

*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: 11/11/20.

11.1.3. Reproductive toxicity

The MOE for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl. In an OECD 421/GLP study, groups of 12 Wistar rats (RccHan:WIST) strain)/sex/dose were administered test material, Amber Xtreme at doses of 0, 225, 750, or 1500 mg/kg/day via the diet during a premating period of 2 weeks, during mating, gestation, and lactation until post-natal day 4. Males were treated for a period of 33 days, and females were treated for a period of 44 days. Relative differences of −28%, −26%, and −14% were observed for the measured concentrations of test material in the diet for the low-, mid-, and high-dose groups, respectively. Based on the actual intake, the dose ranges were 13, 43, and 85 mg/kg/day for the low-, mid-, and high-dose males and 17–16, 78–63, and 108–135 mg/kg/day for the low-, mid-, and high-dose females. There were no treatment-related alterations in fertility or developmental toxicity parameters examined up to the highest dose tested. Thus, the NOAEL for fertility was considered to be 85 mg/kg/day for males and 108 mg/kg/day for females. The developmental toxicity NOAEL was considered to be 108 mg/kg/day, the highest dose tested (RIFM, 2012). The most conservative NOAEL of 85 mg/kg/day was considered for the reproductive toxicity endpoint.

Therefore, the 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl MOE for the reproductive toxicity endpoint can be calculated by dividing the 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl NOAEL in mg/kg/day by the total systemic exposure to 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl, 85/0.00097, or 87629.

In addition, the total systemic exposure for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (0.97 μg/kg/day) is below the TTC (30 μg/kg/day) at the current level of use for the reproductive toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.4. Skin sensitization

Based on the existing data, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is a skin sensitizer with a defined NESIL of 2200 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is a weak skin sensitizer with a defined NESIL of 2200 μg/cm^2. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Toxtree v3.1.0; OECD Toolbox v4.2). However, in a murine local lymph node assay (LLNA), 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was found to be sensitizing with an EC3 value of 47.5% (11875 μg/cm^2) (RIFM, 2003a). In a Confirmation of No Induction in Humans test (CNIH) with 2204 μg/cm^2 of 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2003i).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is a weak sensitizer with a WoE NESIL of 2200 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.50 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/28/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl in

Table 1
Data Summary for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
11,875 [1]	Weak	2204	NA	NA	2200

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor 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} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is below the Cramer Class I TTC value for inhalation exposure effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl. Based on the Creme RIFM Model, the inhalation exposure is 0.0047 mg/day. This exposure is 298 times lower than the Cramer Class I TTC value of 1.4 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: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl 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, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl 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 EPI Suite v4.11 (US EPA, 2012a) identified 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl as possibly persistent but not 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 ≥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.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.2.1. Biodegradation. RIFM, 2003e: A ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B method. Biodegradation of 2% was observed over a period of 28 days.

11.2.2.2.2. Ecotoxicity. RIFM, 2004b: A fish (Rainbow trout) acute toxicity test was conducted according to the OECD 203 method under static conditions. The 96-h LC50 based on the time-weighted mean measured test concentration was reported to be > 0.055 mg/L.

RIFM, 2004c: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. Under the conditions of this study, the 48-h EC50 value based on the mean measured test concentrations was greater than 0.099 mg/L.

RIFM, 2004d: An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 values for biomass and growth rate based on geometric mean measured test concentrations were greater than 0.093 mg/L, and correspondingly the NOEC value was 0.093 mg/L.

RIFM, 2006: A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under controlled conditions. The 21-day NOEC value based on time-weighted mean measured test concentration was 0.034 mg/L.

11.2.2.2.3. Other available data. 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl has been pre-registered for REACH with no additional data at this time.

11.2.3. 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)**	2.8			1000000	0.0028	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.150	0.118	0.337	10000	0.0118	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.055					
Daphnia		0.099	0.034	50	0.68	
Algae		0.093	0.093			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.42	4.42
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 additional assessment is necessary.

*Combined Regional VoU for both CAS #s.

The RIFM PNEC is 0.68 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 11/09/20.

12. 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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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 04/15/21.

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.

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RIFM (Research Institute for Fragrance Materials, Inc), 2003c. Indeno[4,3a-b]furan, decahydro-2,2,7,7,8,9,9-heptamethyl- and 2H-Indeno[4,5b] Furan, Decahydro-2,2,6,6,7,8,8-Heptamethyl (Amber Extreme): Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors & Fragrances, Inc. RIFM report number 47747.

RIFM (Research Institute for Fragrance Materials, Inc), 2003d. Indeno[4,3a-b]furan, decahydro-2,2,7,7,8,9,9-heptamethyl- and 2H-Indeno[4,5b] Furan, Decahydro-2,2,6,6,7,8,8-Heptamethyl (Amber Extreme): Determination of Flash Point. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors & Fragrances, Inc. RIFM report number 47751.

RIFM (Research Institute for Fragrance Materials, Inc), 2003e. Indeno[4,3a-b]furan, decahydro-2,2,7,7,8,9,9-heptamethyl- and 2H-Indeno[4,5b] Furan, Decahydro-2,2,6,6,7,8,8-Heptamethyl (Amber Extreme): Assessment of Ready Biodegradability; CO2 Evolution Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors & Fragrances, Inc. RIFM report number 47754.

RIFM (Research Institute for Fragrance Materials, Inc), 2003f. Indeno[4,3a-b]furan, decahydro-2,2,7,7,8,9,9-heptamethyl- and 2H-Indeno[4,5b] Furan, Decahydro-2,2,6,6,7,8,8-Heptamethyl (Amber Extreme): Determination of Hazardous Physico-Chemical Properties. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors & Fragrances, Inc. RIFM report number 47755.

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