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RIFM fragrance ingredient safety assessment, 8H-indeno(4,5-B)fura-n,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers), CAS Registry Number 338735-71-0

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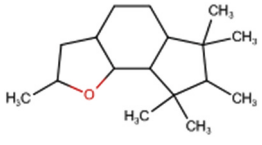
Name: 8H-Indeno(4,5-B)fura-n,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of



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isomers)
CAS Registry Number: 338735-71-0
Additional CAS*
351343-77-6
1H-Indene, 2,3,3a,4,5,7a-hexahydro-1,1,2,3,3-pentamethyl-6-(2-

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propenyl)-*Included because the materials are a commercial mixture

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., 2015a, 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.

This safety assessment is based on the RIFM Criteria Document (Api, 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.

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

8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is not genotoxic and provided a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across analog naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9) provided a calculated MOE >100 for the reproductive toxicity endpoint. Data on read-across analog 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476332-65-7) provided a NESIL of 2200 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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, 2001c; RIFM, 2005)
Repeated Dose Toxicity: NOAEL = 333 mg/k/g/day.	RIFM, (2002h)
Reproductive Toxicity: NOAEL = 800 mg/kg/day.	(ECHA REACH Dossier: [3aR-(3aα,5aβ,9aα,9bβ)]-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b] furan; ECHA, 2015)
Skin Sensitization: NESIL = 2200 μg/cm^2.	RIFM, (2003b)
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: 0% (OECD 301B) for CAS # 338735-71-0	RIFM, (2002f)
Bioaccumulation: Screening-level: 1020 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.274 mg/L	(ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

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

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.274 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0274 μg/L

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

1. Identification

Chemical Name: 8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers)	Chemical Name: 1H-Indene, 2,3,3a,4,5,7a-hexahydro-1,1,2,3,3-pentamethyl-6-(2-propenyl)-
CAS Registry Number: 338735-71-0	**CAS Registry Number:** 351343-77-6
Synonyms: tris amber super; 8H-Indeno (4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl Mixture of isomers	**Synonyms:** 1H-Indene, 2,3,3a,4,5,7a-hexahydro-1,1,2,3,3-pentamethyl-6-(2-propenyl)-
Molecular Formula: $C_{17}H_{30}O$	**Molecular Formula:** $C_{17}H_{28}$
Molecular Weight: 250.42	**Molecular Weight:** 232.41
RIFM Number: 6490	**RIFM Number:** 6510
Stereochemistry: Isomer not specified. Six stereocenters and 64 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. Six stereocenters and 64 total stereoisomers possible.

2. Physical data

CAS # 338735-71-0	CAS # 351343-77-6
Boiling Point: 569±0.5 K at 103.98 kPa (RIFM, 2002c)	**Boiling Point:** Not Available
Flash Point: 128±2 °C (RIFM, 2001a)	**Flash Point:** Not Available
Log K_{OW}: > 6.20 (RIFM, 2002c)	**Log K_{OW}:** Not Available
Melting Point: 253 K (RIFM, 2002c)	**Melting Point:** Not Available
Water Solubility: 1.02 × $10^{(-3)}$ g/L of solution at 20.0±0.5 °C (RIFM, 2002c)	**Water Solubility:** Not Available
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 4.4 Pa at 25 °C (RIFM, 2002b)	**Vapor Pressure:** Not Available
UV Spectra: Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: Not Available	**Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient***

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.17% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.00035 mg/kg/day or 0.025 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0061 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 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, 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

1. **Cramer Classification:** Class III, High

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9)
   d. **Skin Sensitization:** 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476332-65-7)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) and the additional material 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

Dossier available for main CAS # 338735-71-0; accessed 09/28/20; no dossier available for additional CAS # 351343-77-6 as of 09/28/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.24
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	0.56
7	Products applied to the hair with some hand contact	1.9
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)	4.1
10B	Aerosol air freshener	6.6
11	Products with intended skin contact but minimal transfer of fragrance to	0.080

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	skin from inert substrate (feminine hygiene pad)	
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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers), the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 40%, 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, 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) 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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) in ethanol 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, 2001c). Under the conditions of the study, 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) was not mutagenic in the Ames test.

The clastogenic activity of 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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 from each dose level 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, 2005). Under the conditions of the study, 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) does not present a concern for genotoxic potential.

Additional References: RIFM, 2002a.

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

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers). In an OECD TG 407-compliant 28-day oral (intragastric intubation) repeated dose toxicity study, Sprague Dawley Crl:CD (SD) IGS BR rats (5/sex/dose) were administered the test material (Tris amber super) at dose levels of 0 (vehicle control: Arachis oil BP), 15, 150, and 1000 mg/kg/day daily for 28 days. Two recovery groups (5/sex/dose) included high-dose (1000 mg/kg/day) and vehicle controls, which were treated for 28 days and then maintained without treatment for 14 days further. There was an increase in the relative liver weights for both males (statistically significant) and females (not statistically significant) among the high-dose group animals; however, such effects had mostly regressed after the 14-day treatment-free period for the high-dose group recovery animals. Histopathological evaluation revealed alterations in the liver (centrilobular hepatocyte enlargement at 1000 mg/kg/day), kidney (globular accumulations of eosinophilic material in the renal tubular epithelium of males at 150 and 1000 mg/kg/day), and thyroid (follicular cell hypertrophy occasionally associated with depletion of colloid at 1000 mg/kg/day). Effects observed in the kidney were consistent with a condition known as hydrocarbon nephropathy, which only occurs in male rats and is not considered hazardous to human health (Lehman-McKeeman, 1992; and Lehman-McKeeman, 1990). Liver weight increases can be considered adaptive due to the lack of histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage or clinical chemistry alterations (Hall, 2012). The effects observed in the thyroid are considered an adaptive secondary response due to the induction of hepatocyte drug-metabolizing enzymes that may increase the turnover of T4 and secondary thyroid hypertrophy/hyperplasia due to stimulation of the hypothalamus-pituitary-thyroid axis (Hall, 2012). Therefore, a NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2002h).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day or 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 1000/3 or 333 mg/kg/day.

Therefore, the 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) MOE for the repeated dose toxicity endpoint can be calculated by dividing the 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) NOAEL in mg/kg/day by the total systemic exposure to 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers), 333/0.0061, or 54590.

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, 2020b) and a reference dose of 3.33 mg/kg/day.

11.1.2.1.1. Derivation of reference dose (RfD). The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) was calculated by dividing the lowest NOAEL (from the Repeated Dose

and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 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: 11/03/20.

11.1.3. Reproductive toxicity

The MOE for 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers). Read-across material naphtho [2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9; see Section VI) has sufficient reproductive toxicity data. An OECD 422/GLP gavage study was conducted on groups of 10 HanRcc: WIST (SPF) rats/sex/dose. The test material, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, was administered at doses of 0, 100, 400, and 800 mg/kg bw/day. Control rats were given the vehicle alone. The test material was administered to male rats for at least 28 days and to female rats for 16 days prior to pairing, through the pairing, and the gestation period until the F1 generation reached day 4 post-partum. There was no mortality among treated animals. Clinical signs reported during the treatment period included mid- and high-dose group animals pushing their heads through the bedding from day 14 onwards. Since there were no alterations reported in the fertility parameters or the development of the pups until the end of the study, the NOAEL for reproductive toxicity was considered to be 800 mg/kg/day, the highest dose tested (ECHA, 2015). **Therefore, the 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) MOE for the reproductive toxicity endpoint can be calculated by dividing the naphtho [2,1-b] furan, dodecahydro-3a,6,6,9a-tetramethyl- NOAEL in mg/kg/day by the total systemic exposure to 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers), 800/0.0061, or 131148.**

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across to 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476332-65-7), 8H-indeno (4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is considered a skin sensitizer with a defined NESIL of 2200 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers). Based on the existing data and read-across to 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476332-65-7; see Section VI), 8H-indeno (4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is a weak skin sensitizer with a defined NESIL of 2200 μg/cm^2. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test with 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers), no reactions indicative of sensitization were observed (RIFM, 2001b). However, in a murine local lymph node assay (LLNA), read-across material 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% (11,875 μg/cm^2) (RIFM, 2003a). In a Confirmation of No Induction in Humans (CNIH) test with 2000 μg/cm^2 of 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) in 1:3 diethyl phthalate: ethanol, no reactions indicative of sensitization was observed in any of the 109 volunteers (RIFM, 2001d). Additionally, in a CNIH test with 2204 μg/cm^2 of read-across material 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, 2003b).

Based on the available data and read-across to (2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl), 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (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, 2020b) and a reference dose of 3.33 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, 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) in 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, 2009). Based on the lack of absorbance, 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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, 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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers). Based on the Creme RIFM Model, the inhalation exposure is 0.025 mg/day. This exposure is 18.8 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 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.

Table 1
Data summary for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl as read-across for 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers).

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; 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 test or HMT.
[c] WoE NESIL limited to 2 significant figures.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) was performed following the RIFM Environmental Framework (Salvito, 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, 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) 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, 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.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. For CAS # 338735-71-0.

RIFM, 2002f, (2002g): The ready biodegradability of the test material was evaluated according to the OECD 301B method. No biodegradation was observed after 28 days.

11.2.2.2. Ecotoxicity. For CAS # 338735-71-0.

RIFM, 2002d: A fish (Rainbow trout) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 based on the time-weighted mean measured test concentrations was greater than 0.49 mg/L.

RIFM, 2002e: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 96-h LC50 based on the time-weighted mean measured test concentrations was greater than 0.31 mg/L.

RIFM, 2002f: An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 values for growth rate and biomass, based on the mean measured test concentrations, were reported to be greater than 1.9 mg/L.

11.2.2.3. Other available data. 8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) has been registered for REACH with no additional data at this time.

11.2.2.4. Risk assessment refinement. Since 8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	6.0	6.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional VoU for both CAS #s.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.07			1000000	0.00007	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.364	0.274	0.658	10000	0.0274	Neutral Organics

The RIFM PNEC is 0.0274 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: 11/06/20.

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 05/11/21.

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. 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.2021.112644.

Appendix

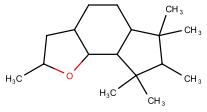
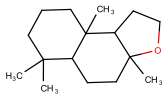
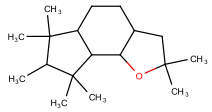
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, 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 EPA, 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (Mixture of isomers)	Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-	2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl
CAS No.	338735-71-0 and 35143-77-6 (mixture)	3738-00-9	476332-65-7
Structure			
Similarity (Tanimoto Score)		0.81	0.95
Read-across Endpoint		• Reproductive toxicity	• Skin sensitization
Molecular Formula	$C_{17}H_{30}O$	$C_{16}H_{20}O$	$C_{18}H_{32}O$
Molecular Weight	250.43	236.40	264.46
Melting Point (°C, EPI Suite)	70.34	74.13	78.02
Boiling Point (°C, EPI Suite)	285.77	276.83	293.01
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.366	0.524	0.213
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	5.06	4.76	5.52
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.113	2.436	0.3807
J_{max} (μg/cm^2/h, SAM)	0.401	0.777	8.120
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.61E+001	4.98 + 001	8.77E+001
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH_2	• Non-binder, without OH or NH_2	
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)	• Toxicant (good reliability)	
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		• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alerts found		• No alerts 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 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) (CAS # 338735-71-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9) and 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476332-65-7) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9) was used as a read-across analog for the target material 8H-indeno (4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) (CAS # 338735-71-0) for the reproductive toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of cyclic ethers.
  - o The target material and the read-across analog share a fused tricyclic ether with methyl groups substituted on the ring.
  - o The key difference between the target material and the read-across analog is that the target material has 6 methyl groups substituted on the cyclic structure, whereas the read-across analog has 4 methyl groups. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the fused tricyclic ether with methyl groups substituted on the ring. 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 have an alert of toxicant with good reliability. The data for the read-across analog confirm that the material has an adequate MOE under the current level of use. Therefore, based on the structural similarity between the target material and the read-across analog, as well as the data for the read-across analog, the *in silico* alert is superseded.
- 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.

- 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476332-65-7) was used as a read-across analog for the target material 8H-indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl (mixture of isomers) (CAS # 338735-71-0) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to the class of cyclic ethers.
  - The target material and the read-across analog share a fused tricyclic ether with methyl groups substituted on the ring.
  - The key difference between the target material and the read-across analog is that the target material has 6 methyl groups substituted on the cyclic structure, whereas the read-across analog has 7 methyl groups. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the fused tricyclic ether with methyl groups substituted on the ring. 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.

References

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