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RIFM fragrance ingredient safety assessment, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-, CAS Registry Number 79771-15-6

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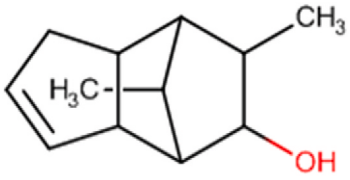


Name: 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-
CAS Registry Number: 79771-15-6
Additional CAS Numbers*: 94248-21-2 3a,4,5,6,7,7a-Hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol
*Included because these materials are a commercial mixture

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; Safford et al., 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 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
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

(*continued on next column*)

(*continued*)

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.

4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- is not genotoxic. Data on read-across materials acetoxydihydrodicyclopentadiene (CAS # 54830-99-8) and acetic acid (CAS # 64-19-7) provided a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across material tricyclo [3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3) provided a No Expected Sensitization Induction Level (NESIL) of 3000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoint was completed based on data and ultraviolet/visible (UV/Vis) spectra; 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material (0.47 mg/day). The environmental endpoints were evaluated; 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- was not found to be Persistent, Bioaccumulative, and Toxic (PBT) 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, 2017c; RIFM, 2017d)
Repeated Dose Toxicity: NOAEL = 464.1 mg/kg/day.	RIFM (2012)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	RIFM (2010)
Skin Sensitization: NESIL = 3000 μg/cm^2.	(RIFM, 1991a; RIFM, 1991b)
Phototoxicity/ Photoallergenicity: Not phototoxic/not expected to be photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 1980a; RIFM, 1981)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 2% (OECD 301 D) for CAS # 94248-21-2	RIFM (2017e)
Bioaccumulation: Screening-level: 93.36 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 12.16 mg/L	(RIFM Framework; Salvito, 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: 12.16 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.01216 μg/L

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

1. Identification

Chemical Name: 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-	**Chemical Name**: 3a,4,5,6,7,7a-Hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol
CAS Registry Number: 79771-15-6	**CAS Registry Number:** 94248-21-2
Synonyms: Dimethyl cyclormol; 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-	**Synonyms:** 3a,4,5,6,7,7a-Hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol; 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-; Dimethyl cyclormol
Molecular Formula: $C_{12}H_{18}O$	**Molecular Formula:** $C_{12}H_{18}O$
Molecular Weight: 178.27	**Molecular Weight:** 178.27
RIFM Number: 7091	**RIFM Number:** 5509
Stereochemistry: Isomer not specified. Seven stereocenters present and 128 stereoisomers possible.	**Stereochemistry:** Isomer not specified. Seven stereocenters present and 128 stereoisomers possible.

2. Physical data

CAS # 79771–15–6	**CAS # 94248–21–2**
Boiling Point: 260.52 °C (EPI Suite)	**Boiling Point:** 250.09 °C (EPI Suite)
Flash Point: >93 °C (Globally Harmonized System [GHS])	**Flash Point:** >93 °C (GHS)
Log K_{OW}: 2.68 (EPI Suite)	**Log K_{OW}:** 3.49 (EPI Suite)
Melting Point: 42.61 °C (EPI Suite)	**Melting Point:** 40.7 °C (EPI Suite)
Water Solubility: 940.3 mg/L (EPI Suite)	**Water Solubility:** 189.8 mg/L (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.00114 mm Hg at 25 °C (EPI Suite), 0.000585 mm Hg at 20 °C (EPI Suite v4.0)	**Vapor Pressure:** 0.00227 mm Hg at 25 °C (EPI Suite), 0.00118 mm Hg at 20 °C (EPI Suite v4.0)
UV Spectra: No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; the 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. 0.1–1 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.12% (RIFM, 2017a)
2. **Inhalation Exposure****: 0.00060 mg/kg/day or 0.048 mg/day (RIFM, 2017a)
3. **Total Systemic Exposure*****: 0.0022 mg/kg/day (RIFM, 2017a)

*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 fine fragrances, inhalation exposure, and total exposure.

**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 IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

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)

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

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Acetoxydihydrodicyclopentadiene (CAS # 54830-99-8) and acetic acid (CAS # 64-19-7)
   c. **Reproductive Toxicity:** Acetoxydihydrodicyclopentadiene (CAS # 54830-99-8) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** Tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- is not reported to occur in food by the VCF.*

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

9. REACH dossier

The combined materials are pre-registered for 2010; no dossier available as of 09/30/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-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)	0.23
2	Products applied to the axillae	0.069
3	Products applied to the face/body using fingertips	0.57

(*continued on next page*)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
4	Products related to fine fragrances	1.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.33
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.33
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.33
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.57
7	Products applied to the hair with some hand contact	0.57
8	Products with significant ano-genital exposure (tampon)	0.11
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.5
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.7
10B	Aerosol air freshener	9.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.11
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 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-, the basis was the reference dose of 4.6 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 3000 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; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl 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, 2014b). 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 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl 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 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl 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, 2017c). Under the conditions of the study, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl was not mutagenic in the Ames test.

The clastogenic activity of 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl 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 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl in DMSO at concentrations up to 1780 μg/mL in the DRF study; micronuclei analysis was conducted at 200 μg/mL in presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl 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, 2017d). Under the conditions of the study, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.2. Repeated dose toxicity

The MOE for 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data for the target material. Read-across materials acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI) have sufficient data for repeated dose toxicity. Based on the available data (NICNAS, 2013; EFSA, 2012; JECFA, 2006; US FDA, 2018), acetic acid does not show specific reproductive or developmental toxicity. Thus, acetic acid does not pose any systemic (repeated dose) toxicity to human health when used in fragrances. An OECD/GLP 408 dietary 90-day study was conducted in Sprague Dawley Crl:CD BR strain rats. Groups of 10 rats/sex/group were administered the test material acetoxydihydrodicyclopentadiene (mixture of isomers) at doses of 0, 200, 2000, 6000, or 20000 ppm (equivalent to a mean achieved doses of 0, 15.3, 154.9, 464.1, or 1504.6 mg/kg/day, respectively). A reduction in overall bodyweight gain was detected in animals of either sex treated with 20000 ppm. Animals of either sex treated with 20000 ppm showed a reduction in overall food consumption, and food efficiency was also adversely affected during periods of the treatment phase. Organ weight analysis revealed statistically significant increases in both absolute and relative adrenal weights among high-dose males. Microscopic examination of the adrenals showed an increase in the incidence of vacuolation of the zona fasciculata in all treated males. This was considered to be an adaptive response to stress. There was a statistically significant increase in both the absolute and relative kidney weight alterations among treated males. Microscopic examination of kidneys revealed treatment-related hyaline droplet nephropathy among all treated males. The α-2u-globulin nature of this finding was confirmed by additional Mallory's Heidenhain staining performed on male kidneys. Kidney changes in males were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). Microscopic alterations in the liver included minimal centrilobular to midzonal hepatocellular hypertrophy in males treated with 2000, 6000, or 20000 ppm test material. Elevated incidences of mostly diffuse vacuolation were found in males from all treatment

groups; this vacuolation did not exceed slight severity degrees. The microscopic alterations in the liver among treated males were not considered to be toxicologically relevant since there were no liver weight increases or related alterations in clinical chemistry parameters. The authors of the study concluded a NOAEL of 6000 ppm for females, based on decreased body weights. However, they did not provide a NOAEL for males due to treatment-related alterations in the kidney. Since the alterations in the kidneys were consistent with α-2u-globulin nephropathy and due to the absence of such effects among treated females, these changes were not considered to be adverse. Thus, the NOAEL for males was also considered to be 6000 ppm, based on decreased body weights among high-dose group animals. A NOAEL of 6000 ppm or 464.1 mg/kg/day was considered for this study (RIFM, 2012; data also available in RIFM, 2014a). **Therefore, the 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the acetoxydihydrodicyclopentadiene NOAEL in mg/kg/day by the total systemic exposure to 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-, 464.1/0.0022 or 210955.**

11.1.3. Derivation of reference dose (RfD)

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 4.6 mg/kg/day.

The RIFM Criteria Document (Api et al., 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 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 464.1 mg/kg/day by the uncertainty factor, 100 = 4.6 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/21.

11.1.4. Reproductive toxicity

The MOE for 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.4.1. Risk assessment. There are no reproductive toxicity data on 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-. Read-across material acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section VI) is expected to hydrolyze to 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- (target material) and acetic acid (CAS # 64-19-7; see Section VI). Based on the available data (EFSA, 2012; NICNAS, 2013; US FDA, 2018), acetic acid does not show specific developmental toxicity or fertility effects. Thus, acetic acid does not pose any systemic (repeated dose), developmental toxicity, or fertility effects on human health when used in fragrances.

Read-across material acetoxydihydrodicyclopentadiene (CAS # 54830-99-8) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. An OECD 421 oral gavage reproduction and developmental toxicity screening test was conducted in Wistar Han:HsdRccHan:WIST strain rats. Groups of 10 rats/sex/dose were administered via oral gavage with test material, acetoxydihydrodicyclopentadiene (mixture of isomers) at doses of 0, 100, 300, or 1000 mg/kg/day in an Arachis oil BP vehicle, for up to 43 consecutive days (including a 2-week maturation phase, pairing, gestation, and early lactation for females). There were no treatment-related developmental effects in the litter parameters evaluated or on any reproductive effects. Thus, the NOAEL for developmental toxicity and fertility was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010). **Therefore, the 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- MOE for the reproductive toxicity endpoint can be calculated by dividing the acetoxydihydrodicyclopentadiene NOAEL in mg/kg/day by the total systemic exposure to 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-, 1000/0.0022 or 454545.**

Additional References: RIFM, 2012; RIFM, 2014a.

Literature Search and Risk Assessment Completed On: 05/31/21.

11.1.5. Skin sensitization

Based on the existing data for additional material 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol (CAS # 94248-21-2) and read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3), 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- is considered a skin sensitizer with a defined NESIL of 3000 μg/cm^2.

11.1.5.1. Risk assessment. No data are available for the target material, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-. Based on the existing data on the additional material, 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol and read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3; see Section VI), the target material is considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (RIFM, 2016a; RIFM, 2016b). However, in a murine local lymph node assay (LLNA), read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- was not found to be sensitizing up to 30% (7500 μg/cm^2) (RIFM, 2004). In a guinea pig maximization test, read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8--methylene- reactions indicative of sensitization were observed at 60% (RIFM, 1992; Environmental Protection Agency, 1991). In a guinea pig Beuhler test, the additional material 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol presented reactions indicative of sensitization at 5% (RIFM, 1980c). Read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- did not present reactions indicative of sensitization (RIFM, 1989b; Environmental Protection Agency, 1991). In 3 Confirmation of No Induction in Humans tests (CNIHs) with 2.5% or (1250 μg/cm^2) in alcohol SDA 39C of 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol and 1% (500 μg/cm^2) in alcohol SD 39C or 3% (1500 μg/cm^2) in alcohol SD 39C of read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol,

Table 1
Data summary for tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- as read-across material for 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-.

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
>7500 [1]	Weak	3000	NA	NA	3000

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.

4-methyl-8-methylene-, no reactions indicative of sensitization were observed in any of the 53, 53, and 50 volunteers, respectively (RIFM, 1980b; RIFM, 1989a; RIFM, 1990; Environmental Protection Agency, 1991). Additionally, in 2 combined CNIHs with 6% (3000 μg/cm^2) of read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8--methylene- in ethanol-based vehicle, no sensitization reactions were observed in any of the 99 volunteers (RIFM, 1991a; RIFM, 1991b).

Based on the available data on read-across material tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene-, summarized in Table 1, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-is considered to be a weak skin sensitizer with a defined NESIL of 3000 μg/cm^2. 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 4.6 mg/kg/day.

Additional References: RIFM, 2017b.

Literature Search and Risk Assessment Completed On: 05/26/21.

11.1.6. Phototoxicity/photoallergenicity

Based on the available data and UV/Vis spectra, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6.1. Risk assessment. 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). In a mouse phototoxicity study on an additional material, 3a,4,5,6,7,7a-Hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol (CAS # 94248-21-2), no reactions indicative of phototoxic responses were observed (RIFM, 1980a). In a human phototoxicity study with 10 human volunteers, there were no observed phototoxic reactions in response to 1% of the additional material 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol (RIFM, 1981). Based on the lack of absorbance and the available *in vivo* study data on the additional material, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- does not present a concern for phototoxicity or photoallergenicity.

11.1.6.2. 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} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

11.1.7. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The material, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.7.1. Risk assessment. There are no inhalation data available on 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.048 mg/day. This exposure is 9.8 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/28/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- 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, 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- 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 identified 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- 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 $\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.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 2017e: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 2% was observed after 28 days.

11.2.2.1.1. Ecotoxicity. No data available.

11.2.2.2. Other available data. 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- has been pre-registered for REACH with no additional data at this time.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	12.16			1000000	0.01216	

11.2.2.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.49	3.49
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use.

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

The RIFM PNEC is 0.01216 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/25/21.

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 09/30/21.

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.2021.112727.

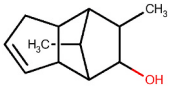
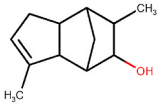
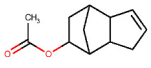
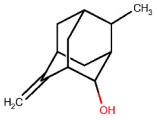
Appendix

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, 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, 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	Read-across Material
Principal Name	4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- ***and*** 3a,4,5,6,7,7a-Hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol	Acetoxydihydrodicyclopentadiene (Mixture of Isomers)	Acetic acid	Tricyclo[3.3.1.1.(3.7)] decan-2-ol, 4-methyl-8-methylene-
CAS No.	79771-15-6 ***and*** 94248-21-2	54830-99-8	64-19-7	122760-84-3
Structure	 ***and*** 			
Similarity (Tanimoto Score)		0.63	0.07	0.56
Read-across Endpoint		• Reproductive Toxicity • Repeated Dose Toxicity	• Reproductive Toxicity • Repeated Dose Toxicity	• Skin Sensitization
Molecular Formula	$C_{12}H_{18}O$ ***and*** $C_{12}H_{18}O$	$C_{12}H_{16}O_2$	$C_2H_4O_2$	$C_{12}H_{18}O$
Molecular Weight	178.27 ***and*** 178.27	192.25	60.05	178.27
Melting Point (°C, EPI Suite)	42.61 ***and*** 40.70	44.07	16.64	50.74
Boiling Point (°C, EPI Suite)	260.52 ***and*** 250.09	253.97	117.90	258.98
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.152 ***and*** 0.302	1.94	2.09E+003	0.14
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.68 ***and*** 3.49	2.98	−0.17	3.23
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	940.3 ***and*** 189.8	137.4	1e+006	318.6
J_{max} (μg/cm^2/h, SAM)	48.872 ***and*** 123.839	22.988	6283.04	126.367
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.64E-001 ***and*** 2.843E-001	1.36E+002	1.45E-002	7.833E-002
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized ***and*** Not categorized	• Not categorized	• Carboxylic acids (Hepatotoxicity) No rank	
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Moderate binders, OH group	• Non-binder, without OH or NH2 group	• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Toxicants (good reliability)	• Toxicant (good reliability)	• Toxicant (low reliability)	
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found for either material			• No alert found
Protein Binding (OECD)	• No alert found for either material			• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH) for either material			• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found for either material			• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found for either material			• No alert found
Metabolism				
		• See Supplemental Data 3	• No metabolites	

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1 ***and*** Supplemental Data 2			• See Supplemental Data 4

Summary

There are insufficient toxicity data on 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- (CAS # 79771-15-6) and 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol (CAS # 94248-21-2) (mixture). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8), acetic acid (CAS # 64-19-7), and tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Read-across ester acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) and read-across acid acetic acid (CAS # 64-19-7) are used as read-across analogs for the target material 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- (CAS # 79771-15-6) and 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol (CAS # 94248-21-2) (mixture) for the repeated dose and reproductive toxicity endpoints.
  - o The read-across ester (CAS # 54830-99-8) is expected to be hydrolyzed into read-across materials acetic acid (CAS # 64-19-7) and 4,7-methano-1H-inden-6-ol (CAS # 5071-81-8) alcohol. The main differences between the target alcohol and the alcohol obtained from the read-across ester hydrolysis are the position of the double bond and the inclusion of 2 methyl groups in the target materials. These differences are toxicologically insignificant.
  - o The target materials and the read-across analogs have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o The read-across material acetic acid is categorized as a carboxylic acid substance with hepatotoxicity alert for repeated dose toxicity by the HESS categorization scheme. It has been shown by numerous studies that carboxylic acids are excreted out from the human body relatively quickly with no toxic effects. The data described in the repeated dose section above show that the MOE of the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - o The target materials and read-across analogs have a toxicant alert for developmental toxicity (CAESAR v2.1.6). The data described in the reproductive toxicity section shows that the MOE is adequate at the current level of use. The predictions are superseded by the data.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target materials and the read-across analogs.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analogs and the target materials.
- Tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3) was used as a read-across analog for the target material 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl- (CAS # 79771-15-6) and 3a,4,5,6,7,7a-hexahydro-2,6(or 3,6)-dimethyl-4,7-methano-1H-inden-5-ol (CAS # 94248-21-2) (mixture) for the skin sensitization endpoint.
  - o The target materials and the read-across analog are structurally similar and belong to a class of unsaturated bridged macrocyclic secondary alcohols.
  - o The target materials and the read-across analog are isomers.
  - o The key difference between the target materials and the read-across analog is that the target materials have an endocyclic vinylene group, whereas the read-across analog has an exocyclic vinyl terminal group. This structural difference is toxicologically insignificant.
  - o The similarity between the target materials and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target materials and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target materials and the read-across analog.
  - o The target materials and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target materials.

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 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? No
Q22. A common component of food? No
Q33. Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No, Class III (High Class)

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