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RIFM fragrance ingredient safety assessment, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-, CAS Registry Number 285977-85-7

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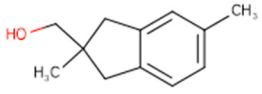

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Name: 1H-Indende-2-methanol, 2,3-dihydro-2,5-dimethyl-

CAS Registry Number: 285977-85-7

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

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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., 2021)
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 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 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.

1H-Indende-2-methanol, 2,3-dihydro-2,5-dimethyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- is not genotoxic. Data on 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra for read-across analog 2-(1,1,2,3,3-pentamethylindan-5-yl)-1-propanol (CAS # 1217-08-9); 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 1999; RIFM, 2013)
Repeated Dose Toxicity: NOAEL = 167 mg/kg/day.	RIFM (2012)
Reproductive Toxicity: Developmental toxicity: NOAEL = 250 mg/kg/day. Fertility: NOAEL = 500 mg/kg/day.	RIFM (2012)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: (2,5-Dimethyl-2,3-dihydro-1H-inden-2-yl)methanol; ECHA, 2019; RIFM, 2001)
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: 7% (OECD 301B)	RIFM (2000)
Bioaccumulation: Screening-level: 46.54 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 4.974 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 et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 4.974 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.4974 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** 1H-Indende-2-methanol, 2,3-dihydro-2,5-dimethyl-
2. **CAS Registry Number:** 285977-85-7
3. **Synonyms:** (2,5-Dimethyl-2,3-dihydro-1H-inden-2-yl)methanol; Lilyflore; 2,3-Dihydro-2,5-dimethyl-1H-indene-2-methanol; 1H-Indende-2-methanol, 2,3-dihydro-2,5-dimethyl-
4. **Molecular Formula:** $C_{12}H_{16}O$
5. **Molecular Weight:** 176.25 g/mol
6. **RIFM Number:** 9435
7. **Stereochemistry:** Stereoisomer not specified. One chiral center is present. Two total enantiomers are possible.

2. Physical data

1. **Boiling Point:** 278.50 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 2.48 (EPI Suite)
4. **Melting Point:** 71.12 °C (EPI Suite)

5. **Water Solubility:** 459.1 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00287 mm Hg at 25 °C (EPI Suite), 0.382 Pa at 25 °C (EPI Suite)
8. **UV Spectra:** Not available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.06% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000032 mg/kg/day or 0.0023 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00086 mg/kg/day (RIFM, 2021)

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

6.1. Cramer Classification

II* (Expert Judgment)

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

*See the Appendix below for details.

6.2. Analogs Selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** 2-(1,1,2,3,3-Pentamethylindan-5-yl)-1-propanol (CAS # 1217-08-9)
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

1H-Indende-2-methanol, 2,3-dihydro-2,5-dimethyl- is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Not pre-registered; no dossier available as of 02/16/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1999). Under the conditions of the study, 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-was not mutagenic in the Ames test.

The clastogenicity of 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-in dimethyl sulfoxide (DMSO) at concentrations up to 1760 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 2013). Under the conditions of the study, 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-does not present a concern for genotoxic potential.

Additional References: RIFM, 2005a.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.2. Repeated dose toxicity

The MOE for 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- 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 on 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-.

In a GLP and OECD 421-compliant study, 10 Wistar Han rats/sex/dose were administered 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- via gavage at doses of 0, 60, 250, and 1000 mg/kg/day for up to 8 weeks (including a 2-week maturation phase, pairing, gestation and early lactation for females). After 3 deaths (2 females and 1 male) at the high dose on the third day of treatment, the high dose was reduced from 1000 mg/kg/day to 500 mg/kg/day. No other mortality occurred throughout the study. Prior to the dose reduction, both sexes at 1000 mg/kg/day showed ataxia, lethargy, noisy respiration, piloerection or prostration, and reduced body weights and food consumption, but these effects disappeared once the dose was reduced to 500 mg/kg/day. The animals that died prior to the dose reduction showed raised limiting ridge in the stomach at necropsy. No other treatment-related adverse effects were observed. Based on no effects seen up to the reduced high dose (500 mg/kg/day), the NOAEL for this study was considered to be 500 mg/kg/day (RIFM, 2012).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 421 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 endpoint is 500/3 or 167 mg/kg/day.

Therefore, the 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- NOAEL in mg/kg/day by the total systemic exposure to 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-, 167/0.00086 or 194186.

In addition, the total systemic exposure to 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- (0.86 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated toxicity endpoint of a Cramer Class II material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/09/21.

11.1.3. Reproductive toxicity

The MOE for 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient repeated dose toxicity data on 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-.

In a GLP and OECD 421-compliant study, 10 Wistar Han rats/sex/dose were administered 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- via gavage at doses of 0, 60, 250, and 1000 mg/kg/day for up to 8 weeks (including a 2-week maturation phase, pairing, gestation and early lactation for females). After 3 deaths (2 females and 1 male) at the high dose on the third day of treatment, the high dose was reduced from 1000 mg/kg/day to 500 mg/kg/day. No other mortality occurred throughout the study. No treatment-related adverse effects were observed in mating performance, fertility, or gestation length. No treatment-related adverse effects were observed in litter sex ratio, offspring growth, and development. Litter size and live birth index were significantly reduced at the high dose. By day 4 post-partum, 3 of the 6 litters had lost more than 3 offspring after birth at the high dose; there were no litters in the controls or other treatment groups that lost more than 1 offspring in the same time period. Based on reduced litter survival at 500 mg/kg/day, the developmental toxicity NOAEL for this study was considered to be 250 mg/kg/day. Based on no effects seen up to the reduced high dose, the fertility NOAEL for this study was considered to be 500 mg/kg/day (RIFM, 2012).

Therefore, the 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- MOE for the developmental toxicity endpoint can be calculated by dividing the 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- NOAEL in mg/kg/day by the total systemic exposure to 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-, 250/0.00086 or 290697.

The 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- MOE for the fertility endpoint can be calculated by dividing the 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- NOAEL in mg/kg/day by the total systemic exposure to 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-, 500/0.00086 or 581395.

In addition, the total systemic exposure to 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- (0.86 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/09/21.

11.1.4. Skin sensitization

Based on the existing data, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- did not lead to skin sensitization reactions when tested at 50% (w/w) in corn oil (ECHA, 2019; RIFM, 2001). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 10% or 5000 μg/cm^2 of 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- in diethyl phthalate, no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2002).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: NICNAS, 2011.

Literature Search and Risk Assessment Completed On: 07/22/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra for the structurally related material 2-(1,1,2,3,3-Pentamethylindan-5-yl)-1-propanol (CAS # 1217-08-9), 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- 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 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- in experimental models. UV/Vis absorption spectra are not available for the target material 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-. UV/Vis absorbance spectra on the structurally related read-across analog 2-

(1,1,2,3,3-pentamethylindan-5-yl)-1-propanol (CAS # 1217-08-9) indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance for the structurally related analog, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were not available for the target material 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-. UV/Vis absorbance spectra on the structurally related material 2-(1,1,2,3,3-pentamethylindan-5-yl)-1-propanol (CAS # 1217-08-9) indicate no 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: 07/26/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- 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 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.0023 mg/day. This exposure is 204.3 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/19/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- 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, 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- 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 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 2000: The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 7% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. RIFM, 2005b: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on measured concentrations was reported to be 27.2 mg/L.

RIFM, 2005d: The acute fish (*Oncorhynchus mykiss*) toxicity test was conducted according to the OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on the arithmetic mean measured concentrations was reported to be 14.4 mg/L (95% CI: 9.49–21.7 mg/L).

RIFM, 2005c: The algae growth inhibition test was conducted according to the OECD 201 guidelines under non-axenic conditions. The 72-h EC50 values based on the arithmetic mean measured concentrations for growth under the curve and growth rate were reported to be 14.4 mg/L and 26.6 mg/L, respectively.

11.2.2.1.3. Other available data. 1H-Indende-2-methanol, 2,3-dihydro-2,5-dimethyl- has not been registered under REACH.

11.2.3. Risk assessment refinement

Since 1H-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- has passed the screening criteria, measured data are included for completeness and have 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	13.8			1000000	0.0138	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	7.683	4.974	6.371	10000	0.4974	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.42	3.42
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.4974 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: 07/15/21.

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 02/16/22.

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.

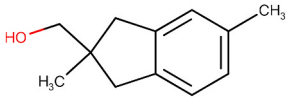
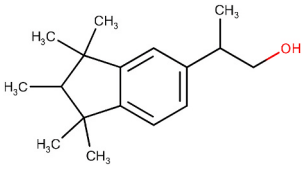
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). 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 alert system.

	Target Material	Read-across Material
Principal Name	1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-	2-(1,1,2,3,3-Pentamethylindan-5-yl)-1-propanol
CAS No.	285977-85-7	1217-08-9
Structure		
Similarity (Tanimoto Score)		0.71
SMILES	Cc1ccc2CC(C)(CO)Cc2c1	CC(CO)c1ccc2c(c1)C(C)(C)C(C)C2(C)C
Endpoint		Phototoxicity/photoallergenicity
Molecular Formula	$C_{12}H_{16}O$	$C_{17}H_{26}O$
Molecular Weight (g/mol)	176.259	246.394
Melting Point (°C, EPI Suite)	71.32	101.31
Boiling Point (°C, EPI Suite)	287.14	333.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.49E-02	3.81E-04
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.23E+02	1.28E+00
Log KOW	3.42	5.62
J_{max} (μg/cm^2/h, SAM)	18.54	0.18
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.77E-02	1.14E-01
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	N/A*	N/A*

*Not applicable for the endpoint under consideration.

Summary

There are insufficient toxicity data on 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- (CAS # 285977-85-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, read-across analog 2-(1,1,2,3,3-pentamethylindan-5-yl)-1-propanol (CAS # 1217-08-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2-(1,1,2,3,3-Pentamethylindan-5-yl)-1-propanol (CAS # 1217-08-9) was used as a read-across analog for the target material 1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl- (CAS # 285977-85-7) for the phototoxicity/photoallergenicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a structural class of aromatic compounds fused to a cyclopentane ring.
  - o The target material and the read-across analog share an aromatic and cyclopentane ring and a primary alcohol.
  - o The key difference between the target material and the read-across analog is in the methyl substitutions on the molecule. The read-across analog has a cyclopentyl ring on the aromatic ring with 5 methyl substituents while the target material has a cyclopentyl ring with 1 methyl substituent and a methyl alcohol substituent. This structural difference does not alter the chromophore and light-absorbing properties of the molecule.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$80%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$10%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.

- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. The data on the read-across analog confirm that the material does not absorb in the UV/Vis range. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the phototoxicity/photoallergenicity endpoint, and the target material can be predicted to not absorb in the UV/Vis range.

Explanation of Cramer Classification

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

Q1. 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.
Q27. Rings with substituents? No.
Q28. More than one aromatic ring? No.
Q30. Aromatic ring with complex substituents? No.
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No.
Q32. It contains only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms or c) a polyoxyethylene ($n \geq 4$) on the aromatic or aliphatic side chain? Yes. Class moderate (Class II)

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