Food and Chemical Toxicology 163 (2022) 112978

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, 2,3-dihydro-1,1-dimethyl-1-H-indene-ar-propanal, CAS Registry Number 300371-33-9

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ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

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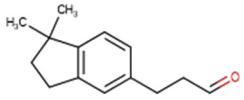
https://doi.org/10.1016/j.fct.2022.112978
Received 10 December 2021; Received in revised form 25 February 2022; Accepted 27 March 2022
Available online 30 March 2022

Version: 121021. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal
CAS Registry Number: 300371-33-9

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., 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
EC50 – Median effective concentration
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LC50 – Median lethal concentration
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

(*continued on next column*)

(*continued*)

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.
2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Target data and data from read-across analog *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0) provide 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal a No Expected Sensitization Induction Level (NESIL) of 1100 □g/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1999c; RIFM, 2016a; RIFM, 2014; Williams et al., 2017)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 1100 □g/cm^2.	(RIFM, 2004; RIFM, 2003b; RIFM, 2002a)
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 301)	RIFM (2000d)
Bioaccumulation: Critical Measured Value: <76 (OECD 305)	RIFM (2017)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* EC50: 1.307 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* EC50: 1.307 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.1307 □g/L
- Revised (Tier II) PEC/PNECs (2015 IFRA VoU): North America and Europe: <1

1. Identification

1. **Chemical Name:** 2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal
2. **CAS Registry Number:** 300371-33-9
3. **Synonyms:** 1H-indene-ar-propanal, 2,3-dihydro-1,1-dimethyl-; Hivernal; DDIP; Hivernal neo; Reaction mass of 3-(3,3-dimethyl-2,3-dihydro-1H-inden-5-yl)propanal and 3-(1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)propanal and 3-(1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)propanal; 2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal
4. **Molecular Formula:** $C_{14}H_{18}O$
5. **Molecular Weight:** 202.29 g/mol
6. **RIFM Number:** 6434

7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 574 ± 0.5 K (301 °C) at 101.06 kPa (RIFM, 2000a)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.48–3.56 (RIFM, 2000b), 4.377 (EPI Suite)
4. **Melting Point**: 77.20 °C (EPI suite)
5. **Water Solubility:** 7.78 mg/L (EPI suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000655 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 10–100 metric tons (IFRA, 2015)

IV. EXPOSURE TO FRAGRANCE INGREDIENT (CREME RIFM AGGREGATE EXPOSURE MODEL v3.1.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.019% (RIFM, 2020a)
2. **Inhalation Exposure*:** 0.000033 mg/kg/day or 0.0024 mg/day (RIFM, 2020a)
3. **Total Systemic Exposure**:** 0.00041 mg/kg/day (RIFM, 2020a)

*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; 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; Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** *p-tert*-Butyldihydrocinnamaldehyde (CAS # 18127-01-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

7. Natural occurrence

2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal is not reported to occur in foods by the VCF*.

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

8. REACH dossier

Available; accessed 11/23/21 (ECHA, 2012b).

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal 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)	0.085
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.51
4	Products related to fine fragrances	0.47
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.12
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.12
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.12
6	Products with oral and lip exposure	0.28
7	Products applied to the hair with some hand contact	0.96
8	Products with significant ano-genital exposure (tampon)	0.050
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.92
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.3
10B	Aerosol air freshener	3.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.8
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 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal, the basis was a skin sensitization NESIL of 1100 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 v3.1.4.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with and without metabolic activation, positive for genotoxicity with metabolic activation, and negative for genotoxicity without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. While the BlueScreen assay on the target material showed positive results, data from additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal 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 TA1535, TA1537, TA98, TA100, and *Escherichia coli* strains WP2uvrA were treated with 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal 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, 1999c). Under the conditions of the study, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal was not mutagenic in the Ames test.

The clastogenic activity of 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG487. Human peripheral blood lymphocytes were treated with 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal in DMSO at concentrations up to 1300 μg/mL in the presence of metabolic activation for 4 h and in the absence of metabolic activation at the 4-h and 24-h timepoints. 2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in non-activated 24-h test systems. However, a statistically significant increase in micronuclei was observed at the 4-h treatment period in the presence and absence of S9 metabolic activation. Despite these increases, a dose response was not observed, and the study was concluded to be equivocal (RIFM, 2014).

To clarify the *in vitro* micronucleus test results, a GLP-compliant 3D reconstructed skin micronucleus assay (RSMN) was conducted to assess the genotoxic potential of 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal in an EpiDerm skin model. EpiDerm tissues were treated with 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal in acetone at 24-h intervals for 48 and 72 h, at concentrations up to 12 mg/mL 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels, and therefore was concluded to be negative for the induction of micronuclei in the RSMN in EpiDerm (RIFM, 2016a).

Additionally, DNA adduct formation and comet analysis were performed using the Turkey Egg Genotoxicity Assay (TEGA). Turkey eggs were treated with 20, 40, and 80 mg/egg of 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal for 3 daily injections (from the 22nd to the 24th day). Comet and nucleotide ^{32}P post-labeling (NPL) assays were performed using samples from turkey eggs treated with 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal. No statistically significant increases in the tail intensity or tail movement were observed in the comet assay, and no DNA adducts were observed in the NPL assay. Under the conditions of the study, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal was considered to be non-genotoxic (Williams et al., 2017).

Based on the data available, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/23/21.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal or any read-across materials. The total systemic exposure to 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal (0.41 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/21.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal or any read-across materials. The total systemic exposure to 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal or any read-across materials evaluated that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal (0.41 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: 04/11/21.

10.1.4. Skin sensitization

Based on the existing data and data on the read-across material, *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0), 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is considered a skin sensitizer with a defined NESIL of 1100 μg/cm^2.

Table 1
Data summary for *p-tert*-butyldihydrocinnamaldehyde as a read-across for 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal.

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
1075 [1]	Weak	1181	4140	NA	1100

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.

10.1.4.1. Risk assessment. Based on the existing data, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is a skin sensitizer. However, the existing data is insufficient to establish the NESIL. Based on read-across to *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0; see Section VI), 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is a sensitizer with a defined NESIL of 1100 μg/cm^2. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), human cell line activation test (h-CLAT), and U-Sens test but negative in the KeratinoSens (RIFM, 2015c; RIFM, 2015b; RIFM, 2015a; RIFM, 2018). In a murine local lymph node assay (LLNA), the read-across material was found to be sensitizing with an EC3 value of 4.3% (1075 μg/cm^2) (RIFM, 2007). The guinea pig studies were available on both the target material and the read-across material. The target material, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal, did not present reactions indicative of sensitization in a guinea pig Buehler test (RIFM, 1999a). However, in a guinea pig maximization test, the target material was found to be sensitizing (RIFM, 2000c). The read-across material was also predicted to be a sensitizer in guinea pig maximization tests (RIFM, 1990; RIFM, 1980b). However, the read-across material was concluded to be sensitizing at 12.5% but non-sensitizing at 5% in a Buehler guinea pig test (RIFM, 1980b). In a Confirmation of No Induction in Humans test (CNIH) with the target material on more than 100 subjects, 1% (500 μg/cm^2) or 5% (2500 μg/cm^2) 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal in diethyl phthalate (DEP) did not result in reactions indicative of sensitization in any of the volunteers (RIFM, 1999b; RIFM, 2002a). However, no information was available on a vehicle control study. In CNIHs with the read-across material, no sensitization reactions were observed in any of the 107 volunteers when 1181 μg/cm^2 in 3:1 diethyl phthalate:ethanol (DEP:EtOH) was used for induction and challenge (RIFM, 2004; RIFM, 2003b). The read-across material was also negative in a human maximization test (RIFM, 1980a).

Based on the weight of evidence (WoE) from structural analysis and data on the read-across material *p-tert*-butyldihydrocinnamaldehyde, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is a sensitizer with a WoE NESIL of 1100 μg/cm^2 (see 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, 2020c).

Additional References: RIFM, 2002b; RIFM, 2003a.

Literature Search and Risk Assessment Completed On: 04/13/21.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal in experimental models. UV/Vis absorption spectra 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, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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: 04/13/21.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal is below the Cramer Class IIII* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal. Based on the Creme RIFM Model, the inhalation exposure is 0.0024 mg/day. This exposure is 195.8 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.

*As per Carthew et al. (2009), Cramer Class II materials default to

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	12.0			1000000	0.012	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.763	1.307	2.839	10000	0.1307	Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** v1.11	6.608	4.328	5.849			Neutral Organics SAR

Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/16/21.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal 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, 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal 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 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012a). 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.

10.2.2. Risk assessment

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

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 2000d:** The biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. Under the conditions of the study, no biodegradation was observed.

RIFM, 2016b: The biodegradability of the test material was evaluated according to the Japanese New Substance Guidance. No biodegradation was observed after 28 days.

RIFM, 2017: The bioaccumulation potential of the test material was evaluated in carp according to the OECD 305 method under flow-through conditions. The steady-state BCF was reported to be less than 76.

10.2.3.2. Ecotoxicity. **RIFM, 2015d:** A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 4.25 mg/L.

RIFM, 2015e: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 value based on geometric mean measured concentration was reported to be 6.75 mg/L and 1.27 mg/L for growth rate and yield, respectively.

RIFM, 2016c: A fish (Zebrafish) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 value based on geometric mean measured concentration was reported to be 3.76 mg/L.

10.2.4. Other available data

2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal has been registered for REACH, and no additional information is available at this time.

10.2.5. Risk assessment refinement

Since 2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal 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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.56	3.56
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 further assessment is necessary.

The RIFM PNEC is 0.1307 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: 04/22/21.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** 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 12/10/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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.2022.112978.

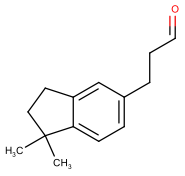
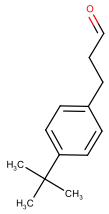
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020b). 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	2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal	*p-tert*-Butyldihydrocinnamaldehyde
CAS No.	300371-33-9	18127-01-0
Structure		
Similarity (Tanimoto Score)		0.59
SMILES	CC1(C)CCc2cc(CCC=O)ccc21	CC(C)(C)c1ccc(CCC=O)cc1
Endpoint		Skin sensitization
Molecular Formula	$C_{14}H_{18}O$	$C_{13}H_{18}O$
Molecular Weight (g/mol)	202.297	190.286

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Melting Point (°C, EPI Suite)	77.20	46.30
Boiling Point (°C, EPI Suite)	299.07	273.66
Vapor Pressure (Pa @ 25 °C, EPI Suite)	8.73E-02	6.65E-01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	7.78E+00	2.11E+01
Log K_{OW}	4.38	3.94
J_{max} (μg/cm^2/h, SAM)	0.96	2.24
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.25E-01	1.90E+00
Skin Sensitization		
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Protein Binding (OECD)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified	Alert for Schiff base formation identified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on material 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal (CAS 300371-33-9). 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, *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- *p-tert*-Butyldihydrocinnamaldehyde (CAS # 18127-01-0) was us/ed as a read-across analog for the target material 2,3-dihydro-1,1-dimethyl-1H-indene-ar-propanal (CAS # 300371-33-9) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of aromatic aldehydes.
  - o The key difference between the target material and the read-across analog is that the target material has a cyclopentyl ring substituted on the benzene, whereas in the read-across analog, a tertiary butyl group is substituted at the para position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - 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 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 have alerts for reactivity towards skin proteins via Schiff base formation. The data confirms that the read-across analog is a sensitizer. *In silico* alerts are consistent with the data.
  - o The target material 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 material.

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? Yes.
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 II (Class intermediate)

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