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RIFM fragrance ingredient safety assessment, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-, CAS Registry Number 6790-58-5

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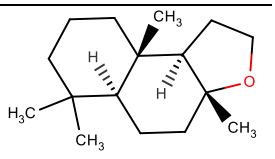

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Name: Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-
CAS Registry Number: 6790-58-5
Additional CAS*:
3738-00-9 - Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-
*Included because the materials are isomers

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

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Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- is not genotoxic and provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on additional material naphtho [2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- (CAS 3738-00-9) provide naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- a calculated MOE >100 for the reproductive toxicity endpoint. Data on the read-across analog 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476,332-65-7) provided a NESIL of 2200 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; naphtho[2,1-b] furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material; exposure is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- 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, 2016a; RIFM, 2009f)
Repeated Dose Toxicity: NOAEL = 267 mg/kg/day. RIFM (2009a)
Reproductive Toxicity: NOAEL = 800 mg/kg/day. RIFM (2009a)
Skin Sensitization: NESIL = 2200 μg/cm^2. RIFM (2003c)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV/Vis Spectra, RIFM Database; RIFM, 1990a; RIFM, 1991a; RIFM, 1979a; RIFM, 1989b; RIFM, 1990b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 100% (OECD 302C) RIFM (1999a)
Bioaccumulation:
Critical Measured Value: BCF (OECD 305): 864 (whole fish) RIFM (2009l)
Ecotoxicity:
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 0.51 mg/L RIFM (2009b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 0.51 mg/L RIFM (2009b)
RIFM PNEC is: 0.51 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

Chemical Name: Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-
CAS Registry Number: 6790-58-5
Synonyms: Ambroxan; Ambroxid; 3aR-(3aalpha,5abeta,9aalpha,9bbeta) Dodecahydro-3a,6,6,9a-tetramethylnaphtho(2,1-b)furan; Fixateur 404; Ambrofix; 3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-b] furan; 8-α,12-Oxido-13,14,15,16-tetranorlabdane; Oxido tetra nor Labdane; Ambroxid cryst; Ambrox super; Cetalox; Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-

Chemical Name: Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-
CAS Registry Number: 3738-00-9
Synonyms: 1,5,5,9-Tetramethyl-13-oxatricyclo(8.3.0.0(4,9))tridecane; 3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-b]furan; Amberiff; Amberlyn; Ambrox DL; Ambroxan; Ambroxid; Ambroxid 30% in hercolyn; Cachalox; Cetalox; Dodecahydro-3a,6,6,9a-tetramethylnaphtho(2,1-b)furan; Fixambrene; Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-; ﾋﾞｼｸﾛｼﾞﾋﾄﾞﾛﾎﾓﾌｱﾙﾈｼﾙｵｷｼﾄﾞ; Naphtho [2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-

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Molecular Formula: $C_{16}H_{28}O$ **Molecular Weight:** 236.39 **RIFM Number:** 1169 **Stereochemistry:** 3aR,5aS,9aS,9bR isomer specified. Four chiral centers and 16 total enantiomers possible.	**Molecular Formula:** $C_{16}H_{28}O$ **Molecular Weight:** 236.39 **RIFM Number:** 5010 **Stereochemistry:** Isomer not specified. Four chiral centers and 16 total enantiomers possible.

2. Physical data

CAS #: 6790-58-5	CAS #: 3738-00-9
Boiling Point: 120 °C (RIFM), 276.83 °C (EPI Suite), 597±2 K (324±2 °C) at 99.4 kPa (RIFM, 2013b)	**Boiling Point:** 276.83 °C (EPI Suite)
Flash Point: >200 °F; CC (Fragrance Materials Association), 161 °C (RIFM), >93 °C (Globally Harmonized System [GHS]), Flash point (corrected) = 155 °C at 1013 hPa (RIFM, 2008b), solubility at pH 4, 7, and 9 is very low (RIFM, 2008d)	**Flash Point:** >93 °C (GHS)
Log K_{OW}: 6.0 at 30 °C (RIFM, 1996b), (RIFM, 2005a), 4.76 (EPI Suite), 5.09 (RIFM, 2013d)	**Log K_{OW}:** 6.0 at 30 °C (RIFM, 1996d); >6.0 at 35 °C (RIFM, 1998c)
Melting Point: 74.13 °C (EPI Suite)	**Melting Point:** 74.13 °C (EPI Suite)
Water Solubility: 2.436 mg/L (EPI Suite), 1.88 mg/L (RIFM, 2009k)	**Water Solubility:** 2.436 mg/L (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.00219 mm Hg at 20 °C (EPI Suite v4.0), 0.00393 mm Hg at 25 °C (EPI Suite), 0.054 Pa at 20 °C (RIFM, 1998d)	**Vapor Pressure:** 0.00219 mm Hg at 20 °C (EPI Suite v4.0), 0.00393 mm Hg at 25 °C (EPI Suite)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: White crystalline mass	**Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient***

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.20% (RIFM, 2016b)
2. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.011 mg/day (RIFM, 2016b)
3. **Total Systemic Exposure**:** 0.0029 mg/kg/day (RIFM, 2016b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics or 97.5th percentile, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476,332-65-7)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- and the additional material are not reported to occur in foods by the VCF*.

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

9. REACH dossier

Dossier available for main CAS 6790-58-5 (accessed 04/14/21); no dossier available for additional CAS # 3738-00-9 as of 04/14/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.17
2	Products applied to the axillae	0.050
3	Products applied to the face/body using fingertips	1.0
4	Products related to fine fragrances	0.94
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.24
5B		0.24

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.24
5D	Baby cream, oil, talc	0.080
6	Products with oral and lip exposure	0.56
7	Products applied to the hair with some hand contact	1.9
8	Products with significant ano-genital exposure (tampon)	0.080
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	6.6
10B	Aerosol air freshener	6.6
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.080
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-, the basis was the reference dose of 2.67 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2200 μg/cm^2.

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

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013a). 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 naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- in solvent 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, 2016a). Under the conditions of the study, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- was not mutagenic in the Ames test.

The clastogenicity of naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung cells were treated with naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-in tetrahydrofuran (THF) at concentrations up to 1200 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 dose of the test material, either with or without S9 metabolic activation (RIFM, 2009f). Under the conditions of the study, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-was considered to be non-clastogenic to human/mammalian cells.

Based on the data available, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- does not present a concern for genotoxic potential.

Additional References: RIFM, 1989c; RIFM, 2008a; RIFM, 2009e.

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

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-. In a GLP and OECD 422-compliant study, 10 WIST (SPF) rats/sex/dose were administered the test material via gavage at doses of 0, 100, 400, or 800 mg/kg/day. Males were dosed for 28 days, while females were dosed for 16 days prior to pairing, through the pairing and gestation periods until the F1 generation reached day 4 postpartum. No mortality occurred throughout the study period. Body temperature was significantly reduced in females at the mid-dose and both sexes at high-dose; this effect followed dose-dependence but remained within historical control ranges. Food consumption was significantly decreased in males at the mid-dose and both sexes at the high-dose, but only during the first week of the pre-pairing period. This was accompanied by significant transient reductions in bodyweight gain in both sexes at high-dose (isolated days during pre-pairing in males, days 2–7 of pre-pairing in females). Platelet levels were significantly increased in males at the mid-dose and high-dose, exceeding historical control ranges at high-dose. Prothrombin time was outside historical control ranges in females at high-dose but was not significantly increased. Cholesterol and globulin levels were increased (only statistically significant for cholesterol) and were outside historical control ranges in both sexes at the mid and high doses. Protein levels were increased (not statistically significant) and outside historical control ranges in males at the mid and high doses. Absolute and relative liver weights were increased in both sexes at mid-dose and high-dose. This was accompanied by centrilobular hepatocellular hypertrophy in both sexes at mid-dose and high-dose, as well as diffuse follicular hypertrophy in the thyroid glands at minor degrees of severity in both sexes at high-dose. The thyroid alterations were considered to be secondary to liver effects. However, liver effects were not considered adverse. Increased severity of hyaline inclusions and tubular basophilia was seen in kidneys of males at mid-dose and high-dose; these were considered to represent α2-microglobulin nephropathy, which is species- and sex-specific and thus not relevant to human health. Based on there having been no toxicologically relevant, treatment-related effects seen up to the highest dose, the NOAEL for this study was considered to be 800 mg/kg/day (RIFM, 2009a).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for fragrance safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 800/3 or 267 mg/kg/day.

Therefore, the naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- MOE for the repeated dose toxicity endpoint can be calculated by dividing the naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- NOAEL in mg/kg/day by the total systemic exposure to naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-, 267/0.0029, or 92,069.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 2.67 mg/kg/day.

Derivation of reference dose (RfD)

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 267 mg/kg/day by the uncertainty factor, 100 = 2.67 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/16/20.

11.1.3. Reproductive toxicity

The MOE for naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on additional material naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-. An OECD 422/GLP gavage study was conducted on groups of 10 HanRcc: WIST(SPF) rats/sex/dose, administered test material, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- at doses of 0, 100, 400 and 800 mg/kg/day. Control rats were given the vehicle alone. The test material was administered to male rats for at least 28 days and to female rats for 16 days prior to pairing through the pairing and gestation periods until the F1 generation reached day 4 post-partum. There was no mortality among treated animals. Clinical signs reported during the treatment period included mid- and high-dose group animals pushing their heads through the bedding from day 14 onwards. Since there were no alterations reported in the fertility parameters or the development of the pups until the end of the study, the NOAEL for reproductive toxicity was considered to be 800 mg/kg/day, the highest dose tested (RIFM, 2009a). **Therefore, the naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- MOE for the reproductive toxicity endpoint can be calculated by dividing the naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- NOAEL in mg/kg/day by the total systemic exposure to naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-, 800/0.0029, or 275,862.**

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476,332-65-7), naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- is a skin sensitizer with a defined NESIL of 2200 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-. Based on the existing data and read-across 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476,332-65-7; see Section VI), naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- is a weak skin sensitizer with a defined NESIL of 2200 μg/cm^2. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- did not present reactions indicative of sensitization (RIFM, 1991b). In a murine local lymph node assay (LLNA), naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- was found to be negative up to maximum tested concentration of 10% which resulted in Stimulation Index (SI) of 1.09 (RIFM, 2013c). However, in another LLNA, read-across 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl was found to be sensitizing with an EC3 value of 47.5% (11,875 μg/cm^2) (RIFM, 2003b). In a human maximization test, no skin sensitization reactions were observed with naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- (RIFM, 1982). In a Confirmation of No Induction in Humans test (CNIH) with 5000 μg/cm^2 in diethyl phthalate (DEP), 5510 μg/cm^2 in 3:1 ethanol:diethyl phthalate (EtOH:DEP), and 2755 μg/cm^2 in 3:1 EtOH:DEP of 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl, no reactions indicative of sensitization was observed in any of the studies with 103, 49, and 51 volunteers, respectively (RIFM, 2003a; RIFM, 1998a; RIFM, 1997b). Additionally, in a CNIH with 2204 μg/cm^2 of read-across 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl in 3:1 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2003c).

Based on the available data on read-across (2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl), 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 2200 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 2.67 mg/kg/day.

Additional References: RIFM, 1971; RIFM, 1991a; RIFM, 1977; RIFM, 1990b; RIFM, 1979a; RIFM, 1979b.

Table 1
Data summary for 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl as read-across for naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-.

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

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

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and available data, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Phototoxicity and photoallergenicity were evaluated in guinea pigs (RIFM, 1990a; RIFM, 1991a; RIFM, 1989b; RIFM, 1990b) at concentrations up to 100% (phototoxicity) and 30% (photoallergenicity), and there was no evidence of phototoxicity or photoallergenicity. Phototoxicity and photoallergenicity were evaluated in volunteers in a photo-CNIH with 5% naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- (RIFM, 1979a). There were no reactions at induction or challenge. Based on the available study data and the lack of absorbance, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate 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, 2009).

Additional References: RIFM, 1976.

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

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to the lack of appropriate data. The exposure level for naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- 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 naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-. Based on the Creme RIFM Model, the inhalation exposure is 0.011 mg/day. This exposure is 42.7 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- 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) did not identify naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- 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, 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.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

For CAS # 6790-58-5.

RIFM, 2010: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 93% was observed after 28 days.

RIFM, 2009j: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 82% was observed after 28 days.

RIFM, 2009i: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 67% was observed after 28 days.

RIFM, 2009h: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 32% was observed after 28 days.

RIFM, 2008c: The ready biodegradability of the test material was evaluated using the manometric respirometry test. The mean biodegradation of −3% ($ThODNH_4$) was observed after 28 days.

RIFM, 2009g: The ready biodegradability of the test material was evaluated using the manometric respirometry test. The biodegradation of 1% was observed after 28 days.

RIFM, 2005b: The ready biodegradability of the test material was

determined by the manometric respirometry test according to the OECD 301F method. The biodegradation rate was 71% after 28 days.

RIFM, 1996a: Biodegradability of the test material was evaluated by the manometric respirometry test according to the OECD 301F method. The biodegradation rate was 68% after 28 days.

RIFM, 1997a: The inherent biodegradability of the test material was determined in a sealed vessel test CO_2 production test using an acclimatized inoculum from a modified semi-continuous activated sludge test according to the OECD 302A method. Filtered activated sludge and 4.5 mg/L of 8-α,12-oxido-13,14,15,16-tetranorlabdane was incubated on a rotary shaker for 28 days. The rate of degradation after 28 days was 16.5%.

For CAS # 3738-00-9.

RIFM, 1999b: The inherent biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 302C guideline. Biodegradation of 100% was observed after 33 days.

RIFM, 1996c: The ready biodegradability of the test material was evaluated in manometric respirometry tests according to the OECD 301F method. The biodegradation of 81% was observed after 32 days.

RIFM, 1998b: The inherent biodegradability of the test material was determined by the manometric respirometry test according to the OECD 302C guidelines. Biodegradation of 52% was observed after 28 days and 61% after 41 days.

RIFM, 1989a: The ready biodegradability of the test material was determined by the respirometric method (modified MITI test according to the OECD 301C method). No biodegradation was observed.

RIFM, 1999a: The inherent biodegradability of the test material was determined by the respirometric method according to the OECD 302C method. Under the conditions of the study, biodegradation of 100% was observed after 28 days.

RIFM, 1992: The ready biodegradability of the test material was evaluated in a closed bottle test, according to the OECD 301D method. No biodegradation was observed after 28 days.

RIFM, 2009l: A fish (Rainbow trout) bioaccumulation assay was conducted with 14C naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- according to the OECD 305 method under flow-thru conditions. The average BCF for the whole fish was reported to be 864.

Ecotoxicity

For CAS # 6790-58-5.

RIFM, 2000: A *Daphnia magna* acute immobilization test (limit test) was conducted according to the OECD 202 method under static conditions. No immobilization was observed at the concentration of 0.92 mg/L (saturated solution).

RIFM, 2009b: The acute toxicity of the test material to zebrafish (*Brachydanio rerio*) was determined in a 96-h static test (limit test) according to the OECD 203 guideline. Under the conditions of the study, the 96 h LC50 value based on the mean measured concentration and loading rate of 100 mg/L was reported to be greater than 0.51 mg/L.

RIFM, 2009d: An algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on mean measured concentrations and loading rate of 100 mg/L, for growth rate and yield, was reported to be greater than 1.4 mg/L.

RIFM, 2009c: A *Daphnia magna* acute immobilization test (limit test) was conducted according to the OECD 202 method under static conditions. Under the conditions of the study, the test material had no toxic effects on *Daphnia magna* up to its water solubility limit in test water at a loading rate of 100 mg/L (1.8 mg/L measured concentration).

For CAS # 3738-00-9.

RIFM, 1993: A *Daphnia magna* acute immobilization test was conducted according to the DIN 38412 Part II 202 method under static conditions. Under the conditions of the study, the EC50 value at 48 h based on nominal test concentration was reported to be 316 mg/L.

RIFM, 1994: A fish (Zebrafish) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. Under the conditions of the study, the LC50 value was graphically determined to be 520 mg/L at 96 h based on nominal concentrations.

Other available data

Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- has been registered under REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.0	6.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	100–1000	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional volume of use.

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

The RIFM PNEC is 0.51 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 11/06/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/14/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.11			1000000	0.00011	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.65	0.476	1.015	10000	0.0476	Neutral Organics
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.51			1000	0.51	
Daphnia		1.8				
Algae		1.4				

the work reported in this paper.

Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112454.

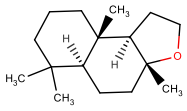
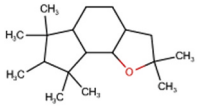
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-	2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl
CAS No.	6790-58-5	476,332-65-7
Structure		
Similarity (Tanimoto Score)		0.89
Endpoint		• Skin sensitization
Molecular Formula	$C_{16}H_{28}O$	$C_{18}H_{32}O$
Molecular Weight	236.399	264.453
Melting Point (°C, EPI Suite)	74.13	78.02
Boiling Point (°C, EPI Suite)	276.83	293.01
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.24E-01	2.13E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.44E+00	3.81E-01
Log KOW	4.76	5.52
J_{max} (μg/cm^2/h, SAM)	0.26	0.05
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.98E+01	8.77E+01
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts 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 naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- (CAS # 6790-58-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 2H-indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476,332-65-7) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl (CAS # 476,332-65-7) was used as a read-across analog for the target material naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- (CAS # 6790-58-5) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of cyclic ethers.
  - o The target material and the read-across analog share a fused tricyclic ether with methyl groups substituted on the ring.
  - o The key difference between the target material and the read-across analog is that the target material has 4 methyl groups substituted on the cyclic structure, whereas the read-across analog has 7 methyl groups. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the fused tricyclic ether with methyl groups substituted on the ring. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - 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 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.

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