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RIFM fragrance ingredient safety assessment, decahydrospiro[furan-2(3H), 5'-[4,7]methano[5H]indene], CAS Registry Number 68480-11-5

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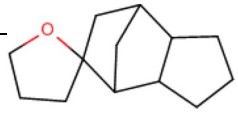

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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.

Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] is not genotoxic. Data on read-across analog naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold for toxicological concern (TTC) for a Cramer Class III material, and the exposure to decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] 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, 2007; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 267 mg/kg/day. RIFM (2009a)
Reproductive Toxicity: NOAEL = 800 mg/kg/day. RIFM (2009a)
Skin Sensitization: No safety concerns at current declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 3% (OECD 301D) (ECHA REACH Dossier: Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene]; ECHA, 2017a)

Bioaccumulation:

Screening-level: 108.3 L/kg (EPI Suite v4.11; US EPA, 2012a

Ecotoxicity:
Screening-level: Fish LC50: 10.73 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 10.73 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.01073 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene]
2. **CAS Registry Number:** 68480-11-5
3. **Synonyms:** Spiro[furan-2(3H),5'-[4,7]methano[5H]indene], decahydro-; Vigoflor; Decahydro-3H-spiro[furan-2,5'-[4,7]methanoindene]; Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene]
4. **Molecular Formula:** $C_{13}H_{20}O$
5. **Molecular Weight:** 192.3
6. **RIFM Number:** 5915
7. **Stereochemistry:** No isomer specified. Five stereocenters and 32 total stereoisomers possible

2. Physical data

1. **Boiling Point:** 248.8 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS)
3. **Log K_{OW}:** 3.59 (EPI Suite)
4. **Melting Point**: 45.76 °C (EPI Suite)
5. **Water Solubility:** 41.28 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0296 mm Hg @ 25 °C (EPI Suite), 0.0173 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0039% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000015 mg/kg/day or 0.0010 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.000043 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015a; 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 4. 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., 2015a; Safford et al., 2017; and 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 III, High

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
III	III	III

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

6. Metabolism

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

7. Natural occurrence (discrete chemical) or composition (NCS)

Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] 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 05/06/19.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] in dimethyl sulfoxide 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, 2007). Under the conditions of the study, decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] was not mutagenic in the Ames test.

The clastogenic activity of decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] in ethanol at concentrations up to 1920 μg/mL in a DRF study. Micronuclei analysis was conducted at 100 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/18/19.

10.1.2. Repeated dose toxicity

The MOE for decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene]. Read-across material, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9; see Section 5) has sufficient repeated dose toxicity data. In an OECD 422 and GLP-compliant subchronic toxicity study, 10 HanRcc: WIST(SPF) rats/sex/dose were administered the test material naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- at doses of 0, 100, 400, and 800 mg/kg/day. Treatment duration in males was at least 28 days. In females, the treatment was initiated 16 days prior to pairing and was continued until the F1 generation reached post-partum day 4. There was no mortality among treated animals. Clinical signs reported during the treatment period included the mid- and high-dose group animals pushing their heads through the bedding from day 14 onwards. Since there were no adverse effects reported during the study duration at the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 800 mg/kg/day (ECHA, 2017b).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 studies. 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 decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] MOE for the reproductive toxicity endpoint can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure to naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, 267/0.000043 or 6209302.

In addition, the total systemic exposure to decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] (0.043 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007**) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.**

*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.

Additional References: RIFM, 2009b.

Literature Search and Risk Assessment Completed On: 04/15/19.

10.1.3. Reproductive toxicity

The MOE for decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene]. Read-across material, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9; see Section 5) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. An OECD/GLP 422 gavage study was conducted on groups of 10 HanRcc: WIST(SPF) rats/sex/dose. The test material was administered at doses of 0, 100, 400, and 800 mg/kg/day in corn oil. 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, and until the F1 generation reached day 4 post-partum. In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. There was no mortality among the 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; ECHA, 2017b). **Therefore, the decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] MOE for the reproductive toxicity endpoint can be calculated by dividing the naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- NOAEL in mg/kg/day by the total systemic exposure to decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene], 800/0.000043 or 18604651.**

In addition, the total systemic exposure to decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] (0.043 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007**;** Laufersweiler et al., 2012**) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/27/19.

10.1.4. Skin sensitization

Based on the existing data and the application of the DST, decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] does not present a concern for skin sensitization under the current declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). However, in a murine local lymph node assay (LLNA), decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] was found to be sensitizing with an EC3 value of 68% (17000 μg/cm^2) (ECHA, 2017a). In guinea pigs, a Draize test resulted in no sensitization with 0.1% decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] in 4:1 acetone:olive oil (RIFM, 1975). Additionally, in multiple confirmatory human repeat insult patch tests (HRIPT) with decahydrospiro[furan-2(3H),5'-[4,7]methano

Table 1
Maximum acceptable concentrations for decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	NRU[b]
2	Products applied to the axillae	0.0015%	5.0×10^{-5}%
3	Products applied to the face using fingertips	0.029%	1.6×10^{-6}%
4	Fine fragrance products	0.027%	0.0060%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	7.8×10^{-5}%
6	Products with oral and lip exposure	0.016%	NRU[b]
7	Products applied to the hair with some hand contact	0.056%	5.6×10^{-7}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.0022%
10	Household care products with mostly hand contact	0.19%	NRU[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	0.012%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

[5H]indene] in petrolatum, no reactions indicative of sensitization were observed in any of the volunteers (RIFM, 1978; RIFM, 1977d; RIFM, 1977c; RIFM, 1977b; RIFM, 1977a). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). Although decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] was predicted *in silico* to not be directly reactive to skin proteins, the reactive DST was applied due to the positive LLNA data. The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/22/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] 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 decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] 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 significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/03/19.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene]. Based on the Creme RIFM Model, the inhalation exposure is 0.0010 mg/day. This exposure is 470 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/05/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] 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, decahydrospiro[furan-2(3H),5'-[4,7]

methano[5H]indene] was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] as possibly being 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.

10.2.1.1. Risk assessment. Based on current VoU (2015), decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] presents no risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. No data available.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.3. Other available data. Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] has been registered for REACH with the following additional data available at this time:

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guidelines. Biodegradation of 3% was observed after 28 days (ECHA, 2017a).

10.2.1.4. Risk assessment refinement. Since decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	10.73			1000000	0.01073	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.59	3.59
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
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 0.01073 μg/L. The revised PEC/PNECs for EU and North America are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 04/01/19.

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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/30/19.

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.

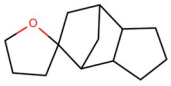
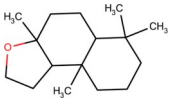
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemicals Agency (ECHA) read-across assessment framework or RAAF (ECHA, 2016).

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

	Target Material	Read-across Material
Principal Name	Decahydrospiro[furan-2(3H),5'-[4,7]methano [5H]indene]	Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-
CAS No.	68480-11-5	3738-00-9
Structure		
Similarity (Tanimoto Score)		0.86
Read-across Endpoint		• Reproductive Toxicity • Repeated Dose Toxicity
Molecular Formula	$C_{13}H_{20}O$	$C_{16}H_{28}O$
Molecular Weight	192.30	236.39
Melting Point (°C, EPI Suite)	45.76	74.13
Boiling Point (°C, EPI Suite)	248.80	276.83
Vapor Pressure (Pa @ 25 °C, EPI Suite)	3.94	0.524
Log K_{OW}(KOWWIN v1.68 in EPI Suite)	3.59	4.76
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	41.28	4.98E + 001
J_{max} (μg/cm^2/h, SAM)	14.559	0.777
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.38E + 000	5.085E + 001
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Toxicant (good reliability)
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 decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] (CAS # 68480-11-5). 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, naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl- (CAS # 3738-00-9) was used as a read-across analog for the target material decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene] (CAS # 68480-11-5) for the reproductive toxicity and repeated dose toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of multicyclic furans.
  - The target material and the read-across analog share a tetrahydrofuran functionality.
  - The key difference between the target material and the read-across analog is that the target material is a spiro multicyclic fused-bridged furan, whereas the read-across analog contains a furan fused to 2 C6 rings and substituted with 4 methyl groups in different positions. These structural differences are toxicologically insignificant.

- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- 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 $\leq 40\%$. While 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.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The read-across analog is predicted to be a toxicant by the CAESAR model for developmental toxicity while the target material is predicted to be a non-toxicant. The data described in the developmental toxicity section above shows that the read-across analog has an adequate MOE at the current level of use. Therefore, the alert will be superseded by the availability of data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111201.

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