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Short Review

RIFM fragrance ingredient safety assessment, tetrahydro-4-methyl-2-phenyl-2H-pyran, CAS Registry Number 94201-73-7

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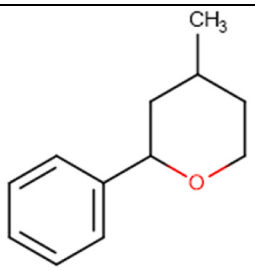

Name: Tetrahydro-4-methyl-2-phenyl-2H-pyran
CAS Registry Number: 94201-73-7
Additional CAS Numbers*:
149713-23-5 2H-Pyran, tetrahydro-4-methyl-2-phenyl-,(2R,4S)-rel
149713-24-6 2H-Pyran, tetrahydro-4-methyl-2-phenyl-, (2R,4R)-rel-*These materials are included in this assessment because they are isomers.

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., 2015, 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.

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(*continued*)

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.

Tetrahydro-4-methyl-2-phenyl-2H-pyran was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydro-4-methyl-2-phenyl-2H-pyran 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 III material, and the exposure to tetrahydro-4-methyl-2-phenyl-2H-pyran is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). Data show that there are no safety concerns for tetrahydro-4-methyl-2-phenyl-2H-pyran for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; tetrahydro-4-methyl-2-phenyl-2H-pyran is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; tetrahydro-4-methyl-2-phenyl-2H-pyran 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 (VoU) 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, 2014b; RIFM, 2014a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization. (RIFM, 2013d; RIFM, 2021b)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant/photoallergen. (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: 46% (OECD 301B) RIFM (2013e)
Bioaccumulation:
Screening-level: 91.8 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 48-h *Daphnia magna* LC50: 4.419 mg/L (ECOSAR v2.0; 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, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 4.419 mg/L (ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 0.4419 μg/L
- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe: <1

1. Identification

1. Chemical Name: Tetrahydro-4-methyl-2-phenyl-2H-pyran	1. Chemical Name: 2H-Pyran, tetrahydro-4-methyl-2-phenyl-, (2R,4S)-rel	1. Chemical Name: 2H-Pyran, tetrahydro-4-methyl-2-phenyl-, (2R,4R)-rel-
2. CAS Registry Number: 94201-73-7 **3. Synonyms:** 2H-Pyran, tetrahydro-4-methyl-2-phenyl-; Doremox;	**2. CAS Registry Number:** 149713-23-5 **3. Synonyms:** 2H-Pyran, tetrahydro-4-methyl-2-phenyl-; Doremox;	**2. CAS Registry Number:** 149713-24-6 **3. Synonyms:** 2H-Pyran, tetrahydro-4-methyl-2-phenyl-; Doremox;

(*continued on next page*)

(*continued*)

1. Chemical Name: Tetrahydro-4-methyl-2-phenyl-2H-pyran	1. Chemical Name: 2H-Pyran, tetrahydro-4-methyl-2-phenyl-, (2R,4S)-rel	1. Chemical Name: 2H-Pyran, tetrahydro-4-methyl-2-phenyl-, (2R,4R)-rel-
Tetrahydro-4-methyl-2-phenyl-2H-pyran **4. Molecular Formula:** $C_{12}H_{16}O$ **5. Molecular Weight:** 176.25 g/mol **6. RIFM Number:** 5508 **7. Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers possible	Tetrahydro-4-methyl-2-phenyl-2H-pyran **4. Molecular Formula:** $C_{12}H_{16}O$ **5. Molecular Weight:** 176.25 g/mol **6. RIFM Number:** 5508 **7. Stereochemistry:** (2R, 4S)-isomer specified	Tetrahydro-4-methyl-2-phenyl-2H-pyran **4. Molecular Formula:** $C_{12}H_{16}O$ **5. Molecular Weight:** 176.25 g/mol **6. RIFM Number:** 5508 **7. Stereochemistry:** (2R,4R)- isomer specified

2. Physical data

CAS # 94201-73-7	CAS # 149713-23-5	CAS # 149713-24-6
1. Boiling Point: 525 ± 2 K (252 ± 2 °C) at 97.7 kPa (RIFM, 2006b), 255.08 °C (EPI Suite v4.11)	**1. Boiling Point:** 255.08 °C (EPI Suite v4.11)	**1. Boiling Point:** 255.08 °C (EPI Suite v4.11)
2. Flash Point: 114 °C (Globally Harmonized System [GHS]), 114 ± 2 °C (RIFM, 2006b)	**2. Flash Point:** 114 °C (GHS)	**2. Flash Point:** Not available
3. Log K_{OW}: 3.43 (RIFM, 2006b), 3.48 (EPI Suite v4.11)	**3. Log K_{OW}:** 3.48 (EPI Suite v4.11)	**3. Log K_{OW}:** 3.48 (EPI Suite v4.11)
4. Melting Point: Less than 253 ± 0.5 K (−20 ± 0.5 °C) (RIFM, 2006b), 21.63 °C (EPI Suite v4.11)	**4. Melting Point**: 21.63 °C (EPI Suite v4.11)	**4. Melting Point**: 21.63 °C (EPI Suite v4.11)
5. Water Solubility: 0.213 g/kg of solution at 20 ± 0.5 °C (RIFM, 2006b), 61.27 mg/L at 25 °C (EPI Suite v4.11)	**5. Water Solubility:** 61.27 mg/L at 25 °C (EPI Suite v4.11)	**5. Water Solubility:** 61.27 mg/L at 25 °C (EPI Suite v4.11)
6. Specific Gravity: Not Available	**6. Specific Gravity:** Not available	**6. Specific Gravity:** Not available
7. Vapor Pressure: 3.44 Pa at 25 °C (RIFM, 2013f), 0.0207 mm Hg at 25 °C (EPI Suite v4.11), 0.013 mm Hg at 20 °C (EPI Suite v4.0)	**7. Vapor Pressure:** 0.0207 mm Hg at 25 °C (EPI Suite v4.11)	**7. Vapor Pressure:** 0.0207 mm Hg at 25 °C (EPI Suite v4.11)
8. UV Spectra: Not available	**8. UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**8. UV Spectra:** Not available
9. Appearance/ Organoleptic: Not available	**9. Appearance/ Organoleptic:** Not available	**9. Appearance/ Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 10–100 metric ton per year (IFRA, 2019).

4. Exposure to fragrance ingredient* (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0015% (RIFM, 2021a)
2. **Inhalation Exposure****: 0.00049 mg/kg/day or 0.042 mg/day (RIFM, 2021a)
3. **Total Systemic Exposure*****: 0.00067 mg/kg/day (RIFM, 2021a)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5 (OECD, 2021)
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

Tetrahydro-4-methyl-2-phenyl-2H-pyran (CAS # 94201-73-7), 2H-pyran, tetrahydro-4-methyl-2-phenyl-,(2R,4S)-rel (CAS # 149713-23-5); and 2H-pyran, tetrahydro-4-methyl-2-phenyl-, (2R,4R)-rel- (CAS # 149713-24-6) 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

Available for tetrahydro-4-methyl-2-phenyl-2H-pyran (CAS # 94201-73-7) (ECHA, 2014); accessed on 09/08/22. Not available for

2H-pyran, tetrahydro-4-methyl-2-phenyl-,(2R,4S)-rel (CAS # 14971 3-23-5). Not available for 2H-Pyran, tetrahydro-4-methyl-2-phenyl-, (2R,4R)-rel- (CAS # 149713-24-6).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, tetrahydro-4-methyl-2-phenyl-2H-pyran does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Tetrahydro-4-methyl-2-phenyl-2H-pyran was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with metabolic activation, negative for cytotoxicity without 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 (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of tetrahydro-4-methyl-2-phenyl-2H-pyran has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with tetrahydro-4-methyl-2-phenyl-2H-pyran in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. A 3.1-fold increase in the mean number of revertant colonies was observed at 50 μg/plate in strain TA1537 absence of S9 (RIFM, 2014b). However, this fold increase was only observed in the confirmatory assay and was attributed to a relatively low count of the mean number of revertant colonies in the concurrent vehicle control. To address this, a repeat assay was conducted with TA1537 in the absence of S9 at concentrations of 6.25, 12.5, 25.0, 50.0, 160, 500, 1600, and 5000 μg/plate. The test material was cytotoxic at concentrations ≥1600 μg/plate in strain TA1537 without S9, and no precipitate was observed at any concentration. No increases in the mean number of revertant colonies were observed at any concentration. Under the conditions of the study, tetrahydro-4-methyl-2-phenyl-2H-pyran was not mutagenic in the Ames test.

The clastogenic activity of tetrahydro-4-methyl-2-phenyl-2H-pyran 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 tetrahydro-4-methyl-2-phenyl-2H-pyran in DMSO at concentrations up to 1765 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 500 μg/mL in the presence and absence of metabolic activation. Tetrahydro-4-methyl-2-phenyl-2H-pyran did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2014a). Under the conditions of the study, tetrahydro-4-methyl-2-phenyl-2H-pyran was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, tetrahydro-4-methyl-2-phenyl-2H-pyran does not present a concern for genotoxic potential.

Additional References: RIFM, 2006a.

Literature Search and Risk Assessment Completed On: 11/11/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on tetrahydro-4-methyl-2-phenyl-2H-pyran or any read-across materials. The total systemic exposure to tetrahydro-4-methyl-2-phenyl-2H-pyran is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on tetrahydro-4-methyl-2-phenyl-2H-pyran or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to tetrahydro-4-methyl-2-phenyl-2H-pyran (0.67 μg/kg/day) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material (1.5 μg/kg/day; Kroes et al., 2007) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on tetrahydro-4-methyl-2-phenyl-2H-pyran or any read-across materials. The total systemic exposure to tetrahydro-4-methyl-2-phenyl-2H-pyran is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on tetrahydro-4-methyl-2-phenyl-2H-pyran or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to tetrahydro-4-methyl-2-phenyl-2H-pyran (0.67 μg/kg/day) is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/22.

11.1.4. Skin sensitization

Based on the existing data, tetrahydro-4-methyl-2-phenyl-2H-pyran does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, tetrahydro-4-methyl-2-phenyl-2H-pyran is not considered a skin sensitizer. The data are summarized in Table 1. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). In a murine local lymph node assay (LLNA), tetrahydro-4-methyl-2-phenyl-2H-pyran was found to be non-sensitizing when tested up to 100% (25000 μg/cm^2) (RIFM, 2013d). While a guinea pig Buehler test did present reactions indicative of sensitization, similar reactions were seen in the negative control group, and no reactions indicative of sensitization were seen in the rechallenge (RIFM, 1992). In a Confirmation of No Induction in Humans test (CNIH) with 5905 μg/cm^2 of tetrahydro-4-methyl-2-phenyl-2H-pyran in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2021b).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, tetrahydro-4-methyl-2-phenyl-2H-pyran does not present a concern for skin sensitization.

Additional References: RIFM, 1995.

Literature Search and Risk Assessment Completed On: 11/10/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, tetrahydro-4-methyl-2-phenyl-2H-pyran would not be expected to present a concern

Table 1
Summary of existing data on tetrahydro-4-methyl-2-phenyl-2H-pyran.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal 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	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	5909	N/A	N/A	N/A	Negative up to 25000 (100%)	N/A	Inconclusive
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox 4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	N/A	N/A	N/A		No alert found	No alert found; Radical Reactions	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC (ECETOC, 2003).

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for tetrahydro-4-methyl-2-phenyl-2H-pyran 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 photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, tetrahydro-4-methyl-2-phenyl-2H-pyran does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. 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 photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/26/22.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for tetrahydro-4-methyl-2-phenyl-2H-pyran 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 tetrahydro-4-methyl-2-phenyl-2H-pyran. Based on the Creme RIFM Model, the inhalation exposure is 0.042 mg/day. This exposure is 11.2 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: 11/08/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydro-4-methyl-2-phenyl-2H-pyran 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, tetrahydro-4-methyl-2-phenyl-2H-pyran 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 tetrahydro-4-methyl-2-phenyl-2H-pyran as possibly being 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, 2017). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current VoU (2019), tetrahydro-

4-methyl-2-phenyl-2H-pyran presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 2013e:** The ready biodegradability of the test material was evaluated according to the OECD 301B method. Under the conditions of this study, 46% degradation was observed after 28 days.

11.2.1.2.2. Ecotoxicity. **RIFM, 2013b:** A 72-h algal growth inhibition test was conducted according to the OECD 201 method. Under the test conditions and based on geometric mean measured concentrations, the 72-h EC10 for yield inhibition and growth rate reduction was 5.8 and 5.4 mg/L, respectively. The EC50 for growth rate and yield was 12 (10−14, 95% CL) and 8.3 mg/L, respectively. The NOEC and LOEC for both growth rate and yield were 4.4 and 14 mg/L, respectively.

RIFM, 2013c: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 21 mg/L with 95% confidence limits of 12–38 mg/L based on the 0-h measured concentrations.

11.2.1.2.3. Other available data. Tetrahydro-4-methyl-2-phenyl-2H-pyran has been registered under REACH with no additional data at this time.

11.2.1.3. Risk assessment refinement. Since tetrahydro-4-methyl-2-phenyl-2H-pyran has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivations.

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

Endpoints used to calculate PNEC are underlined.

The RIFM PNEC is 0.4419 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: 10/31/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	13.53			1000000	0.01353	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	6.788	4.419	5.791	10000	0.4419	Neutral Organic SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.43	3.43
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band*	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional VoU for all CAS #s.

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

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 06/22/23.

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.

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