



RIFM fragrance ingredient safety assessment, tetrahydro-2-(*p*-tolylloxy)-2H-pyrane, CAS Registry Number 13481-09-9

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ARTICLE INFO

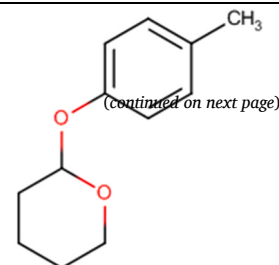
Handling Editor: Dr. Jose Luis Domingo

Version: 031422. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient

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Safety Assessments is here: fragrancesafetyresource.elsevier.com.

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<https://doi.org/10.1016/j.fct.2022.113203>

Received 14 March 2022; Accepted 1 June 2022

Available online 4 June 2022

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CAS Registry Number: 13481-09-9

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

DRF - Dose Range Finding

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LOEL - Lowest Observed Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.

QRA - Quantitative Risk Assessment

QSAR - Quantitative Structure-Activity Relationship

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern

UV/Vis spectra - Ultraviolet/Visible spectra

VCF - Volatile Compounds in Food

VoU - Volume of Use

vPvB - (very) Persistent, (very) Bioaccumulative

WoE - Weight of Evidence

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

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

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

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

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

Tetrahydro-2-(*p*-tolylxy)-2H-pyran was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydro-2-(*p*-tolylxy)-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-2-(*p*-tolylxy)-2H-pyran is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials ($64 \mu\text{g}/\text{cm}^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; tetrahydro-2-(*p*-tolylxy)-2H-pyran is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; tetrahydro-2-(*p*-tolylxy)-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 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, 2021; RIFM, 2014)

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 under the declared use levels; exposure is below the DST.

Phototoxicity/Photoallergenicity: Not (UV/Vis Spectra; RIFM Database) expected to be phototoxic/photoallergenic.

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment**Hazard Assessment:**

Persistence: Screening-level: 2.63 (EPI Suite v4.11; US EPA, 2012a) (BIOWIN 3)

Bioaccumulation: Screening-level: 118.3 (EPI Suite v4.11; US EPA, 2012a) L/kg

Ecotoxicity: Screening-level: Fish LC50: 9.51 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: 9.51 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00951 $\mu\text{g}/\text{L}$

• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

- Chemical Name:** Tetrahydro-2-(*p*-tolylxy)-2H-pyran
- CAS Registry Number:** 13481-09-9
- Synonyms:** 4-Methylphenyl 2-tetrahydropyranyl ether; 2H-Pyran, tetrahydro-2-(4-methylphenoxy)-; *p*-Cresetol; 2-(4-Methylphenoxy) tetrahydro-2H-pyran; Tetrahydro-2-(*p*-tolylxy)-2H-pyran
- Molecular Formula:** $\text{C}_{12}\text{H}_{16}\text{O}_2$
- Molecular Weight:** 192.25 g/mol
- RIFM Number:** 5405
- Stereochemistry:** Stereoisomer not specified. One stereocenter and a total of 2 isomers are possible.

2. Physical data

- Boiling Point:** 277.17 °C (EPI Suite)
- Flash Point:** Not Available
- Log K_{ow}:** 3.65 (EPI Suite)
- Melting Point:** 47.57 °C (EPI Suite)
- Water Solubility:** 36.81 mg/L (EPI Suite)
- Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.00224 mm Hg at 20 °C (EPI Suite v4.0), 0.00404 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000 \text{ L mol}^{-1} \bullet \text{ cm}^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

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

1. **95th Percentile Concentration in Fine Fragrance:** 0.0025% (RIFM, 2020)
2. **Inhalation Exposure*:** 0.0000001 mg/kg/day or 0.000080 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.000015 mg/kg/day (RIFM, 2020)

*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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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:** None
- e. **Phototoxicity/Photoallergenicity:** None
- f. **Local Respiratory Toxicity:** None
- g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

Tetrahydro-2-(*p*-tolylxy)-2H-pyran is not reported to occur in

Table 1

Maximum acceptable concentrations for tetrahydro-2-(*p*-tolylxy)-2H-pyran 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%	$1.0 \times 10^{-4}\%$
3	Products applied to the face using fingertips	0.029%	$3.1 \times 10^{-5}\%$
4	Fine fragrance products	0.027%	0.0025%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	$4.2 \times 10^{-4}\%$
6	Products with oral and lip exposure	0.016%	NRU ^b
7	Products applied to the hair with some hand contact	0.056%	$2.8 \times 10^{-5}\%$
8	Products with significant anogenital exposure	0.0029%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.054%	$7.7 \times 10^{-4}\%$
10	Household care products with mostly hand contact	0.19%	$2.3 \times 10^{-5}\%$
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	0.0014%

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.

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

Tetrahydro-2-(*p*-tolylxy)-2H-pyran has been preregistered for 2010; no dossier available as of 03/14/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, tetrahydro-2-(*p*-tolylxy)-2H-pyrane does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Tetrahydro-2-(*p*-tolylxy)-2H-pyrane was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity with metabolic activation and negative for both cytotoxicity and genotoxicity without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. While the BlueScreen assay on the target material showed positive results, additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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-2-(*p*-tolylxy)-2H-pyrane in dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. A 1.6-fold increase in the mean number of revertant colonies was observed in strain TA100 in the presence of S9 (RIFM, 2021). However, the increase was not dose-responsive, within the 99% historical control limit, and not reproducible, so it was not considered biologically relevant. Under the conditions of the study, tetrahydro-2-(*p*-tolylxy)-2H-pyrane was not mutagenic in the Ames test.

The clastogenic activity of tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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-2-(*p*-tolylxy)-2H-pyrane in DMSO at concentrations up to 1925 µg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1925 µg/mL in the presence and absence of metabolic activation. Tetrahydro-2-(*p*-tolylxy)-2H-pyrane did not induce binucleated cells with micronuclei in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, tetrahydro-2-(*p*-tolylxy)-2H-pyrane was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, tetrahydro-2-(*p*-tolylxy)-2H-pyrane does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on tetrahydro-2-(*p*-tolylxy)-2H-pyrane or any read-across materials. The total systemic exposure to tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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-2-(*p*-tolylxy)-2H-pyrane or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to tetrahydro-2-(*p*-tolylxy)-2H-pyrane (0.015 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/14/

22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on tetrahydro-2-(*p*-tolylxy)-2H-pyrane or any read-across materials. The total systemic exposure to tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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-2-(*p*-tolylxy)-2H-pyrane or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to tetrahydro-2-(*p*-tolylxy)-2H-pyrane (0.015 µg/kg/day) is below the TTC (1.5 µg/kg/day; Kroes et al., 2007; Lauferweiler 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: 03/14/22.

11.1.4. Skin sensitization

Based on the existing data, tetrahydro-2-(*p*-tolylxy)-2H-pyrane does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for tetrahydro-2-(*p*-tolylxy)-2H-pyrane. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a Confirmation of No Induction in Humans test (CNIH) with 0.2% or 155.04 µg/cm² of tetrahydro-2-(*p*-tolylxy)-2H-pyrane in an unknown vehicle, reactions indicative of sensitization were observed in 1/42 volunteers (RIFM, 1965a). In another CNIH with 0.10% or 77.52 µg/cm² of tetrahydro-2-(*p*-tolylxy)-2H-pyrane, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1965b). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 µg/cm² (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). 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 tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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: 03/14/22.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, tetrahydro-2-(*p*-tolylxy)-2H-pyrane would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for tetrahydro-2-(*p*-tolylxy)-2H-pyrane in experimental models. 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 et al., 2009). Based on the lack of absorbance, tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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, $1000 \text{ L mol}^{-1} \bullet \text{ cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/14/22.

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-2-(*p*-tolylxy)-2H-pyrane 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-2-(*p*-tolylxy)-2H-pyrane. Based on the Creme RIFM Model, the inhalation exposure is 0.000080 mg/day. This exposure is 5875 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: 03/14/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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

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 $\geq 2000 \text{ L/kg}$. 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), tetrahydro-2-(*p*-tolylxy)-2H-pyrane presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

No data available.

Ecotoxicity

No data available.

Other available data

Tetrahydro-2-(*p*-tolylxy)-2H-pyrane has been preregistered for REACH with no additional information available at this time.

11.2.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$)

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>9.51</u>			1000000	0.00951	

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, tetrahydro-2-(*p*-tolylxy)-2H-pyrane 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 is < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified tetrahydro-2-(*p*-tolylxy)-2H-pyrane as possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.65	3.65
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<u><1</u>	<u><1</u>
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 0.00951 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA 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: 03/14/22.

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>
- **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://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/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.nih.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 03/14/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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