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RIFM fragrance ingredient safety assessment, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one, CAS Registry Number 32764-98-0

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ABSTRACT

The existing information supports the use of this material as described in this safety assessment. Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data and read-across to 5-hydroxy-7-decenoic acid δ-lactone (CAS # 25,524-95-2) show that there are no safety concerns for tetrahydro-6-(3-pentenyl)-2H-pyran-2-one for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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

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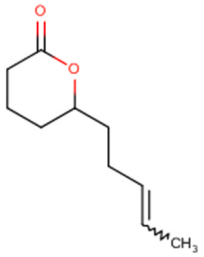
current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Version: 100,621. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one

CAS Registry Number: 32,764-98-0



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
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

(*continued on next column*)

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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-6-(3-pentenyl)-2H-pyran-2-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data and read-across to 5-hydroxy-7-decenoic acid δ-lactone (CAS # 25,524-95-2) show that there are no safety concerns for tetrahydro-6-(3-pentenyl)-2H-pyran-2-one for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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, 2013a; RIFM, 2013d)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use. (RIFM, 2020b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 1979)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 87% (OECD 301 F)	RIFM (2012)
Bioaccumulation:	
Screening-level: 16.56 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 124.4 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: 124.4 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.1244 μg/L

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

1. Identification

1. **Chemical Name:** Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one
2. **CAS Registry Number:** 32,764-98-0
3. **Synonyms:** 5-Hydroxy-8-decenoic acid δ-lactone; 2H-Pyran-2-one, tetrahydro-6-(3-pentenyl)-; 6-Pent-3-en-1-yltetrahydro-2H-pyran-2-

one; 8-Decen-5-olide; 6-(Pent-3-en-1-yl)tetrahydro-2H-pyran-2-one; Tetrahydro-6-(3-penten-1-yl)-2H-pyran-2-one; 5-Hydroxydec-8-enoic acid lactone; Jasmolactone; 2H-Pyran-2-one, tetrahydro-6-(3-penten-1-yl)-; Reaction mass of 6-[(3 E)-pent-3-en-1-yl]tetrahydro-2H-pyran-2-one and 6-[(3Z)-pent-3-en-1-yl]tetrahydro-2H-pyran-2-one; N 431; Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one

4. **Molecular Formula:** $C_{10}H_{16}O_2$
5. **Molecular Weight:** 168.23
6. **RIFM Number:** 5659
7. **Stereochemistry:** Specific isomer not specified. One chiral center and 1 geometric center is present, giving a total of 4 isomers.

2. Physical data

1. **Boiling Point:** 556 ± 2 K (283 ± 2 °C) at 97.2 kPa (RIFM, 2004b), 287.95 °C (EPI Suite)
2. **Flash Point:** 145 ± 2 °C (RIFM, 2004b), 142 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.3 (RIFM, 2013f), 2.0/2.1 (RIFM, 2013c), 2.35 (EPI Suite)
4. **Melting Point**: less than 253 ± 0.5 K (<−20 ± 0.5 °C) (RIFM, 2004b), 17.72 °C (EPI Suite)
5. **Water Solubility:** 5.69 g/L at 20 °C (RIFM, 2013f), 614.3 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.12 Pa at 20 °C (8.8×10^{-4} mm Hg) (RIFM, 2013f), 0.22 Pa at 25 °C (1.7×10^{-3} mm Hg) (RIFM, 2013f), 0.00227 mm Hg at 20 °C (EPI Suite v4.0), 0.00369 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm. Molar absorption coefficient (9.2 L mol^{-1} • cm^{-1}; condition not specified) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.1.2)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.040% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000062 mg/kg/day or 0.0045 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00098 mg/kg/day (RIFM, 2018)

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

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 5-Hydroxy-7-decenoic acid δ-lactone (CAS # 25,524-95-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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.

9. REACH dossier

Available; accessed 09/19/21 (ECHA, 2014).

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-6-(3-pentenyl)-2H-pyran-2-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with and without metabolic activation, positive for genotoxicity without metabolic activation, and negative for genotoxicity with metabolic activation (RIFM, 2013b). 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-6-(3-pentenyl)-2H-pyran-2-one 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 tetrahydro-6-(3-pentenyl)-2H-pyran-2-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Small increases in the mean number of revertant colonies were observed at 15 and 150 μg/plate in strain TA100 in the absence of S9 (RIFM, 2013a). However, the maximum increase was only 1.25-fold, there was no dose-dependence observed, the result was not reproducible, and the values were within the historical control limit. Therefore, this result was not considered to be biologically relevant. Under the conditions of the study, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one was not mutagenic in the Ames test.

The clastogenic activity of tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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-6-(3-pentenyl)-2H-pyran-2-one in DMSO at concentrations up to 1680 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1680 μg/mL in the presence and absence of metabolic activation. Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one did not induce binucleated cells with micronuclei when tested up to cytotoxic levels or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2013d). Under the conditions of the study, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one does not present a concern for genotoxic potential.

Additional References: RIFM, 2004a.

Literature Search and Risk Assessment Completed On: 12/11/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on tetrahydro-6-(3-pentenyl)-2H-pyran-2-one or any read-across materials. The total systemic exposure to tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on tetrahydro-6-(3-pentenyl)-2H-pyran-2-one or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (0.98 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/25/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on tetrahydro-6-(3-pentenyl)-2H-pyran-2-one or any read-across materials. The total systemic exposure to tetrahydro-6-(3-pentenyl)-2H-pyran-2-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on tetrahydro-6-(3-pentenyl)-2H-pyran-2-one or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (0.98 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/02/20.

11.1.4. Skin sensitization

Based on the existing data and read-across material 5-hydroxy-7-decenoic acid δ-lactone (CAS # 25,524-95-2), tetrahydro-6-(3-pentenyl)-2H-pyran-2-one presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for tetrahydro-6-(3-pentenyl)-2H-pyran-2-one. Based on the existing data and read-across material 5-hydroxy-7-decenoic acid δ-lactone (CAS # 25,524-95-2; see Section VI), tetrahydro-6-(3-pentenyl)-2H-pyran-2-one presents no concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.2). In a guinea pig Buehler test, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one did not present reactions indicative of sensitization at 10% in propylene glycol (ECHA, 2014: 001 WoE; RIFM, 1971). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 0.84% or 992 μg/cm^2 of read-across material 5-hydroxy-7-decenoic acid δ-lactone in 1:3 ethanol: diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 106 volunteers (RIFM, 2020b). In another CNIH with 1.25% or 969 μg/cm^2 of read-across material 5-hydroxy-7--decenoic acid δ-lactone in 98.75% alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1972).

Based on the weight of evidence (WoE) from the animal study and human studies on the read-across material 5-hydroxy-7-decenoic acid δ-lactone, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1979; ECHA, 2014.

Literature Search and Risk Assessment Completed On: 11/30/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and human study data, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm for tetrahydro-6-(3-pentenyl)-2H-pyran-2-one. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In a human study, 10% tetrahydro-6-(3-pentenyl)-2H-pyran-2-one was not found to be phototoxic or photoallergenic (RIFM, 1979). Based on the lack of absorbance and human study data, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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 minor absorbance in the range of 290–700 nm. The molar absorption coefficient (9.2 L mol^{-1} • cm^{-1}; condition not specified) 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: 12/03/20.

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-6-(3-pentenyl)-2H-pyran-2-one 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-6-(3-pentenyl)-2H-pyran-2-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0045 mg/day. This exposure is 104.4 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/10/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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) did not identify tetrahydro-6-(3-pentenyl)-2H-pyran-2-one as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), tetrahydro-6-(3-pentenyl)-2H-pyran-2-one presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. **RIFM, 2012:** The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301 F guideline. Biodegradation of 87% was observed after 28 days.

RIFM, 2013i: The ready biodegradability of the test material was evaluated using the CO_2 evolution test (modified strum test) according to the OECD 301 B guideline. Mean biodegradation of 57% was observed after 29 days.

RIFM, 2013g: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 71% was observed after 28 days.

11.2.3.2. Ecotoxicity. **RIFM, 2013h:** The *Daphnia magna* immobilization test was conducted according to the OECD 202 guideline under static conditions (limit test). The 48-h EC50 value based on analytically confirmed nominal concentration was reported to be greater than 100 mg/L.

RIFM, 2013e: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value for growth rate reduction exceeded a time-weighted average concentration of 88 mg/L. The 72-EC50 for yield inhibition based on time-weighted average concentrations was 31 mg/L (95% CI: 23–42 mg/L).

11.2.4. Other available data

Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one has been registered for REACH, with no additional information available at this time.

11.2.4.1. Risk assessment refinement. Since tetrahydro-6-(3-pentenyl)-2H-pyran-2-one has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.3	2.3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.1244 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/03/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	124.4			1000000	0.1244	

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/31/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix G. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112734.

Appendix

Read-across Justification

Methods

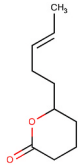
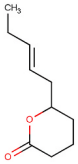
The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), 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, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one	5-Hydroxy-7-decenoic acid ∂-lactone
CAS No.	32,764-98-0	25,524-95-2

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Structure		
Similarity (Tanimoto Score)		0.75
Endpoint		• Skin sensitization
Molecular Formula	$C_{10}H_{16}O_2$	$C_{10}H_{16}O_2$
Molecular Weight	168.236	168.236
Melting Point (°C, EPI Suite)	17.72	17.72
Boiling Point (°C, EPI Suite)	287.95	287.95
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.92E-01	4.92E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6.14 E+02	6.14 E+02
Log K_{OW}	2.35	2.35
J_{max} (μg/cm^2/h, SAM)	14.95	14.95
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.01 E+01	5.01 E+01
Skin Sensitization		
Protein Binding (OASIS v1.1)	Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents	Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents
Protein Binding (OECD)	Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates	Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents	Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS 32764-98-0). 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, 5-hydroxy-7-decenoic acid ∂-lactone (CAS # 25,524-95-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 5-Hydroxy-7-decenoic acid ∂-lactone (CAS # 25,524-95-2) was used as a read-across analog for the target material tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS 32764-98-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the family of lactones.
  - o The target material and the read-across analog share a ∂-lactone ring.
  - o The key difference between the target material and the read-across analog is in the position of the vinylene bond. The target has it at the 7 position, whereas the read-across analog has it at the 8 position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an alert of acylation and thereafter reactivity with skin proteins. The alert is triggered due to the acyl substructure in the lactone ring. The data on the target read-across analog confirms that it presents no concern for skin sensitization under the current, declared levels of use. Therefore, based on the structural similarity between the target material and the read-across analog, and the data for the read-across analog, the predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). toxTree.tree.cramer.CramerTreeResult 1 N,2 N,3 N,5 N,6 N,7Y,8Y, 9 N (20Y,

21 N, 18Y)

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q8. Lactone or cyclic diester? No.
Q9. Lactone, fused to another ring, or 5- or 6-membered alpha,beta-unsaturated lactone? No.
Q19. Open chain? No.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? No.
Q21. Three or more different functional groups? No.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories). Yes Class II (Class intermediate).

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