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RIFM fragrance ingredient safety assessment, tetrahydro-2-isobutyl-4-methyl-2H-pyrane, CAS Registry Number 13477-62-8

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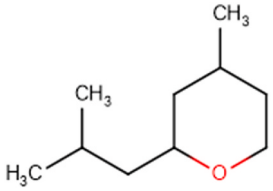

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Name: Tetrahydro-2-isobutyl-4-methyl-2H-pyrane
CAS Registry Number: 13477-62-8

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor

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(*continued*)

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.

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

Tetrahydro-2-isobutyl-4-methyl-2H-pyrane was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydro-2-isobutyl-4-methyl-2H-pyrane is not genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints, and show that there are no safety concerns for tetrahydro-2-isobutyl-4-methyl-2H-pyrane for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; tetrahydro-2-isobutyl-4-methyl-2H-pyrane is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to tetrahydro-2-isobutyl-4-methyl-2H-pyrane is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; tetrahydro-2-isobutyl-4-methyl-2H-pyrane 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1989; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 167 mg/kg/day. RIFM, (2018b)
Reproductive Toxicity: Developmental toxicity NOAEL = 150 mg/kg/day. Fertility NOAEL = 500 mg/kg/day. RIFM, (2018b)
Skin Sensitization: No concern for skin sensitization. RIFM, (2019)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.
(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: 75% after 60 days (OECD 310) RIFM, (2015)
Bioaccumulation:
Screening-level: 121.3 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 48-h *Daphnia magna* LC50: 2.728 mg/L (EPI Suite v4.11; 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 et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 2.728 mg/L (EPI Suite v4.11; US EPA, 2012b)
RIFM PNEC is: 0.272 μg/L μg/L
- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe: <1

1. Identification

1. **Chemical Name:** tetrahydro-2-isobutyl-4-methyl-2H-pyrane
2. **CAS Registry Number:** 13477-62-8
3. **Synonyms:** Dihydrorose oxide; 2H-Pyran, tetrahydro-4-methyl-2-(2-methylpropyl)-; 2-Isobutyl-4-methyltetrahydro-2H-pyran; Dihydrorosan; Dihydrorosenoxid; Tetrahydro-2-isobutyl-4-methyl-2H-pyrane
4. **Molecular Formula:** $C_{10}H_{20}O$
5. **Molecular Weight:** 156.26 g/mol
6. **RIFM Number:** 5404
7. **Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 181.94 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.3/4.5 (RIFM, 1999b), 3.66 (EPI Suite), 4.4, 4.7, and 5.2 for 28.5, 53.0, and 18.6% peak areas, respectively (RIFM, 2014)
4. **Melting Point**: 31.71 °C (EPI Suite)
5. **Water Solubility:** 52.98 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.852 mm Hg at 20 °C (EPI Suite v4.0), 1.21 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.039% (RIFM, 2018a)
2. **Inhalation Exposure*:** 0.00054 mg/kg/day or 0.035 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2018a)

*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; 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; 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. **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-2-isobutyl-4-methyl-2H-pyrane 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 on 01/28/22 (ECHA, 2019).

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-isobutyl-4-methyl-2H-pyrane does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of tetrahydro-2-isobutyl-4-methyl-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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with tetrahydro-2-isobutyl-4-methyl-2H-pyrane in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1989). Under the conditions of the study, tetrahydro-2-isobutyl-4-methyl-2H-pyrane was not mutagenic in the Ames test.

The clastogenic activity of tetrahydro-2-isobutyl-4-methyl-2H-pyrane was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. V79 cells were treated with tetrahydro-2-isobutyl-4-methyl-2H-pyrane in ethanol at concentrations up to 1600 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 150 μg/mL in the presence and absence of S9 for 4 h and the absence of metabolic activation for 24 h. Tetrahydro-2-isobutyl-4-methyl-2H-pyrane did not induce biologically relevant increases in binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, tetrahydro-2-isobutyl-4-methyl-2H-pyrane was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: RIFM, 2016.

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.2. Repeated dose toxicity

The MOE for tetrahydro-2-isobutyl-4-methyl-2H-pyrane is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data for tetrahydro-2-isobutyl-4-methyl-2H-pyrane. In an OECD 422 and GLP-complaint study, 10 Wistar rats/sex/dose were administered tetrahydro-2-isobutyl-4-methyl-2H-pyrane through oral gavage at the doses of 0, 50, 150, and 500 mg/kg/day for 35–55 days. In both sexes, the treatment duration was initiated 2 weeks prior to mating. Male

animals were treated up to 1 week after mating, while female animals were treated up to 3 weeks post-mating. No treatment-related mortality was reported during the study. In addition, no treatment-related alterations were reported for body weight, food consumption, macroscopy, biochemistry, hematology, organ weights, histopathology, or functional observation battery. Based on the lack of adverse effects observed up to the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 500 mg/kg/day (RIFM, 2018b).

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

Thus, the derived NOAEL for the repeated dose toxicity data is 500/3 or 167 mg/kg/day.

Therefore, the tetrahydro-2-isobutyl-4-methyl-2H-pyrane MOE for the repeated dose toxicity endpoint can be calculated by dividing the tetrahydro-2-isobutyl-4-methyl-2H-pyrane NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-2-isobutyl-4-methyl-2H-pyrane, 167/0.0012, or 139167.

In addition, the total systemic exposure to tetrahydro-2-isobutyl-4-methyl-2H-pyrane (1.2 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/08/21.

11.1.3. Reproductive toxicity

The MOE for tetrahydro-2-isobutyl-4-methyl-2H-pyrane is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on tetrahydro-2-isobutyl-4-methyl-2H-pyrane (dihydrorosan). In an OECD 422/GLP study conducted in Wistar rats, groups of 10 rats/sex/dose were administered via oral gavage test material dihydrorosan at doses of 0, 50, 150, or 500 mg/kg/day in corn oil. Males were treated for 2 weeks premating, during mating, and 7 days post-mating, while females were treated for 2 weeks premating, during mating, through gestation, and for 3 weeks of lactation up to the day of scheduled euthanasia. The body weights of high-dose group pups were below the control group throughout the lactation period until postnatal day (PND) 13, and the difference became statistically significant for female pups on PND 1 and in both sexes combined on PNDs 1 and 4. However, recovery was observed during PNDs 7 and 13, where the pup body weights were no longer statistically significantly different from the control group. No treatment-related changes in bodyweight gain of F1 pups were noted in all treatment groups, and there were no associated effects on pup well-being or survival. There were no treatment-related adverse effects observed for fertility up to the highest dose tested; thus, the NOAEL for fertility was considered to be 500 mg/kg/day. The NOAEL for developmental toxicity was conservatively considered to be 150 mg/kg/day, based on decreased pup body weight on PNDs 1 and 4 (RIFM, 2018b).

The tetrahydro-2-isobutyl-4-methyl-2H-pyrane MOE for the developmental toxicity endpoint can be calculated by dividing the tetrahydro-2-isobutyl-4-methyl-2H-pyrane NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-2-isobutyl-4-methyl-2H-pyrane, 150/0.0012, or 125000.

The tetrahydro-2-isobutyl-4-methyl-2H-pyrane MOE for the fertility endpoint can be calculated by dividing the tetrahydro-2-isobutyl-4-methyl-2H-pyrane NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-2-isobutyl-4-methyl-2H-pyrane, 500/0.0012, or 416667.

In addition, the total systemic exposure to tetrahydro-2-isobutyl-4-methyl-2H-pyrane (1.2 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/08/21.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Based on the existing data, tetrahydro-2-isobutyl-4-methyl-2H-pyrane is not considered to be a skin sensitizer (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 v4.2). Tetrahydro-2-isobutyl-4-methyl-2H-pyrane was predicted to be non-sensitizing in a direct peptide reactivity assay (DPRA) and LuSens assay (RIFM, 2019).

Based on the weight of evidence (WoE) from structural analysis and *in vitro* studies, tetrahydro-2-isobutyl-4-methyl-2H-pyrane does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/20/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, tetrahydro-2-isobutyl-4-methyl-2H-pyrane would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for tetrahydro-2-isobutyl-4-methyl-2H-pyrane 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-2-isobutyl-4-methyl-2H-pyrane 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: 01/11/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for tetrahydro-2-isobutyl-4-methyl-2H-pyrane is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are limited inhalation data available on tetrahydro-2-isobutyl-4-methyl-2H-pyrane. Based on the Creme RIFM Model, the inhalation exposure is 0.035 mg/day. This exposure is 13.4 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.

Additional References: RIFM, 1993.

Literature Search and Risk Assessment Completed On: 01/17/22.

Table 1
Summary of existing data on tetrahydro-2-isobutyl-4-methyl-2H-pyrane.

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 Weighted Mean EC3 Value μg/cm^2	GPMT[d]	Buehler[d]
No evidence of sensitization[f]	NA	NA	NA	NA	NA	NA	NA
	***In vitro* Data[e]**				***In silico* protein binding alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	Negative (DPRA)	Negative (LuSens)	NA		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; LOEL = lowest observed effect level; KE = Key Event; NA = 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] Studies conducted according to the OECD TG 406 are included in the table.

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

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydro-2-isobutyl-4-methyl-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 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-2-isobutyl-4-methyl-2H-pyrane 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-2-isobutyl-4-methyl-2H-pyrane 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, 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-2-isobutyl-4-methyl-2H-pyrane 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, 2015**: The inherent biodegradability of the test material was evaluated according to the OECD 310 method. After 60 days, biodegradation of 75% was observed.

RIFM, 1999a: The inherent biodegradability of the test material was evaluated according to the OECD 302 C method. After 28 days, biodegradation of 15% was observed.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. Tetrahydro-2-isobutyl-4-methyl-2H-pyrane has been registered for REACH, and the following additional data is available (ECHA, 2019):

The fish (*Dania rerio*) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 was reported to be 77.6 mg/L.

The *Daphnia* acute immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 33.2 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 with respect to growth rate was reported to be 79.7 mg/L.

11.2.1.5. Risk assessment refinement. Since the tetrahydro-2-isobutyl-4-methyl-2H-pyrane has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.346			1000000	0.000346	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	4.121	2.728	3.835	10000	0.2728	Vinyl/allyl Ketones

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.2	5.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	1–10	1–10
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 0.272 μg/L 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: 05/24/22.

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/

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 06/17/22.

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.

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