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RIFM fragrance ingredient safety assessment, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate, CAS Registry Number 131766-73-9

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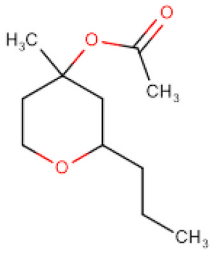

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Name: Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate
CAS Registry Number: 131766-73-9

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

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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 (RIFM, 2015a; Safford et al., 2015a; Safford et al., 2017; Comiskey 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, 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-4-methyl-2-propyl-2H-pyran-4-yl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate is not genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500-71-0) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data provided tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate a No Expected Sensitization Induction Level (NESIL) of 11000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate is not expected to be phototoxic/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-4-methyl-2-propyl-2H-pyran-4-yl acetate is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1991c; RIFM, 1992d; RIFM, 1993b)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day.	RIFM (1993a)
Reproductive Toxicity: Developmental toxicity: NOAEL = 437.8 mg/kg/day. Fertility: NOAEL = 1113 mg/kg/day.	(RIFM, 2015c; ECHA REACH Dossier: A Mixture of *cis*-Tetrahydro-2-isobutyl-4-methylpyran-4-ol; *trans*-Tetrahydro-2-isobutyl-4-methylpyran-4-ol; ECHA, 2010)
Skin Sensitization: NESIL = 11000 μg/cm^2.	RIFM (2013a)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ 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: 38% (OECD 301D)	RIFM (1991d)
Bioaccumulation: Screening-level: 30.22 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 123.7 mg/L	(RIFM Framework; Salvito, 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, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 123.7 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.1237 μg/L

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

1. Identification

1. **Chemical Name:** Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate
2. **CAS Registry Number:** 131766-73-9
3. **Synonyms:** Clarycet; 2H-Pyran-4-ol, tetrahydro-4-methyl-2-propyl-, acetate; Sagecete; Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate
4. **Molecular Formula:** $C_{11}H_{20}O_3$
5. **Molecular Weight:** 200.27
6. **RIFM Number:** 6339
7. **Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 205.5–238.5 °C (RIFM, 1992h), 245.92 °C (EPI Suite)
2. **Flash Point:** 101 °C (Globally Harmonized System), 104.5 °C (RIFM, 1992h)

3. **Log K_{OW}**: 2.39 at 23 °C (RIFM, 1992h), 2.75 (EPI Suite)
4. **Melting Point**: 33.22 °C (EPI Suite)
5. **Water Solubility:** 196.1 mg/L (EPI Suite)
6. **Specific Gravity:** 0.98 (RIFM, 1991a)
7. **Vapor Pressure:** 0.0277 mm Hg at 25 °C (EPI Suite), 0.016 mm Hg at 20 °C (EPI Suite v4.0)
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. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.18% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.00059 mg/kg/day or 0.039 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00060 mg/kg/day (RIFM, 2021)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (RIFM, 2015a; Safford, 2015; Safford, 2017; and Comiskey, 2017).

5. Derivation of systemic absorption

1. **Dermal:** 43.78% on read-across material 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500- 71-0)

RIFM, 2013b: An OECD 428/GLP *in vitro* dermal penetration study was conducted on 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500-71-0) using rat skin. The diffusion of ^{14}C-pyranol into and through rat skin was assessed by single topical application of target concentrations of 9500 μg/cm^2 (950 mg/mL; pure) and 1000 μg/cm^2 (100 mg/mL; solution in corn oil) of test material to split-thickness skin preparations under semi-occlusive conditions. During the study period, receptor fluids were collected from each cell at several time points (1, 2, 4, 6, 8, 10, and 24 h after application) in order to determine kinetic parameters (lag phase, absorption rate, and Kp). At the end of the sampling period, the test material was recovered from all compartments of each diffusion cell. The results of recovery are summarized as non-absorbed dose (donor chamber, skin washing, tape strips 1–2, and charcoal filter), the amount associated with skin preparation (skin and tape strips 3–6), and absorbed dose (receptor fluid, receptor chamber washing, receptor samples including washout). The mean absorbed doses were 14.80% and 36.27% for skin treated with the high dose (950 mg/mL) and low dose (100 mg/mL), respectively. The amounts of test material associated with the skin after the exposure period amounted to 3.12% and 7.51% for the high dose and low dose, respectively. The sum of the absorbed dose and the amounts recovered in skin preparation was calculated to determine the dermal absorption of pyranol, which corresponded to 17.92% and 43.78% of the applied dose for the high dose and low dose, respectively. The total recovery was 101.47% and 99.25% for the high and low doses, respectively. Thus, a dermal absorption value of 43.78% was used for this safety assessment.

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:** 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500-71-0)
   d. **Skin Sensitization:** None
   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-4-methyl-2-propyl-2H-pyran-4-yl acetate 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 10/05/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.010
2	Products applied to the axillae	0.25
3	Products applied to the face/body using fingertips	0.010
4	Products related to fine fragrances	0.59
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.99
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.031

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.010
5D	Baby cream, oil, talc	0.0035
6	Products with oral and lip exposure	0.010
7	Products applied to the hair with some hand contact	0.40
8	Products with significant ano-genital exposure (tampon)	0.0035
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.0
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.24
10B	Aerosol air freshener	0.010
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0035
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	27

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate, the basis was the reference dose of 0.50 mg/kg/day, a predicted skin absorption of 80%, and a skin sensitization NESIL of 11000 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate 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/preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate 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, 1991c). Under the conditions of the study, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was not mutagenic in the Ames test.

The clastogenicity of tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the proportion of aberrant cells were observed at 62.5, 250, and 500 μg/mL in the presence of S9 in the 16-h harvest and at 250 and 500 μg/mL in the presence of S9 for the 24-h harvest (RIFM, 1992d). Under the conditions of the study, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate has shown evidence of clastogenic activity only in the presence of S9 in the *in vitro* chromosome aberration assay. A follow-up *in vivo* micronucleus test was conducted.

The clastogenic activity of tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered by intragastric gavage to groups of male and female CD-1 mice. The dose of 1600 mg/kg body weight was administered. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1993b). Under the conditions of the study, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.2. Repeated dose toxicity

The MOE for tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate 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 the target material. In a GLP and OECD 407-compliant study, 5 Sprague Dawley rats via gavage at doses of 0, 15, 150, and 1000 mg/kg/day for 28 days. No mortality occurred throughout the study period. Slightly abnormal gait (waddling) was seen in both sexes at the high dose. Water consumption was increased in both sexes at the high dose. Packed cell value (PCV), hemoglobin (Hb), and red blood cell (RBC) count values were significantly decreased in females at the high dose. Globulin, total protein, and phosphate levels were increased in both sexes at the high dose, while chloride levels were decreased in both sexes at the high dose. Relative liver weights, enlarged liver incidences, and centrilobular hepatocyte enlargement were significantly increased in both sexes at the high dose. Adrenal weights and adrenal gland cortical width were increased in females at the high dose and kidney weights were increased in males at the high dose. Based on clinical signs, hematology effects, blood biochemistry, and organ weight changes at 1000 mg/kg/day, the NOAEL for this study was considered to be 150 mg/kg/day (RIFM, 1993a).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study (ECHA, 2012b). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 150/3 or 50 mg/kg/day.

Therefore, the tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate, 50/0.0006 or 83333.

In addition, the total systemic exposure tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate (0.60 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a

Cramer Class III material at the current level of use.

Derivation of reference dose (RfD)

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.50 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.50 mg/kg/day.

*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: 05/21/21.

11.1.3. Reproductive toxicity

The MOE for tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate. Read-across material 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500-71-0; pyranol; see Section VI) has sufficient developmental toxicity data. An OECD 414/GLP dermal prenatal developmental toxicity study was conducted in female Wistar rats. Groups of 25 pregnant female rats were treated with test material pyranol at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil to the intact shaven dorsal skin using a semi-occlusive dressing (6 h/day) from gestation days (GD) 6 through 19. All dams were euthanized on GD 20 and assessed by gross pathology. There were no treatment-related adverse effects observed on fetal morphology up to the highest dose tested. The NOAEL for developmental toxicity was considered to be 1000 mg/kg/day (RIFM, 2015c). To account for bioavailability following dermal application, data from a rat *in vitro* study (RIFM, 2013b; see Section V) was used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 43.78% of the applied dose, the revised developmental toxicity NOAEL from the dermal study is 437.8 mg/kg/day. **Therefore, the tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate, 437.8/0.0006 or 729667.**

There are insufficient fertility data on tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate. Read-across material 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500-71-0; pyranol; see Section VI) has sufficient fertility data. An OECD 443/GLP extended 1-generation reproductive toxicity study was conducted in Wistar rats. The test material pyranol was administered in the diet at doses of 0, 1000, 4000, or 12500 ppm (corresponding to the mean achieved doses of approximately 0, 90, 359, and 1113 mg/kg/day, respectively, as per [ECHA, 2010]) to groups of F0 parental generation animals (25 rats/sex/dose) and F1 generation pups that were assigned to cohort 1A (20 rats/sex/-dose) or cohort 1B (25 rats/sex/dose). To account for the increased food intake of the F0 dams during lactation, pyranol concentrations in the diet were reduced by 50% (i.e., 500, 2000, and 6250 ppm). F0 males and females were exposed to the test material for 10 weeks prior to and during mating until necropsy on either postnatal days (PND) 21 or 22. F1 generation pups that were prenatally exposed to pyranol were examined for developmental and systemic toxicity beginning at PND 0 through adolescence and adulthood (necropsy PND was not specified). In addition to systemic toxicity parameters, F0 parental animals were evaluated for fertility, estrous cycling, and sperm integrity. There were no treatment-related effects observed for fertility, gestation, implantation, intrauterine embryo-fetal lethality, or live birth indices. Male and female fertility indices of 88%–100% were within the normal range of biological variation for the Wistar rat strain. A single dam that received the highest dose was reported to have 7 stillborn pups; however, this observation was considered to be incidental and not related to treatment. In F1 pups, there were no developmental effects observed up to PND 13. Based on the absence of treatment-related fertility effects up to the highest dose tested, the NOAEL for fertility for F0 parental males and females was considered to be 12500 ppm or 1113 mg/kg/day (ECHA, 2010).

An OECD 421/GLP dermal reproductive/developmental toxicity screening test conducted in Wistar rats with test material pyranol also concluded a fertility NOAEL of 1000 mg/kg/day, the highest dose tested (RIFM, 2015b; see Table 1 for study details), which supports the OECD 443 study. A NOAEL of 1113 mg/kg/day from the more robust OECD 443 dietary study was selected for the fertility endpoint. **Therefore, the tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate MOE for the fertility endpoint can be calculated by dividing the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate, 1113/0.0006 or 1855000.**

In addition, the total systemic exposure tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate (0.60 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: RIFM, 1993a; RIFM, 2010.

Literature Search and Risk Assessment Completed On: 05/31/21.

11.1.4. Skin sensitization

Based on the existing data, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate is considered a skin sensitizer with a defined NESIL of 11000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens test (RIFM, 2016a; RIFM, 2016b). It was found to be positive in human cell line activation test (h-CLAT) (RIFM, 2017b). In a murine local lymph node assay (LLNA), tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was found to be non-sensitizing up to 30% (RIFM, 2004). In guinea pig maximization tests, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate presented reactions indicative of sensitization (RIFM, 1992a). In a guinea pig Buehler test, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate did not present reactions indicative of sensitization up to 15% (RIFM, 1992b). Additionally, in 2 sets of Confirmation of No Induction in Humans tests (CNIHs) with 10% (5510 μg/cm^2) in alcohol SD39C and 3:1 alcohol SD39C:diethyl phthalate or 15% (8264 μg/cm^2) in alcohol SD39C, no reactions indicative of sensitization were observed in any of the 55 and 52 volunteers, respectively (RIFM, 1992f; RIFM, 1992g).

Table 1
Details of OECD 421 reproductive/developmental toxicity screening test.

Duration in detail	GLP/ Guideline	No. of animals/ dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/ LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
2-week premating, 3-week mating in both sexes, through gestation to approximately 2 weeks of lactation	OECD 421/GLP	10/sex/dose (Wistar rats)	Dermal exposure (6 h/day) to intact shaven dorsal skin using semi-occlusive dressing (corn oil)	0, 100, 300, or 1000 mg/ kg/day	Fertility NOAEL = 1000 mg/kg/ day	No treatment-related adverse up to the highest dose tested	RIFM (2015b)

Similarly, in another 3 sets of CNIHs with 15% (8264 μg/cm^2) in 3:1 alcohol SD39C:diethyl phthalate or 10% (5510 μg/cm^2) in 1:3 ethanol: diethyl phthalate (EtOH:DEP); or 20% (11019 μg/cm^2) in 1:3 EtOH: DEP, no reactions indicative of sensitization were observed in any of the 50, 112, and 106 volunteers, respectively (RIFM, 1992e; RIFM, 2012; RIFM, 2013a).

Based on the weight of evidence (WoE) from structural analysis as well as animal and human studies, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate is a weak sensitizer with a WoE NESIL of 11000 μg/cm^2 (Table 2). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.50 mg/kg/day.

Additional References: RIFM, 2017a.

Literature Search and Risk Assessment Completed On: 05/26/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate 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-4-methyl-2-propyl-2H-pyran-4-yl acetate 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 phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate 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 absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

Table 2
Data Summary for tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human 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
>7500	Weak	11019	NA	NA	11000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.039 mg/day. This exposure is 12.1 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/28/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA 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-4-methyl-2-propyl-2H-pyran-4-yl acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate as possibly being persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and*

bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012b). 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-4-methyl-2-propyl-2H-pyran-4-yl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1991d: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guidelines. Biodegradation of 38% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. RIFM, 1991b: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 110 mg/L (95% CI: 91mg/L–130 mg/L).

RIFM, 1992c: A 96-h fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on nominal test concentration was reported to be > 100 mg/L.

11.2.2.1.3. Other available data. Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate has been registered for REACH with the following additional data available at this time (ECHA, 2012a):

An algae growth inhibition test was conducted according to OECD 201 method under static conditions. The 72-h EC50 and NOEC values based on mean measured concentration for growth rate and biomass were reported to be > 77 mg/L and 47 mg/L, respectively.

11.2.3. Risk assessment refinement

Since tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate 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 Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.39	2.39
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1237 μg/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 VoU.

Literature Search and Risk Assessment Completed On: 05/25/21.

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://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 10/05/21.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	123.7			1000000	0.1237	

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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112863.

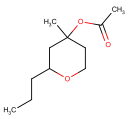
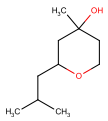
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate	2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol
CAS No.	131766-73-9	63500-71-0
Structure		
Similarity (Tanimoto Score)		0.71
Read-across Endpoint		• Reproductive Toxicity
Molecular Formula	$C_{11}H_{20}O_3$	$C_{10}H_{20}O_2$
Molecular Weight	200.27	172.26
Melting Point (°C, EPI Suite)	33.22	24.55
Boiling Point (°C, EPI Suite)	245.92	229.55
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.69	1.59
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.75	2.16
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	196.1	2773
J_{max} (μg/cm^2/h, SAM)	31.233	19.724
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.39E-002	1.71E-003
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, impaired OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)	• Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 1

Summary

There are insufficient toxicity data on tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate (CAS # 131766-73-9). 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, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500-71-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol (CAS # 63500-71-0) was used as a read-across analog for the target material tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate (CAS # 131766-73-9) for the reproductive toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of oxygen-containing tetrahydropyrans.
  - o The target material and the read-across analog share a 4-methyltetrahydropyran ring.
  - o The key difference between the target material and the read-across analog is that the target material is an acetyl ester with a propyl chain substituent at position 2 of the ring whereas the read-across is an alcohol with an isobutyl chain substituent in position 2. The target material would give rise to a similar alcohol product upon hydrolysis of the ester and these structural differences are toxicologically insignificant for the endpoints.
  - 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 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.

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