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Short review

RIFM fragrance ingredient safety assessment, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran, CAS Registry Number 16409-43-1

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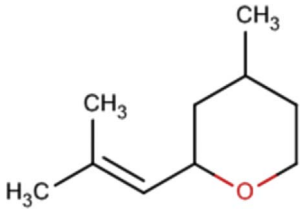
Version: 042617. This version replaces any previous versions.

Name: Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran

CAS Registry Number: 16409-43-1

Additional CAS Numbers*:
4610-11-1 (+)-cis-Rose oxide
3033-23-6 Rose oxide levo

*These materials are included in this assessment because they are a mixture of isomers.



Abbreviation list:

2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach.
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice

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IFRA - The International Fragrance Association
LOEL - Lowest Observable 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
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
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultra Violet/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 under the limits 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 reviews 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (*i.e.*, 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic, provided an acceptable MOE > 100 for the repeated dose and reproductive toxicity endpoints, and it does not have skin sensitization potential. The developmental and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.0015 mg/kg/day and 0.47 mg/day, respectively); exposure < TTC (acceptable). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra and the material is not phototoxic/photoallergenic. The environmental endpoints were evaluated and this material was not found to be a PBT; its risk quotients, based on the current volume of use in Europe and North America were acceptable (PEC/PNEC < 1).

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2002; RIFM, 2012c; RIFM, 2012d)

Repeated Dose Toxicity: NOAEL = 100 mg/kg/day. (RIFM, 2012b)

Developmental Toxicity: No NOAEL available. Exposure is below the TTC. **Reproductive Toxicity:** NOAEL = 100 mg/kg/day. (RIFM, 2012b)

Skin Sensitization: Not sensitizing. (RIFM, 1993a)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra RIFM DB)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 79% (OECD 301 F) (RIFM, 2012a)

Bioaccumulation: Screening Level: 107 l/kg (EPI SUITE ver 4.1, 2000–2011)

Ecotoxicity: Critical Ecotoxicity Endpoint: 48-hour *Daphnia magna* EC50: 33.2 mg/l (RIFM, 2008b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 48 h *Daphnia magna* EC50: 33.2 mg/l (RIFM, 2008b)

RIFM PNEC is: 33.2 μg/l

- Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe < 1

1. Identification

Chemical Name: Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran	**Chemical Name:** (+)-cis-Rose oxide	**Chemical Name:** Rose oxide levo
CAS Registry Number: 16409-43-1	**CAS Registry Number:** 4610-11-1	**CAS Registry Number:** 3033-23-6
Synonyms: 2-(2′-Methyl-1′-propenyl)-4-methyltetrahydro-pyran; 2H-Pyran, tetrahydro-4-methyl-2-(2-methyl-1-propenyl)-; Rosenoxide; Rosoxide; Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran; Rose Oxide Racemic; 2-(2-ﾒﾁﾙ-1-ﾌﾟﾛﾍﾟﾆﾙ)-4-ﾒﾁﾙﾃﾄﾗﾋﾄﾞﾛﾋﾟﾗﾝ; 2-(2-ﾒﾁﾙ-1-ﾌﾟﾛﾍﾟﾆﾙ)-4-ﾒﾁﾙﾃﾄﾗﾊｲﾄﾞﾛﾋﾟﾗﾝ; 2-(2-ﾒﾁﾙ-1-ﾌﾟﾛﾍﾟﾆﾙ)-4-ﾒﾁﾙﾃﾄﾗﾊｲﾄﾞﾛﾋﾟﾗﾝ; 2-(2-ﾒﾁﾙ-1-ﾌﾟﾛﾍﾟﾆﾙ)-4-ﾒﾁﾙﾃﾄﾗﾊｲﾄﾞﾛﾋﾟﾗﾝ; 4-Methyl-2-(2-methylprop-1-en-1-yl) tetrahydro-2H-pyran; Rosenoxid L; Rosenoxid inaktiv high cis; (14)C-Rose oxide 90; Rose oxide	**Synonyms:** 4-Methyl-2-(2-methylprop-1-en-1-yl) tetrahydro-2H-pyran; 2H-Pyran, tetrahydro-4-methyl-2-(2-methyl-1-propenyl)-, (2R-cis)-; (2R-cis)-Tetrahydro-4-methyl-2-(2-methyl-1-propenyl)-2H-pyran	**Synonyms:** 4-Methyl-2-(2-methylprop-1-en-1-yl)tetrahydro-2H-pyran; levo-2-(2′-Methyl-1′-propenyl)-4-methyltetrahydropyran; 2H-Pyran, tetrahydro-4-methyl-2-(2-methylpropenyl)-, (−)-; *cis*-Rose oxide; L-Rose oxide; (2S-cis)-Tetrahydro-4-methyl-2-(2-methyl-1-propenyl)-2H-pyran; 2-(2′-ﾒﾁﾙ-1′-ﾌﾟﾛﾍﾟﾆﾙ)-4-ﾒﾁﾙﾃﾄﾗﾋﾄﾞﾛﾋﾟﾗﾝ
Molecular Formula: $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$
Molecular Weight: 154.25	**Molecular Weight:** 154.53	**Molecular Weight:** 154.25
RIFM Number: 32	**RIFM Number:** N/A	**RIFM Number:** 478

2. Physical data*

1 **Boiling Point:** 194.97 °C [EPI Suite]
2 **Flash Point:** 151°F; CC [FMA database]
3. **Log K_{OW}**: log Pow = 3.58 [RIFM, 2013a], for two isomers. Log Pow 3.6 & 3.7 @ 30 °C [RIFM, 1996a], 3.58 [EPI Suite]
4. **Melting Point:** no melting temp between −100 °C and 30 °C. [BASF, 2013g], −29.92 °C [EPI Suite]
5. **Water Solubility:** 0.92 g/l +/− 0.05 g/l at T = 20.0 °C +/- 0.5 °C [BASF, 2013g], 63.97 mg/L [EPI Suite]
6. **Specific Gravity:** 0.869 [FMA database]
7. **Vapor Pressure:** p20 °C = 0.53 hPa; p25 °C = 0.77 hPa; p50 °C = 4.0 hPa [RIFM, 2013a], 0.456 mm Hg @ 20 °C [EPI Suite 4.0], 0.3 mm Hg 20 °C [FMA database], 0.657 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Does not significantly absorb in the region of 290–700 nm; molar absorption coefficient below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless, mobile liquid with a penetrating, very diffusive, gassy-green, floral odor with a distinctive geranium top-note

*Physical data are identical for all materials included in this assessment.

3. Exposure***

1. Volume of Use (worldwide band): 100–1000 metric tons per year (IFRA, 2011)
2. 95th Percentile Concentration in Hydroalcoholics: 0.053% (RIFM, 2013d)
3. Inhalation Exposure*: 0.00011 mg/kg/day or 0.0083 mg/day (RIFM, 2013d)
4. Total Systemic Exposure**: 0.00022 mg/kg/day (RIFM, 2013d)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al., 2017).

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

4. Derivation of systemic absorption

1. Dermal: 17.25%
RIFM, 2013b: An OECD 428 GLP *in vitro* skin absorption study was conducted with ^{14}C-Rose oxide 90 (tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran) using human skin. The diffusion of ^{14}C-Rose oxide 90 into and through human skin was assessed by a single topical application of target doses of 8700 and 87 μg/cm^2 of test substance to split thickness skin preparations mounted on Franz-type diffusion cells. The applied high dose corresponds to the expected exposure of workers to the pure product and the low dose to the exposure of consumers to a leave-on product. The study was performed using 8 diffusion cells for each dose. Valid results were obtained from 5 to 8 cells for the high and low dose, respectively. Diffusion cells were operated in static mode with ethanol/tap water (1:1/v:v) for the pure test substance (high-dose) and tap water for the 1% volume dilution (low-dose) as receptor fluid. After application, the opening of each donor chamber was covered with a charcoal filter fixed to Fixomull® Stretch adhesive fleece (semi-occlusive conditions). During the study period, defined amounts of the receptor fluid were collected from each cell at several time points (1, 2, 4, 6, 8, 12 and 24 h). At the end of the sampling period, the test substance was recovered from all compartments of each diffusion cell. The results of recovery were summarized as non-absorbed dose (donor chamber, skin washing, tape strips 1–2 (desquamation of the skin) and charcoal filter), amount associated with the skin preparation (skin and tape strips 3–6) and absorbed dose (receptor fluid, receptor chamber washing, receptor samples including wash out). In the low- and high-dose groups, mean absorbed dose amounted to 7.97 and 17.25%, respectively. The amount of non-absorbed dose (donor chamber washing, skin washes, tape strip sample 1, 2 and charcoal filter) corresponded to 88.36 and 77.59%, respectively for the low- and high-dose applications. The highest amounts of activity were recovered in the charcoal filters. These

activities accounted for 67.50 and 87.30% of dose for the high and low doses, respectively, demonstrating that the major part of applied rose oxide 90 evaporated from the skin during the exposure period. Total recovery corresponded to 96.33 and 94.84% of the applied dose, respectively for the low and high dose applications. In the low-dose group, no absorption lag time was observed. In contrast, a mean absorption lag time of 1.66 h was determined in the high-dose group. The presence of a lag time in the high dose group and the limited amount absorbed in the low dose group underline the functional diffusion barrier of the skin against the test substance preparations. The most conservative skin absorption value of 17.25% was used for the safety assessment of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran.

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree 2.6	OECD QSAR Toolbox 3.1
III	III	III

2. **Analogues Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read across justification: None

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran is reported to occur in the following foods* but is not found in natural complex substances (NCS):

Apple brandy (*Calvados*)
Black currants (*Ribes nigrum* L.)
Grape brandy.
Passion fruit (*Passiflora* species).
Thyme (*Thymus* species).
Wine.

(+)-cis-Rose oxide and rose oxide levo are not reported to occur in foods by the VCF* and are not found in natural complex substances (NCS).

*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 contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran has a dossier available; accessed on 12/13/13. (+)-cis-Rose oxide and rose oxide levo are pre-registered for 2010, no dossier available as of 04/26/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 were treated with tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2002). Under the conditions of the study, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was not mutagenic in the Ames test. A mammalian cell gene mutation assay (HPRT) was also conducted according to OECD TG 476 and GLP guidelines. Chinese hamster lung cells (V79) were treated with tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran in DMSO at concentrations up to 770 μg/mL for 4 and 24 h. Effects were evaluated both with and without metabolic activation. No significant increases in the frequency of mutant colonies were observed with any dose of the test item, either with or without metabolic activation (RIFM, 2012d).

The clastogenic activity of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran 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 in corn oil via oral administration, to groups of male NMRI mice (5/sex/dose). Doses of 250, 500 or 1000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, the bone marrow was extracted and examined for polychromatic erythrocytes. The single oral administration of the test material led to a weak, dose-related increase in the number of polychromatic erythrocytes containing micronuclei when scoring an increased sample of 4000 PCEs per animal in some selected test groups due to large inter-animal variability. However, no statistical significance was calculated for any of the dose groups. A repeat experiment was performed and similar results were obtained when compared to the first experiment. Additionally, a clear negative response was observed in the 48-hour exposure. Overall, these marginal increases in micronuclei were not considered biologically relevant. Under the experimental conditions, tetrahydro-4-methyl-2-(2-methylpropen-1-yl) pyran has no chromosome damaging (clastogenic) effects nor does it lead to any impairment of chromosome distribution in the course of mitosis (aneugenic activity) in bone marrow cells (RIFM, 2012c). Under the conditions of the study, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was not considered to be clastogenic in the *in vivo* micronucleus test.

Based on the data available, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran does not present a concern for genotoxicity.

Additional References: RIFM, 2001.

Literature Search and Risk Assessment Completed on: 10/19/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for tetrahydro-4-methyl-2-(2-

methylpropen-1-yl)pyran is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (rose oxide) for the repeated dose toxicity endpoint. An OECD 407 gavage 28-day subchronic toxicity study conducted with test material, rose oxide was administered to 5 Wistar rats/sex/dose at dose levels of 0 (corn oil), 100, 300 and 1000 mg/kg/day. Due to treatment-related alterations in the hematological and clinical chemistry parameters among male and females of the high dose group, the NOAEL for the repeated dose toxicity endpoint was considered to be 300 mg/kg/day for males and females. There were increases in the relative and absolute liver and kidney weights among the high dose males and females and the mid dose females. Due to the absence of any histopathological correlates, these were considered as treatment related adaptive responses. The presence of alpha-2μ-globulin deposition was confirmed in male rats of the control and treatment groups, and was not considered a risk towards human health (Lehman-McKeeman et al., 1990; Lehman-McKeeman and Caudill, 1992). There was an increase in relative spleen weight among males of the high dose group and this was correlated to the extramedullary hematopoiesis in the spleen during microscopic analysis. This was considered to be secondary to the anemia detected during hematological analysis in males and females of the high dose group and was regarded as an adaptive response (RIFM, 2012b).

A 90-day dietary subchronic study was conducted on groups of 10–16 rats/sex with test material, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran as an emulsion in gum arabic, as adsorbates on microcrystalline cellulose, or as a solution in ethanol or peanut oil. The average dietary intake of the test material in males was 2.51 mg/kg/day and 2.81 mg/kg/day in females. No significant changes were observed in the organ weights, clinical chemistry or hematology parameters (Posternak et al., 1969). A NOAEL could not be derived since this study was limited to only one dose tested. A NOAEL of 300 mg/kg/day was selected for the repeated dose toxicity endpoint.

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

Thus, the derived NOAEL for the repeated dose toxicity data is 300/3 or 100 mg/kg/day.

Therefore, the tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran MOE for the repeated dose toxicity endpoint can be calculated by dividing the tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran, 100/0.00022 or 454545.

When correcting for skin absorption (see Section 4), the total systemic exposure to tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (0.22 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) 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: RIFM, 1989; RIFM, 2015a; RIFM, 2015b; RIFM, 2015c; RIFM, 2013c; RIFM, 2010; RIFM, 1993e.

Literature Search and Risk Assessment Completed on: 10/25/2016.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental toxicity data on tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran or any read across materials. The total systemic exposure to tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran is below the TTC for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

The margin of exposure for tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran or any of the combined materials. In addition, there are no developmental toxicity data on any of the read across materials that can be used to support the developmental toxicity endpoint. When correcting for skin absorption (see Section 4), the total systemic exposure to tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (0.22 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

An OECD 407 28-day study conducted with test material, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was administered via gavage at doses of 0, 100, 300 and 1000 mg/kg/day to groups of 5/rats/sex/dose. In addition to the systemic toxicity parameters, female estrous cycles were observed for a period of 2 weeks. The male sperm morphology, motility, cauda epididymides sperm count and testis sperm head count were also recorded following necropsy and organ weight analysis. The males of the mid and high dose group were observed to have a decrease in sperm motility and total sperm head counts along with an increase in the abnormal sperm counts. There was a significant increase in absolute and relative mean epididymides weights and immature ducts in all males (slight to severe), interstitial edema in all males (minimal to slight) and intraductal granulocytic infiltration in 2 of 5 males (minimal) among high dose males. Mid dose males also showed presence of immature ducts in all males (minimal to slight) and interstitial edema in 1 of 5 males (minimal). There were no treatment-related effects reported among the treated females in terms of estrous cycle measurements and reproductive organ analysis. Thus the NOAEL for the male testicular toxicity was considered to be 100 mg/kg/day and the NOAEL for females ovarian toxicity was considered to be 1000 mg/kg/day (BASF, 2012a; #64294). The most conservative NOAEL of 100 mg/kg/day was considered for the reproductive toxicity endpoint covering the male testicular toxicity and female ovarian toxicity. Therefore, the tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran MOE for the reproductive toxicity endpoint can be calculated by dividing the tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran, 100/0.00022 or 454545.

When correcting for skin absorption (see Section 4), the total systemic exposure to tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (0.22 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: Posternak et al., 1969; RIFM, 1989; RIFM, 2015a; RIFM, 2015b; RIFM, 2015c; RIFM, 2013c; RIFM, 2010; RIFM, 1993e.

Literature Search and Risk Assessment Completed on: 10/25/2016.

10.1.4. Skin sensitization

Based on available data, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on available data, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox version 3.1). In guinea pig test methods, no results indicative of sensitization were observed (RIFM, 1993a; RIFM, 1993b; RIFM, 1993c; RIFM, 1993d). Additionally, no reactions indicative of skin sensitization were observed in the human maximization test or repeated insult patch tests (RIFM, 1964; RIFM, 1978; RIFM, 1973). Based on weight of evidence from structural analysis, animal and human data, tetrahydro-4-methyl-2-(2-

methylpropen-1-yl)pyran does not present a concern for skin sensitization.

Additional References: Klecak, 1985; RIFM, 1963.

Literature Search and Risk Assessment Completed on: 01/17/2014.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran in experimental models. UV/Vis absorption spectra indicate no significant absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern (1000 L $mol^{-1} \cdot cm^{-1}$) for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/13/2016.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are limited inhalation data available on tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran. Based on the Creme RIFM model, the inhalation exposure is 0.0083 mg/day. This exposure is 56.6 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, 1997a.

Literature Search and Risk Assessment Completed on: 10/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was performed following the RIFM Environmental Framework (Salvito et al., 2002) that provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was identified as a fragrance material with 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 version 4.1 did not identify tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran as persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (*e.g.*, OECD guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (*e.g.*, USEPA's BIOWIN and BCFBAF found in EPI SUITE version 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. **RIFM, 2012a**: The ready biodegradability of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was determined by the Manometric Respirometry Test according to OECD 301F guidelines. 30 mg/l of the test material undergoes 79% biodegradation after 28 days in the test conditions. The 10-day window criterion was also fulfilled (10% biodegradation on day 7 and 62% on day 17).

RIFM, 1997b: To determine the inherent biodegradability of the test substance, the sealed vessel test according to the OECD 302A method was conducted using an acclimatized inoculum from a modified Semi-Continuous Activated Sludge (SCAS) test. The degradability of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was reported to be 65.8%.

RIFM, 1993f: The biodegradability of the test material was evaluated in a modified ready test according to the OECD 301B method. Biodegradation of 29.6% was observed after 56 days.

RIFM, 1994: In a standard OECD 301B ready test, biodegradation of 4.6% was observed after 28 days.

RIFM, 1996b: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the test, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran underwent less than 15% biodegradation.

RIFM, 1998: The inherent biodegradability of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was determined by the Manometric Respirometry Test according to OECD 302C guidelines. Test material underwent 95% biodegradation after 31 days (92% after 28 days).

RIFM, 2008a: Biodegradation of the test material was evaluated according to the ISO 14593 method. After 28 days, biodegradation of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was less than 10%.

RIFM, 1999; **RIFM, 1996c**; **RIFM, 1996d**: The biodegradability of different samples of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was evaluated using the BOD test for insoluble substances (BODIS). After 28 days, the biodegradation of 1%, 3% and 57% was observed.

10.2.2.1.2. Ecotoxicity. **RIFM, 2008b**: A 48 h *Daphnia magna* acute toxicity test was conducted according to the OECD 202 method. The 48 h EC50 was reported to be 33.2 mg/l.

RIFM, 2008c: A 96 h fish (*Danio rerio*) acute toxicity test was conducted with the test material according to the OECD 203 method. The acute LC50 at 24, 48, 72 and 96 h was reported to be 77.6 mg/l.

RIFM, 2008c: In a 72-hour algal growth study, cultures of *Pseudokirchneriella subcapitata* were exposed to the test material at mean measured concentrations of 0.68, 2.13, 7.26, 25.7 and 80.9 mg/l under static conditions in accordance with OECD 201 guideline. The 72 h EbC50 of 36.0 mg/l and ErC50 of 79.7 mg/l based on mean measured concentrations was reported.

10.2.2.1.3. Other available data. Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran has been registered under REACH with full dossier available but no additional data.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	(Fish)	(Daphnia)				
RIFM Framework Screening Level **(Tier 1)**	8.783 mg/l			1,000,000	0.008783 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.625 mg/l	1.491 mg/l	1.762 mg/l	10,000	0.0625 µg/l	Vinyl/Alyl Ethers
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.853 mg/l	3.188 mg/l	4.336 mg/l			Neutral Organic SAR
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	77.6 mg/l					
Daphnia		33.2 mg/l		1000	33.2 µg/l	
Algae		36.0 mg/l				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.58	3.58
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 33.2 µg/l. The revised PEC/PNECs for EU and NA < 1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 01/17/2014.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.011.

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