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Short Review

RIFM fragrance ingredient safety assessment, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-, CAS Registry Number 128489-02-1

A.M. Api [a], A. Bartlett [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], A. Bryant-Freidrich [d], G.A. Burton Jr. [e], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [f], W. Dekant [g], C. Deodhar [a], K. Farrell [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], H. Moustakas [a], J. Muldoon [a], T.M. Penning [i], G. Ritacco [a], N. Sadekar [a], I. Schember [a], T.W. Schultz [j], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, Pharmaceutical Sciences, Wayne State University, 42 W. Warren Ave., Detroit, MI, 48202, USA*
[e] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[f] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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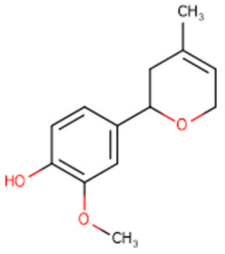

Name: Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-CAS Registry Number: 128489-02-1

Additional Materials*: 2-Methoxy-4-(tetrahydro-4-methylene-2H-pyran-2-yl)phenol (CAS # 128489-04-3)

*Included because the materials are isomers

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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; B. Safford et al., 2015; B. 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
ISS - Instituto Superiore di Sanita (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
TTC - Threshold of Toxicological Concern

(*continued on next column*)

(*continued*)

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.

Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- is not genotoxic. Data on phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. These data were extrapolated to derive a point of departure (PoD) for the reproductive toxicity endpoint. Data show that there are no safety concerns for phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- 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 phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- 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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 18.3 mg/kg/day. (RIFM, 1991a)
Reproductive Toxicity: NOAEL = 1.83 mg/kg/day. (RIFM, 1991a)
Skin Sensitization: Not a concern for skin sensitization. (RIFM, 1991b)
Photoirritation/Photoallergenicity: Not photoirritating/not expected to be photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 2017)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 2.7 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 29 L/kg (EPI Suite v4.11; US EPA; 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 73.01 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 73.01 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.07301 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name**: Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-	1. **Chemical Name**: 2-Methoxy-4-(tetrahydro-4-methylene-2H-pyran-2-yl) phenol
2. **CAS Registry Number:** 128489-02-1	2. **CAS Registry Number:** 128489-04-3
3. **Synonyms:** 4-(3,6-Dihydro-4-methyl-2H-pyran-2-yl)-2-methoxyphenol; Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-	3. **Synonyms:** 2-Methoxy-4-(tetrahydro-4-methylene-2H-pyran-2-yl)phenol; Eugewhite; Phenol, 2-methoxy-4-(tetrahydro-4-methylene-2H-pyran-2-yl)-
4. **Molecular Formula:** $C_{13}H_{16}O_3$	4. **Molecular Formula:** $C_{13}H_{16}O_3$
5. **Molecular Weight:** 220.26 g/mol	5. **Molecular Weight:** 220.26 g/mol
6. **RIFM Number:** 6337	6. **RIFM Number:** 6338
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers are possible.	7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data

CAS # 128489-02-1	CAS # 128489-04-3
1. **Boiling Point:** 334.65 °C (EPI Suite v4.11)	1. **Boiling Point:** decomposes at 266–271 °C at atmospheric pressure (RIFM, 1991e); 330.96 °C (EPI Suite v4.11)
2. **Flash Point:** Not Available	2. **Flash Point:** 178 °C
3. **Log K_{OW}:** 2.74 (EPI Suite v4.11)	3. **Log K_{OW}:** 2.82 (EPI Suite v4.11); 2.31 at 21 °C (RIFM, 1991e)
4. **Melting Point**: 107.11 °C (EPI Suite v4.11)	4. **Melting Point**: 105.6 °C (EPI Suite v4.11)
5. **Water Solubility:** 157.1 mg/L (EPI Suite v4.11)	5. **Water Solubility:** 2.06 ± 0.06 g/L at 20 °C (RIFM, 1991c); 134.6 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** Not Available	6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.37e-005 mm Hg at 25 °C (EPI Suite v4.11), 0.00000651 mm Hg at 20 °C (EPI Suite v4.0)	7. **Vapor Pressure:**; 1.76e-005 mm Hg at 25 °C (EPI Suite v4.11), 0.00000843 mm Hg at 20 °C (EPI Suite v4.0), 3.525 × 10^{-3} Pa (RIFM, 1991e)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm under the biologically relevant neutral condition and under the acidic condition; molar absorption coefficients (865 and 599 L mol^{-1} • cm^{-1}, under neutral and acidic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1}). Significant absorbance was observed under basic conditions, with a corresponding molar absorption coefficient (4475 L mol^{-1} • cm^{-1}) above the benchmark	8. **UV Spectra:** Minor absorbance between 290 and 700 nm under the biologically relevant neutral condition and under the acidic condition; molar absorption coefficients (202 and 258 L mol^{-1} • cm^{-1} under neutral and acidic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1}). Significant absorbance was observed under basic conditions, with a corresponding molar absorption coefficient (1443 L mol^{-1} • cm^{-1}) above the benchmark
9. **Appearance/Organoleptic:** Not Available	9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1 0.1–1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient* (Creme RIFM aggregate exposure model v3.1.3)

1. **95th Percentile Concentration in Fine Fragrance:** 1.78% (RIFM, 2020)
2. **Inhalation Exposure**:** 0.000033 mg/kg/day or 0.0024 mg/day (RIFM, 2020)
3. **Total Systemic Exposure***:** 0.0080 mg/kg/day (RIFM, 2020)

*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 fine fragrance, inhalation exposure, and total exposure.

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

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

5. Derivation of systemic absorption

1. **Dermal:** 80% Skin Absorption Model (SAM)

Name	Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-
J_{max} (μg/cm^2/h)	12.5[1]
Skin Absorption Class	80%

1. J_{max} was calculated based on measured log K_{ow} = 2.31 (RIFM, 1991e) and water solubility = 2060 mg/L at 20 °C (RIFM, 1991e).
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 v4.5
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

Neither material is 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

Neither material has been pre-registered; no dossiers are available as of 01/02/24.

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, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity without metabolic activation, positive for cytotoxicity with metabolic activation, and negative for genotoxicity with metabolic activation (RIFM, 2014c). These positive results were observed at cytotoxic concentrations that were within the acceptable range for the BlueScreen assay (positive: <80% relative cell density). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- 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, 2014a). Under the conditions of the study, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- was not mutagenic in the Ames test.

The clastogenic activity of phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- in DMSO at concentrations up to 2203 μg/mL in the dose range finding study; micronuclei analysis was conducted at concentrations up to 800 μg/mL in the presence and absence of metabolic activation. Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- did induce binucleated cells with micronuclei when tested at 1048 μg/mL in the 3-h treatment in the absence of an S9 activation system (RIFM, 2014b). However, the micronucleated binucleated frequencies at these concentrations (0.60%) were within the vehicle historical control ranges (0.25%–1.00%). Therefore, the statistically significant increases at these concentrations were considered biologically non-relevant and not indicative of clastogenic effects. Under the conditions of the study, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/05/23.

11.1.2. Repeated dose toxicity

The MOE for phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- 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 on phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-. In an OECD 407-compliant study, groups of 5 CD rats/sex/dose were administered phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- via gavage (vehicle: corn oil) at doses of 0, 5, 55, and 1000 mg/kg/day for 28 days. No mortality occurred throughout the study. There were no treatment-related adverse effects in clinical signs, food consumption, macroscopic examination, or microscopic examination. Bodyweight gains were significantly reduced in males at the high dose (−65%). Thrombotest time was slightly but significantly reduced in males at the high dose (5%). Neutrophil levels were significantly reduced in females of all treated groups (−68%, −51%, and −57% at the low, mid, and high doses, respectively), but values remained within historical control ranges. Urea nitrogen levels were significantly increased in males at the high dose (54%), but values remained within historical control ranges. Creatinine levels were slightly but significantly increased in males at the high dose (20%). Phosphorus levels were significantly reduced in females of all treated groups (10%, 10%, and 22% at the low, mid, and high doses, respectively), but values for the low-dose and mid-dose groups remained within historical control ranges. Relative liver weights were significantly increased in both sexes at the high dose (13% in males, 8% in females). Based on reduced bodyweight gains at 1000 mg/kg/day, the repeated dose NOAEL for this study was considered to be 55 mg/kg/day (RIFM, 1991a).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 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 55/3 or 18.3 mg/kg/day.

Therefore, the phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- NOAEL in mg/kg/day by the total systemic exposure to phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-, 18.3/0.0080 or 2288.

*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: 06/26/23.

11.1.3. Reproductive toxicity

The MOE for phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no fertility data or developmental toxicity data on phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- or on any read-across materials that can be used to support the reproductive toxicity endpoint. After refinement based on an 80% skin absorption rate determined by the RIFM SAM; see Section V), the total systemic exposure to phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- (8.0 μg/kg/day) is above 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.

As the repeated dose toxicity data on phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- are sufficient to draw a NOAEL (subchronic study), the repeated dose toxicity PoD can be adjusted to a reproductive toxicity PoD using an uncertainty factor (UF) and a Developmental and Reproductive Toxicity (DART) factor (Blackburn et al., 2015; Wu et al., 2013). In an OECD 407-compliant study, groups of 5 CD rats/sex/dose were administered phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- via gavage (vehicle: corn oil) at doses of 0, 5, 55, and 1000 mg/kg/day for 28 days. Based on reduced bodyweight gains at 1000 mg/kg/day, the repeated dose NOAEL for this study was considered to be 55 mg/kg/day (RIFM, 1991a).

Because the repeated dose toxicity data on phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- are sufficient to draw a NOAEL (sub-acute study), this PoD can be adjusted to a reproductive toxicity PoD using 2 uncertainty factors (UFs): (1) a duration factor of 3x to convert sub-acute to subchronic, and (2) a Developmental and Reproductive Toxicity (DART) factor.

To determine the value of the DART factor, the structure of phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- was analyzed using P&G DART Automated Tree (v1.7) to investigate its potential to cause DART reactivity or toxicity. The structure was first compared with a library of structures known to be negative for DART effects, but no matches were found in this library. The structure of the material was then compared to all structures in the DART Precedent database. The DART Precedent database includes all possible chemical structures enumerated from the substructures and rules for allowable substituents for all 25 subcategories of DART toxicants (Blackburn et al., 2015; Wu et al., 2013). There were no matches with a sufficient mapping score found in this library. The structure was next compared to all structures in the DART Substructure/Scaffold database to determine the degree of 'scaffold' match, and any/all overlaps of portions of the material structure with the scaffolds in the database are reported. The DART DT scaffold database includes all the 'scaffold' or core structures derived from the substructures defined for each of the 25 categories of DART toxicants (Blackburn et al., 2015; Wu et al., 2013). A scaffold match was detected with subcategory 2b-3-2 in that the structure is within the unsaturated 4-alkylphenol derivatives. However, the overlap between the structure of interest and the scaffold group was small. In the absence of matches to any of the libraries of structures (DART negative, DART precedence) other than a small scaffold match, a database uncertainty factor of 10x is applied. The 10x DART UF is maintained as a conservative approach, as DART potential is unknown because the DART DT is unable to provide sufficient information on the potential for DART precedence.

The cumulative product of the duration and DART UFs is $3 \times 10 = 30$.

Thus, the reproductive toxicity NOAEL for the developmental toxicity and fertility endpoints can be calculated by dividing the repeated dose toxicity NOAEL by the cumulative product of the UFs, $55/30 = 1.83$ mg/kg/day.

Therefore, the phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- MOE for the developmental toxicity and fertility endpoints can be calculated by dividing the phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- NOAEL in mg/kg/day by the total systemic exposure to phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-, 1.83/0.0080 or 229.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/27/23.

11.1.4. Skin sensitization

Based on the existing data, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- is not considered a skin sensitizer. The data are summarized in Table 1. This material is predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.5). A guinea pig Buehler test did not present reactions indicative of sensitization in isomer 2-methoxy-4-(tetrahydro-4-methylene-2H-pyran-2-yl)phenol (RIFM, 1991b). Additionally, in 2 separate Confirmation of No Induction in Humans (CNIH) tests with 5000 μg/cm^2 of isomer 2-methoxy-4-(tetrahydro-4-methylene-2H--pyran-2-yl)phenol in alcohol SD39C, no reactions indicative of sensitization were observed in any of the 51 volunteers (RIFM, 1991c; RIFM, 1991d).

Based on the weight of evidence (WoE) from structural analysis, an animal study, and human studies, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/28/

Table 1
Summary of existing data on phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- and isomer 2-methoxy-4-(tetrahydro-4-methylene-2H-pyran-2-yl)phenol.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL (induction) μg/cm^2	WoE NESIL μg/cm^2	LLNA Weighted Mean EC3 Value μg/cm^2	GPMT	Buehler[b]
No evidence of sensitization[c]	5000	N/A	N/A	N/A	N/A	N/A	Negative
	***In vitro* Data**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	N/A	N/A	N/A		No alert found	Radical reactions; SN2; Michael addition; Nucleophilic addition	Schiff base formation; Michael addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = 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] Studies conducted according to the OECD TG 406 are included in the table.

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

23.

11.1.5. Photoirritation/photoallergenicity

Based on the lack of absorbance at the biologically relevant neutral condition and the *in vitro* study data, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- does not present a concern for photoirritation. Based on the lack of absorbance at the biologically relevant neutral condition, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- would not be expected to present a concern for photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm under neutral and acidic conditions and significant absorbance under basic conditions. The corresponding molar absorption coefficients for neutral and acidic conditions were below the benchmark of concern for photoirritation and photoallergenicity; the molar absorbance coefficient under basic conditions was above the benchmark (Henry et al., 2009). Acidic and basic conditions in this assay are defined as pH < 2 and pH > 10. As such, they are not considered biologically relevant as the route of exposure is dermal. In an *in vitro* 3T3-Neutral Red Uptake phototoxicity assay (OECD TG 432), the isomer to the target material, 2-methoxy-4-(tetrahydro-4-methylene-2H-pyran-2-yl)phenol (CAS # 128489-04-3), was not predicted to be photoirritating (RIFM, 2017). Based on the lack of absorbance at the biologically relevant neutral condition and the *in vitro* study data, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- does not present a concern for photoirritation. Based on the lack of absorbance at the biologically relevant neutral condition, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- would not be expected to present a concern for photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm under the biologically relevant neutral condition and under the acidic condition. The molar absorption coefficients (865 and 599 L mol^{-1} • cm^{-1}, under neutral and acidic conditions, respectively) are below the benchmark of concern for photoirritating and photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009). Significant absorbance was observed under basic conditions, and the corresponding molar absorbance (4475 L mol^{-1} • cm^{-1}) was above the benchmark.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/08/23.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- 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 phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy-. Based on the Creme RIFM Model, the inhalation exposure is 0.0024 mg/day. This exposure is 195.8 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- 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 of 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, phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- as possibly being 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 $\geq$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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy- presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Phenol, 4-(3,6-dihydro-4-methyl-2H-pyran-2-yl)-2-methoxy has been pre-registered for REACH with no additional data at this time.

11.2.1.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	73.01			1000000	0.07301	

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

Exposure	Europe	North America
Log K_{ow} Used	2.7	2.7
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 0.07301 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: 04/20/23.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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://pubchem.ncbi.nlm.nih.gov/source/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 01/02/24.

Declaration of competing interest

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

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