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Short Review

RIFM fragrance ingredient safety assessment, 4,6-dimethyl-2H-pyran-2-one, CAS Registry Number 675-09-2

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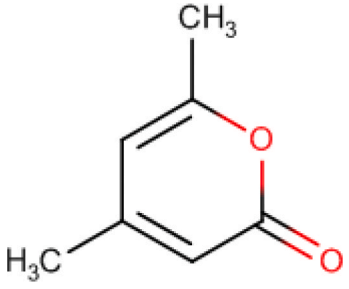
Name: 4,6-Dimethyl-2H-pyran-2-one CAS Registry Number: 675-09-2



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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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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

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NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

4,6-Dimethyl-2H-pyran-2-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog 5-hydroxy-2,4-decadienoic acid δ-lactone (CAS # 27593-23-3) show that 4,6-dimethyl-2H-pyran-2-one is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 4,6-dimethyl-2H-pyran-2-one is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; 4,6-dimethyl-2H-pyran-2-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4,6-dimethyl-2H-pyran-2-one was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 1982a; RIFM, 2014)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.

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Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (RIFM, 1982c; RIFM, 1982d)
Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 11% (OECD 302 C) RIFM (2009c)
Bioaccumulation: Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1016 mg/L (EPI Suite v4.11; US EPA, 2012a)
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: 1016 mg/L (RIFM Framework; Salvito, 2002) (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 1.016 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 4,6-Dimethyl-2H-pyran-2-one
2. **CAS Registry Number:** 675-09-2
3. **Synonyms:** Mesitene lactone; 2H-Pyran-2-one, 4,6-dimethyl-; Levistamel; Lavyrone; 4,6-Dimethyl-2H-pyran-2-one
4. **Molecular Formula:** $C_7H_8O_2$
5. **Molecular Weight:** 124.13
6. **RIFM Number:** 5209
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 238.97 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 1.1 (RIFM, 2009a), 0.85 (EPI Suite)
4. **Melting Point:** 4.46 °C (EPI Suite)
5. **Water Solubility:** 18220 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0112 mm Hg at 20 °C (EPI Suite v4.0), 0.0196 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with peak absorbance at 300 nm returning to baseline by 330 nm. Molar absorption coefficients (3520, 3180, and 3131 L mol^{-1} · cm^{-1} for neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} · cm^{-1}).
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

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

1. 95th Percentile Concentration in Fine Fragrance: 0.025% (RIFM, 2016)
2. Inhalation Exposure*: 0.000027 mg/kg/day or 0.0021 mg/day (RIFM, 2016)
3. Total Systemic Exposure**: 0.00083 mg/kg/day (RIFM, 2016)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** 5-Hydroxy-2,4-decadienoic acid δ-lactone (CAS # 27593-23-3)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   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 (discrete chemical) or composition (NCS)

4,6-Dimethyl-2H-pyran-2-one is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. Reach dossier

Pre-registered for 2010; no dossier available as of 10/26/20.

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, 4,6-dimethyl-2H-pyran-2-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 4,6-dimethyl-2H-pyran-2-one has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 4,6-dimethyl-2H-pyran-2-one in ethanol at concentrations up to 50 mg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM,1982a). Under the conditions of the study, 4, 6-dimethyl-2H-pyran-2-one was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 4,6-dimethyl-2H-pyran-2-one; however, read-across can be made to 5-hydroxy-2,4-decadienoic acid δ-lactone (CAS # 27593-23-3; see Section 6).

The clastogenic activity of 5-hydroxy-2,4-decadienoic acid δ-lactone 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 5-hydroxy-2,4-decadienoic acid δ-lactone in dimethyl sulfoxide (DMSO) at concentrations up to 1663 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 800 μg/mL in the presence and absence of metabolic activation. 5-hydroxy-2,4-decadienoic acid δ-lactone did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, 5-hydroxy-2,4-decadienoic acid δ-lactone was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 4,6-dimethyl-2H-pyran-2-one.

Based on the data available, 5-hydroxy-2,4-decadienoic acid δ-lactone does not present a concern for genotoxic potential, and this can be extended to 4,6-dimethyl-2H-pyran-2-one.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/02/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 4,6-dimethyl-2H-pyran-2-one or any read-across materials. The total systemic exposure to 4,6-dimethyl-2H-pyran-2-one is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4,6-dimethyl-2H-pyran-2-one or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.83 μg/kg/day) is below the TTC for 4,6-dimethyl-2H-pyran-2-one (1.5 μg/kg/day; Kroes, 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/22/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4,6-dimethyl-2H-pyran-2-one or any read-across materials. The total systemic exposure to 4,6-dimethyl-2H-pyran-2-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 4,6-dimethyl-2H-pyran-2-one or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.83 μg/kg/day) is below the TTC for 4,6-dimethyl-2H-pyran-2-one (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/18/20.

11.1.4. Skin sensitization

Based on the existing data and the application of DST, 4,6-dimethyl-2H-pyran-2-one does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 4,6-dimethyl-2H-pyran-2-one. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; OECD toolbox v4.2). In a guinea pig maximization test, 4,6-dimethyl-2H-pyran-2-one did not present reactions indicative of sensitization up to 100% (RIFM, 1982b). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 4,6-dimethyl-2H-pyran-2-one that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/01/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available *in vivo* study data, 4,6-dimethyl-2H-pyran-2-one would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm. The corresponding molar absorption coefficients (3520, 3180, and 3131 L mol^{-1} cm^{-1} for neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In phototoxicity and photoallergenicity studies conducted in guinea pigs, there was no evidence of phototoxicity or photoallergenicity (RIFM, 1982d; RIFM, 1982c). Based on *in vivo* study data, 4,6-dimethyl-2H-pyran-2-one does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. Spectra indicate significant absorbance between 290 and 700 nm, with peak absorbance at 300 nm and returning to baseline by 330 nm. Molar absorption coefficients (3520, 3180, and 3131 L mol^{-1} · cm^{-1} for neutral, acidic, and basic conditions, respectively) are above 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: 06/18/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4,6-dimethyl-2H-pyran-2-one is below the Cramer Class III TTC value for inhalation exposure local effects.

Table 1
Maximum acceptable concentrations for 4,6-dimethyl-2H-pyran-2-one that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	0.013%
3	Products applied to the face using fingertips	0.41%	0.0013%
4	Fine fragrance products	0.39%	0.025%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.013%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	0.0012%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0032%
10	Household care products with mostly hand contact	2.7%	0.0029%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.063%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.6.1. Risk assessment. There are no inhalation data available on 4,6-dimethyl-2H-pyran-2-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0021 mg/day. This exposure is 224 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: 05/08/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4,6-dimethyl-2H-pyran-2-one was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ),

expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 4,6-dimethyl-2H-pyran-2-one was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 4,6-dimethyl-2H-pyran-2-one as possibly 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 4,6-dimethyl-2H-pyran-2-one presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 2009c: The inherent biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 302C guideline. Biodegradation of 11% was observed after 31 days.

RIFM, 2009b: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. No biodegradation was observed after 29 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 4,6-Dimethyl-2H-pyran-2-one has been pre-registered for REACH with no additional data available at this time.

11.2.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	1.1	1.1
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 1.016 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 volumes of use.

Literature Search and Risk Assessment Completed On: 06/16/20.

12. Literature Search*

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>1016</u>			1000000	1.016	

- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/30/20.

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.2020.111893.

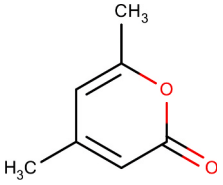
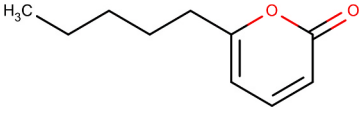
Appendix

Read-across Justification

Methods

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

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

	Target Material	Read-across Material
Principal Name	4,6-Dimethyl-2H-pyran-2-one	5-Hydroxy-2,4-decadienoic acid δ-lactone
CAS No.	675-09-2	27593-23-3
Structure		
Similarity (Tanimoto Score)		0.53
Endpoint		• Genotoxicity
Molecular Formula	$C_7H_8O_2$	$C_{10}H_{14}O_2$
Molecular Weight	124.139	166.22
Melting Point (°C, EPI Suite)	51.50	12.92
Boiling Point (°C, EPI Suite)	245.00	290.38
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.61E+00	4.33E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.82E+04	7.42E+02
Log KOW	0.85	2.27
J_{max} (μg/cm^2/h, SAM)	118.20	16.77
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.66E+01	1.52E+02
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 4,6-dimethyl-2H-pyran-2-one (CAS # 675-09-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 5-hydroxy-2,4-decadienoic acid δ-lactone (CAS # 27593-23-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 5-Hydroxy-2,4-decadienoic acid δ-lactone (CAS # 27593-23-3) was used as a read-across analog for the target material 4,6-dimethyl-2H-pyran-2-one (CAS # 675-09-2) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of δ-lactones.
  - o The target material and the read-across analog share a δ-lactone substructure.
  - o The key difference between the target material and the read-across analog is that the target material has a methyl substitution on the 4- and 6-positions, whereas the read-across analog has a pentyl substitution at the 6-position. This structural difference is toxicologically insignificant for the genotoxicity endpoint.
  - 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 There are no alerts for the target material and the read-across analog for the genotoxicity endpoint. Therefore, *in silico* alerts are consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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