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Short Review

RIFM fragrance ingredient safety assessment, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one, CAS Registry Number 68555-63-5

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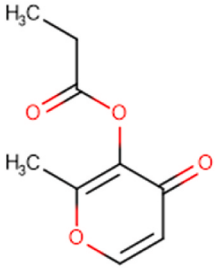

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Name: 2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one CAS Registry Number: 68555-63-5

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
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)

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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., 2015; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api 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.

2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs maltol (CAS # 118-71-8) and propionic acid (79-09-4) show that 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one is not expected to be genotoxic. Data on read-across analogs ethyl maltol (CAS # 4940-11-8) and propionic acid (CAS # 79-09-4) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog ethyl maltol (CAS # 4940-11-8) show that there are no safety concerns for 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one 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; 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one 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 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA, 2011; RIFM, 2012a; RIFM, 2012b; RIFM, 2013b)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day.	(OECD, 2007; ECHA, 2018)
Reproductive Toxicity: Developmental toxicity and Fertility NOAEL = 200 mg/kg/day.	(OECD, 2007; ECHA, 2018)
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.	
Photoirritation/Photoallergenicity: Not photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 2019)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Screening-level: 2.9 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 3.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 1038 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)	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 1038 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 1.038 μg/L

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

1. Identification

1. **Chemical Name:** 2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one
2. **CAS Registry Number:** 68555-63-5
3. **Synonyms:** Maltol propionate; 4H-Pyran-4-one, 2-methyl-3-(1-oxopropoxy)-; Veltol propionate; 2-Methyl-4-oxo-4H-pyran-3-yl propionate; 2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one
4. **Molecular Formula:** $C_9H_{10}O_4$
5. **Molecular Weight:** 182.17 g/mol
6. **RIFM Number:** 5923
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 279.83 °C (EPI Suite v4.11)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 1.28 (EPI Suite)
4. **Melting Point**: 64.26 °C (EPI Suite v4.11)
5. **Water Solubility:** 4348 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00243 mm Hg at 25 °C (EPI Suite v4.11), 0.00133 mm Hg at 20 °C (EPI Suite v4.0)

8. **UV Spectra:** Minor absorbance between 290 and 700 nm under the biologically relevant neutral condition. The corresponding molar absorption coefficient (449 L mol^{-1} • cm^{-1}, under neutral conditions) is below the benchmark. Under basic conditions, there was significant absorbance between 290 and 700 nm, with peak absorbance at 322 nm and returning to baseline by 370 nm (RIFM, 2017d). The molar absorption coefficients (3284 L mol^{-1} • cm^{-1}, under basic condition) is 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, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00011% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000023 mg/kg/day or 0.0017 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.000023 mg/kg/day (RIFM, 2021)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class III, High.

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
III	III	III

6.2. Analogs selected

a. **Genotoxicity:** Maltol (CAS # 118-71-8) and propionic acid (CAS # 79-09-4)
b. **Repeated Dose Toxicity:** Ethyl maltol (CAS # 4940-11-8) and propionic acid (CAS # 79-09-4)
c. **Reproductive Toxicity:** Ethyl maltol (CAS # 4940-11-8) and propionic acid (CAS # 79-09-4)
d. **Skin Sensitization:** Weight of evidence (WoE) for non-reactive DST - ethyl maltol (CAS # 4940-11-8)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-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

2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one has been pre-registered for 2010; no dossier is available as of 10/21/22.

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, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity without metabolic activation and negative for both cytotoxicity and genotoxicity with metabolic activation. The positive results were observed at cytotoxic concentrations that were within the acceptable range for the BlueScreen assay (positive: <80% relative cell density) (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one; however, read-across can be made to maltol and propionic acid (CAS # 118-71-8 and 79-09-4, respectively; see Section VI).

The mutagenic activity of maltol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with maltol 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, 2012a). Under the conditions of the study, maltol was not mutagenic in the Ames test, and this can be extended to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one.

The mutagenic activity of propionic acid 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 propionic acid in water 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 (ECHA, 2011). Under the conditions of the study, propionic acid was not mutagenic in the Ames test, and this can be extended to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one.

The clastogenic activity of maltol 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 maltol in DMSO at concentrations up to 1262 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1262 μg/mL in the presence and absence of metabolic activation. Maltol induced binucleated cells with micronuclei when tested at 800.0 and 1262 μg/mL in the 3-h treatment in the presence of an S9 activation system and at 400.0, 800.0, and 1262 μg/mL in the 3-h treatment in the absence of an S9 activation system (RIFM, 2012b). Under the conditions of the study, maltol was considered to be clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one.

In order to verify the biological relevance of the results in the *in vitro* micronucleus test, the genotoxic activity of maltol was evaluated in a combined *in vivo* COMET/micronucleus test conducted in compliance with GLP regulations. The test material was administered in 0.5% (w/v) aqueous methylcellulose via oral gavage to groups of male Han Wistar rats (no gender differences were observed in the DRF study). Doses of 70, 350, and 700 mg/kg were administered for 3 consecutive days. Mice from each dose level were euthanized 3 h after the last dose, and bone marrow was collected and examined for micronuclei evaluation; the liver was used for the COMET assay analysis. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in bone marrow or induce a significant increase in DNA damage in the liver (RIFM, 2013b). Under the conditions of the study, maltol was considered to be non-genotoxic in the combined *in vivo* COMET/micronucleus test, and this can be extended to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one.

The clastogenic activity of propionic acid was evaluated in an *in vivo* micronucleus test conducted in an equivalent manner to OECD TG 474. The test material was administered in physiological saline via intraperitoneal injection to groups of male and female Chinese hamsters. A single dose of 125 mg/kg body weight was administered. Hamsters from each dose level were euthanized at 12, 24, or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, propionic acid was considered not to be clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one.

Based on the data available, maltol and propionic acid do not present a concern for genotoxic potential, and this can be extended to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/22.

11.1.2. Repeated dose toxicity

The MOE for 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one. Read-across materials ethyl maltol (2-ethyl-3-hydroxy-4-pyrone; CAS # 4940-11-8) and propionic acid (CAS # 79-09-4; see Section VI) have sufficient repeated dose toxicity data.

In a pre-GLP, non-guideline, chronic toxicity study, groups of 25 Charles River albino rats/sex/dose were administered ethyl maltol via diet at doses of 0, 50, 100, and 200 mg/kg/day for 2 years. The parameters inspected included clinical signs, body weights, food consumption, hematology, urinalysis, gross pathology, and histopathology. No mortality was observed throughout the treatment period. There were no treatment-related adverse effects observed on clinical signs, body weights, food consumption, hematology, urinalysis, organ weights, gross pathology, or histopathology. Based on no adverse effects seen up to the highest dose, the repeated dose toxicity NOAEL for this study was considered to be 200 mg/kg/day (ECHA, 2018).

In a pre-GLP, non-guideline, subchronic toxicity study, groups of 10 Charles River albino rats/sex/dose were administered ethyl maltol via diet at doses of 0, 250, 500, and 1000 mg/kg/day for 90 days. The parameters inspected included clinical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. No mortality was observed throughout the treatment period. There were no treatment-related adverse effects observed on clinical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights, or gross pathology. Histopathological examination revealed kidney lesions (extremely dilated, acellular glomerular tuft with protein loss into Bowman's space and cast formation within the lumina of dilated corticomedullary tubules) in high-dose animals. Based on kidney lesions observed at 1000 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 500 mg/kg/day (ECHA, 2018).

Across both studies, no adverse effects were seen up to a dose of 500 mg/kg/day. Therefore, the NOAEL of 500 mg/kg/day was selected for the repeated dose toxicity endpoint for ethyl maltol.

There are sufficient repeated dose toxicity data on propionic acid. A non-GLP, 90-day dietary study was conducted according to guidelines similar to OECD TG 408 on groups of 20 Sprague Dawley rats/sex. The animals were treated with 0%, 0.62%, 1.25%, 2.5%, or 5% propionic acid in a pulverized diet for 91 days. The concentrations are equal to approximately 0, 312, 625, 1250, or 2500 mg/kg/day (as per the conversion factors for old rats, available in the JECFA guidelines for the preparation of toxicological working papers on food additives). In parallel, 10 animals were included in the control, and 0.62% and 5% groups were assigned to the post-exposure recovery groups for respective doses and fed the control diet for 6 weeks. There was a 12% decrease in the relative kidney weights among high-dose males. In high-dose females, there were 5% and 9% increases in the relative weights of the heart and liver, respectively. Examination of tissues revealed no lesions except local changes of the mucosa of the forestomach in rats in the 5% treatment group, which included acanthosis, hyperkeratosis, and proliferation of the epithelium. The changes observed in the forestomach were not observed in the recovery group, and there were no differences in the relative or absolute organ weights. There were no adverse effects on the reproductive organs. The forestomach is a species-specific organ and is not found among humans; therefore, the effects observed in the rat forestomach were considered to be of no relevance to humans. In addition, since the changes in the liver and kidney weights were not associated with any histopathological alterations, they were not considered to be adverse. The NOAEL for systemic toxicity was considered to be 5% or 2500 mg/kg/day, the highest dose tested (OECD, 2007; ECHA, 2011).

In an OECD 409 study, propionic acid was fed in the diet to groups of 8 male and 8 female beagle dogs for approximately 100 days. The dogs received 0%, 0.3%, 1.0%, or 3.0% propionic acid (0, 196, 660, and 1848 mg/kg/day for males and 0, 210, 696, and 1832 mg/kg/day for females) in the diet. An additional 8 animals (4/sex) were assigned to the control and high-dose groups to be maintained for an additional 6-week recovery interval. There were no effects of treatment on the dogs except

for local diffuse epithelial hyperplasia of the mucosa of the esophagus in 3 dogs in the highest-dose group. At the end of the recovery interval, the incidence of lesions of the esophagus was the same in the control and high-dose group animals. The incidence of focal epithelial hyperplasia in lower-dose animals was comparable to controls. The NOAEL for systemic toxicity was considered to be 3% propionic acid (1848 mg/kg/day for males and 1832 mg/kg/day for females) in the diet, the highest dose tested (OECD, 2007; ECHA, 2011).

The most conservative NOAEL for the repeated dose toxicity endpoint was considered to be 1832 mg/kg/day from the study conducted on beagle dogs.

Considering studies on both ethyl maltol and propionic acid, a conservative NOAEL of 500 mg/kg/day was selected for the safety assessment.

Therefore, the 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl maltol NOAEL in mg/kg/day by the total systemic exposure to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one, 500/0.00023, or 21739130.

In addition, the total systemic exposure to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one (0.023 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/22.

11.1.3. Reproductive toxicity

The MOE for 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one. Read-across materials, ethyl maltol (CAS # 4940-11-8) and propionic acid (CAS # 79-09-4); see Section VI), have sufficient reproductive toxicity data.

In a pre-GLP non-guideline chronic toxicity study, groups of 25 Charles River albino rats/sex/dose were administered ethyl maltol via diet at doses of 0, 50, 100, and 200 mg/kg/day for 2 years. Between 15 and 21 and 30−36 weeks, 10 Charles River albino rats/sex/dose were mated to produce 2 separate litters. The resulting offspring were counted, weighed, and examined for abnormal development at birth and during lactation. At weaning, they were euthanized and examined for internal malformations. In the parent groups, 5 of each sex at each level were autopsied after 1 year on the test, the remainder after the full study duration of 2 years. At termination, further examinations were made for gross necropsy, organ weights, and tissue histopathology. The estrous cycle and sperm parameters of parental animals were not examined. No mortality was observed throughout the study period. There were no treatment-related adverse effects on conception rate, gestation, parturition, lactation, pup survival, pup weights, gross pathology, or any other developmental parameters. Based on no treatment-related adverse effects seen up to the highest dose, the developmental toxicity and fertility NOAEL for this study was considered to be 200 mg/kg/day (ECHA, 2018).

There are sufficient developmental toxicity data on propionic acid. Calcium propionate, the calcium salt of propionic acid, was administered via oral gavage to 21–24 pregnant female Wistar rats per group from gestation days (GDs) 6–15 at doses of 0, 3, 14, 65, or 300 mg/kg/day. There were no treatment-related effects reported among the treated females or the development of the fetuses up to the highest dose tested. The NOAEL for maternal toxicity and the development of the fetus was considered to be 300 mg/kg/day, the highest dose tested (OECD, 2007).

In another study, calcium propionate, the calcium salt of propionic acid, was administered via oral gavage to 21–22 pregnant female golden outbred Syrian hamsters per dose group from GDs 6–10 at doses of 0, 4, 19, 86, or 400 mg/kg/day. There were no treatment-related effects reported among the treated females or the development of the fetuses up to the highest dose tested. The NOAEL for maternal toxicity and the development of the fetus was considered to be 400 mg/kg/day, the highest dose tested (OECD, 2007).

In another study, calcium propionate, the calcium salt of propionic acid, was administered via oral gavage to 9–11 pregnant female Dutch-belted rabbits per dose group from GDs 6–18 at doses of 0, 4, 19, 86, or 400 mg/kg/day. There were no treatment-related effects reported among the treated females or the development of the fetuses up to the highest dose tested. The NOAEL for maternal toxicity and the development of the fetus was considered to be 400 mg/kg/day, the highest dose tested (OECD, 2007).

There are sufficient fertility data on propionic acid. A 90-day dietary study was conducted on groups of 20 Sprague Dawley rats/sex. The animals were treated with 0%, 0.62%, 1.25%, 2.5%, or 5% propionic acid in a pulverized diet for 91 days. The concentrations are equal to approximately 0, 312, 625, 1250, or 2500 mg/kg/day (as per the conversion factors for old rats, available in the JECFA guidelines for the preparation of toxicological working papers on food additives). There were no effects of propionic acid treatment on the male or female reproductive organ weights or histopathology up to the highest dose tested. The NOAEL for fertility effects was considered to be 5% or 2500 mg/kg/day (OECD, 2007; ECHA, 2011).

In an OECD 409 study, propionic acid was fed in the diet to groups of 8 male and female beagle dogs for approximately 100 days. The dogs received 0%, 0.3%, 1.0%, or 3.0% propionic acid (0, 196, 660, and 1848 mg/kg/day for males and 0, 210, 696, and 1832 mg/kg/day for females) in the diet. An additional 8 animals (4/sex) were assigned to the control and high-dose groups to be maintained for an additional 6-week recovery interval. There were no significant changes in the relative or absolute weight of the testes or ovaries in the treatment group animals relative to controls, and there were no histopathological alterations in the male and female reproductive organs in animals fed propionic acid in the diet for 90 days. The NOAEL for fertility effects was considered to be 3% propionic acid (1848 mg/kg/day for males and 1832 mg/kg/day for females) in the diet, the highest dose tested (OECD, 2007). The most conservative NOAEL of 1832 mg/kg/day from female dogs was considered for fertility effects.

Considering studies on both ethyl maltol and propionic acid, a conservative NOAEL of 200 mg/kg/day for developmental toxicity and fertility was considered for the safety assessment.

Therefore, the 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one MOE for the reproductive toxicity endpoint can be calculated by dividing the ethyl maltol NOAEL in mg/kg/day by the total systemic exposure to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one, 200/0.00023 or 8695652.

In addition, the total systemic exposure to 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one (0.023 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/22.

11.1.4. Skin sensitization

Based on the existing data on weight of evidence (WoE) material ethyl maltol, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization data are available for 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one. Therefore, WoE material ethyl maltol (CAS # 4940-11-8; see Section VI) was used for the risk assessment of 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one. The data on

the WoE material are summarized in Table 1. The chemical structure of the WoE material and the target material indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). However, WoE material ethyl maltol was predicted to be negative an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens, but positive in the human cell line activation test (h-CLAT) (RIFM, 2017c; RIFM, 2017a; RIFM, 2017b). Based on the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a), ethyl maltol was determined *in vitro* to be a non-sensitizer. In a human maximization test, no reactions to WoE material ethyl maltol were observed at 6900 μg/cm^2 (Kligman, 1974, #1779). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 5906 μg/cm^2 of WoE ethyl maltol in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 111 volunteers (RIFM, 2015).

Based on the existing data on the WoE material, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent supported 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: 10/11/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and *in vitro* study data, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, under the biologically relevant neutral condition, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one would not be expected to present a concern for photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the critical range of 290–700 nm under neutral conditions and significant absorbance under basic conditions. Under neutral conditions, the molar absorption coefficients are below the benchmark of concern for photoirritation/photoallergenicity. Under basic conditions, the corresponding molar absorption coefficient is above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). However, the acidic and basic conditions in this assay are defined as pH 2 or less and pH 10 or greater, respectively, and are not biologically relevant for our purposes, where the route of exposure is topical. In a 3T3-Neutral Red Uptake photoirritation test, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one was not predicted to have photoirritating potential (RIFM, 2019). Based on the available UV/Vis absorption spectra and *in vitro* study data, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, 2-methyl-3-(1-oxopropoxy)-4H--pyran-4-one 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 between 290 and 700 nm under the biologically relevant neutral condition. The corresponding molar absorption coefficients (449 L mol^{-1} • cm^{-1}, under neutral conditions) are below the benchmark. Under basic conditions, there was significant absorbance between 290 and 700 nm, with peak absorbance at 322 nm and returning to baseline by 370 nm. The molar absorption coefficient (3284 L mol^{-1} • cm^{-1}, under basic conditions) is above the benchmark of concern for photoirritating and photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/12/22.

Table 1
Summary of existing data on ethyl maltol as WoE material for using non-reactive DST to evaluate 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL[2] (induction) μg/cm²	WoE NESIL[3] μg/cm²	LLNA[4] Weighted Mean EC3 Value μg/cm²	GPMT[5]	Buehler[5]
No evidence of sensitization[7]	5906	6900	N/A	N/A	N/A	N/A	N/A
	In vitro Data[6]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Negative	Positive		Michael addition	Michael addition	Michael addition

Table 2
Supported concentrations for 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Supported Concentrations[b] (%) 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[c]
2	Products applied to the axillae	0.021	NRU[c]
3	Products applied to the face using fingertips	0.41	NRU[c]
4	Fine fragrance products	0.39	1.1×10^{-4}
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10	NRU[c]
6	Products with oral and lip exposure	0.23	NRU[c]
7	Products applied to the hair with some hand contact	0.79	NRU[c]
8	Products with significant ano-genital exposure	0.041	No Data[d]
9	Products with body and hand exposure, primarily rinse-off	0.75	6.6×10^{-6}
10	Household care products with mostly hand contact	2.7	NRU[c]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5	No Data[d]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.019

Note:
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] These levels represent maximum acceptable concentrations based on the DST. However, additional studies may show it could be used at higher levels.
[c] No reported use.
[d] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one 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 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0017 mg/day. This exposure is 276.5 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: 10/12/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-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 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, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-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) did not identify 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one 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, 2017a). 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).

11.2.2. Risk assessment

Based on the current VoU (2019), 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.1.2.1. Biodegradation. No data available.
11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.3. Other available data. 2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one has been pre-registered for REACH with no additional data 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1038			1000000	1.038	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.28	1.28
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 1.038 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: 10/04/22.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 03/27/23.

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.2023.113796.

Appendix

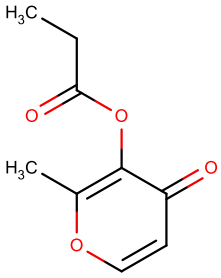
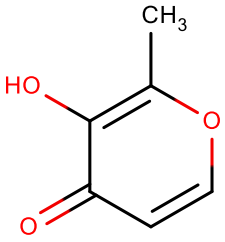
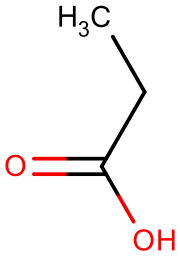
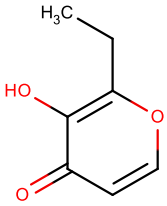
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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 Chemicals Agency read-across assessment framework (ECHA, 2017b).

- 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 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021b).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one	Maltol	Propionic acid	Ethyl maltol
CAS No.	68555-63-5	118-71-8	79-09-4	4940-11-8
Structure				
Similarity (Tanimoto Score)		Not applicable*	Not applicable*	0.51
SMILES	CCC(=O)OC1C(=O)C=COC=1C	CC1OC=CC(=O)C = 1O	CCC(O)=O	CCC1OC=CC(=O)C = 1O
Endpoint		Genotoxicity	Genotoxicity Repeated dose toxicity Reproductive toxicity	Skin sensitization Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_9H_{10}O_4$	$C_6H_6O_3$	$C_3H_6O_2$	$C_7H_8O_3$
Molecular Weight (g/mol)	182.175	126.111	74.079	140.138
Melting Point (°C, EPI Suite)	64.26	161.50	−21.10	70.54
Boiling Point (°C, EPI Suite)	279.83	267.24	141.10	283.37
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.24E-01	5.71E-03	4.71E+02	1.93E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.35E+03	1.09E+04	1.00E+06	2.42E+04
Log K_{OW}	1.28	0.09	0.33	0.63
J_{max} (μg/cm²/h, SAM)	12.52	18.13	10128.08	70.33
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	9.51E-02	1.55E-04	4.51E-02	2.07E-04
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	AN2|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds	No alert found	
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found	No alert found	
Carcinogenicity (ISS)	α,β-Unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity	α,β-Unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	AN2|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	α,β-Unsaturated carbonyls	α,β-Unsaturated carbonyls	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	α,β-Unsaturated carbonyls|H-acceptor-path3-H-acceptor	α,β-Unsaturated carbonyls|H-acceptor-path3-H-acceptor	No alert found	
Oncologic Classification	Not classified	Not classified	Not classified	
Repeated Dose Toxicity				
Repeated Dose (HESS)	Not categorized		Carboxylic acids (Hepatotoxicity) No rank|	Not categorized

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
			Glycolic acid (Renal Toxicity) Alert	
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, without OH or NH_2 group		Non-binder, non-cyclic structure	Non-binder, impaired OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Toxicant (low reliability)	Non-toxicant (low reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	Michael addition|Michael addition ≫ Michael addition on quinoid type compounds|Michael addition ≫ Michael addition on quinoid-type compounds ≫ Pyranones, Pyridones (and related nitrogen chemicals)			Michael addition|Michael addition ≫ Michael addition on quinoid-type compounds|Michael addition ≫ Michael addition on quinoid-type compounds ≫ Pyranones, Pyridones (and related nitrogen chemicals)
Protein Binding (OECD)	Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates|Michael addition|Michael addition ≫ Quinones and Quinone-type Chemicals|Michael addition ≫ Quinones and Quinone-type Chemicals ≫ Pyranones (and related nitrogen chemicals)			Michael addition|Michael addition ≫ Quinones and Quinone-type Chemicals|Michael addition ≫ Quinones and Quinone-type Chemicals ≫ Pyranones (and related nitrogen chemicals)
Protein Binding Potency	Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Substituted 1-Alken-3-ones (MA)			Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Substituted 1-Alken-3-ones (MA)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Michael Addition|Michael Addition ≫ Michael addition on quinoid-type compounds|Michael Addition ≫ Michael addition on quinoid-type compounds ≫ Pyranones, Pyridones (and related nitrogen chemicals)			Michael Addition|Michael Addition ≫ Michael addition on quinoid-type compounds|Michael Addition ≫ Michael addition on quinoid-type compounds ≫ Pyranones, Pyridones (and related nitrogen chemicals)
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Michael Acceptor identified.			Alert for Michael Acceptor identified.
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	No metabolites formed	See Supplemental Data 3

*Tanimoto score not reported as the read-across analogs are metabolites of the target material and not structural analogs.

Summary

There are insufficient toxicity data on 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one (CAS # 68555-63-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, maltol (CAS # 118-71-8), propionic acid (CAS # 79-09-4), and ethyl maltol (CAS # 4940-11-8) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target material, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one (CAS # 68555-63-5), was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.5). The target material is predicted to be metabolized to maltol (CAS # 118-71-8) and propionic acid (CAS # 79-09-4) in the first step with 0.440 pre-calculated and 0.950 intrinsic probability. Hence, maltol (CAS # 118-71-8) and propionic acid (CAS # 79-09-4) can be used as read-across analogs for the target material. Due to a lack of data for the repeated dose and reproductive toxicity endpoints on maltol, the metabolite analog ethyl maltol (CAS # 4940-11-8) was used. Read-across analogs maltol (CAS # 118-71-8), propionic acid (CAS # 79-09-4), and ethyl maltol (CAS # 4940-11-8) were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.30.1.11). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided.

Conclusions

- Read-across alcohol maltol (CAS # 118-71-8) and read-across acid propionic acid (CAS # 79-09-4) are used as read-across analogs for the target ester, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one (CAS # 68555-63-5), for the genotoxicity endpoint.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.

- The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
- According to the QSAR OECD Toolbox v4.5, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material. The read-across analog, maltol (CAS # 118-71-8), has an alert for Schiff base formation that the target material does not have. According to these predictions, the read-across analog is expected to be more reactive compared to the target material.

- Read-across alcohol analog ethyl maltol (CAS # 4940-11-8) and read-across acid propionic acid (CAS # 79-09-4) are used as read-across analogs for the target ester, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one (CAS # 68555-63-5), for the repeated dose toxicity and reproductive toxicity endpoints.
  - An analog of the alcohol produced from ester hydrolysis along with the corresponding acid are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the acid and a similar alcohol comparable to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - According to the QSAR OECD Toolbox v4.5, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material. The read-across analog propionic acid (CAS # 79-09-4) has alerts for renal toxicity and hepatotoxicity for repeated dose toxicity and is identified as a toxicant for reproductive toxicity, whereas the target material has no alerts and is identified as a non-toxicant. According to these predictions, the read-across analog is expected to be more reactive compared to the target material.
- Ethyl maltol (CAS # 4940-11-8) was used as a read-across analog for the target material, 2-methyl-3-(1-oxopropoxy)-4H-pyran-4-one (CAS # 68555-63-5), for the skin sensitization endpoints.
  - The target material and the read-across analog are structurally similar and belong to the keto-enol-pyrans group.
  - The key difference between the target material and the read-across analog is the target material is an ester and has a methyl group on the ring, whereas the read-across analog is an alcohol and has an ethyl group on the ring. Since the ester will metabolize quickly to a comparable alcohol analog, this structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have alerts for Michael addition to quinones and quinone-type chemicals for protein binding by OASIS and as a Michael acceptor for skin sensitization reactivity domain by Toxtree. The data on the read-across analog confirms that the material does not pose a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - 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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