Food and Chemical Toxicology 159 (2022) 112646

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-, CAS Registry Number 27538-09-6

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

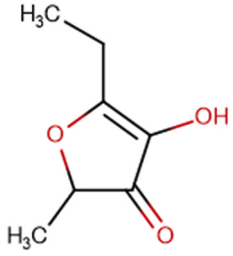
[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *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] *University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *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*
[k] *The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 090221. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: 3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl-CAS Registry Number: 27538-09-6
27538-10-9 2-Ethyl-4-hydroxy-5-methylfuran-3(2H)-one
*Included because the materials are isomers



Abbreviation/Definition List:

(*continued on next column*)

(*continued*)

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., 2020)
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

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2021.112646
Received 3 September 2021; Accepted 25 October 2021
Available online 29 October 2021

(*continued*)

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

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

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

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

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

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

3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is not genotoxic. Data on read-across material 4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. Data and read-across to 4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3) provided 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- a No Expected Sensitization Induction Level (NESIL) of 590 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data; 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is not expected to be phototoxic/photoallergenic. The developmental toxicity and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material; exposure to 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is below the TTC (0.009 mg/kg/day and 0.47 mg/day). The environmental endpoints were evaluated; 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- 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.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1981; RIFM, 1988; RIFM, 2005)
Repeated Dose Toxicity: NOAEL = 194.25 mg/kg/day.	RIFM (2003)
Reproductive Toxicity: Developmental toxicity: No NOAEL available. Exposure is below TTC. Fertility NOAEL = 400 mg/kg/day.	JECFA (2018)
Skin Sensitization: NESIL = 590 μg/cm^2.	RIFM (2015b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(RIFM, 2017; RIFM, 1991b; RIFM, 1991d)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 76% (OECD 301C)	(RIFM, 1991e)
Bioaccumulation:	
Screening-level: 3.42 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 763.9 mg/L	(RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 763.9 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.7639 μg/L

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

1. Identification

Chemical Name: 3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl-	Chemical Name: 2-Ethyl-4-hydroxy-5-methylfuran-3(2H)-one
CAS Registry Number: 27538-09-6	**CAS Registry Number:** 27538-10-9
Synonyms: 5-Ethyl-4-hydroxy-2-methyl-3(2H)-furanone; Homofuronol; Homopineapple compound; 5-Ethyl-4-hydroxy-2-methylfuran-3(2H)-one; 3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl-	**Synonyms:** 3(2H)-Furanone, 2-ethyl-4-hydroxy-5-methyl-; 2-Ethyl-4-hydroxy-5-methylfuran-3(2H)-one
Molecular Formula: $C_7H_{10}O_3$	**Molecular Formula:** $C_7H_{10}O_3$
Molecular Weight: 142.15	**Molecular Weight:** 142.15
RIFM Number: 5014	**RIFM Number:** 5635
Stereochemistry: Isomer not specified. One stereocenter and 2 enantiomers possible.	**Stereochemistry:** Isomer not specified. One stereocenter and 2 enantiomers possible.

2. Physical data

CAS # 27538-09-6	CAS # 27538-10-9
Boiling Point: 275.21 °C (EPI Suite)	**Boiling Point:** 275.21 °C (EPI Suite)
Flash Point: >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA] Database)	**Flash Point:** Not Available
Log K_{OW}: 1.31 (EPI Suite)	**Log K_{OW}:** 1.31 (EPI Suite)
Melting Point: 60.62 °C (EPI Suite)	**Melting Point**: 60.62 °C (EPI Suite)
Water Solubility: 6178 mg/L (EPI Suite)	**Water Solubility:** 6178 mg/L (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.000152 mm Hg at 20 °C (EPI Suite v4.0), 0.1 mm Hg at	**Vapor Pressure:** 0.000152 mm Hg at 20 °C (EPI Suite v4.0), 0.000304 mm Hg at 25 °C (EPI Suite)

(*continued on next page*)

(*continued*)

20 °C (FMA Database), 0.000304 mm Hg at 25 °C (EPI Suite)	
UV Spectra: Significant absorbance in the range of 290–700 nm, with peak at 290 nm (under neutral conditions) and returning to baseline by 330 nm. Molar absorption coefficient is above the benchmark of concern (1000 L mol^{-1} •cm^{-1})	**UV Spectra:** Significant absorbance in the range of 290–700 nm, with peak at 290 nm (under neutral conditions) and returning to baseline by 320 nm. Molar absorption coefficient is above the benchmark of concern (1000 L mol^{-1} •cm^{-1})
Appearance/Organoleptic: Not Available	**Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0.4)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.018% (RIFM, 2019)
2. **Inhalation Exposure******:** 0.00013 mg/kg/day or 0.0090 mg/day (RIFM, 2019)
3. **Total Systemic Exposure*******:** 0.00088 mg/kg/day (RIFM, 2019)

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

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	III	III

*See the Appendix below for details.

6.2. Analogs Selected

a. **Genotoxicity:** Weight of Evidence (WoE) 4-hydroxy-2, 5-dimethyl-3 (2H)-furanone (CAS # 3658-77-3)
b. **Repeated Dose Toxicity:** 4-Hydroxy-2,5-dimethyl-3(2H)-furanone (CAS 3658-77-3)
c. **Reproductive Toxicity:** 4-Hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3)
d. **Skin Sensitization:** 4-Hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3)
e. **Phototoxicity/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

3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl- is reported to occur in the following foods by the VCF*:

Coffee	Shoyu (fermented soya hydrolysate)
Melon	Swiss cheeses
Milk and milk products	Wine

Ethyl-4-hydroxy-5-methylfuran-3(2H)-one is reported to occur in the following foods by the VCF:

Cashew apple (*Anacardium occidentale*)	Durian (*Durio zibethinus*)
Cheddar cheese	Lovage (*Levisticum officinale* Koch)
Cheese, various types	Melon
Citrus fruits	Sherry
Coffee	Shoyu (fermented soya hydrolysate)
Cupuacu (*Theobroma grandiflorum* Spreng.)	Wine

*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

3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl- has been pre-registered for 2010; no dossier available as of 07/26/21; dossier for ethyl-4-hydroxy-5-methylfuran-3(2H)-one available; accessed on 07/26/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3 (2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.045
2	Products applied to the axillae	0.014
3	Products applied to the face/body using fingertips	0.27
4	Products related to fine fragrances	0.25
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.064
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.064
5C		0.064

(*continued on next page*)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	
5D	Baby cream, oil, talc	0.021
6	Products with oral and lip exposure	0.15
7	Products applied to the hair with some hand contact	0.52
8	Products with significant ano-genital exposure (tampon)	0.021
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.49
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.98
10B	Aerosol air freshener	1.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.021
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-, the basis was the reference dose of 1.94 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 590 μg/cm^2.

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

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- in dimethyl sulfoxide (DMSO) at concentrations ranging from 1.25 to 10 μL/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1981). Under the conditions of the study, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was not mutagenic in the Ames test.

The mutagenic activity of 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- has also been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and TA102 were treated with 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- in DMSO at concentrations ranging from 0.25 to 25 mg/plate. The test material increased the mutant frequency of strains TA97 and TA100 and to a lesser degree of TA98 and TA102. The effect was independent of metabolic activation by the liver enzymes (RIFM, 1988). Based on the conditions of the study, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was considered mutagenic in the Ames assay.

Two *in vivo* studies listed in an EFSA Opinion report were considered to be positive in the mouse micronucleus study (EFSA, 2015). In 1 of the studies, evidence of chromosomal aberration induction in mouse germ cells was considered to have limitations because it was based on an increase of premature disjunction of sex chromosomes and autosomes at metaphase I. In another study, induction of sister chromatid exchanges (SCE) in spermatogonia and induction of micronuclei in early sperm cells was reported. The relevance of SCE in spermatogonia as an indicator of heritable genetic damage was considered limited. In addition, observed effects in the germ cells could be the result of the mal-segregation of chromosomes which is generally considered a thresholded event. Alternatively, they could be the result of the (thresholded) generation of reactive oxygen species. The clastogenic activity of 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was evaluated in a newer *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via the oral route to groups of male and female NMRI mice. Doses of 312.5, 625, and 1250 mg/kg body weight were administered for 24 h, and 1250 mg/kg body weight was administered for 48 h. Mice from the highest dose levels were euthanized at 24 and 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 (RIFM, 2005). Under the conditions of the study, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was considered to be not clastogenic in the new *in vivo* micronucleus test.

There was an oral male fertility study (considered equivalent to a dominant lethal study) performed on a weight of evidence material, 4-hydroxy-2, 5-dimethyl-3(2H)-furanone (CAS # 3658-77-3), according to ICH 4.1.1 that was concluded to be negative, which, in combination with results from a new *in vivo* micronucleus study, discounts the germ cell effects observed in the 2 old *in vivo* micronucleus studies. As an additional weight of evidence, concern for carcinogenicity was alleviated since the read-across material was not carcinogenic in a valid chronic assay in rats. After consideration of all the available data, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was considered not to pose a genotoxic risk (EFSA, 2011) at the current level of use (0.75 μg/kg/day) in fragrances. Based on the position of the Scientific Opinion of the EFSA Expert Panel, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- had no safety concerns with respect to genotoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/09/21.

11.1.2. Repeated dose toxicity

The MOE is adequate for the repeated dose endpoint at the current level of use.

11.1.2.1. Risk assessment. There are limited repeated dose toxicity data on 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-. In a dietary 90-day subchronic toxicity study conducted in rats, no adverse effects were observed at a dose of 1.43 mg/kg/day, the only dosage tested (RIFM, 1978). The results in the study were not considered in determining the NOAEL of the material in this safety assessment since the study was performed using only a single dose level.

There are sufficient data on the read-across material 4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS 3658-77-3; see Section VI) for repeated dose toxicity endpoint. An OECD 451 dietary 24-month carcinogenicity study was conducted in rats. Groups of 60 rats/sex/dose were administered a dietary admixture of test material 4-hydroxy-2,5-dimethyl-3(2H)-furanone in doses of 0, 100, 200, or 400 mg/kg/day in a 0.2% ascorbic acid in propylene glycol vehicle for 24 months. The NOAEL was determined to be 200 mg/kg/day (194.25 and 195.90 mg/kg/day in males and females, respectively), based on reduced bodyweight gains and survival among the higher dose group animals (RIFM, 2003).

Therefore, the 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 4-hydroxy-2,5-dimethyl-3(2H)-furanone NOAEL in mg/kg/day by the total systemic exposure to 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-, 194.25/0.00088 or 220738.

In addition, the total systemic exposure to 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- (0.88 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Section 10 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose (RfD) of 1.94 mg/kg/day.

11.1.2.2. Derivation of RfD. The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 194.25 mg/kg/day by the uncertainty factor, 100 = 1.94 mg/kg/day.

Additional References: RIFM, 2003; Posternak (1969); Roscher (1997); JECFA, 2018; Rennhard (1971); Kimura (1980); Barrand (1987).

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.3. Reproductive toxicity

There are no developmental toxicity data on 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- or on any read-across materials. The total systemic exposure to 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is below the TTC for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

The MOE for 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is adequate for the fertility endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- or on any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- (0.88 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no fertility data on 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-. Read-across material 4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3; see Section 6) has sufficient male reproductive toxicity data. An oral gavage 2-phase male reproductive study was conducted in male Crl:CD(SD) rats to determine the potential effects of read-across material 4-hydroxy-2,5-dimethyl-3(2H)-furanone on mating, fertility, and gonadal function. Groups of 25 male rats/dose were administered test material 4-hydroxy-2,5-dimethyl-3(2H)-furanone via oral gavage at doses of 0, 100, 500, or 1000 mg/kg/day in propylene glycol. Males received 14 daily doses prior to mating with untreated phase I females and 63 daily doses prior to mating with untreated phase II females until females were euthanized (total of 91–93 doses). The females with evidence of mating were euthanized on gestation day (GD) 15, and females without evidence of mating were euthanized 8 days following completion of the cohabitation period; the males were euthanized following completion of postmortem examination of the phase II females with evidence of mating. There were no significant treatment-related adverse effects at any dose levels. In the absence of any effects observed on spermatogenic parameters, organ weights, reproductive performance, and embryonic survival, the NOAEL for male reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2008). There are no female reproductive toxicity data on 4-hydroxy-2,5-dimethyl-3(2H)-furanone. Read-across material maltol (CAS # 118-71-8; see Section VI) has sufficient female reproductive toxicity data. A dietary 3-generation reproductive toxicity study conducted in male and female rats considered the NOAEL for reproductive toxicity to be 400 mg/kg/day, the highest dose tested (JECFA, 2018). The most conservative NOAEL of 400 mg/kg/day from the 3-generation study was selected for the reproductive toxicity endpoint.

Therefore, the 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- MOE for the fertility endpoint can be calculated by dividing the maltol NOAEL in mg/kg/day by the total systemic exposure to 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-, 400/0.00088 or 454545.

In addition, the total systemic exposure to 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- (0.88 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: RIFM, 1978; Posternak (1969); Kataoka (1997); Roscher (1997); RIFM, 2003; RIFM, 2000.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to 4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3), 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is considered a skin sensitizer.

11.1.4.1. Risk assessment. Based on the existing data and read-across to 4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3; see Section 6), 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is considered a moderate skin sensitizer. The chemical structure indicates that this material is not predicted to react directly with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). A guinea pig maximization test with 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was inconclusive with reactions observed in both test and control groups (RIFM, 1991a). A Buehler study with 0.5% 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- did not result in skin sensitization reactions (RIFM, 1980a). In a murine local lymph node assay (LLNA), the material was found to be sensitizing with an EC3 value of 1.8% or 450 μg/cm^2 (RIFM, 2001; ECHA, 2018). In Confirmation of No Induction in Humans tests (CNIHs) with 1181 μg/cm^2 of 4-hydroxy-2,5-dimethyl-3(2H)-furanone in 3:1 DEP:EtOH, both positive and negative results were reported (RIFM, 2015a; RIFM, 2010). 3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl- up to 1% (500 μg/cm^2) in a CNIH did not result in sensitization reactions in any of the subjects tested (RIFM, 1991c; RIFM, 1980b). In a separate CNIH in 108 subjects using 590 μg/cm^2 of 4-hydroxy-2,5-dimethyl-3(2H)-furanone in 3:1 DEP:EtOH, no sensitization reactions were observed (RIFM, 2015b).

Based on the available data on read-across material 4-hydroxy-2,5-dimethyl-3(2H)-furanone, summarized in Table 1, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- is considered to be a moderate skin sensitizer with a defined NESIL of 590 μg/cm^2. Section 10 provides the maximum

Table 1
Data summary of 4-hydroxy-2,5-dimethyl-3(2H)-furanone as read-across for 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-.

LLNA weighted mean EC3 value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data [a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL (induction) μg/cm^2	WoE NESIL [b] μg/cm^2
450 [1]	Moderate	590	NA	1181	590

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

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

[b] WoE NESIL limited to 2 significant figures.

acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 1.94 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available *in vitro* and *in vivo* experimental data, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- would not be expected to present a concern for phototoxicity. Based on the available *in vivo* study data, 3 (2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- would not be expected to present a concern for photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate significant absorbance in the critical range of 290–700 nm, with peak absorbance, under neutral conditions, at 290 nm and returning to baseline by 330 nm. The molar absorption coefficient is above the benchmark of concern for phototoxicity/photoallergenicity (Henry, 2009). Phototoxicity was evaluated in a 3T3-Neutral Red Uptake phototoxicity assay; 3 (2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was not predicted to have phototoxic potential (RIFM, 2017). The phototoxicity and photoallergenicity of 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was evaluated in guinea pigs; there were no reactions indicative of either phototoxicity or photoallergenicity (RIFM, 1991b; RIFM, 1991d). Based on *in vitro* and *in vivo* experimental data, 3(2H)-furanone, 5-ethyl-4--hydroxy-2-methyl- would not be expected to present a concern for phototoxicity. Based on *in vivo* study data, 3(2H)-furanone, 5-ethyl-4--hydroxy-2-methyl- 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 generated for 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl-. The spectra demonstrate that the material absorbs in the range of 290–700 nm, with peak absorbance, under neutral conditions, at 290 nm and returning to baseline by 330 nm. The molar absorption coefficient for λ max is above 1000 L mol^{-1} • cm^{-1}, the benchmark of concern for phototoxic effects (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- 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 3 (2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.0090 mg/day. This exposure is 52.2 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- 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 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- 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, 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), 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation:*** RIFM (1991e): The ready biodegradability of the test material was evaluated according to OECD 301 Guidelines. Under the conditions of the study, the biodegradation of the test material was 76% after 28 days.

Ecotoxicity: No data are available.

Other available data: 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- has been pre-registered for REACH with no additional information 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 Framework: Salvito, 2002)

Exposure	Europe (EU)	North America (NA)

(*continued on next page*)

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	763.9			1000000	0.7639	

(*continued*)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.31	1.31
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use for both CAS numbers.

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

The RIFM PNEC is 0.7639 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: 06/25/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/02/21.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112646.

Appendix

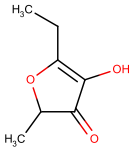
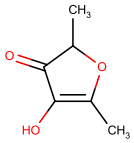
Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	3(2H)-Furanone, 5-ethyl-4-hydroxy-2-methyl-	4-Hydroxy-2,5-dimethyl-3(2H)-furanone
CAS No.	27538-09-6	3658-77-3
Structure		
Similarity (Tanimoto Score)		0.89
Read-across Endpoint		• Repeated Dose Toxicity • Fertility • Skin Sensitization • Genotoxicity (WoE)
Molecular Formula	$C_7H_{10}O_3$	$C_6H_8O_3$
Molecular Weight	142.15	128.12
Melting Point (°C, EPI Suite)	60.62	56.94
Boiling Point (°C, EPI Suite)	275.21	258.62
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.0871	0.0773
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.31	0.82
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6178	1.85e+004
J_{max} (μg/cm^2/h, SAM)	264.69	377.53
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.98	1.49
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, impaired OH or NH2 group	• Non-binder, impaired OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)	• Non-toxicant (moderate reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Moderately reactive (GSH)| Moderately reactive (GSH) ≫ Substituted 1-Alkane-3-one (MA)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
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 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- (CAS # 27538-09-6). 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, 4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3) and maltol (CAS # 118-71-8) were identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 4-Hydroxy-2,5-dimethyl-3(2H)-furanone (CAS # 3658-77-3) was used as a read-across analog for the target material 3(2H)-furanone, 5-ethyl-4-hydroxy-2-methyl- (CAS # 27538-09-6) for the fertility, skin sensitization, and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of oxygen-containing heterocycles.
  - o The target material and the read-across analog share a furanone structure.
  - o The key difference between the target material and the read-across analog is that the target has a methyl group in position 2, whereas the read-across analog has an ethyl group at the same position. This structural difference is toxicologically insignificant.
  - o 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 comparison of their toxicological properties.

- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The read-across analog has an alert for being moderately reactive according to GSH rules. The data described in the skin sensitization section confirm that the substance is a skin sensitizer. Therefore, the alert is consistent with the 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.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

1N,2N,3N,5N,6N,7Y,8N,10N,11N,12N,22N,33N CC II.

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q8. Lactone or cyclic diester? No.
Q10. 3-membered heterocycles? No.
Q11. Has a heterocyclic ring with complex substituents? No.
Q12. Heteroaromatic? No.
Q22. A common component of food? Yes. Class II (Class intermediate)

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Barrand, M.A., Callingham, B.R., Hider, R.C., 1987. Effects of the pyrones, maltol and ethyl maltol, on iron absorption from the rat small intestine. J. Pharm. Pharmacol. 39, 203–211.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

ECHA, 2018. 4-Hydroxy-2,5-dimethyl-3(2H)-furanone Registration Dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/22015/1.

EFSA, 2011. Scientific Opinion on Flavouring Group Evaluation 220, Revision 1 (FGE.220Rev1): alpha,beta-Unsaturated Ketones and Precursors from Chemical Subgroup 4.4 of FGE.19: 3(2H)-Furanones. Retrieved from. https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2011.1841.

EFSA, 2015. Scientific Opinion on Flavouring Group Evaluation 99 Revision 1 (FGE.99Rev1): Consideration of Furanone Derivatives Evaluated by the JECFA (63rd, 65th and 69th Meetings). https://doi.org/10.2903/j.efsa.2015.4286. Retrieved from.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

JECFA, 2018. Safety Evaluations of Groups of Related Flavouring Agents: Maltol and Related Substances. http://www.inchem.org/documents/jecfa/jecmono/v56je07.pdf.

Kataoka, S., Liu, W., Albright, K., Storkson, J., Pariza, M., 1997. Inhibition of benzo[a]pyrene-induced mouse forestomach neoplasia and reduction of H2O2 concentration in human polymorphonuclear leucoytes by flavour components of Japanese-style fermented soy sauce. Food Chem. Toxicol. 35 (5), 449–457.

Kimura, R., Matsui, S., Ito, S., Aimoto, T., Murata, T., 1980. Central depressant effects of maltol analogs in mice. Chem. Pharm. Bull. 28 (9), 2570–2579.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance skin sensitization evaluation and human testing, dermatitis. https://doi.org/10.1097/DER.0000000000000684. November 16, 2020. Volume Publish Ahead of Print Issue. Retrieved from.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA, p. 7. Retrieved from. http://www.oecd.org/, 2015.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

Posternak, J.M., Linder, A., Vodoz, C.A., 1969. Summaries of toxicological data. Toxicological tests on flavoring matters. Food Chem. Toxicol. 7, 405–407.

Rennhard, H.H., 1971. The metabolism of ethyl maltol and maltol in the dog. J. Agric. Food Chem. 19 (1), 152–154.

RIFM (Research Institute for Fragrance Materials, Inc), 1978. 90-Day Feeding Study on 2-Ethyl-4-Hydroxy-5-Methyl-3(2H)furanone in Sprague-Dawley Rats. Private Communication to FEMA. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Cox, G.E. & Re, T.A. RIFM report number 21593.

RIFM (Research Institute for Fragrance Materials, Inc), 1980a. Delayed Contact Hypersensitivity of 2-oxabicyclo[2.2.2]octane, 1,5-Dimethyl-3-(2-Propen-1-Yl (Allyl Cyclo Octyl Ether) in a guinea Pig Sensitization (Buehler and Griffith). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF Incorporated. RIFM report number 47726.

RIFM (Research Institute for Fragrance Materials, Inc), 1980b. Repeated Insult Patch Test with Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 52308.

RIFM (Research Institute for Fragrance Materials, Inc), 1981. Mutagenicity Evaluation of 2-Ethyl-4-Hydroxy-5-Methyl-3(2h)-Furanone (Homofuronol) in the Ames Salmonella/mammalian Liver Microsome Plate Incorporation Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57243.

RIFM (Research Institute for Fragrance Materials, Inc), 1988. Mutagenicity Evaluation of 2-Ethyl-4-Hydroxy-5-Methyl-3(2h)-Furanone (Homofuronol) with the Ames Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57244.

RIFM (Research Institute for Fragrance Materials, Inc), 1991a. Determination of Contact Hypersensitivity in Albino guinea Pigs by the Maximization Test to 2-Ethyl-4-

Hydroxy-5-Methyl-3(2h)-Furanone (Homofuronol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 44272.
RIFM (Research Institute for Fragrance Materials, Inc), 1991b. Determination of Phototoxicity in Albino guinea Pigs with 2-Ethyl-4-Hydroxy-5-Methyl-3(2h)-Furanone (Homofuronol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 44275.
RIFM (Research Institute for Fragrance Materials, Inc), 1991c. Repeated Insult Patch Test with 2-Ethyl-4-Hydroxy-5-Methyl-3(2h)-Furanone (Homofuronol) in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 44276.
RIFM (Research Institute for Fragrance Materials, Inc), 1991d. Determination of Photoallergenicity in Albino guinea Pigs with 2-Ethyl-4-Hydroxy-5-Methyl-3(2h)-Furanone (Homofuronol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 44277.
RIFM (Research Institute for Fragrance Materials, Inc), 1991e. Preliminary Test for the Evaluation of Ready Biodegradability of 2-Ethyl-4-Hydroxy-5-Methyl-3(2h)-Furanone (Homofuronol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57242.
RIFM (Research Institute for Fragrance Materials, Inc), 2000. 4-Hydroxy-2,5-dimethyl-3(2H)-furanone: A 3-Month Dietary Range-Finding Toxicity Study in Rats. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich. RIFM report number 74075.
RIFM (Research Institute for Fragrance Materials, Inc), 2001. Murine Local Lymph Node Assay with 4-Hydroxy-2,5-Dimethyl-3(2h)-Furanone (Furaneol). RIFM, Woodcliff Lake, NJ, USA [Amendment Attached] Unpublished report from Firmenich SA. RIFM report number 60432.
RIFM (Research Institute for Fragrance Materials, Inc), 2003. 24-Month Dietary Carcinogenicity Study in Rats for 4-Hydroxy-2,5-Dimethyl-3(2h)-Furanone (Furaneol). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich. RIFM report number 52789.
RIFM (Research Institute for Fragrance Materials, Inc), 2005. Micronucleus Assay in Bone Marrow Cells of the Mouse with 2-Ethyl-4-Hydroxy-5-Methyl-3(2h)-Furanone. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 48787.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Oral Male Fertility Study of 4-Hydroxy-2,5-Dimethyl-3(2h)-Furanone (Furaneol) in Rats. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71181.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Repeated Insult Patch Test of 4-Hydroxy-2,5-Dimethyl-3(2h)-Furanone (Furaneol) at 1.0% in 75% Diethyl Phthalate (DEP)/25% Ethanol. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 60433.
RIFM (Research Institute for Fragrance Materials, Inc), 2015a. Repeat Insult Patch Test with 4-Hydroxy-2,5-Dimethyl-3(2h)-Furanone. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 68926.
RIFM (Research Institute for Fragrance Materials, Inc), 2015b. Repeated Insult Patch Test (RIPT) with 4-Hydroxy-2,5-Dimethyl-3(2h)-Furanone (Furaneol). RIFM Report Number 69745. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017. 2-Ethyl-4-hydroxy-5-methylfuran-3(2H)-one: Neutral Red Uptake Phototoxicity Assay in Balb/c 3T3 Mouse Fibroblasts. RIFM Report Number 71841. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2019. Exposure Survey 25. October 2019.
RIFM (Research Institute for Fragrance Materials, Inc), 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76775.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Roscher, R., Koch, H., Herderich, M., Schreier, P., Schwab, W., 1997. Identification of 2,5-dimethyl-4-hydroxy-3[2H]-furanone beta-delta-glucuronide as the major metabolite of a strawberry flavour constituent in humans. Food Chem. Toxicol. 35 (8), 777–782.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.