Food and Chemical Toxicology 183 (2024) 114221

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone, CAS Registry Number 698-10-2

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

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

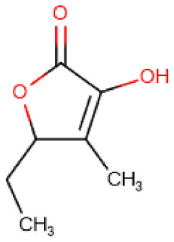
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

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

https://doi.org/10.1016/j.fct.2023.114221
Received 17 February 2023; Received in revised form 24 September 2023; Accepted 19 November 2023
Available online 26 November 2023
0278-6915/© 2023 Elsevier Ltd. All rights reserved.

Version: 021523. 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: 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone
CAS Registry Number: 698-10-2

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 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, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that

(*continued on next column*)

(*continued*)

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.

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

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2011a; RIFM, 2011b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Photoirritation/Photoallergenicity: Not photoirritating. Not expected to be photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 2018)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 3.1 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 3.1 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 9523 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: Fish LC50: 9523 mg/L ((RIFM Framework; Salvito, 2002)
RIFM PNEC is: 9.523 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: <1

1. Identification

1. **Chemical Name:** 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone
2. **CAS Registry Number:** 698-10-2
3. **Synonyms:** 2,4-Dihydroxy-3-methyl-2-hexenoic acid, γ-lactone; 2-Ethyl-3-methyl-4-hydroxydihydro-(2,5)-furan-5-one; 2(5H)-Furanone, 5-ethyl-3-hydroxy-4-methyl-; 2-Hydroxy-3-methyl-γ-2-hexenolactone; Maple furanone; 5-Ethyl-3-hydroxy-4-methylfuran-2

(5H)-one; Methyl ethyl hydroxyfuranone; 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone
4. **Molecular Formula:** $C_7H_{10}O_3$
5. **Molecular Weight:** 142.15 g/mol
6. **RIFM Number:** 6172
7. **Stereochemistry:** No isomer specified. One stereocenter is present, and 2 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 80 °C at 0.05 mm Hg (Fragrance Materials Association [FMA]), 303.49 °C (EPI Suite)
2. **Flash Point:** >200 °F; closed cup (FMA), >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 0.05 (EPI Suite)
4. **Melting Point**: 52.96 °C (EPI Suite)
5. **Water Solubility:** 74390 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000287 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 5.96e-005 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm under the biologically relevant neutral condition, as well as under the acidic condition; molar absorption coefficients (120 and 42 L $mol^{-1} \bullet cm^{-1}$ for neutral and acidic conditions, respectively) are below the benchmark (1000 L $mol^{-1} \bullet cm^{-1}$). Significant absorbance between 290 and 700 nm under basic conditions. Molar absorbance (2890 L $mol^{-1} \bullet cm^{-1}$ for basic conditions) is above the benchmark (1000 L $mol^{-1} \bullet cm^{-1}$).
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 v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.11% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000011 mg/kg/day or 0.00076 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00082 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford, 2015a; Safford, 2017; 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, 2015; Safford, 2015a; Safford, 2017; 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:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

None.

7. Metabolism

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

8. Natural occurrence

5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone is reported to occur in the following foods by the VCF*.

Beer	Sherry
Cocoa category	Shrimps (prawn)
Coffee	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

5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone has been pre-registered for 2010; no dossier available as of 08/23/22.

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, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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 TA102 were treated with 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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, 2011a). Under the conditions of the study, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone was not mutagenic in the Ames test.

The clastogenic activity of 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone in DMSO at concentrations up to 1422 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2011b). Under the conditions of the study, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone was considered to be non-clastogenic in the *in vitro* micronucleus test.

Additional References: RIFM, 2013

Literature Search and Risk Assessment Completed On: 08/19/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone or any read-across materials. The total systemic exposure to 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone (0.82 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: Posternak et al., 1969

Literature Search and Risk Assessment Completed On: 08/17/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone or any read-across materials. The total systemic exposure to 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no repeated dose toxicity data on 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone (0.82 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: 08/17/22.

11.1.4. Skin sensitization

Based on existing data and the application of DST, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone does not present a safety concern for skin sensitization under the current declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone (see Table 1 below). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.5). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford, 2011; Roberts et al., 2015; Safford, 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 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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: 07/18/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and *in vitro* study data, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone does not present a concern for photoirritation. Based on available UV/Vis absorption spectra, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone would not be expected to present a concern for photoallergy.

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 and acidic conditions. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Significant absorbance was evident under basic conditions, with a peak absorbance at 290 nm and returning to baseline by 340 nm. 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, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone was not predicted to have photoirritating potential (RIFM, 2018). Based on the available *in vitro* study data and the lack of UV/Vis absorbance under the biologically relevant, neutral condition, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone does present a concern for photoirritation. Based on the lack of UV/Vis absorbance under the biologically relevant, neutral condition, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone would not be expected to present a concern for photoallergy.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were generated for 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone. The spectra indicated that the material has minor absorption in the range of 290–700 nm under the biologically relevant neutral condition and also under acidic conditions; molar absorption coefficients (120 and 42 L mol^{-1} • cm^{-1} for neutral and acidic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1}) of concern for

Table 1
Summary of existing data on 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone.

	Human Data				Animal Data		
WoE Skin Sensitization Potency Category[1]	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]
Human potency category unknown; Current exposure level below the DST for non-reactive materials.	NA	NA	NA	NA	NA	NA	NA
	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
	NA	NA	NA		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[5]Studies conducted according to the OECD TG 406 are included in the table.
[6]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

photoirritating effects. Significant absorbance was observed under basic conditions. The corresponding molar absorption coefficient was 2890 L mol^{-1} • cm^{-1} under basic conditions respectively, which is above 1000 L mol^{-1} • cm^{-1}, the benchmark of concern for photoirritating effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/29/22.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone. Based on the Creme RIFM Model, the inhalation exposure is 0.00076 mg/day. This exposure is 618.4 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: 07/13/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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 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, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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).

Table 2
Supported concentrations for 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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	5.0×10^{-5}
2	Products applied to the axillae	0.021	1.1×10^{-4}
3	Products applied to the face using fingertips	0.41	4.6×10^{-5}
4	Fine fragrance products	0.39	0.11
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10	0.016
6	Products with oral and lip exposure	0.23	2.4×10^{-4}
7	Products applied to the hair with some hand contact	0.79	1.2×10^{-7}
8	Products with significant ano-genital exposure	0.041	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75	8.3×10^{-5}
10	Household care products with mostly hand contact	2.7	6.4×10^{-4}
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.13

[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] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone 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, 2017). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. Biodegradation:
No data available.
Ecotoxicity:
No data available.

11.2.1.3. Other available data. 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone has been pre-registered for REACH with no additional data at this time.

11.2.2. 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)**	9523			1000000	9.523	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.05	0.05
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 9.523 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 07/27/22.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 02/15/23.

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. 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.

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.

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.

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.

Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis-based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. Toxicol. Vitro 32, 248–260. Apr.

ECHA, 2017. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. Toxicol. Vitro 37, 178–188.

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), 2019. Volume of Use Survey, January-December 2019.

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., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

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

RIFM (Research Institute for Fragrance Materials, Inc.), 2011a. 5-Ethyl-3-hydroxy-4-methyl-2(5H)furanone: Reverse Mutation in Five Histidine-Requiring Strains of Salmonella typhimurium. Unpublished Report from Bowen, R. RIFM Report Number 73590. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011b. 5-Ethyl-3-hydroxy-4-methyl-2(5H)furanone: Induction of Micronuclei in Cultured Human Peripheral Blood Lymphocytes. Unpublished Report from Lloyd, M. RIFM Report Number 73591. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone (Methyl Ethyl Hydroxyfuranone): Bacterial Reverse Mutation with Salmonella typhimurium and Escherichia coli. Unpublished Report from Symrise. RIFM Report Number 68074. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Report on the Testing of 5-Ethyl-3-Hydroxy-4-Methyl-2(5h)-Furanone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 67462. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone: Neutral Red Uptake Photoxocity Assay in Balb/c 3T3 Mouse Fibroblasts. RIFM Report Number 74250. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2021. Exposure Survey 30. January 2021.

Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

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., 2015b. 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.

Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.

Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.

Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.

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.

Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. Mutagenesis 37 (1), 13–23, 2022.

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.