



Short Review

RIFM fragrance ingredient safety assessment, methyl 2-furoate, CAS Registry Number 611-13-2



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, M. Date^a, 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, M. Na^a, T.M. Penningⁱ, 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, Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmö, 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, 48109, 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 Würzburg, 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

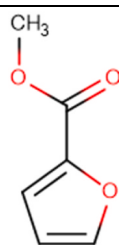
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Name: Methyl 2-furoate

CAS Registry Number: 611-13-2



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

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* Corresponding author.

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

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

DRF - Dose Range Finding

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LOEL - Lowest Observed Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.

QRA - Quantitative Risk Assessment

QSAR - Quantitative Structure-Activity Relationship

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern

UV/Vis spectra - Ultraviolet/Visible spectra

VCF - Volatile Compounds in Food

VoU - Volume of Use

vPvB - (very) Persistent, (very) Bioaccumulative

WoE - Weight of Evidence

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

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

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

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

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

Methyl 2-furoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog isobutyl 3-(2-furan)propionate (CAS # 105-01-1) show that methyl 2-furoate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to methyl 2-furoate is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal

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Sensitization Threshold (DST) for non-reactive materials (900 $\mu\text{g}/\text{cm}^2$); exposure is below the DST. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl 2-furoate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; methyl 2-furoate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are < 1 .

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (WHO, 1999; RIFM, 2015; RIFM, 2013b)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.

Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 3.06 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 1394 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 1394 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 1.394 $\mu\text{g}/\text{L}$ $\mu\text{g}/\text{L}$

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

1. Identification

- 1. Chemical Name:** Methyl 2-furoate
- 2. CAS Registry Number:** 611-13-2
- 3. Synonyms:** 2-Furancarboxylic acid, methyl ester; Methyl furoate; Methyl pyromucate; Methyl 2-furoate
- 4. Molecular Formula:** $\text{C}_6\text{H}_8\text{O}_3$
- 5. Molecular Weight:** 126.11 g/mol
- 6. RIFM Number:** 848
- 7. Stereochemistry:** No stereoisomer possible.

2. Physical data

- 1. Boiling Point:** 181 °C (Fragrance Materials Association [FMA]), 159.67 °C (EPI Suite)
- 2. Flash Point:** 73 °C (Globally Harmonized System), 164 °F; closed cup (FMA)
- 3. Log K_{ow}:** 0.95 (EPI Suite)
- 4. Melting Point:** 19.07 °C (EPI Suite)
- 5. Water Solubility:** 13320 mg/L (EPI Suite)
- 6. Specific Gravity:** 1.179 (FMA), 1.1758 (EOA, 1976 Sample 76–201)
- 7. Vapor Pressure:** 1.2 mm Hg 20 °C (FMA), 0.629 mm Hg at 20 °C (EPI Suite v4.0), 0.906 mm Hg at 25 °C (EPI Suite)
- 8. UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 $\text{L mol}^{-1} \bullet \text{cm}^{-1}$)

9. **Appearance/Organoleptic:** Colorless liquid, berry-like fruity, winey, and rather heavy odor of some moderate to poor tenacity. Some observers find a nauseating or fungus-like tobacco odor. Sweet-tart heavy fruity taste, often compared to ethyl lactate (Arctander, 1969).

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 v1.0)

- 95th Percentile Concentration in Fine Fragrance: 0.0066% (RIFM, 2017)
- Inhalation Exposure*: 0.0000057 mg/kg/day or 0.00045 mg/day (RIFM, 2017)
- Total Systemic Exposure**: 0.00016 mg/kg/day (RIFM, 2017)

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

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

5. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- 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

- Genotoxicity:** Weight of evidence (WoE): Isobutyl 3-(2-furan)propionate (CAS # 105-01-1)
- Repeated Dose Toxicity:** None
- Reproductive Toxicity:** None
- Skin Sensitization:** None
- Photoirritation/Photoallergenicity:** None
- Local Respiratory Toxicity:** None
- 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

Methyl 2-furoate is reported to occur in the following foods by the VCF*:

Almond (roasted) (<i>Prunus amygdalus</i>)	Papaya (<i>Carica papaya</i> L.)
Cocoa category	Plum (<i>Prunus</i> species)
Coffee	Tamarind (<i>Tamarindus indica</i> L.)
Guava and feyoa	Honey
Mountain papaya (<i>C. candamarcensis</i> , <i>C. pubescens</i>)	Grape brandy

*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. This is a partial list.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 06/20/22.

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, methyl 2-furoate does not present a concern for genotoxicity.

11.1.1.1. *Risk assessment.* Methyl 2-furoate was assessed in the Blue-Screen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity at the highest concentration tested (1261 µg/mL) with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

Limited mutagenic activity data is available for methyl 2-furoate. A bacterial reverse mutation assay was conducted using the standard plate incorporation method. *Salmonella typhimurium* strains TA98 and TA100 were treated with methyl 2-furoate in dimethyl sulfoxide (DMSO) at concentrations up to 100 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the absence of S9 (NCBI, 2022). Under the conditions of the study, methyl 2-furoate was not mutagenic in the Ames test. Additionally, this material may hydrolyze to form furoic acid and methanol; furoic acid is easily excreted as a glycine conjugate after human systemic exposure (WHO, 1999).

Due to the limited data assessing the mutagenic activity of methyl 2-furoate, data from read-across analog isobutyl 3-(2-furan)propionate (CAS # 105-01-1; see Section VI) can be used as WoE. The mutagenic activity of isobutyl 3-(2-furan)propionate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with isobutyl 3-(2-furan)propionate in 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, 2015). Under the conditions of the study, isobutyl 3-(2-furan) propionate was not mutagenic in the Ames test, and this can be extended to methyl 2-furoate.

The clastogenic activity of methyl 2-furoate 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 methyl 2-furoate in DMSO at concentrations up to 1260 µg/mL in the dose range finding (DRF) study, and micronuclei analysis was conducted at concentrations up to 1260 µg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h. Methyl 2-furoate 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, 2013b). Under the conditions of the study, methyl 2-furoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the current existing data and use levels, methyl 2-furoate and read-across material isobutyl 3-(2-furan)propionate do not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on methyl 2-furoate or any read-across materials. The total systemic exposure to methyl 2-furoate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on methyl 2-furoate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to methyl 2-furoate (0.16 µg/kg/day) is below the TTC (9 µg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/12/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on methyl 2-furoate or any read-across materials. The total systemic exposure to methyl 2-furoate is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Table 1

Summary of existing data on methyl 2-furoate.

WoE Skin Sensitization Potency Category ^a	Human Data	Animal Data					
	NOEL-CNIH (induction) µg/cm ²	NOEL-HMT (induction) µg/cm ²	LOEL ^b (induction) µg/cm ²	WoE NESIL ³ µg/cm ²	LLNA ^c Weighted Mean EC3 Value µg/cm ²	GPMT ^d	Buehler ^d
Human potency category unknown; Current exposure level below the DST for non-reactive materials.	NA	6900	NA	NA	NA	NA	NA
	<i>In vitro</i> Data^e	<i>In silico</i> protein binding alerts (OECD Toolbox v4.2)	KE 3	Target Material	Autoxidation simulator	Metabolism simulator	
	KE 1	KE 2	NA	No alert found	No alert found	No alert found	
	NA	NA	NA				

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

³WoE NESIL limited to 2 significant figures.

^a WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

^b Data derived from CNIH or HMT.

^c Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

^d Studies conducted according to the OECD TG 406 are included in the table.

^e Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl 2-furoate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to methyl 2-furoate (0.16 µg/kg/day) is below the TTC (9 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/12/22.

11.1.4. Skin sensitization

Based on existing data and the application of DST, methyl 2-furoate 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 methyl 2-furoate (Table 1). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a human maximization test, no skin sensitization reactions were observed at 6900 µg/cm² of methyl 2-furoate (RIFM, 1976). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm² (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 methyl 2-furoate that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels 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: 01/06/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, methyl 2-furoate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for methyl 2-furoate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding

Table 2

Supported concentrations for methyl 2-furoate 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	3.7×10^{-5}
2	Products applied to the axillae	0.021	NRU ^c
3	Products applied to the face using fingertips	0.41	2.2×10^{-5}
4	Fine fragrance products	0.39	0.0095
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10	1.5×10^{-4}
6	Products with oral and lip exposure	0.23	0.014
7	Products applied to the hair with some hand contact	0.79	NRU ^c
8	Products with significant anogenital exposure	0.041	No Data ^d
9	Products with body and hand exposure, primarily rinse-off	0.75	3.8×10^{-4}
10	Household care products with mostly hand contact	2.7	3.1×10^{-4}
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5	No Data ^d
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.012

Note.

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.

^b These levels represent supported concentrations based on the DST. However, additional studies may show it could be used at higher levels.

^c No reported use.

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

molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, methyl 2-furoate does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/22.

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 methyl 2-furoate 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 methyl 2-furoate. Based on the Creme RIFM Model, the inhalation exposure is 0.00045 mg/day. This exposure is 1044 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.

*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: 01/19/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl 2-furoate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW} , and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, methyl 2-furoate 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 methyl 2-furoate as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq 2000 \text{ L/kg}$. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2019), methyl 2-furoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.1. Key studies

11.2.1.2.1. *Biodegradation*. No data available.

11.2.1.2.2. *Ecotoxicity*. No data available.

11.2.1.2.3. *Other available data*. Methyl 2-furoate has been pre-registered for REACH, with no additional data available 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 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>1394</u>			1000000	1.394	

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

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	0.95	0.95
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 1.394 µg/L 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: 05/24/22.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2022.113448>.

Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria ([Date et al., 2020](#)). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in [Schultz et al. \(2015\)](#) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment ([OECD, 2015](#)) and the European Chemical Agency read-across assessment framework ([ECHA, 2017b](#)).

- **ECHA:** <https://echa.europa.eu/>
- **NTP:** <https://ntp.niehs.nih.gov/>
- **OECD Toolbox:** <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubChem:** <https://pubchem.ncbi.nlm.nih.gov/>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **National Library of Medicine's Toxicology Information Services:** <https://toxnet.nlm.nih.gov/>

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

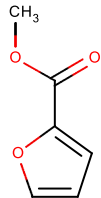
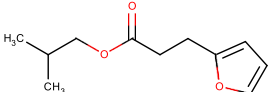
Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 06/20/22.

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.

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{\max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	WoE Material
Principal Name	Methyl 2-furoate	Isobutyl 3-(2-furan)propionate
CAS No.	611-13-2	105-01-1
Structure		
Similarity (Tanimoto Score)		0.34
Endpoint		Genotoxicity (Mutagenicity)
Molecular Formula	C ₆ H ₆ O ₃	C ₁₁ H ₁₆ O ₃
Molecular Weight (g/mol)	126.11	196.25
Melting Point (°C, EPI Suite)	-19.07	26.87
Boiling Point (°C, EPI Suite)	181.30	246.19
Vapor Pressure (Pa @ 25°C, EPI Suite)	120.79	4.15
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	13320.00	64.04
Log K_{OW}	1.00	3.34
J_{max} (µg/cm²/h, SAM)	105.74	3.36
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	3.51	4.45
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition Michael addition >> P450-Mediated Activation of Heterocyclic Ring Systems Michael addition >> P450-Mediated Activation of Heterocyclic Ring Systems >> Furans	Michael addition Michael addition >> P450-Mediated Activation of Heterocyclic Ring Systems Michael addition >> P450-Mediated Activation of Heterocyclic Ring Systems >> Furans
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	H-acceptor-path3-H-acceptor	No alert found
Oncologic Classification	Not classified	Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on methyl 2-furoate (CAS # 611-13-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, isobutyl 3-(2-furan)propionate (CAS # 105-01-1) was identified as a WoE analog with sufficient data for toxicological evaluation.

Conclusions

- Isobutyl 3-(2-furan)propionate (CAS # 105-01-1) was used as a WoE analog for the target material, methyl 2-furoate (CAS # 611-13-2), for the genotoxicity endpoint.
 - The target material and the WoE analog belong to a class of aliphatic esters.
 - The key difference between the target material and the WoE analog is that the target is a furoate ester while the WoE analog is a propionate ester. Moreover, there is a methyl fragment on the alcohol side in the target material, whereas there is an isobutyl fragment on the alcohol side in the WoE analog. These structural differences are toxicologically insignificant.
 - The similarity between the target material and the WoE analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
 - The physical–chemical properties of the target material and the WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
 - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the WoE analog.
 - Both the target material and WoE analog have a Michael addition alert for DNA binding (OECD QSAR Toolbox v4.2). This alert is due to the presence of a furan ring which can lead to a Michael addition upon ring-opening. The data on the WoE analog confirm that the substance does not pose a concern for genotoxicity. Therefore, based on the structural similarity between the target material and the WoE analog and the data on the WoE analog, the *in silico* alerts are superseded by the data.
 - The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between 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.

- Q1 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
- Q16 Common terpene (see Cramer et al., 1978 for detailed explanation)? No
- Q17 Readily hydrolyzed to a common terpene? No
- Q19 Open chain? No
- Q23 Aromatic? No
- Q24 Monocarbocyclic with simple substituents? No
- Q25 Cyclopropane (see explanation in Cramer et al., 1978)? No
- Q26 Monocycloalkanone or a bicyclo compound? Yes, Intermediate (Class II)

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