Food and Chemical Toxicology 192 (2024) 114943

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 5-methylfurfural, CAS registry number 620-02-0

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ARTICLE INFO

Handling Editor: Bryan Delaney

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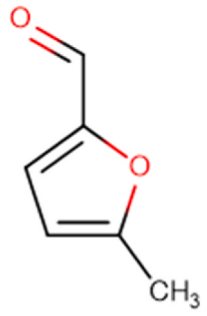
https://doi.org/10.1016/j.fct.2024.114943
Received 2 August 2024; Accepted 17 August 2024
Available online 20 August 2024

Version: 073,024. 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 Research Institute for Fragrance Materials (RIFM) Fragrance Ingredient Safety Assessments is here: http://fragrancematerialsafetyresource.elsevier.com/.



Name: 5-Methylfurfural
CAS Registry Number: 620-02-0

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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, 2024) 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food

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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 material was not evaluated for photoallergy due to a lack of suitable data and validated *in vitro* tests.

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. This material was not evaluated for photoallergy due to a lack of suitable data and validated *in vitro* tests.

5-Methylfurfural was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog furfural (CAS # 98-01-1) show that 5-methylfurfural is not expected to be genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints, and that there are no safety concerns for 5-methylfurfural for skin sensitization under the current declared levels of use. The photoirritation endpoint was evaluated based on target data; 5-methylfurfural does not present a concern for photoirritation under the current declared levels of use. 5-Methylfurfural was not evaluated for photoallergenicity due to a lack of suitable data and validated *in vitro* tests. To address this data gap, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 5-methylfurfural. The environmental endpoints were evaluated; 5-methylfurfural 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 expected to be genotoxic.	(Mortelmans et al., 1986; McGregor et al., 1988; EPA, 1996; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 3 mg/kg/day.	ECHA (2011)
Reproductive Toxicity: Developmental toxicity NOAEL = 100 mg/kg/day. Fertility NOAEL = 60 mg/kg/day.	(ECHA, 2011) (ECHA REACH Dossier: 2-Furaldehyde; ECHA, 2011)
Skin Sensitization: No concern for skin sensitization.	(RIFM, 2003; ECHA, 2011 [001 Key Experimental Result]; RIFM, 1997; ECHA, 2011 [002 Supporting Experimental Result])
Photoirritation/Photoallergenicity: Not photoirritating; not evaluated for photoallergy.	RIFM (2017)
Local Respiratory Toxicity: NOAEC = 8 mg/m^3.	ECHA (2011)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 85% (OECD 301F)	RIFM (2020)
Bioaccumulation: Screening-level: 3.1 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 513.7 mg/L	(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	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 513.7 mg/L	(Salvito et al., 2002)

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RIFM PNEC is: 0.5137 μg/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe; not applicable cleared at the screening-level

1. Identification

1. **Chemical Name:** 5-Methylfurfural
2. **CAS Registry Number:** 620-02-0
3. **Synonyms:** 2-Furancarboxaldehyde, 5-methyl-; 5-Methyl-2-furaldehyde; 5-ﾒﾁﾙﾌﾙﾌﾗｰﾙ; 2-Formyl-5-methylfuran; 2-Formyl-5-methyltetrahydrofuran; 2-Methyl-5-formylfuran; 2-Methyl-5-furaldehyde; 5-Methylfuran-2-aldehyde; 5-Methylfuran-2-carbaldehyde; 5-Methylfurfuraldehyde; 5-Methylfurfural
4. **Molecular Formula:** $C_6H_6O_2$
5. **Molecular Weight:** 110.11 g/mol
6. **RIFM Number:** 1029
7. **Stereochemistry:** No stereocenter is present, and no stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 187 °C (Fragrance Materials Association [FMA]), 165.68 °C (EPI Suite v4.11)
2. **Flash Point:** 71 °C (Globally Harmonized System), 160 °F; closed cup (FMA)
3. **Log K_{OW}:** 1.38 (EPI Suite v4.11)
4. **Melting Point**: −11.22 °C (EPI Suite v4.11)
5. **Water Solubility:** 29,110 mg/L at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** 1.107 (FMA)
7. **Vapor Pressure:** 1.1 mm Hg at 20 °C (FMA), 0.686 mm Hg (EPI Suite v4.11)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline by 330 nm; molar absorption coefficients (6106, 7824, and 9034 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with a spicy-sweet, warm, and slightly caramelly odor

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0077% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000081 mg/kg/day or 0.0060 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0005 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024).

**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, 2017; Safford et al., 2015, 2017, 2024).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate (Expert Judgment)

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

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** Furfural (CAS # 98-01-1)
   b. **Repeated Dose Toxicity:** Furfural (CAS # 98-01-1)
   c. **Reproductive Toxicity:** Furfural (CAS # 98-01-1)
   d. **Skin Sensitization:** Furfural (CAS # 98-01-1)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Furfural (CAS # 98-01-1)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

5-Methylfurfural is reported to occur in the following foods by the VCF*.

Beer	Honey
Cocoa category	*Mangifera* species
Coconut (*Cocos nucifera* L.)	Tea
Coffee	Whiskey
Grape brandy	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. This is a partial list.

9. REACH dossier

5-Methylfurfural has been pre-registered for 2010; no dossier available as of 07/30/24.

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-methylfurfural does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no sufficient studies assessing the

mutagenic activity of 5-methylfurfural; however, read-across can be made to furfural (CAS # 98-01-1; see Section VI). The mutagenic activity of furfural has been evaluated in a bacterial reverse mutation assay conducted with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with furfural 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 (ECHA, 2011). Under the conditions of the study, furfural was not mutagenic in the Ames test.

In another bacterial mutation study conducted equivalent to OECD TG using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 at concentrations up to 10,000 μg/plate, negative results were observed in one trial and ambiguous in another trial where there were increases only at higher toxic doses (Mortelmans et al., 1986), but these increases cannot be considered to be biologically relevant since they were only observed at toxic doses.

A mammalian cell gene mutation assay (mouse lymphoma assay) was conducted, equivalent to OECD TG 476 guidelines. MLA cells were treated with furfural in distilled water at concentrations up to 800 μg/mL for 4 h. Effects were evaluated only without metabolic activation. Statistically significant increases in the frequency of mutant colonies were observed without metabolic activation (McGregor et al., 1988). Under the conditions of the study, furfural was mutagenic to mammalian cells *in vitro*.

Additionally, an *in vivo* transgenic rodent assay was also conducted in GLP conditions as per EPA OPP 84-2 guidelines. Furfural was administered once daily by oral gavage for 28 consecutive days. It was dissolved in corn oil and administered at dose levels of 37.5, 75, 150, and 300 mg/kg/day. There was no increase in mutant frequency at any dose tested, and hence, furfural was concluded to be negative for mutagenicity (ECHA, 2011), and this can be extended to 5-methyl furfural.

There are no sufficient studies assessing the clastogenic activity of 5-methyl furfural; however, read-across can be made to furfural (CAS # 98-01-1; see Section VI). The clastogenicity of furfural was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary (CHO) cells were treated with furfural in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural chromosomal aberrations were observed both with and without the S9 metabolic activation test condition (EPA, 1996). Under the conditions of the study, furfural was clastogenic in the *in vitro* chromosome aberration assay.

The clastogenic activity of furfural was evaluated in an *in vivo* chromosomal aberration test conducted in accordance with OECD TG 475. The test material was administered in phosphate-buffered saline (PBS) via the intraperitoneal route of administration to groups of male B6C3F1 mice. Doses of 50, 100, or 200 mg/kg body weight were administered. Mice from each dose level were euthanized at 17 or 36 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 chromosomal aberrations in the bone marrow (ECHA, 2011). Under the conditions of the study, furfural was not clastogenic in the *in vivo* chromosomal aberration test, and this can be extended to 5-methylfurfural.

Taken together with negative bacterial mutagenicity studies in conjunction with *in vivo* transgenic rodent study along with *in vivo* bone marrow micronucleus test being negative furfural is not considered to have any genotoxic potential, and this can be extended to 5-methylfurfural.

Additional References: Florin et al., 1980; Stich et al., 1981; Aeschbacher (1989); Kong et al., 1988; Shahabuddin and Hadi, 1991; Shahabudin and Hadi, 1990; Uddin and Hadi, 1995; Shinohara et al., 1986.

Literature Search and Risk Assessment Completed On: 07/19/24.

11.1.2. Repeated dose toxicity

The MOE for 5-methylfurfural is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 5-methylfurfural. Read-across material furfural (CAS # 98-01-1; see Section VI) has sufficient repeated dose toxicity data.

An OECD 408/GLP (90-day oral toxicity study) test was conducted in Fischer 344 rats. Groups of 10 rats/sex/dose were administered test material furfural via the oral route at doses of 0, 30, 60, 90, or 180 mg/kg/day in diet (actual ingested, males: 0, 26, 53, 82, or 160 mg/kg; and females: 0, 28, 57, 86, or 170 mg/kg). No treatment-related mortality was observed. In addition, no treatment-related clinical signs or bodyweight changes were observed at any dose groups. A decrease in red blood cell count in males dosed at 180 mg/kg/day and increased corpuscular volume and mean corpuscular hemoglobin in males dosed at 90 and 180 mg/kg/day were observed. Females at the high dose showed decreased alkaline phosphatase activity, increased γ-glutamyltransferase activity, increased plasma concentration of albumin, and decreased plasma concentration of potassium. Males at 180 mg/kg/day showed decreased alanine aminotransferase activity, increased plasma concentration of albumin, and increased albumin:globulin ratio. The absolute and relative weights of the liver were increased in males at 180 mg/kg/per day at necropsy. However, no gross pathological changes were observed. Microscopic examination revealed changes in the liver (perilobular region was characterized by cells having less coarse cytoplasm, an increased occurrence of clumps of eosinophils, a less dense periphery, and more prominent nucleoli in the nucleus) in 5/10 males at 90 mg/kg/day and 10/10 males at 180 mg/kg/day. No treatment-related effects were observed in the livers of females. Thus, the NOAEL for the study was considered to be 60 (53) mg/kg/day based on effects seen in the liver of male rats (ECHA, 2011).

In an OECD 451 carcinogenicity study, groups of 50 Fischer 344 rats/sex/dose were administered furfural via oral gavage at doses of 0, 30, or 60 mg/kg/day. No treatment-related mortality was observed. In addition, no treatment-related clinical signs or bodyweight changes were observed at any dose groups. Mild liver toxicity occurred at increased incidences in both furfural-treated groups of male rats (mild centrilobular necrosis, in control 3/50, low dose 9/50, high dose 12/50). Squamous cell carcinomas (in one low-dose male) and papillomas (in 2 high-dose males, one low and one high-dose female) were seen in the forestomach. At 60 mg/kg/day, there was some evidence of carcinogenic activity for male rats, based on the occurrence of uncommon cholangiocarcinomas in 2 animals (historical vehicle control: 3/2145 male rats) and bile duct dysplasia with fibrosis in 2 other animals. A NOAEL was not established for this study; the LOAEL was considered to be 30 mg/kg/day based on liver toxicity seen in male rats (ECHA, 2011).

An OECD TG 412 (subacute inhalation toxicity: 28-day study) was conducted in a group of 5 Fischer 344 rats/sex/dose via inhalation route where animals were treated for 6 h/day at 0, 20, 40, 80, 160, 320, 640, and 1280 mg/m^3. At the end of the first exposure day, all animals exposed to 1280 mg/m3 were found dead. Up to day 8, 5 animals of the 640 mg/m^3 group were found dead, and exposure to this group was discontinued. Statistically significant increases in absolute and relative liver weights were observed in males at 80 mg/m3 for the 6-h/day exposure. Statistically significant increases in relative spleen weights were also observed in males at 80 mg/m^3. These changes were considered to be due to biological variation in the absence of a dose relationship. Respiratory effects like metaplasia and atypical hyperplasia of the transitional respiratory epithelium in the anterior part of the nose and epithelial disarrangement of the olfactory epithelium were observed in all dose groups. Thus, the NOAEC for systemic effects for the 6 h/day

Table 1
Summary of existing data on furfural as read-across for 5-methylfurfural.

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

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = 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 the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 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.
[7]Determined based on Criteria for the RIFM safety evaluation process for fragrance ingredients (Api et al., 2015).

exposure was considered to be 320 mg/m3 (equivalent to 90 mg/kg/day), based on mortality seen at higher doses (ECHA, 2011).

Further, an OECD 410 (repeated dose dermal toxicity: 21/28-day study) was also conducted at 250, 500, and 1000 mg/kg/day. The test material was applied to groups of 10 Wistar rats/sex/dose for 6 h/day and 5 days/week. A high incidence of mortality was seen at 1000 mg/kg/day, and this test group was discontinued. Increased mortality, adverse clinical signs, and increased motor activity were seen at 500 mg/kg/day. Thus, NOAEL was considered to be 250 mg/kg/day (ECHA, 2011).

Considering the results of all these studies, a NOAEL of 3 mg/kg/day (LOAEL 30/10 = 3 mg/kg/day) was considered from the OECD 451 carcinogenicity study based on liver toxicity seen in male rats.

Therefore, the 5-methylfurfural MOE for the repeated dose toxicity endpoint can be calculated by dividing the furfural NOAEL in mg/kg/day by the total systemic exposure to 5-methylfurfural, 3/0.0005, or 6000.

In addition, the total systemic exposure to furfural (0.5 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: 07/23/24.

11.1.3. Reproductive toxicity

The MOE for 5-methylfurfural is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 5-methylfurfural. Read-across material furfural (CAS # 98-01-1; see Section VI) has sufficient reproductive toxicity data.

In an OECD 414- and GLP-compliant prenatal developmental toxicity study (EPA OTS 798.4900), 25 female Sprague Dawley rats/group were administered dose levels of 0, 50, 100, and 150 mg/kg/day in water via oral gavage from gestation days (GDs) 6–15. Dosing was terminated between GDs 10–14 for the 150 mg/kg/day group due to significant maternal toxicity. The animals were retained in the study to assess reversibility. For the 100 and 150 mg/kg/day groups, 3 and 16 females, respectively, died between gestation days 6 and 15. Body weight and food consumption were adversely affected at 150 mg/kg/day. A slightly reduced mean fetal body weight in the 150 mg/kg/day group was observed. No treatment-related developmental toxicity parameters were affected at 50 and 100 mg/kg/day, and a complete assessment of the potential prenatal toxicity of the test material in the 150 mg/kg/day group was precluded by maternal mortalities, a reduced number of litters available for evaluation, and limited duration of administration. Thus, the NOAEL for developmental toxicity was considered to be 100 mg/kg/day (ECHA, 2011).

In another OECD 414- and GLP-compliant prenatal developmental toxicity study (EPA OTS 798.4900), 24 female New Zealand White rabbits/group were administered dose levels of 0, 30, 100, and 300 mg/kg/day in methylcellulose/deionized water via oral gavage from GDs 6–28. No treatment-related mortality or clinical signs were observed at any dose groups. A statistically significant decrease in mean maternal food consumption at 300 mg/kg/day was observed as compared to the control group throughout the treatment period (GDs 6–29), and an overall lower mean bodyweight gain was also observed in the high-dose groups. A statistically significant decrease in mean fetal body weight was observed in the high-dose groups. Skeletal malformations were noted in all groups, including the control group. The findings were considered not to be treatment-related because they were noted in single fetuses in a manner that was not dose-related and occurred in the control group as well. Mean fetal body weights in the high-dose group animals were significantly lower than the concurrent control group and were considered to be related to the test material. There were no fetal treatment malformations or developmental variations noted at any dose level. Thus, the NOAEL was considered to be 100 mg/kg/day, based on lower mean fetal body weights observed at 300 mg/kg/day (ECHA, 2011).

In an OECD 416- and GLP-compliant study, groups of 30 Sprague Dawley rats/sex/dose were administered test material at doses of 20, 40, or 60 mg/kg/day via oral gavage in deionized water. Animals were dosed once daily for 70 consecutive days prior to mating. Dose administration for the F0 and F1 males continued throughout mating and through the day prior to euthanasia. The F0 and F1 females continued to be dosed continuously throughout mating, gestation, and lactation until the day prior to euthanasia. No treatment-related mortality was observed. In addition, no treatment-related food consumption and body weight changes were observed at any dose groups for P0 parental animals. No treatment-related macroscopic findings or changes in organ weights were noted. Reproductive parameters for males and females were unaffected by the administration of the test material at all dose levels. For the F1 generation, no treatment-related mortality or body weight changes were observed. No treatment-related macroscopic findings or changes in organ weights were noted at any dose groups. Further, no treatment-related effects were observed with respect to F2 generation pups. Thus, the NOAEL for developmental toxicity and fertility was considered to be 60 mg/kg/day, the highest dose tested (ECHA, 2011).

Considering all the studies, the developmental toxicity was considered to be 100 mg/kg/day, based on the OECD 414 studies on rats and rabbits. The fertility NOAEL was considered to be 60 mg/kg/day, based on the OECD 416 study in rats.

Therefore, the 5-methylfurfural MOE for the developmental toxicity endpoint can be calculated by dividing the furfural NOAEL in mg/kg/day by the total systemic exposure to 5-methylfurfural, 100/0.0005, or 200,000.

Therefore, the 5-methylfurfural MOE for the fertility endpoint can be calculated by dividing the furfural NOAEL in mg/kg/day by the total systemic exposure to 5-methylfurfural, 60/0.0005, or 120,000.

In addition, the total systemic exposure to furfural (0.5 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: 07/23/24.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material furfural (CAS # 98-01-1; see Section VI), 5-methylfurfural presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 5-methylfurfural. Therefore, furfural (CAS # 98-01-1; see Section VI) was used for the risk assessment of 5-methylfurfural. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 5-methylfurfural is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.4). In a guinea pig maximization test, read-across material furfural did not lead to skin sensitization reactions (RIFM, 2003; ECHA, 2011 [001 Key Experimental Result]). A guinea pig Buehler test did not present reactions indicative of sensitization (RIFM, 1997; ECHA, 2011 [002 Supporting Experimental Result]). In a human maximization test, no skin sensitization reactions were observed with the target material or the read-across material (RIFM, 1975; RIFM, 1977).

Based on the weight of evidence (WoE) from structural analysis, animal studies, and human studies on the read-across material, as well as the target material, 5-methylfurfural does not present a concern for skin sensitization.

Additional References: Watanabe et al., 2001; Klecak (1985).

Literature Search and Risk Assessment Completed On: 07/16/24.

11.1.5. Photoirritation/photoallergenicity

Based on the available *in vitro* study data, 5-methylfurfural would not be expected to present a concern for photoirritation. 5-Methylfurfural was not evaluated for photoallergy due to a lack of suitable data and validated *in vitro* tests. To address this data gap, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 5-methylfurfural.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm. The corresponding molar absorption coefficients are above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In a 3T3-Neutral Red Uptake phototoxicity assay (OECD TG 432), 5-methylfurfural was not predicted to be a photoirritant (RIFM, 2017). Based on the available *in vitro* study data, 5-methylfurfural would not be expected to present a concern for photoirritation. 5-Methylfurfural was not evaluated for photoallergy due to a lack of suitable data and validated *in vitro* tests. To address this data gap, RIFM is sponsoring an *in vitro* photoallergy

research program to evaluate the photoallergy potential of 5-methylfurfural.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate significant absorbance in the range of 290–700 nm, with peak absorbance at 290 nm and returning to baseline by 330 nm. The molar absorption coefficients (6106, 7824, and 9034 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritant or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/01/24.

11.1.6. Local respiratory toxicity

There are no inhalation data available on 5-methylfurfural; however, in a 4-week inhalation study for the analog furfural (CAS # 98-01-1; see Section VI), a NOAEC of 8 mg/m^3 was reported (ECHA, 2011).

11.1.6.1. Risk assessment. The calculated chronic inhalation exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In an OECD 412 guideline study, 10 male and female Sprague Dawley rats per group were exposed to furfural at 1, 2, 4, 8, and 20 mg/m^3 (ECHA, 2011). The exposures were carried out for 28 days, at 6 h a day and 5 days per week, amounting to 20 exposures. Standard observations included clinical observations, food consumption, body weight, ophthalmoscopic examination, hematology, clinical chemistry, gross pathology, and histopathology. Observations in the local respiratory tissues included exposure-related inflammatory changes in the nasal cavity of 3 males and 5 females in the highest concentration group. The changes were localized at level 3 of the nasal cavity and were characterized by very slight respiratory epithelial cell hyperplasia associated with a very slight mixed inflammatory cell infiltrate. Similar changes were observed in 1 male and 1 female at the highest concentration in the nasal cavity at level 2. No other exposure-related effects were observed in the local respiratory tissues in the highest concentration groups. No effects were observed in any other exposure groups. Therefore, a NOAEC for local effects is identified at 8 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is.

- (8 mg/m^3) × (1 m^3/1000 L) = 0.008 mg/L
- Minute ventilation of 0.17 L/min* for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.008 mg/L) × (61.2 L/d) = 0.4896 mg/day
- (0.4896 mg/day)/(0.0016 kg lung weight of rat**) = 306 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0060 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.009 mg/kg lung weight/day, resulting in a MOE of 34,000 (i.e., [306 mg/kg lung weight of rat/-day]/[0.009 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0060 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/18/24.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 5-methylfurfural was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio of Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 5-methylfurfural 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 5-methylfurfural as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 5-methylfurfural does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. ***Biodegradation:***

RIFM, 2020: A ready biodegradability study was conducted in a manometric respirometry test according to the OECD 301F method. Biodegradation of 85% was observed after 28 days.

Ecotoxicity:

No data available.

11.2.1.2.1. Other available data. 5-Methylfurfural 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)**	513.7			1000000	0.5137	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.3	1.3
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 0.5137 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: 07/16/24.

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 07/30/24.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.114943.

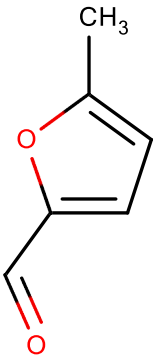
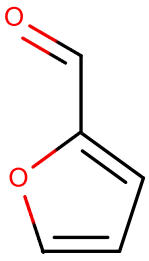
Appendix

Read-across Justification:

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	5-Methylfurfural	Furfural
CAS No.	620-02-0	98-01-1
Structure		
Similarity (Tanimoto Score)		0.84
SMILES	Cc1ccc (C═O)o1	O=Cc1ccco1
Endpoint		Genotoxicity Skin sensitization Repeated dose toxicity Reproductive toxicity Local respiratory toxicity
Molecular Formula	$C_6H_6O_2$	$C_5H_4O_2$
Molecular Weight (g/mol)	110.112	96.085
Melting Point (°C, EPI Suite)	−11.22	−38.10
Boiling Point (°C, EPI Suite)	187.00	161.70
Vapor Pressure (Pa @ 25°C, EPI Suite)	9.15E+01	2.95E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.91E+04	7.41E+04
Log K_{OW}	0.67	0.41
J_{max} (μg/cm^2/h, SAM)	201.80	479.17
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.50E+00	3.82E-01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
DNA Binding (OECD QSAR Toolbox v4.5)	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)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	Simple aldehyde	Simple aldehyde
***In Vivo* Mutagenicity (Micronucleus, ISS)**	H-acceptor-path3-H-acceptor|Simple aldehyde	H-acceptor-path3-H-acceptor|Simple aldehyde
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 5-methylfurfural (CAS # 620-02-0). 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, furfural (CAS # 98-01-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Furfural (CAS # 98-01-1) was used as a read-across analog for the target material, 5-methylfurfural (CAS # 620-02-0), for the genotoxicity, repeated dose toxicity, reproductive toxicity, skin sensitization, and local respiratory toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the furan group.
  - o The key difference between the target material and the read-across analog is the target material has an additional methyl group compared to the read-across analog. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o For genotoxicity, there are Michael addition alerts due to the potential activation of the furan ring for DNA binding by the OECD QSAR Toolbox and simple aldehyde alerts for genotoxic carcinogenicity from ISS. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
  - o For skin sensitization, there are Schiff base formation alerts for protein binding by OASIS and skin sensitization reactivity by Toxtree. The data on the read-across analog confirms that the material does not pose a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
  - o There are no alerts for repeated dose toxicity, reproductive toxicity, or local respiratory toxicity. *In silico* alerts are consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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).

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? Yes.
Q8	Lactone or cyclic diester? No.
Q10	3-membered heterocycles? No.
Q11	Has a heterocyclic ring with complex substituents? No.
Q12	Heteroaromatic? Yes.
Q13	Does the ring bear any substituents? Yes.
Q14	More than one aromatic ring? No.
Q22	A common component of food? Yes. Class Intermediate (Class II).

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