(b) (4)

Methyl-2-furoate

Toxicity monograph (with existing HCVs)

May 2018

Prepared by:

(b) (4)

(b) (4)

TABLE OF CONTENTS

Methyl-2-furoate

Toxicity monograph (with existing HCVs)

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of methyl-2-furoate (CAS RN[1] 611-13-2), focussing on the inhalation route of exposure, with inclusion of existing Health Criteria Values (HCVs) where available. Searches were also performed on CAS RN 1334-76-5 which represents methyl furoate (mixed isomers)[2]. Data on the inhalation of tobacco smoke containing the substance (if available) have not been included in this monograph.

EXPERTISE

(b) (4)

TOXICITY DATA SEARCH CRITERIA[4]

Searches of (b) (4) see Appendix for details) identified the EFSA (2011) review, on which this monograph is based. Earlier reviews by EFSA (2009) and JECFA (2001) were also consulted for additional information on the studies cited in EFSA (2011). A subsequent search of the primary literature was restricted (b) (4) and Toxline (the toxicity subset of Medline, via TOXNET) in an attempt to identify more recent data since the 2011 review. The remainder of the TOXNET system (which includes HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB) and eChemPortal was also consulted. Since the key review focussed on the use of methyl-2-furoate in food and, as such, could not necessarily be relied upon to identify all critical local and systemic inhalation data, no date restriction was placed on searches in PubMed tailored to identify such information (and also cardiopulmonary data).

All searches were conducted in May 2018 using the CAS RNs and (in PubMed only) the name and/or synonym(s) identified below, as appropriate.

The data summarised in this report refers to the unheated form unless otherwise stated.

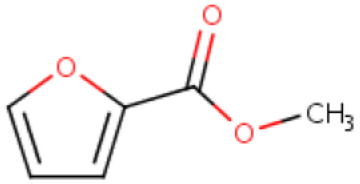
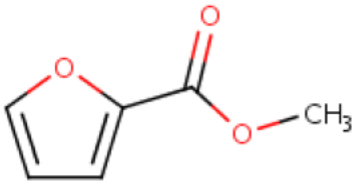
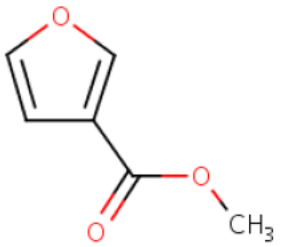
---

[1] Chemical Abstracts Service Registry Number.

[2] A mixture of methyl-2-furoate and methyl-3-furoate (ratio unspecified). Searches were not performed on methyl-3-furoate (CAS RN 13129-23-2) and data on this isomer is not currently included in this monograph.

(b) (4) searching (b) (4) accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier		
Name	Methyl-2-furoate	Methyl furoate (mixed isomers)[5]
Synonyms(s)	Methylfuranoate 2-Furanmethanol, 5-methyl- (5-Methyl-2-furyl)methanol	Methylfuranoate (mixed isomers)
CAS RN	611-13-2	1334-76-5
REACH registration number[6]	Not REACH registered	Not REACH registered
Molecular formula	$C_6H_6O_3$	$C_6H_6O_3$
Molecular weight	126.11	126.11
Structure	 Methyl-2-furoate	 Methyl-2-furoate  Methyl-3-furoate
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** Not available	**Harmonised classification:** Not available
	REACH joint registrants: Not available	**REACH joint registrants:** Not available

ADME[7]

No relevant data were identified on the ADME of inhaled methyl-2-furoate[8] or methyl furoate (mixed isomers).

[5] A mixture of methyl-2-furoate and methyl-3-furoate (ratio unspecified).
[6] REACH registration numbers are substance and company specific. Therefore, the substance-specific part of the registration number is included here, from data disseminated on the ECHA 'registered substance' website.
[7] Absorption, Distribution, Metabolism and Excretion.
[8] ADME predictions could be estimated on the basis of the structure and physic-chemical properties, if required.

No relevant data were identified regarding the oral absorption or distribution of methyl-2-furoate. As a furoate ester it is predicted to be hydrolysed directly to 2-furoic acid and the corresponding alcohol. Furoic acid forms a Coenzyme A (CoA) thioester, which may be either metabolised to a glycine conjugate or condensed with acetyl CoA to form 2-furanacryloyl CoA, which is then further conjugated with glycine. Both end metabolites are excreted in the urine (JECFA, 2001).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Skin irritation

Expert-group opinion

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Human

Methyl-2-furoate was not irritating to 27 subjects when applied at 10% in petrolatum under an occluded patch for 48 hours (Epstein, 1976). [See also Skin sensitisation section.]

Non-human

Methyl-2-furoate was moderately irritating when applied undiluted to intact or abraded rabbit skin under an occluded patch for 24 hours (Moreno, 1976).

Eye irritation

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Other local effects

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Skin sensitisation

Expert-group opinion

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Human

In a maximisation test[9], no skin sensitisation reactions were produced when 27 subjects were tested with methyl-2-furoate at 10% in petrolatum (Epstein, 1976). [See also Skin irritation section.]

[9] The test procedure typically involves an initial induction phase of five 48-hour covered patch tests, followed 10-14 days later by a 48-hour covered challenge patch.

Non-human

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Oral allergy/intolerance

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS

Single dose toxicity

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Repeated dose toxicity

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Expert-group opinion

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Human

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Non-human

According to a publicly-available TSCA[10] submission letter to the US EPA[11], briefly summarising the key findings of a draft study report, albino rats (5/sex/group) received a single gavage administration of methyl-2-furoate[12] (in corn oil) at 178, 300 or 507 mg/kg bw. Endpoints assessed included mortality, clinical effects, body weight and gross necropsy [no further details given]. There were 0/10, 5/10 and 10/10 deaths at 178, 300 and 507 mg/kg bw, respectively, with all deaths occurring within 3 days of dosing. Dose-related clinical findings included abnormal respiration, hyperactivity, prostration, tremors and impaired muscle coordination. Other observed adverse effects included ocular discharge, abnormal excretion, loss of body weight, vocalisation, loss of use of hindquarters, hypothermia and hair loss. All surviving animals, except for the sole surviving male at 300 mg/kg bw, appeared normal within 12 days post-dosing. Pulmonary or urinary abnormalities were observed at necropsy in six of the rats that died and intestinal, ocular, renal, hepatic or thymus findings[13] were seen in the other animals that died. A LD_{50} value[14] of 300 mg/kg bw was calculated (Great Lakes Chemical Corporation, 1998). [See Cardiopulmonary effects section and Other toxicity considerations section.]

A dermal LD_{50} value >1250 mg/kg bw has been reported for methyl-2-furoate in rabbits (Moreno, 1976).

[10] Toxic Substances Control Act (TSCA).
[11] US Environmental Protection Agency (EPA).
[12] CAS RN 611-13-2.
[13] No further details provided.
[14] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.

ere administered 50, 75, 100, 200 or 250 mg methyl-2-furoate/kg bw by intraperitoneal injection. A LD_{50} of 100 mg/kg bw was established (Phatak and Emerson, 1936).

Repeated dose toxicity

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

GENOTOXICITY

Expert-group opinions

In its evaluation of furfuryl alcohol and related substances, JECFA provided genotoxicity data for furfuryl alcohol, furfural and 5-methylfurfural but did not provide an overall conclusion on the genotoxic potential of the 15 furfuryl derivatives evaluated [including methyl-2-furoate] (JECFA, 2001). However, this did not preclude a conclusion on their safety as food additives or establishment of a group ADI[15]. [See Existing Health Criteria Values (HCVs) section for further details.]

In its evaluations of furfuryl alcohol and related flavouring substances, EFSA Expert Panels concluded that the available data, including that on furfuryl acetate, furfuryl alcohol, furfural, 5-methylfurfural and methyl-2-furoate, "do not give rise to concern with respect to genotoxicity" (EFSA, 2009, 2011).

Mammals (*in vivo*)

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Mammalian cells (*in vitro*)

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

Micro-organisms

Methyl-2-furoate lacked mutagenic activity in a [limited] bacterial reverse mutation (Ames) assay using *Salmonella typhimurium* strains TA98 and TA100 at 100 µg/plate, in the absence of S9[16] (Ichikawa *et al.*, 1986)[17]. [Current OECD guidelines recommend testing in at least five bacterial strains at up to 5 mg/plate in the presence and absence of mammalian metabolic activation.]

Other

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

CARCINOGENICITY

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

[15] Acceptable Daily Intake.

[16] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.

[17] EFSA, 2009 and 2011 also cite this study stating that use of metabolic activation is "not reported".

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No relevant data were identified on methyl-2-furoate or methyl furoate (mixed isomers).

CARDIOPULMONARY EFFECTS[18]

In an acute toxicity test where male and female albino rats received 178, 300 or 507 mg methyl-2-furoate/kg bw in corn oil by gavage, dose-related abnormal respiration was observed. At necropsy pulmonary abnormalities[19] were observed in six of the fifteen rats that died[20] (Great Lakes Chemical Corporation, 1998). [See Single dose toxicity section for further details, and also Other toxicity Considerations section.]

OTHER TOXICITY CONSIDERATIONS

Dose-related tremors, impaired muscle control and loss of use of hindquarters[21] were observed in an acute toxicity test where male and female albino rats received 178, 300 and 507 mg methyl-2-furoate/kg bw in corn oil by gavage (Great Lakes Chemical Corporation, 1998). [See Single dose toxicity section for further details, and also Cardiopulmonary effects section.]

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific inhalation HCVs were identified for methyl-2-furoate or methyl furoate (mixed isomers).

A group ADI of 0-0.5 mg/kg bw has been established by JECFA for furfural, furfuryl alcohol, furfuryl acetate, furfuryl propionate, furfuryl pentanoate, furfuryl octanoate, furfuryl 3-methylbutanoate, methyl 2-furoate, propyl 2-furoate, amyl 2-furoate, hexyl 2-furoate, and octyl 2-furoate, based on a NOEL[22] of 53 mg/kg bw/day in a 13-week feeding study in rats given furfural, followed by application of a safety factor of 100. This NOEL was considered appropriate for methyl 2-furoate as it is hydrolysed to furoic acid, the major metabolite of furfural, providing the basis for the inclusion of methyl-2-furoate in the group ADI (EFSA, 2009, 2011; JECFA, 2001).

JECFA and, more recently, EFSA, have also concluded that methyl-2-furoate is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive. In the earlier JECFA assessment, estimated intakes were 35 or 37 µg/person/day in the EU and US, respectively (JECFA, 2001). At the time of the EFSA review, these were 30 or 37 µg/person/day in the EU and US, respectively (EFSA, 2011).

[18] Potential effects on the heart, blood vessels and/or respiratory tract.
[19] No further details provided.
[20] 5/10 animals died at 300 mg/kg bw and all 10 died at 507 mg/kg bw..
[21] No further details provided.
[22] No-Observed-Effect Level.

REFERENCES

CCRIS (1990). Chemical Carcinogenesis Research Information System. Record for methyl-2-furanoate (CAS RN: 611-13-2). https://www.toxnet.nlm.nih.gov/newtoxnet/ccris.htm

EFSA (2009). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Flavouring Group Evaluation 66 (FGE.66)1: Consideration of furfuryl alcohol and related flavouring substances evaluated by JECFA (55th meeting) structurally related to furfuryl and furan derivatives with and without additional side chain substituents and heteroatoms evaluated by EFSA in FGE.13 (2005). EFSA Journal ON-752, 1-39. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2009.752

EFSA (2011). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 66, Revision 1 (FGE.66Rev1): Consideration of furfuryl alcohol and related flavouring substances evaluated by JECFA (55th meeting). EFSA Journal 9(9), 2314. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2314

Epstein WL (1976). Report to RIFM, 8 October. [Cited in Opdyke, 1979.]

Great Lakes Chemical Corporation (1998). Letter from Lakes Chemical Corp. to USEPA reporting the results of acute oral toxicity study in rats with methyl-2-furoate, dated 5 February 1998. TSCA Section 8(e) notification for methyl-2-furoate.

Ichikawa M, Yamamoto K, Tanaka A, Swaminathan S, Hatcher JF, Erturk E, and Bryan GT (1986). Mutagenicity of 3,4-diphenyl-5-nitrofuran analogs in *Salmonella typhimurium*. Carcinogenesis 7, 1339-1344. [Cited in CCRIS, 1990; EFSA, 2009, 2011.]

JECFA (2001). Safety evaluation of certain food additives and contaminants. Furfuryl alcohol and related substances. Prepared by the fifty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series No. 46. http://www.inchem.org/documents/jecfa/jecmono/v46je08.htm

Moreno OM (1976). Report to RIFM, 7 September. [Cited in Opdyke, 1979.]

Opdyke DLJ (1979). Fragrance Raw Materials Monographs: Methyl furoate. Food and Cosmetics Toxicology 17, 869.

Phatak NM and Emerson GA (1936). Toxicity and local anesthetic activity of alkyl esters of 2-furoic acid. Journal of Pharmacology and Experimental Therapeutics 58, 174-177.

APPENDIX: (b) (4)

(b) (4)

(b) (4) includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, (b) (4) covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, PSD and VMD) and advisory committee (e.g. COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- (b) (4)