(b) (4)

5-Methylfurfural

Toxicity monograph (with existing HCVs)

October 2016

(b) (4)

(b) (4)

TABLE OF CONTENTS

(b) (4)

Version 1

5-Methylfurfural

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of 5-methylfurfural (CAS RN[1] 620-02-0), focusing on the inhalation route of exposure. Data on the inhalation of tobacco smoke containing the ingredient (if available) have not been included in this monograph.

EXPERTISE

(b) (4)

TOXICITY DATA SEARCH CRITERIA

Searches of (b) (4) (see Appendix for details) identified several recent and relevant expert group reports that formed the basis for this assessment. The most recent are EFSA, 2011a-c. Since the key reviews focused on the use of 5-methylfurfural in food, a subsequent search of the primary literature was conducted in (b) (4) PubMed (including Medline) and Toxline (via TOXNET, with PubMed hits removed), in an attempt to identify other critical data that would not have been considered by the regulatory authorities. The RTECS databank was also consulted. All searches were conducted in October 2016 using the CAS RN, name and/or synonyms identified below, as appropriate.

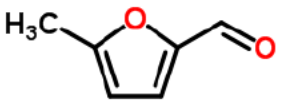
The data summarised in this report refers to the unheated form unless otherwise stated.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier / status	
Name	5-Methylfurfural
Synonym(s)	5-Methyl-2-furaldehyde 5-Methylfuran-2-carbaldehyde

[1] Chemical Abstracts Service Registry Number.

(b) (4)

CAS RN	620-02-0
FEMA	2702
E-number	210-622-6
REACH registration number	Not REACH registered
Molecular formula	$C_6H_6O_2$
Molecular weight	110.1
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** None available
	REACH joint registrants: None available

ADME

No substance-specific inhalation data were identified.

5-Methylfurfural can be oxidised to the primary alcohol 5-hydroxymethylfurfuraldehyde (5-HMF) (EFSA, 2011a,b). [See also Genotoxicity section.]

The glycine conjugate of 5-methylfuroic acid (>40% of the dose) and 5-methylfuryl methyl ketone (7-8% of the dose) were the major and minor urinary metabolites, respectively, in rats given an oral dose of 80, 120 or 160 mg/kg bw (Jodynis-Liebert, 1985, 1988). The ketone, which is thought to be formed directly from the acid, can be excreted before or after reduction to the corresponding alcohol (JECFA, 2001[3]).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

[3] JECFA, 2001, has been used as a key expert group report for this monograph and includes additional information on the metabolism and excretion of ^{14}C-labelled 5-methylfurfural in rats and mice [citing Godfrey *et al*. (1999) Journal of Toxicology and Environmental Health, Part A, 57, 199-210]. However, after consulting EFSA, 2011a,c, as well as the primary reference, it is clear that the study was, in fact, performed with the related substance 5-hydroxymethylfurfural. Presumably a typographical error was made in the JECFA report.

Skin irritation

Human

Exposure of 25 subjects to 5-methylfurfural at 2% in petrolatum under a closed patch for 48 hours did not produce skin irritation (Epstein, 1977). [See also Skin sensitisation section.]

Non-human

No substance-specific data were identified.

Eye irritation

No substance-specific data were identified.

Other local effects

No substance-specific data were identified.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No substance-specific data were identified.

Skin sensitisation

Human

No sensitisation effects were seen in a maximization test[4] in which 25 subjects were tested with 5-methylfurfural at 2%[5] in petrolatum using a 48-hour closed patch [no further details in citing source] (Epstein, 1977). [See also Skin irritation section.]

Non-human

In an open epicutaneous test, a 2% solution of 5-methylfurfural or vehicle only[6] was applied to the clipped skin of at least 6 guinea pigs for 21 days (either daily for 3 weeks or 5 times/week for 4 weeks). No sensitisation reactions were detected up to 72 hours after challenge on days 21 or 35 with the minimal irritating concentration[7] of 5-methylfurfural (Klecak, 1985).

Oral allergy/intolerance

No substance-specific data were identified.

INHALATION TOXICITY STUDIES

No substance-specific data were identified.

[4] 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.

[5] A second report (Klecak, 1985) also mentions that 2% 5-methylfurfural was not sensitising in humans. The report simply states that either a maximization test or repeated insult patch test was performed, but no further details are provided. It is unclear if the report is referring to the study by Epstein (1977).

[6] Vehicle not specified.

[7] Concentration not specified.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Human

No substance-specific data were identified.

Non-human

An oral LD_{50} value[8] of 2200 mg/kg bw was reported for rats [no further details in citing source][9] (Moreno, 1978).

Repeated dose toxicity

No substance-specific data were identified.

GENOTOXICITY

Expert-group opinion

5-Methylfurfural contains a structural alert for genotoxicity (EFSA, 2011b). However, although 5-methylfurfural is expected to be oxidised to 5-HMF, which can in turn be metabolised to 5-[(sulphoxy)methyl]furfural (5-SMF), a compound that shows genotoxic potential *in vitro*, the EFSA CEF Panel[10] concluded that, "notwithstanding the indications of *in vitro* genotoxicity in conditions that favour the formation of 5-SMF and the limited *in vivo* genotoxicity study, the essentially negative results of the carcinogenicity study in rats and mice indicate therefore that 5-HMF is of no concern under the conditions of intended use… This conclusion is also applicable to 5-methylfurfural…" (EFSA, 2011a).

In a subsequent report published the same year, the CEF panel also concluded that "sufficient data have been provided to mitigate this concern with respect to genotoxic potential of [5-HMF] *in vivo*… and accordingly there is no concern for 5-methylfurfural" (EFSA, 2011b).

Micro-organisms

5-Methylfurfural was not mutagenic in a bacterial reverse mutation (Ames) assay at up to 96.1 mg/plate in *Salmonella typhimurium* strains TA98, TA100 and TA102, when tested with and without S9[11] (Aeschbacher *et al*., 1989).

Another Ames assay in *S. typhimurium* strains TA100, TA1535 and TA1537, using 5-methylfurfural at much lower concentrations (0.091-0.363 mg/plate[12]), with and without S9, also produced results indicating a lack of mutagenicity [the reason for the low test doses is not explained] (Shinohara *et al*., 1986). A "spot test" (a limited Ames test) in TA98 and TA100 at a low dose (0.3 mg/plate) did not contradict these findings (Florin *et al*., 1980).

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[8] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.

[9] An online databank also reported an LD_{50} value of 2200 mg/kg bw for rats, although the route of exposure was unspecified and it is unclear whether the report is referring to the same study (Anon., 2001).

[10] EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids.

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

[12] The key expert group reports for this monograph (EFSA, 2011a-c; JECFA, 2001) state that dose range for the study by Shinohara *et al*. (1986) was 0.079-0.316 mg/plate; however, the original reference states that the dose range was 0.825-3.3 µmol/plate (corresponding to 0.091-0.363 mg/plate, based on a molecular weight of 110.1 g/mol). The reason for the discrepancy is unclear.

A rec assay for DNA damage[13] in *Bacillus subtilis* strains H17 (rec+) and M45 (rec-), using concentrations of 0.55, 55 or 5500 µg/disc, with and without S9, produced positive results at the two highest doses (Shinohara *et al.*, 1986).

In a poorly-described study, 5-methylfurfural [dose not specified] was not genotoxic in SOS or UMU chromotests[14] [no further details] (Kong *et al.*, 1988).

One study found that 5-methylfurfural inhibited the mutagenic effects of three known mutagens (benzo(a)pyrene, 2-aminofluorene and Trp-P-1) in bacterial reverse mutation assays using *S. typhimurium* strains TA98 and TA100 (Kong *et al.*, 1989).

Mammalian cells (*in vitro*)

When tested at 2.2-4.1 mg/ml, with and without S9, sister chromatid exchanges (SCEs) were induced in Chinese hamster ovary (CHO) cells (Stich *et al.*, 1981a,b).

Mammals (*in vivo*)

No substance-specific data were identified.

Other

A few studies have reported that 5-methylfurfural can induce DNA strand breaks *in vitro* (Shahabuddin *et al.*, 1990, 1991; Uddin and Hadi, 1995).

CARCINOGENICITY

No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No substance-specific data were identified.

CARDIOPULMONARY EFFECTS[15]

No substance-specific data were identified.

EXISTING HEALTH CRITERIA VALUES (HCVs)

No HCVs were identified.

"No safety concern" from the use of 5-methylfurfural as a food flavouring agent based on current estimated levels of intake of up to approximately 0.18 mg/day (EFSA, 2011a-c) or

[13] An indicative test, based on DNA repair.

[14] Although not specified in the source (Kong *et al.*, 1988), SOS and UMU chromotests are typically performed in *Escherichia coli* and *Salmonella typhimurium*, respectively.

[15] Potential effects on the heart, blood vessels and/or respiratory tract.

0.16 mg/day (JECFA, 2001) in Europe, and 0.025 mg/day in the USA (EFSA, 2011a-c; JECFA, 2001).

In 1965, 5-methylfurfural was determined to be generally recognised as safe (GRAS) by the FEMA Expert Panel (Hall and Oser, 1965).

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APPENDIX: The (b) (4) database and databank

(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) **Toxicity Profiles**