(b) (4)

2-Methyltetrahydrofuran-3-one

Toxicity monograph (with existing HCVs)

May 2018

Prepared by:

(b) (4)

(b) (4)

TABLE OF CONTENTS

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of 2-methyltetrahydrofuran-3-one (CAS RN[1] 3188-00-9), focussing on the inhalation route of exposure, with inclusion of existing Health Criteria Values (HCVs) where available. Data on the inhalation of tobacco smoke containing the substance (if available) have not been included in this monograph.

EXPERTISE

(b) was founded[2] in 1961 to provide independent, high-quality research, information and advice on chemical toxicology to industry and governmental departments. Its risk assessors have been working together for many years (more than 40 years in some instances) and have a record of objectivity and scientific excellence. All senior and principal scientists in the current team are accredited and listed in the European (Eurotox) and UK Royal Society of Biology/British Toxicology Society Registers of Toxicologists and are thus bound by their specific codes of conduct.

TOXICITY DATA SEARCH CRITERIA[3]

Searches of the (b) (4) database (see Appendix for details) identified the JECFA (2006) review on which this monograph is based. Other more recent, but less extensive reviews, namely EFSA (2008, 2016) and JECFA (2017), were also consulted for additional information. 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 2006 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 2-methyltetrahydrofuran-3-one 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 RN and (on PubMed only) name and/or synonym(s) identified below, as appropriate.

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

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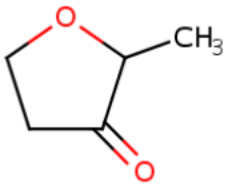
[1] Chemical Abstracts Service Registry Number.

[2] as the (b) (4)

[3] Disclaimer: searches are valid and complete as of the date of searching. (b(accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	2-Methyltetrahydrofuran-3-one
Synonyms(s)	4,5-Dihydro-2-methylfuran-3(2H)-one 3(2H)-Furanone, dihydro-2-methyl-
CAS RN	3188-00-9
REACH registration number[4]	Not REACH registered
Molecular formula	$C_5H_8O_2$
Molecular weight	100.12
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** Not available
	REACH joint registrants: Not available

ADME[5]

No relevant data were identified on the ADME of inhaled 2-methyltetrahydrofuran-3-one[6].

Based on the available experimental data[7], JECFA concluded that tetrahydrofuran and furanone derivatives [including 2-methyltetrahydrofuran-3-one] would be expected to be rapidly absorbed and eliminated, primarily in the urine following conjugation with glucuronic acid. JECFA also concluded that all 18 substances evaluated [including 2-methyltetrahydrofuran-3-one] would be metabolised to innocuous products (JECFA, 2006).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

[4] 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.
[5] Absorption, Distribution, Metabolism and Excretion.
[6] ADME predictions could be estimated on the basis of the structure and physic-chemical properties, if required.
[7] In rodents and humans for 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF) and in rodents for 4-hydroxy-2-ethyl-5-methyl-3(2H)-furanone (HEMF).

Skin irritation
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
No substance-specific data were identified.

Oral allergy/intolerance
No substance-specific data were identified.

INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS
Single dose toxicity
No substance-specific data were identified.

Repeated dose toxicity
No substance-specific data were identified.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES
Single dose toxicity
Expert-group opinion

In an addendum to its 2006 evaluation of tetrahydrofuran and furanone derivatives, JECFA concluded that for previously evaluated flavouring agents [including 2-methyltetrahydrofuran-3-one], oral LD_{50} values[8] in rats ranged from 1731 to 4000 mg/kg bw thus demonstrating their low acute oral toxicity (JECFA, 2017).

Human

No substance-specific data were identified.

Non-human

Oral LD_{50} values of 1860 and >2000 mg/kg bw have been reported for mice and rats respectively (Driscoll, 1996; Moran *et al*., 1980).

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

Repeated dose toxicity

Expert-group opinion

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

In an early limited unpublished subchronic toxicity study involving only a single low tested dose level, groups of weanling Sprague-Dawley rats (23/sex/group) were given 2-methyltetrahydrofuran-3-one in the diet for 13 weeks at doses of 0 or about 91.6 mg/kg bw/day in males and 91.2 mg/kg bw/day in females. Endpoints assessed included weekly assessment of food consumption and body weight changes, daily clinical observations[9], urinalysis[10] (in weeks 6 and 13), haematology and clinical chemistry[11], and necropsy and histological examination [extent of the examination unspecified from citing JECFA review]. It is unclear if any organs were weighed. No significant adverse effects were reported in treated animals, compared to the controls (Shellenberger, 1970), indicating a study NOAEL[12] of 91.6 and 91.2 mg/kg bw/day in male and female rats, respectively. [Current OECD test guidelines[13] recommend the use of a minimum of three dose groups, typically at up to 1000 mg/kg bw/day. Detailed reporting of the examination and weighing of the major organs[14] at necropsy are required, as is a detailed histopathological examination of all gross lesions and a wide-range of organs and tissues.] [See also Cardiopulmonary effects section.]

GENOTOXICITY

Expert-group opinions

In an addendum to its 2006 evaluation of tetrahydrofuran and furanone derivatives, JECFA concluded that "the overall evidence [on representative candidate substances[15]] confirms the absence of mutagenicity and genotoxicity for flavouring agents belonging to the group of tetrahydrofuran and furanone derivatives" including 2-methyltetrahydrofuran-3-one (JECFA, 2017).

In its evaluations of tetrahydrofuran derivatives, EFSA concluded that "genotoxicity data are available only for a limited number of substances, and the genotoxicity could not be assessed adequately". However, this lack of data did not preclude the evaluation of the safety of these substances [including 2-methyltetrahydrofuran-3-one] as food flavourings (EFSA, 2008, 2016).

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[9] Including physiological and behavioural effects, and mortality.

[10] Urinary pH, specific gravity, microscopic examination of sediment and qualitative estimate of albumin, glucose, occult blood, ketones, and bilirubin concentration.

[11] Erythrocyte volume fraction, haemoglobin, and erythrocyte, leukocyte and differential leukocyte counts. Blood glucose, blood urea nitrogen, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase and serum alkaline phosphatase. Performed on 8/sex/group following necropsy at week 6 and on all remaining animals in week 13. Serum electrolyte concentrations (sodium, potassium, calcium, and chloride) were measured in week 13 only.

[12] No-Observed-Adverse-Effect Level.

[13] OECD TG 408. Repeated Dose 90-day Oral Toxicity Study in Rodents.

[14] Liver, kidneys, adrenals, testes, epididymides, uterus, thymus, spleen, brain and heart.

[15] Candidate substances: 4-acetyl-2,5-dimethyl-3(2H)-furanone, 2,5-dimethyl-3(2H)-furanone, tetrahydrofurfuryl alcohol, 2-ethyl-4-hydroxy-5-methyl-3(2H)-furanone and 4-acetoxy-2,5-dimethyl-3(2H)-furanone.

Mammals (*in vivo*)
No substance-specific data were identified.

Mammalian cells (*in vitro*)
No substance-specific data were identified.

Micro-organisms
No substance-specific data were identified.

Other
No substance-specific data were identified.

CARCINOGENICITY
No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY
No substance-specific data were identified.

CARDIOPULMONARY EFFECTS[16]
No significant adverse effects were reported in groups of rats (23/sex/group) fed 2-methyltetrahydrofuran-3-one in the diet for 13 weeks at about 91.4 mg/kg bw/day. Although the extent of gross and histological examination was not specified in the citing JECFA review, it presumably involved the heart and lungs (Shellenberger, 1970). [See also Repeated dose toxicity section.]

OTHER TOXICITY CONSIDERATIONS
No substance-specific data were identified.

EXISTING HEALTH CRITERIA VALUES (HCVs)
No existing HCVs were identified for 2-methyltetrahydrofuran-3-one.

JECFA and, more recently, EFSA, have concluded that 2-methyltetrahydrofuran-3-one is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive. At the time of the EFSA review, these were 20.5 or 9 µg/person/day in the EU and US, respectively (EFSA, 2016). In the earlier JECFA assessment, estimated intakes were 24 or 9 µg/person/day in the EU and US, respectively (JECFA, 2006).

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

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[17] Incorrectly cited in JECFA (2006) as Moran EJ and Easterday OO (1980).

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**