(b) (4)

1-Methylpyrrole-2-carboxaldehyde

Toxicity monograph (with existing HCVs)

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1-Methylpyrrole-2-carboxaldehyde

Toxicity monograph (with existing HCVs)

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of 1-methylpyrrole-2-carboxaldehyde (CAS RN[1] 1192-58-1), 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) (4) 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 (2012) review, on which this monograph is based. EFSA (2008) was also consulted for additional information. A subsequent search of the primary literature was restricted to (b) (4) and Toxline (the toxicity subset of Medline, via TOXNET) in an attempt to identify more recent data since the 2012 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 1-methylpyrrole-2-carboxaldehyde 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 (in PubMed only) name and/or synonyms identified below, as appropriate.

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

[1] Chemical Abstracts Service Registry Number.

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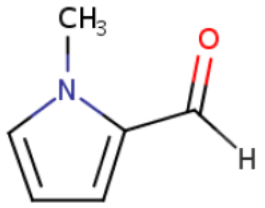
[3] Disclaimer: searches are valid and complete as of the date of searching. (b) accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	1-Methylpyrrole-2-carboxaldehyde
Synonyms(s)	2-Formyl-1-methylpyrrole 1-Methyl-1H-pyrrole-2-carboxaldehyde
CAS RN	1192-58-1
REACH registration number[4]	Not REACH registered
Molecular formula	C_6H_7NO
Molecular weight	109.13
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 1-methylpyrrole-2-carboxaldehyde[6].

In its evaluation of a group of 28 pyridine, pyrrole, indole and quinoline derivatives, an EFSA Expert Panel noted that no data are available on the metabolism of 1-methylpyrrole-2-carboxaldehyde (a N-substituted pyrrole). Data on its oral absorption and elimination were also lacking from the review (EFSA, 2008).

In its evaluation of a group of 11 pyridine, pyrrole and quinoline derivatives, JECFA predicted the metabolism of 1-methylpyrrole-2-carboxaldehyde to be hydroxylation of the pyrrole ring, with excretion in the urine as the corresponding glucuronic acid conjugate and/or oxidation of the aldehyde group to the corresponding carboxylic acid. Alkyl side-chain oxidation was

[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.

also considered as a possible route of metabolism followed by glucuronic acid conjugation and excretion, or oxidation to the corresponding carboxylic acid (JECFA, 2012).

Both EFSA and JECFA concluded that 1-methylpyrrole-2-carboxaldehyde cannot be anticipated or predicted to be "metabolised to innocuous products" (EFSA, 2008; JECFA, 2012).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

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

No substance-specific data were identified.

Oral LD_{50} values[7] between 60 to 3500 mg/kg bw have been reported by JECFA (2006) for six of 28 candidate substances of the group comprising pyridine, pyrrole [including 1-methylpyrrole-2-carboxaldehyde], indole and quinoline derivatives) and nine structurally related substances (EFSA, 2008).

More recently, no oral LD_{50} values were assessed for the pyridine, pyrrole [including 1-methylpyrrole-2-carboxaldehyde] and quinoline derivatives evaluated by JECFA in 2012. However, they did conclude that the "oral acute toxicity of [these] flavouring agents … is low", based on reported oral LD_{50} values in rats, mice and rabbits ranging from 459 to 2295 mg/kg bw for the structurally related material 5-ethyl-2-methylpyridine (JECFA, 2012).

Human
No substance-specific data were identified.

Non-human
No substance-specific data were identified.

Repeated dose toxicity
No substance-specific data were identified.

GENOTOXICITY

Expert-group opinions
In its 2006 evaluation of 22 pyridine, pyrrole and quinoline derivatives, JECFA concluded that on this basis of the available evidence, these substances do not demonstrate genotoxic potential. This conclusion was extended to seven of the 11 additional compounds[8] [including 1-methylpyrrole-2-carboxaldehyde] evaluated in 2012 (JECFA, 2012).

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.

[7] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.
[8] Excluding 1-(2-Hydroxyphenyl)-3-(pyridin-4yl)propan-1-one, 1-(2-Hydroxy-4-isobutoxyphenyl)-3(pyridin-2-yl)propan-1-one and 1-(2-Hydroxy-4-methoxyphenyl)3-(pyridin-2-yl)propan-1-one.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No substance-specific data were identified.

CARDIOPULMONARY EFFECTS[9]

No substance-specific data were identified.

OTHER TOXICITY CONSIDERATIONS

No substance-specific data were identified.

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific existing HCVs were identified.

In their respective evaluations of 28 and 11 pyridine, pyrrole, indole and quinoline derivatives, both EFSA (2008) and JECFA (2012) concluded that additional data was required on 1-methylpyrrole-2-carboxaldehyde in order to fully evaluate its safety as a food flavouring agent.

1-Methylpyrrole-2-carboxaldehyde is no longer supported by Industry for use as a flavouring substance in Europe (DG SANCO, 2013; EFSA, 2011, 2013).

REFERENCES

DG SANCO (2013). Directorate General for Health and Consumer Affairs. Information from DG SANCO 14/05 2013, concerning a list of 18 non-supported substances. FLAVIS.2.26. [Cited in EFSA, 2013.]

EFSA (2008). European Food Safety Authority. EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC). Scientific Opinion on pyridine, pyrrole, indole and quinoline derivatives from chemical group 28 Flavouring Group Evaluation 24, Revision 1. EFSA Journal 792, 1-63. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/792.pdf

EFSA (2011). European Food Safety Authority. List of substances for which the Commission withdraw its request to EFSA for an opinion. FLAVIS/2.23Rev1. [Cited in EFSA, 2013.]

EFSA (2013). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 24, Revision 2 (FGE.24Rev2). EFSA Journal 11(11), 3453. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3453

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

JECFA (2006). Safety evaluation of certain food additives and contaminants. Sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series 54. [Cited in EFSA, 2008; JECFA, 2012].

JECFA (2012). Safety evaluation of certain food additives. Prepared by the seventy-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 67. http://apps.who.int/iris/bitstream/handle/10665/77763/9789241660679_eng.pdf?sequence=1

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