(b) (4)

3-Methylcyclohexane-1,2-dione

Toxicity monograph (with existing HCVs)

May 2018

Prepared by:

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of 3-methylcyclohexane-1,2-dione (CAS RN[1] 3008-43-3), 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 (1999) review, on which this monograph is based. More recent, but less extensive, reviews by EFSA (2009, 2014 and 2015) were 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 1999 JECFA 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 3-methyl-1,2-hexanedione 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 to identify such information (and also cardiopulmonary data).

All searches were conducted in May 2018 using the CAS RN 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.

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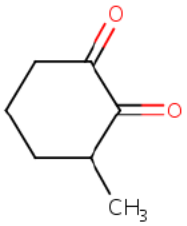
[1] Chemical Abstracts Service Registry Number.

[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	3-Methylcyclohexane-1,2-dione
Synonyms(s)	3-Methyl-1,2-cyclohexanedione 1-Methyl-2,3-cyclohexadione Cyclohexane-1,2-dione, 3-methyl-
CAS RN	3008-43-3
REACH registration number	Not REACH registered
Molecular formula	$C_7H_{10}O_2$
Molecular weight	126.15
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** None Available
	REACH joint registrants: None Available

ADME[4]

No relevant data were identified on the ADME of inhaled 3-methyl-1,2-cyclohexanedione[5].

According to JECFA (1999), "In rats and mice, orally administered aliphatic alpha-diketones are rapidly absorbed from the gastrointestinal tract". At low levels of exposure humans will metabolise alicyclic diketones (such as 3-methylcyclohexane-1,2-dione) by reduction to the corresponding diol, followed by glucuronic acid conjugation and excretion.

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

[4] Absorption, Distribution, Metabolism and Excretion.

[5] ADME predictions could be estimated on the basis of the structure and physic-chemical properties, if required.

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

JECFA considered the acute oral toxicity of aliphatic acyclic and alicyclic alpha-diketones and related alpha-hydroxyketones (including 3-methylcyclohexane-1,2-dione) to be low, based on oral LD_{50} values[6] for seven candidate substances which were within the range 990->8000 mg/kg bw (JECFA, 1999).

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

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

Expert-group opinion
No substance-specific data were identified.

Human
No substance-specific data were identified.

Non-human
Male Sprague-Dawley rats (10 per group) were given 3-methylcyclohexane-1,2-dione in the diet for 13 weeks at 0, 5, 50 or 675 mg/kg bw/day. For the high dose group, during week six[7], the dose was increased to 1350 mg/kg bw/day. Endpoints assessed included food consumption, body weight, haematology, necropsy and histopathological examination[8]. Decreased food consumption with subsequent decreased body weight gain was observed at the highest dose, the effects becoming more marked in week 6 when the dose was increased. On this basis the study investigators determined an NOEL[9] of 50 mg/kg bw/day (Wheldon and Krajkeman, 1967). In its assessment of this early study, JECFA concluded that no adverse effects were observed at any dose level when compared to the control animals (JECFA, 1999) suggesting a study NOAEL[10] of 675-1350 mg/kg bw/day. [See also Cardiopulmonary effects section.]

GENOTOXICITY

Expert-group opinions
In its evaluations of α,β-unsaturated alicyclic ketones and precursors, the EFSA CEF Panel[11] concluded that there was no safety concern with respect to genotoxicity for 3-methylcyclohexane-1,2-dione (EFSA, 2009, 2014, 2015).

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.

[7] It is not clear from the citing source if this dose increase occurred during week 6 only or from week 6 for the remainder of the study.
[8] No details provided on the extent of macro- or microscopic examination were provided in the citing source
[9] No Observed-Effect Level.
[10] No Observed-Adverse-Effect Level.
[11] EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids.

CARCINOGENICITY

Expert-group opinions

In its evaluations of α,β-unsaturated alicyclic ketones and precursors, the EFSA CEF Panel concluded that the lack of carcinogenicity seen with the related substance 3-ethyl-2-hydroxy-2-cyclopenten-1-one was representative for 3-methylcyclohexane-1,2-dione (EFSA, 2009, 2014, 2015).

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In its evaluations of α,β-unsaturated alicyclic ketones and precursors, the EFSA CEF Panel concluded that the lack of carcinogenicity seen with the related substance 3-ethyl-2-hydroxy-2-cyclopenten-1-one was representative for 3-methylcyclohexane-1,2-dione [as described above]. The study that was the basis of this conclusion on carcinogenicity, also assessed the reproductive performance and developmental effects of 3-ethyl-2-hydroxy-2-cyclopenten-1-one across three successive generations following dietary exposure to up to 200 mg/kg bw/day. No adverse effects were seen (EFSA, 2009). Presumably, therefore, the reassuring reproductive and developmental toxicity findings from this study on the related substance 3-ethyl-2-hydroxy-2-cyclopenten-1-one can be considered representative for 3-methylcyclohexane-1,2-dione.

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

CARDIOPULMONARY EFFECTS[12]

No treatment-related effects were reported following the necropsy and histological examination (presumably including the heart and lungs) of male rats fed 3-methylcyclohexane-1,2-dione in the diet at up to 675-1350 mg/kg bw/day for 13 weeks (Wheldon and Krajkeman, 1967). [See also Repeated dose toxicity section.]

OTHER TOXICITY CONSIDERATIONS

No substance-specific data were identified.

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

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific existing HCVs were identified.

JECFA and, more recently, EFSA, have concluded that 3-methylcyclohexane-1,2-dione is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive of 1.3-2 or 8 µg/person/day in the EU and US respectively (EFSA, 2009, 2014, 2015; JECFA, 1999).

REFERENCES

EFSA (2009). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 213: alpha,beta-Unsaturated alicyclic ketones and precursors from chemical subgroup 2.7 of FGE.19. EFSA Journal. ON-879, 1-27. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/879.pdf

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JECFA (1999). Safety evaluation of certain food additives. Prepared by the fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 42. World Health Organization, Geneva. http://www.inchem.org/documents/jecfa/jecmono/v042je20.htm

Wheldon GH and Krajkeman AJ (1967). The effects of ten food-flavoring additives administered to rats over a period of thirteen weeks. Unpublished report from Huntington Research Center. Submitted to WHO by the Flavor and Extract Manufacturers' Association of the United States, Washington DC, United States [cited in JECFA, 1999].

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

(b) (4)

(b) 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
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