(b) (4)

2(5H)-Furanone

Toxicity monograph (with existing HCVs)

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of 2(5H)-furanone (CAS RN[1] 497-23-4), 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]

(b)) has access to a wide range of data sources, including the unique (b) (4) databank (see the Appendix for details), PubMed, the TOXNET system of databases and databanks (which includes Toxline (the toxicity subset of Medline), HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB), and eChemPortal.

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.

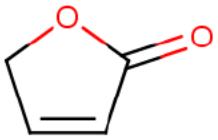
IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	2(5H)-Furanone
Synonyms(s)	Furan-2(5H)-one Butenolide 2-Buten-4-olide

[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.

	gamma-Crotolactone 2-Oxo-2,5-dihydrofuran Isocrotonolactone *gamma*-Hydroxycrotonic acid lactone 4-Hydroxy-2-butenoic acid *gamma*-lactone
CAS RN	497-23-4
REACH registration number[4]	Not REACH registered
Molecular formula	$C_4H_4O_2$
Molecular weight	84.07
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(5H)-furanone.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that 4-hydroxy-2-butenoic acid γ-lactone "would be predicted to be readily hydrolysed to the corresponding hydroxycarboxylic acid" and "would undergo β-oxidative cleavage to yield metabolites that are completely metabolized in the fatty acid pathway and citric acid cycle" (JECFA, 2011).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

Expert-group opinion

No substance-specific data were identified.

Human

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.

Non-human

Repeated inhalation exposure (6 hr/day, 5 days/wk, 13 wks) of hamsters to "butenolide"[6] vapour at a concentration of 446 mg/m³ of air resulted in nasal discharge and was considered indicative of a "slight but definite" local effect of the substance on the mucous membranes of the nose (and mouth) (Feron *et al.*, 1979). [See also Eye irritation and Inhalation toxicity studies – systemic effects sections.]

Skin irritation

Expert-group opinion

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

Erythema and induration[7] were observed 24 hours after a [presumably covered] skin application of "butenolide"[8] (100 µg/mL [0.01% w/v] in ethyl acetate) to male guinea pigs (Bhavanishankar *et al.*, 1988).

Eye irritation

Hamsters showed signs of eye irritation following repeated exposure to "butenolide"[9] vapour at 446 mg/m³ (6 hr/day, 5 days/wk, 13 wks) (Feron *et al.*, 1979). [See also Respiratory tract irritation and Inhalation toxicity studies – systemic effects sections.]

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.

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[6] A citation of this study indicated that the test material was in fact 4-acetamido-4-hydroxy-2-butenoic acid γ-lactone (Wang *et al.*, 2009).

[7] An increase in the fibrous elements in tissue commonly associated with inflammation and marked by loss of elasticity and pliability.

[8] A citation of this study indicated that the test material was in fact 4-acetamido-4-hydroxy-2-butenoic acid γ-lactone (Wang *et al.*, 2009).

[9] A citation of this study indicated that the test material was in fact 4-acetamido-4-hydroxy-2-butenoic acid γ-lactone (Wang *et al.*, 2009).

INHALATION TOXICITY S(b) (4) – SYSTEMIC EFFECTS

Single dose toxicity

The 4-hour LC_{50} value[10] of butenolide was determined to be 1400 mg/m³ in hamsters (Kruysse, 1974).

Repeated dose toxicity

Groups of Syrian golden hamsters (10/sex) were exposed to "butenolide"[11] vapour at concentrations of 0, 18.7, 85 or 446 mg/m³ for 6 hours/day on 5 days/week for 13 weeks. Evaluated parameters included growth, clinical signs, haematology, serum chemistry and urinalysis. The major organs were weighed and a range of organs (including the nose, larynx and trachea with main bronchi) were examined microscopically. At the highest tested concentration, males displayed slightly reduced growth, slightly increased liver weight and a minor reduction in eosinophil count; microscopic effects were limited to nasal metaplasia (both sexes). No gross pathological changes were apparent. The study NOEC[12] was established as 85 mg/m³, though the actual NOAEC[13] was considered to be somewhat higher and was placed at 225 mg/m³ (Feron *et al.*, 1979). [See also Respiratory tract irritation and Eye irritation sections.]

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

No substance-specific data were identified.

Repeated dose toxicity

No substance-specific data were identified.

GENOTOXICITY

Expert-group opinions

In its evaluation of various lactones, the European Food Safety Authority (EFSA) considered that furan-2(5H)-one "did not induce mutations" in a bacterial reverse mutation assay. However, the substance "unequivocally induced micronuclei" *in vitro* in the presence of S9[14] (and gave equivocal results in its absence), leading the Panel to conclude that "furan-2(5H)-one raise[d] concern with respect to genotoxicity *in vitro*" (EFSA, 2013).

Mammals (*in vivo*)

No substance-specific data were identified.

Mammalian cells (*in vitro*)

The clastogenic potential of furan-2(5H)-one was investigated in an OECD Test Guideline 487-compliant micronucleus assay, conducted according to GLP[15]. Human lymphocytes were exposed

[10] Lethal Concentration 50, i.e. the concentration that is lethal to 50% of the exposed group.
[11] A citation of this study indicated that the test material was in fact 4-acetamido-4-hydroxy-2-butenoic acid γ-lactone (Wang *et al.*, 2009).
[12] No-observed-effect concentration.
[13] No-observed-adverse-effect concentration.
[14] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.
[15] Good laboratory practice.

to concentrations of up to 475 µg/mL in the presence and absence of S9 (3-hr incubation with 21-hr recovery period) or for 24 hours at up to 72.5 µg/mL without S9. A significant increase in micronuclei frequency was observed in the presence of S9, while results in the other two assays were equivocal (Whitwell, 2012).

Micro-organisms

In an OECD Test Guideline 471 bacterial reverse mutation assay, conducted to GLP, furan-2(5H)-one displayed no evidence of mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 when tested at up to 5 mg/plate both in the presence and absence of S9 (Bowen, 2011).

A similar lack of mutagenic potential was observed in a limited Ames test in *S. typhimurium* strains TA98 and TA100, in the presence of S9 at 50 µg/mL (Lafont *et al.*, 1983).

No indication of DNA damage[16] was seen in a rec assay in the *Bacillus subtilis* H17/M45 system conducted with butenolide [concentration unspecified] in the absence of metabolic activation (Ueno and Kubota, 1976).

Other

No substance-specific data were identified.

CARCINOGENICITY

No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Expert-group opinions

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No standard substance-specific data were identified.

Intraperitoneal treatment of female rats with 2-buten-4-olide at 100 mg kg bw/day for two weeks delayed the estrous cycle and influenced various hormonal parameters (Shitsukawa *et al.*, 1990).

A dose-dependent (and age-correlated) reduction in growth was observed in rat pups following intraperitoneal injection with 2-buten-4-olide at 50 or 75 mg/kg bw on post-natal days 0-2, 4-6 and 12-14, implicating the substance as an endogenous feeding suppressant (Mathur, 2010).

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

The HSDB record for 2(5H)-furanone cites a number of studies that investigate the endocrine modulating effects of this substance (HSDB, 2014). These are considered of limited value to the current assessment and have not been further summarised.

CARDIOPULMONARY EFFECTS[17]

No substance-specific data were identified.

OTHER TOXICITY CONSIDERATIONS

The HSDB record for 2(5H)-furanone cites a number of studies that investigate the feeding suppressant nature of this substance; various behavioural studies have also been described (HSDB, 2014). These are considered of limited value to the current assessment and have not been further summarised.

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific existing HCVs were identified.

JECFA and EFSA have concluded that 2(5H)-furanone is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive in the EU of 0.01 and 0.61 µg/person/day, respectively (EFSA, 2009, 2013; JECFA, 2011).

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

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

(b) (4)

(b) (4) (cludes 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