(b) (4)

4-Hydroxybenzyl alcohol

Toxicity monograph (with existing HCVs)

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Prepared by:
(b) (4)

(b) (4)

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INTRODUCTION

(b) (4) toxicology advice & consulting was asked to produce a toxicity monograph of 4-hydroxybenzyl alcohol (CAS RN[1] 623-05-2), 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

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TOXICITY DATA SEARCH CRITERIA[3]

(b) (4) access to a wide range of data sources, including the (b) (4) (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.

In addition, the industry REACH registration dossier[4] disseminated on the ECHA website was consulted for critical ADME and/or toxicity data, and also derived no-effect levels (DNELs). None were included in this intermediate REACH registration dossier.

All searches were conducted in May 2018 using the CAS RN(s) and (in PubMed only) name and/or synonym(s) identified below, as appropriate.

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[1] Chemical Abstracts Service Registry Number

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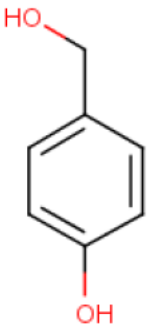
[3] Disclaimer: searches are valid and complete as of the date (b searching. (b) accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

[4] Information on Registered Substances comes from registration dossiers which have been assigned a registration number. The assignment of a registration number does however not guarantee that the information in the dossier is correct or that the dossier is compliant with Regulation (EC) No 1907/2006 (the REACH Regulation). This information has not been reviewed or verified by the Agency or any other authority. The content is subject to change without prior notice.

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

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	4-Hydroxybenzyl alcohol
Synonyms(s)	Benzenemethanol, 4-hydroxy- 4-Hydroxybenzenemethanol 4-(Hydroxymethyl)phenol p-alcohol phenol 4-Methylolphenol 4-MP
CAS RN	623-05-2
REACH registration number[5]	01-2120093505-53-xxxx
Molecular formula	$C_7H_8O_2$
Molecular weight	124.14
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** None available
	REACH joint registrants: Skin Irrit. 2. Causes skin irritation (H315) Eye Irrit. 2. Causes serious eye irritation (H319) STOT SE 3. May cause respiratory irritation (H335)

[5] 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.

ADME[6]

No relevant data were identified on the ADME of inhaled 4-hydroxybenzyl alcohol.

In an evaluation of a group of hydroxy- and alkoxy-substituted benzyl derivatives (including 4-hydroxybenzyl alcohol), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered that these substances are "rapidly absorbed [in the gastrointestinal tract], metabolized, and excreted in the urine mainly as sulfate and glucuronic acid conjugates of the corresponding hydroxybenzoic acid derivatives. All of the flavouring agents in this group are expected to be metabolized to innocuous products" (JECFA, 2002).

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

Expert-group opinion

No substance-specific data were identified.

Human

Four out of a group of 10 patients with allergic contact dermatitis to at least 1 of 6 simple methylol phenols (MP; including 4-MP [4-hydroxybenzyl alcohol]) reacted to a patch test with 4-hydroxybenzyl alcohol at 81% w/v in ethanol. Two patients also reacted at a concentration of 8.1% but not at 0.81% (Bruze and Zimerson, 1997).

Non-human

4-MP was assessed for skin sensitisation potential in what appears to be a well-conducted guinea pig maximisation test (GPMT). Females (24 in the test group) were induced by

[6] Absorption, Distribution, Metabolism and Excretion.

intradermal injection with a 5% solution of 4-MP in combination with an adjuvant. A second induction, involving topical application of a 25% 4-MP solution under a 48-hr occlusive patch, was made 24 hours after treatment with 10% sodium lauryl sulphate (SLS))[7]. Two weeks after the topical inductions, animals (test and control groups) received challenge doses of 15% under 24-hr occlusive patches; animals were similarly rechallenged 1 week later. Both challenge phases produced positive reactions in 19/24 animals (compared to 3/12 for controls). As such, 4-MP was considered to be a moderate sensitiser in this GPMT (Bruze, 1986).

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

An Expert Panel of the Flavor and Extract Manufacturers Association (FEMA) considered the acute oral toxicity of hydroxy- and alkoxy-benzyl derivatives (including 4-hydroxybenzyl alcohol) to be low, based on oral LD_{50} values[8] in excess of 1000 mg/kg bw for the majority of the 46 candidate substances (Adams *et al.*, 2005).

Human

No substance-specific data were identified.

Non-human

There was no mortality following a single gavage administration of p-alcohol phenol to pregnant rats (16-21/group) at up to 1000 mg/kg bw. Growth (measured over a 3-day period) was also unaffected (Kavlock, 1990). [See also Reproductive and developmental toxicity section.]

Repeated dose toxicity

No substance-specific data were identified.

[7] Although the exact timescale was not specified, application of SLS is usually made 5-7 days after intradermal injection followed a day later by the second induction.

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

GENOTOXICITY

Expert-group opinions

In its evaluation of hydroxy- and alkoxy-substituted benzyl derivatives (including 4-hydroxybenzyl alcohol), JECFA considered that these substances "do not have genotoxic potential *in vivo*" (JECFA, 2002).

Mammals (*in vivo*)

No substance-specific data were identified.

Mammalian cells (*in vitro*)

No substance-specific data were identified.

Micro-organisms

In a (very) limited bacterial reverse mutation (Ames) assay, 4-hydroxybenzyl alcohol was not mutagenic in *Salmonella typhimurium* strain TA100 when tested at up to 2 mg/plate in the absence of mammalian metabolic activation (Ball *et al*., 1984).

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 substance-specific fertility data were identified.

In a non-guideline investigation, p-alcohol phenol was administered to pregnant rats (16-21/group) by oral gavage at 0, 333, 667 or 1000 mg/kg bw on day 11 of gestation. There were no treatment-related effects on any of the evaluated parameters: number pregnant, litter size, perinatal loss, pup weight and litter biomass (Kavlock, 1990). [See also Toxicity studies – other exposure routes section.]

CARDIOPULMONARY EFFECTS[9]

No substance-specific data were identified.

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

OTHER TOXICITY CONSIDERATIONS

No relevant substance-specific data were identified.

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific existing HCVs were identified.

JECFA and, more recently, the European Food Safety Authority (EFSA), have concluded that 4-hydroxybenzyl alcohol is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive of 5.2-6 or 0.06 µg/person/day in the EU and US, respectively (EFSA, 2008; JECFA, 2002).

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Kavlock RJ (1990). Structure-activity relationships in the developmental toxicity of substituted phenols: in vivo effects. Teratology 41, 43-59.

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

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(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