(b) (4)

Benzyl alcohol

Toxicity monograph (with existing HCVs)

June 2017

Prepared by:

(b) (4)

(b) (4)

(b) (4)

TABLE OF CONTENTS

(b) (4)

Benzyl alcohol

Toxicity monograph (with existing HCVs)

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of benzyl g on the inhalation route of exposure. Data on the inhalation of tobacco smoke containing the ingredient (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 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 professional conduct.

TOXICITY DATA SEARCH CRITERIA

Searches of the (b) (4) database (see Appendix for details) identified several recent and potentially relevant expert group reports, notably Scognamiglio *et al.* (2012). A subsequent search of the primary literature was conducted (b) (4) and Toxline (the toxicity subset of Medline, via TOXNET) in an attempt to identify more recent data. The remainder of the TOXNET system (which includes HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB) was also consulted. Since the key review could not necessarily be relied upon specifically to identify cardiopulmonary data, no date restriction was placed on searches in PubMed tailored to identify such information. Finally, the industry REACH dossier[3] was consulted for inhalation data and for endpoints for which there were otherwise data gaps or limited data. All searches were conducted in June 2017 using the CAS RN(s), name and/or synonym(s) identified in the table below, as appropriate.

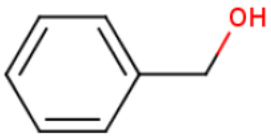
[1] Chemical Abstracts Service Registry Number.

[2] (b) (4)

[3] 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.

(b) (4)

IDENTIFICATION

Identifier	
Name	Benzyl alcohol
Synonyms	Phenylcarbinol Phenylmethanol
CAS RN	100-51-6
REACH registration number	01-2119492630-38-xxxx
Molecular formula	C_7H_8O
Molecular weight	108.14
Structure	
Classification, according to EU CLP (EC 1272/2008)[4]	**Harmonised classification:** Acute Tox. 4. Harmful if swallowed (H302) Acute Tox. 4. Harmful if inhaled (H332)
	REACH joint registrants (2553 of 3241 notifiers[5]): Acute Tox. 4. Harmful if swallowed (H302) Acute Tox. 4. Harmful if inhaled (H332)

KEY PHYSICAL AND CHEMICAL PROPERTIES

Property	Value	Reference
Melting point	-15°C [freezing point]	NTP, 1989; OECD, 2002
Boiling point	205°C	NTP, 1989; OECD, 2002
Vapour pressure	0.02 mmHg at 20°C	OECD, 2002
Henry's Law constant	0.000000337 atm-m^3/mol at 25 °C	EpiSuite
Water solubility	40 g/L at 20°C ("Sparingly soluble")	NTP, 1989; OECD, 2002
Log octanol/air partition coefficient	-4.861	EpiSuite

[4] In humans, skin sensitisation is considered a critical effect of benzyl alcohol. As such, classification for such effects seems prudent.

[5] A further 203 joint registrants propose an additional classification: Eye Irrit. 2. Causes serious eye irritation (H319).

(b) (4)

Log octanol/water partition coefficient	1.1	OECD, 2002
Particle size distribution	Not identified	-
Flash point	101°C (closed cup)	OECD, 2002
Flammability	Not identified	
Explosivity	Explosive limits: lower 1.3% (by volume); upper 13.0% (by volume) at 170°C and 760 mmHg	OECD, 2002
Self-ignition temperature	435°C	OECD, 2002

ADME

No relevant data were identified on the absorption of inhaled benzyl alcohol[6]. Inhalation absorption is assumed to be 100% (Api *et al.*, 2015).

According to OECD (2002), "all benzyl compounds are rapidly absorbed [following ingestion], and rapidly and completely excreted in the urine … Benzyl alcohol, benzoic acid and its sodium and potassium salt can be considered as a single category regarding human health, as they are all rapidly metabolised and excreted via a common pathway within 24 hrs". Benzyl alcohol is rapidly metabolised to benzaldehyde, and then benzoic acid, which is conjugated to form hippuric acid (80%) and benzoyl glucuronide (20%), and is eliminated in the urine. Saturation of metabolic pathways only occurs at high doses (more than 500 mg/kg bw/day by oral gavage) (OECD, 2002)[7].

In studies on human skin samples, the dermal absorption of benzyl alcohol is generally less than 5%, although 35.5% was absorbed in a 6-hour study on skin samples from premature babies (Scognamiglio *et al.*, 2012).

TOXICOLOGY

INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS

Single dose toxicity

Human

No substance-specific data were identified.

Non-human

The following LC_{50} values[8] have been observed in rats:

2-hour LC_{50} 4422 mg/m³ (Smyth *et al.*, 1951).

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

[7] As such, reviews on benzoic acid (and its common salts) and benzaldehyde would be useful to consult for a more comprehensive understanding of the ADME and toxicity of benzyl alcohol (b) would be happy to assist further with this if required.

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

(b) (4)

4-hour LC_{50} >4178 mg/m³ (Anon., 1990).
4-hour LC_{50} ~8845 mg/m³ (Carpenter *et al.*, 1949).
8-hour LC_{50} 4422 mg/m³ (NTP, 1989)[9].

Repeated dose toxicity

Expert-group opinion

"Limited information indicates that the chemical is not likely to cause serious damage to health from repeated inhalation exposure" (NICNAS, 2015).

Human

Transient headaches, dizziness, nausea, diarrhoea and weight loss have been reported in workers exposed for an undetermined duration to a "high vapor concentration" of a mixture containing benzyl alcohol, benzene, and ester solvents [dermal exposure was possibly also involved] (Treon and Stasik, 1983).

Non-human

In a 4-week study, rats (10/sex/group) were exposed to aerosolised benzyl alcohol via (nose-only) inhalation (for 6 hours/day, 5 days/week). The mean exposure concentrations were 0, 41, 102, 290 and 1072 mg/m³. Benzyl alcohol was described as "well tolerated", even at the highest concentration, with no adverse effects on food consumption, growth, clinical pathology, organ weights, or gross and microscopic pathology [of an undisclosed range of tissues and organs]. The no-observed-effect concentration (NOEC) was considered to be 1072 mg/m³ (RIFM, 2009). [See also Respiratory tract irritation section.]

In a 5-day study, inhalation exposure[10] of rats (5/sex/group) to benzyl alcohol (6 hours/day) at 0, 44, 440 and 2200 mg/m³ resulted in emaciation/reduced body weight, reduced food consumption, reduced organ weights (including the liver, spleen, brain, heart and lungs; likely secondary to decreased body weight), splenic atrophy and [presumably reduced] "hemopoiesis" [formation of blood cellular components in the bone marrow] at the highest concentration. No mortalities were observed. The no-observed-adverse-effect concentration (NOAEC) was considered to be 440 mg/m³ (equivalent to about 42 mg/kg bw/day) (RIFM, 2001). [See also Respiratory tract irritation and Cardiopulmonary effects sections.]

TOXICITY STUDIES – OTHER EXPOSURE ROUTES – SYSTEMIC EFFECTS

Single dose toxicity

Expert-group opinion

Benzyl alcohol exhibits low acute oral and dermal toxicity (OECD, 2002).

Human

According to the US Environmental Protection Agency (US EPA, 2009), "available data in humans are limited to case reports where exposure to benzyl alcohol occurred with other solvents or when administered as a bacteriostatic agent with other medications. These reports [provide] no dose-response in humans for quantitative assessments".

[9] Cited as an LC_{Lo}

[10] Type of inhalation exposure (i.e. nose-only or whole body) was not specified in the citing source.

(b) (4)

Non-human

Oral rat LD_{50} 1230-3010 mg/kg bw (cited in Scognamiglio *et al.*, 2012).
Oral mouse LD_{50} 1580 mg/kg bw (Jenner *et al.*, 1964).
Dermal rabbit LD_{50} 2000 mg/kg bw (NPIRI, 1974).

Benzyl alcohol (270 mg/kg bw) exerted a hepatotprotective effect in mice treated with 400 mg/kg bw acetaminophen (Du *et al.*, 2015).

Repeated dose toxicity

Expert-group opinion

Benzyl alcohol exhibits low repeated dose toxicity (OECD, 2002).

Human

Several reports have linked intravenous/intravascular administration of solutions containing benzyl alcohol as a preservative to "gasping syndrome" (involving seizures, unresponsiveness, signs of metabolic acidosis, and death) in low birth weight infants exposed for at least 2 days. Exposures generally were in excess of about 100 mg/kg bw/day (US EPA, 2009). [See also Cardiopulmonary effects section.]

Non-human

In reliable 13-week oral studies performed under the auspices of the US National Toxicology Program, benzyl alcohol (in corn oil) was administered to rats and mice (10/sex/species/dose) at 0, 50, 100, 200, 400 or 800 mg/kg bw/day, by gavage, on 5 days/week. High mortality was observed in top dose male rats, and all treated mice; many described as "gavage related". NTP experts noted that some of the deaths "may have been caused by a combination of the gavage procedure and chemical toxicity" since there was evidence of neurotoxicity at the top dose. Histopathological lesions in the brain, thymus, skeletal muscle and kidney were seen in top dose rats. Reduced growth was seen in female rats and mice from 200 mg/kg bw/day (NTP, 1989). In a subsequent review, Scognamiglio *et al.* (2012) considered the no-observed-adverse-effect level (NOAEL) for both rats and mice to be 100 mg/kg bw/day, with the critical effect being reduced growth in females. In the US EPA's evaluation of this study, the NOAEL was considered to be 400 mg/kg bw/day, based on mortality in rats and signs of neurotoxicity in both species at the top dose (US EPA, 2009). [See also Other toxicity considerations section.]

As part of the same series of investigations, rodents (50/sex/species/dose) were treated for 2 years (on 5 days/week) via oral gavage with benzyl alcohol at 0, 200 or 400 mg/kg bw/day (rats) or 0, 100 or 200 mg/kg bw/day (mice)[11]. No clear treatment-related effects were observed on growth or histopathology. In both dose groups, a statistically significant reduction in female rat survival was observed, but many of the early deaths were again considered related to the gavage procedure [i.e. presumably gavage errors] (NTP, 1989). [See also Carcinogenicity, Reproductive and developmental toxicity, Respiratory tract irritation and Cardiopulmonary effects sections.]

[11] Mice were unintentionally given α-methylbenzyl alcohol for 4 days during week 80 with no observed toxicity.

(b) (4)

"Gasping syndrome", ranging from audible/loud breathing, to blue skin and increased abdominal breathing, was seen within 3 weeks of the start of treatment in juvenile rats (10/sex/dose) given benzyl alcohol at 300 or 600 mg/kg bw/day by gavage from PND[12] 22. Rats were treated for 6 weeks. Other effects included reduced growth and excess salivation. No adverse effects were observed on haematology, blood chemistry, or histopathology. The study NOAEL was 100 mg/kg bw/day (Foulon *et al.*, 2005).

GENOTOXICITY

Expert-group opinion

"Benzyl alcohol has produced mixed results in genotoxicity assays; however, the data suggest that [it] is not likely [to be] a potent genotoxic agent" (US EPA, 2009).

Mammals (*in vivo*)

Benzyl alcohol failed to induce chromosome damage (micronucleus formation) in the bone marrow of male mice treated with a single intraperitoneal injection of up to 200 mg/kg bw, or four daily injections of 100 mg/kg bw/day (Hayashi *et al.*, 1988).

Evidence of DNA damage was seen in the stomach, colon and bladder cells of mice administered 400 mg/kg bw via gavage (Sasaki *et al.*, 2000).

Mammalian cells (*in vitro*)

In reliable studies on Chinese hamster ovary cells, benzyl alcohol induced chromosome aberrations in the presence (but not absence) of S9[13], and produced an 'equivocal' increase (with and without S9) in the incidence of cells with sister chromatid exchanges. It also induced mutations in mouse lymphoma cells, but only at cytotoxic concentrations and in the absence of S9 (NTP, 1989).

Evidence of DNA damage was seen in Comet assays using human lymphocyte cultures (Demir *et al.*, 2010).

Micro-organisms

Benzyl alcohol was not mutagenic in bacterial reverse mutation (Ames) assays (in the presence and absence of S9), including in a good-quality NTP study (NTP, 1989).

CARCINOGENICITY

Human

No substance-specific data were identified.

Non-human

No evidence of carcinogenic potential was observed in good quality studies in rodents (50/sex/species/dose level) administered benzyl alcohol (5 days/week) via gavage for 2 yr. Mice were treated with up to 200 mg/kg bw/day, while rats received up to 400 mg/kg bw/day (NTP, 1989). According to the US EPA, there is "inadequate information to assess

[12] Postnatal day.

[13] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.

(b) (4)

carcinogenic potential" based on the available data, as significant systemic toxicity was not seen at the highest tested dose levels, and a high incidence of deaths occurred in female rats (considered unrelated to benzyl alcohol) (US EPA, 2009). [See also Toxicity studies – other exposure routes – systemic effects, Reproductive and developmental toxicity, Respiratory tract irritation and Cardiopulmonary effects sections.]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Expert-group opinion

Benzyl alcohol is "non-reprotoxic" (OECD, 2002).

Human

No substance-specific data were identified.

Non-human

Studies focussed on the fertility effects of benzyl alcohol were not identified. However, no adverse effects on the reproductive organs were reported in repeated dose (up to lifetime) oral studies (NTP, 1989). [See also Toxicity studies – other exposure routes – systemic effects, Carcinogenicity, Respiratory tract irritation and Cardiopulmonary effects sections.]

Developmental toxicity was not seen in the absence of maternal toxicity in screening assays on mice treated via gavage with 0 or 750 mg/kg bw/day on GD[14] 6-13 (Hardin *et al.*, 1987; Hazelden, 1983), or administered 0 or 550 mg/kg bw/day on GD 6-15 (York *et al.*, 1986). The US EPA notes that these data "are not adequate to fully evaluate the ability of benzyl alcohol to induce developmental toxicity because the presence of visceral or skeletal malformations are not systematically evaluated in any of the studies" (US EPA, 2009).

Sexual maturation was not adversely affected in juvenile rats (10/sex/dose) given benzyl alcohol by gavage from PND 22 for 6 weeks at up to 600 mg/kg bw/day (Foulon *et al.*, 2005).

LOCAL TOLERANCE

Respiratory tract irritation

Expert-group opinion

An EFSA FEEDAP Panel considered it prudent to treat all compounds under assessment [including benzyl alcohol] as irritants to the respiratory tract and harmful if swallowed (EFSA, 2012).

In a 4-week study, nose-only exposure of rats to aerosolised benzyl alcohol (for 6 hours/day, 5 days/week) at up to 1072 mg/m^3 was "well tolerated". No adverse macroscopic or microscopic findings (which presumably included detailed evaluation of the tissues of the respiratory tract) and no organ weight changes (presumably including the lung) were reported (RIFM, 2009). [See also Inhalation toxicity studies – systemic effects and Cardiopulmonary effects sections.]

[14] Gestation day.

(b) (4)

In a 5-day study, rats (5/sex/group) were exposed to benzyl alcohol (6 hours/day) at up to 2200 mg/m³. "Necropsy revealed no morphological signs of toxicity in the lungs of any animals". Increased relative lung weights in both sexes in the top-dose group were considered likely secondary to decreased body weight (RIFM, 2001). [See also Inhalation toxicity studies – systemic effects and Cardiopulmonary effects sections.]

During the 2-year gavage study in rats, a dose-related increase in pulmonary tract inflammation (including haemorrhage and edema as well as foreign material deposition in the respiratory tract and lung (males only)) was apparent. The investigators noted that this could have been the result of gavage "accidents" with direct deposition of material within the lung or due to the anaesthetic properties of the compound (NTP, 1989). [See also Toxicity studies – other exposure routes – systemic effects, Carcinogenicity, Reproductive and developmental toxicity and Cardiopulmonary effects sections.]

Skin irritation

Expert-group opinion

Benzyl alcohol is slightly irritating to the skin (OECD, 2002).

Human

A number of human skin irritation studies are available. For example, in the 3-week induction phase of a human repeated insult patch test (HRIPT), benzyl alcohol[15] was applied on alternate weekdays to the skin of a total of 420 subjects for 24 hours (covered contact) at concentrations of 3, 5, 7.5, 15 or 20%. Treatment produced irritant reactions in 0/107 individuals at 3%, 2/101 at 5%, 3/110[16] at 7.5%, 3/46 at 15% and 5/56 at 20% (RIFM, 2002; RIFM, 2003; RIFM, 2004a; RIFM, 2004b; RIFM, 2005a). Further studies are described in Scognamiglio *et al.* (2012), and these show a similar concentration-related pattern of irritation.

Non-human

Benzyl alcohol [presumably undiluted] was not irritating to the skin of rabbits in a guideline study (Bayer AG, 1990). It was slightly irritating in a non-guideline rabbit study (Smyth *et al.*, 1951).

Eye irritation

Expert-group opinion

Benzyl alcohol is irritating to the eyes (OECD, 2002).

Human

No substance-specific data were identified.

Non-human

Benzyl alcohol [presumably undiluted] was moderately irritating to the eyes of rabbits in a guideline study (Bayer AG, 1990). It was highly irritating to rabbit eyes in another study with "limited data" (Smyth *et al.*, 1951).

[15] In diethyl phthalate:ethanol (3:1).

[16] With another 25 of the 110 showing "slight to mild irritation".

(b) (4)

Other local effects

The odour threshold for benzyl alcohol has been reported to be 25 mg/m³ [no further study details are given] (Jensen *et al.*, 2001).

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No substance-specific data were identified.

Skin sensitisation

Expert-group opinion

Sensitisation is considered the critical effect of benzyl alcohol by the International Fragrance Association (IFRA, 2009). Benzyl alcohol is also an "established contact [allergen] in humans" according to SCCS (2012). Benzyl alcohol is on the list of fragrance allergens designated by the EU (EMA, 2016).

Human

IFRA lists the no-expected-sensitisation-induction level (NESIL) as 5900 µg/cm². For induction in humans, IFRA provides a general lowest-observed-effect level (LOEL) of 8858 µg/cm², and no-observed-effect levels (NOELs) in the human repeated insult patch test (HRIPT) and human maximisation test (HMT) of 5906 and 6897 µg/cm², respectively [no further study details are provided] (IFRA, 2009).

Various human skin sensitisation studies have been conducted with benzyl alcohol. The following summary table of the results of some of these unpublished reports is taken from a review (Scognamiglio *et al.*, 2012):

Method	Concentration	Results		Reference
		Reactions	Incidence (%)	
HRIPT[17]	20%	5/56	8.9	RIFM, 2002
HRIPT	15%	5/46	10.9	RIFM, 2003
HRIPT	7.5%	3/110	2.7	RIFM, 2004a
HRIPT	5%	2/101	1.9	RIFM, 2005a
HRIPT	3%	0/107	0	RIFM, 2004b
HMT[18]	10%	0/25	0	RIFM, 1970
HMT	10%	0/24	0	RIFM, 1979

[17] Benzyl alcohol was applied (via occlusive patch) to the upper arms/backs of volunteers for 24 hours. The same sites were treated each Monday, Wednesday and Friday for a total of nine applications. 10-14 days later, a 24-hour challenge patch was applied to a fresh site. Reactions were scored 24, 48, 72 and/or 96 hour after challenge application.

[18] Benzyl alcohol was applied to the same site on the forearms or backs of subjects for five alternate-day 48-hour periods. Patch sites were pre-treated with sodium lauryl sulphate (SLS). 10-14 days later, 48-hour occlusive challenge patches were applied to fresh sites (also pre-treated with SLS). Reactions were scored at patch removal and at 48 and 72 hours.

(b) (4)

In 38 reports on diagnostic patch testing in dermatitis patients using various concentrations of benzyl alcohol (in most cases 5%, usually in petrolatum), sensitisation frequency was usually about 0-3%, although incidences of 7.8% and 20% were reported in two studies (Scognamiglio *et al.*, 2012).

Non-human

Based on laboratory animal data, IFRA considers the sensitising potential of benzyl alcohol to be "weak" (IFRA, 2009).

Mixed results have been seen for benzyl alcohol in laboratory tests (e.g. on guinea pigs) (OECD, 2002; Scognamiglio *et al.*, 2012). In a mouse local lymph node assay, benzyl alcohol[19] was not sensitising at up to 50%, the highest tested concentration. The EC3 value[20] was more than 50% (also given as 12,500 µg/cm^2) (RIFM, 2005b).

OTHER TOXICITY CONSIDERATIONS

Some evidence of neurotoxicity has been seen in humans and laboratory animals exposed to benzyl alcohol. Sedative effects were seen in mice exposed to an unspecified concentration acutely via inhalation (Buchbauer *et al.*, 1993), although such effects were not noted in repeated dose studies on rats at up to 2200 mg/m^3 (RIFM, 2001, 2009). A "high vapor concentration" of a mixture of benzyl alcohol, benzene and ester solvents was linked to effects in workers including headaches and dizziness (Treon and Stasik, 1983). In 13-week gavage studies, evidence of neurotoxicity (including staggering, respiratory difficulty and lethargy) was seen in rats and mice administered 800 mg/kg bw/day on 5 days/week; such signs were absent at 400 mg/kg bw/day in this subchronic study and also in 2-yr gavage studies (NTP, 1989).

A REACH dossier is available on benzyl alcohol (Chemical Inspection & Regulation Service Limited *et al.*, 2017)[21].

CARDIOPULMONARY EFFECTS[22]

Nebulisers of bacteriostatic saline containing benzyl alcohol as a preservative can cause bronchitis in healthy adults (SCENIHR, 2016).

"Gasping syndrome" (involving slow heartbeat and gasping) has been associated with intravenous/intravascular administration of solutions containing benzyl alcohol as a

[19] In ethanol:diethyl phthalate (1:3).
[20] OECD test guideline 429 defines the stimulation index (SI) as the ratio of lymphocyte proliferation in a treated group to that in the vehicle control group. An SI of ≥3 is considered positive and the estimated concentration three (EC3) is the estimated concentration of a test substance needed to produce an SI of 3.
[21] From the disclaimer on the ECHA website: "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 REACH. ECHA cannot guarantee the correctness of the information in the databases and the REACH Regulation does not permit it to make modifications to the data provided by registrants. Use the information with care. Reproduction or further distribution of the information may be subject to copyright laws and might require the permission of the owner of that information."
[22] Potential effects on the heart, blood vessels and/or respiratory tract.

(b) (4)

preservative in low birth weight infants exposed for at least 2 days. Exposures generally were in excess of about 100 mg/kg bw/day (US EPA, 2009). "Gasping syndrome" was also reported in young rats treated orally with at least 300 mg/kg bw/day for 3-6 weeks, but not at 100 mg/kg bw/day (Foulon *et al.*, 2005). [See also Toxicity studies – other exposure routes – systemic effects section.]

There were no treatment-related gross or microscopic lesions detected in the heart or lungs of rats exposed to benzyl alcohol (at up to 1072 mg/m³) in a 4-week inhalation study. There were no effects on the weights of these organs (RIFM, 2009 cited in Chemical Inspection & Regulation Service Limited *et al.*, 2017). [See also Inhalation toxicity studies – systemic effects and Respiratory tract irritation sections.]

However, heart and lung weights were reduced and "haemopoiesis" [presumably reduced] at 2200 mg/m³ (the highest tested concentration) in a 5-day study in rats; these are likely secondary to decreased body weight (RIFM, 2001). [See also Inhalation toxicity studies – systemic effects and Respiratory tract irritation sections.]

No treatment-related histopathologic effects were apparent in the heart and lungs of mice or rats gavaged with benzyl alcohol at up to respective doses of 200 and 400 mg/kg bw/day for 2 years (NTP, 1989). [See also Toxicity studies – other exposure routes – systemic effects, Carcinogenicity, Reproductive and developmental toxicity and Respiratory tract irritation sections.]

Slight transient bradypnoea was apparent in rats following single exposure to benzyl alcohol at 4178 mg/m3 (Anon., 1990).

Benzyl alcohol had no effect on cardiorespiratory function in healthy cats (8/group), when administered as part of an anaesthetic procedure (2% in an 8 mg/kg bw preparation) on up to six occasions with 48-hour intervals (Taylor *et al.*, 2012).

Benzyl alcohol (0.5%) was used as part of a vehicle control in an investigation of the cardiopulmonary effects of intramuscular injection with MMB4 DMS[23] in dogs (Roche *et al.*, 2013).

The antiarrhythmic dose [presumably intravenous administration to dogs and rats] for benzyl alcohol equates to 0.2-0.4 ml/kg of a 4% solution in physiologic saline (Eichbaum and Yasaka, 1976).

[23] 1,1'-methylenebis[4-[(hydroxyimino)methyl]-pyridinium] dimethanesulfonate.

(b) (4)

EXISTING HEALTH CRITERIA VALUES (HCVs)

Inhalation HCVs	Value	Critical effect(s) and effect level (e.g. NOAEC)	Reference
Health precaution guide value (RW I)	0.4 mg/m³	LOAEL of 800 mg/kg bw/day for neurotoxicity in rats following subchronic oral exposure [presumably the NTP (1989) gavage studies].	Anon., 2010[24]
Health hazard guide value (RW II)	4 mg/m³		
Lowest concentration of interest (LCI)[25]	0.1 mg/m³	The critical effects were apparently "irritation" and neurotoxicity [no further details are provided]	Jensen *et al.*, 2001
Workplace environmental exposure limit (WEEL)[26]	10 ppm [44 mg/m³]	[Not specified]	AIHA, 2013
Long-term systemic derived no-effect level (DNEL) (worker)	22 mg/m³	Dose descriptor starting point (after route-to-route extrapolation): NOAEC[27]	Chemical Inspection & Regulation Service Limited *et al.*, 2017
Acute systemic DNEL (worker)	110 mg/m³	"Acute toxicity"; extrapolated from long-term DNEL	
Long-term systemic DNEL (general population)	5.4 mg/m³	Dose descriptor starting point (after route-to-route extrapolation): NOAEC[28]	
Acute systemic DNEL (general population)	27 mg/m³	"Acute toxicity"; extrapolated from long-term DNEL	

[24] From the German Working Group on Indoor Air Guidelines.
[25] LCI defined as the concentration of a particular volatile substance present in indoor air, which, according to the authors' knowledge at the time of drafting, at continued exposure has no consequences on human health and/or comfort. The LCI value was apparently obtained by dividing the NOAEL (or LOAEL) for the effects found at the lowest concentrations by certain safety factors, and corrected for continuous (24 hours/day) lifetime exposure and including consideration of sensitive groups (e.g. children and asthmatics).
[26] As an 8-hour time-weighted average.
[27] Derived from a repeated dose inhalation toxicity study. An overall AF of 25 was applied to the corrected NOAEC for workers (539 mg/m³); study NOAEC 1072 mg/m³.
[28] Derived from a repeated dose inhalation toxicity study. An overall AF of 50 was applied to the corrected NOAEC for the general population (268 mg/m³); study NOAEC 1072 mg/m³.

(b) (4)

HCVs (other exposure routes[29])	Value	Critical effect(s) and effect level (e.g. NOAEC)	Reference
Oral acceptable daily intake (ADI)[30]	5 mg/kg bw (as benzoic acid equivalents[31] [4.4 mg/kg bw as benzyl alcohol])	NOAEL of 500 mg benzoic acid/kg bw/day in rats treated over a lifetime in the diet (the highest tested dose)	JECFA, 1962, 2002
Oral chronic provisional reference dose (p-RfD)	0.1 mg/kg bw/day	NOAEL of 200 mg/kg bw/day in a good quality chronic oral study in mice (the highest tested dose, adjusted to 143 mg/kg bw/day for continuous exposure)	US EPA, 2009

JECFA and, more recently, the European Food Safety Authority (EFSA), have concluded that benzyl alcohol 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 13 or 37 mg/person/day in the EU and US, respectively (EFSA, 2009). In the earlier JECFA assessment, estimated intakes were 16 or 17 mg/person/day in the EU and US, respectively (JECFA, 2002).

REFERENCES

AIHA (2013). American Industrial Hygiene Association. Guide to occupational exposure values. 2013 ERPG/WEEL Handbook. http://www.aiha.org/get-involved/AIHAGuidelineFoundation/WEELs/Documents/2011WEELValues.pdf

Anon. (1990). Study report [cited in Chemical Inspection & Regulation Service Limited *et al.*, 2017].

Anon. (2010). [Indoor air guide values for benzyl alcohol.] Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 53, 984-7 [from abstract only; article in German].

Api AM, Belsito D, Bhatia S, Bruze M, Calow P, Dagli ML, Dekant W, Fryer AD, Kromidas L, La Cava S, Lalko JF, Lapczynski A, Liebler DC, Politano VT, Ritacco G, Salvito D, Schultz TW, Shen J, Sipes IG, Wall B and Wilcox DK (2015). RIFM fragrance ingredient safety assessment, Benzyl alcohol, CAS Registry Number 100-51-6. Food and Chemical Toxicology 84 (Suppl.), S1-S14.

Bayer AG (1990). Report No. 19232, 6. 7. 1990 [cited in OECD, 2002].

Buchbauer G, Jirovetz L, Jäger W, Plank C and Dietrich H (1993). Fragrance compounds and essential oils with sedative effects upon inhalation. Journal of Pharmaceutical Sciences 82, 660-664.

[29] Oral and dermal DNELs are available in Chemical Inspection & Regulation Service Limited *et al.* (2017).
[30] This ADI is also supported by the EC Scientific Committee on Food (SCF, 2002).
[31] For benzoic acid, benzoate salts (calcium, potassium, and sodium), benzaldehyde, benzyl acetate, benzyl alcohol, and benzyl benzoate.

(b) (4)

Carpenter CP, Smyth Jr HF and Pozzani UC (1949). The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. The Journal of Industrial Hygiene and Toxicolology 31, 343–346 [cited in Scognamiglio *et al.*, 2012].

Chemical Inspection & Regulation Service Limited *et al.* (2017). European Chemicals Agency. REACH dossier on benzyl alcohol. First published 03-Mar-2011, last modified 03-Jun-2017. https://echa.europa.eu/registration-dossier/-/registered-dossier/14748

ChemSpider. Royal Society of Chemistry chemical structure database. Accessed 6 June 2017. http://www.chemspider.com/

Demir E, Kocaoğlu S and Kaya B (2010). Assessment of genotoxic effects of benzyl derivatives by the comet assay. Food and Chemical Toxicology 48, 1239-1242.

Du K, McGill MR, Xie Y and Jaeschke H (2015). Benzyl alcohol protects against acetaminophen hepatotoxicity by inhibiting cytochrome P450 enzymes but causes mitochondrial dysfunction and cell death at higher doses. Food and Chemical Toxicology 86, 253-261 [abstract only].

EFSA (2009). European Food Safety Authority. Scientific opinion of the panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Flavouring Group Evaluation 54, Revision 1 (FGE.54Rev1): Consideration of benzyl derivatives evaluated by JECFA (57th meeting) structurally related to benzyl alcohols, benzaldehydes, a related acetal, benzoic acids and related esters evaluated by EFSA in FGE.20Rev1 (2009). EFSA Journal, 1025, 1-73. http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/abstract

EFSA (2012). European Food Safety Authority. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). Scientific opinion on the safety and efficacy of benzyl alcohols, aldehydes, acids, esters and acetals (chemical group 23) when used as flavourings for all animal species. EFSA Journal 10(7), 2785. http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2785/epdf

Eichbaum FW and Yasaka WJ (1976). Antiarrhythmic effect of solvents: propylene glycol, benzyl alcohol. Basic Research in Cardiology 71, 355-370 [abstract only].

EMA (2016). European Medicines Agency. Information in the package leaflet for fragrances containing allergens in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) Draft. 28 April 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500206000.pdf

EPISuite. US Environmental Protection Agency's (EPA), Estimation Programs Interface Suite (EPISuite™). Accessed 6 June 2017. The database is available to download at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm [cited in ChemSpider].

Foulon O, Mungapen L, Gaoua W and Forster R (2005). Benzyl alcohol: safety assessment in juvenile rats. Toxicologist 84, 55 [Meeting abstract].

Hardin BD, Schuler RL, Burg JR, Booth GM, Hazelden KP, MacKenzie KM, Piccirillo VJ and Smith KN (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratogenesis, Carcinogenesis and Mutagenesis 7, 29-48 [cited in US EPA, 2009].

(b) (4)

Hayashi M, Kishi M, Sofuni T and Ishidate M Jr (1988). Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food and Chemical Toxicology 26, 487-500.

Hazelden KP (1983). Screening of priority chemicals for potential reproductive hazard. NIOSH, Public Health Service, US Department of Health, Education, and Welfare [cited in US EPA, 2009].

IFRA (2009). International Fragrance Association. IFRA Standard on benzyl alcohol. 14 October 2009. http://www.ifraorg.org/en-us/standards-library/snew#.U19w3PldWn-

JECFA (1962). Evaluation of the toxicity of a number of antimicrobials and antioxidants. Sixth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 228. World Health Organization, Geneva. http://whqlibdoc.who.int/trs/WHO_TRS_228.pdf

JECFA (2002). Safety evaluation of certain food additives and contaminants. Benzyl derivatives. Prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 48. World Health Organization, Geneva. http://www.inchem.org/documents/jecfa/jecmono/v48je14.htm

Jenner PM, Hagan EC, Taylor JM, Cook EL and Fitzhugh OG (1964). Food flavorings and compounds of related structure I. Acute oral toxicity. Food and Cosmetics Toxicology 2, 327-343 [cited in Scognamiglio *et al.*, 2012].

Jensen LK, Larsen A, Mølhave L, Hansen MK and Knudsen B (2001). Health evaluation of volatile organic compound (VOC) emissions from wood and wood-based materials. Archives of Environmental Health 56, 419-432.

NICNAS (2015). Australian National Industrial Chemicals Notification and Assessment Scheme. Inventory Multi-tiered Assessment and Prioritisation (IMAP). Human Health Tier II Assessment for Benzenemethanol. https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1784

NPIRI (1974). Raw Mater. Data Handbook Vol. 1, 6 [cited in OECD, 2002].

NTP (1989). National Toxicology Program. Toxicology and carcinogenesis studies of benzyl alcohol (CAS No. 100-51-6) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 343. NTP Technical Report Series No. 343. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr343.pdf

OECD (2002). Organisation for Economic Co-operation and Development. SIDS Initial Assessment Report for 13th SIAM (Bern, 7th - 9th November 2001). Benzoates: benzoic acid, sodium benzoate, potassium benzoate, benzyl alcohol. http://webnet.oecd.org/Hpv/UI/handler.axd?id=fab24d3a-687d-4e90-9447-48a3217b3e71

RIFM (1970). Research Institute for Fragrance Materials. The contact sensitizing potential of fragrance materials in humans. RIFM report No. 1760, 7 October [cited in Scognamiglio *et al.*, 2012].

RIFM (1979). Research Institute for Fragrance Materials. Report on human maximization studies. RIFM report No. 1697, 25 May [cited in Scognamiglio *et al.*, 2012].

(b) (4)

RIFM (2001). Research Institute for Fragrance Materials. Benzyl alcohol: a 5 day inhalation toxicity study in the rat. Unpublished report from A Dotti *et al.*, 23 April. RIFM report No. 54635 [cited in Scognamiglio *et al.*, 2012].

RIFM (2002). Research Institute for Fragrance Materials. Repeated insult patch test (RIPT) with benzyl alcohol. RIFM report No. 44247, 3 March [cited in Scognamiglio *et al.*, 2012].

RIFM (2003). Research Institute for Fragrance Materials. Repeated insult patch test (RIPT) with benzyl alcohol. RIFM report No. 44246, 3 November [cited in Scognamiglio *et al.*, 2012].

RIFM (2004a). Research Institute for Fragrance Materials. Repeated insult patch test with benzyl alcohol (modified Draize procedure). RIFM report No. 45131, 30 April [cited in Scognamiglio *et al.*, 2012].

RIFM (2004b). Research Institute for Fragrance Materials. Repeated insult patch test with benzyl alcohol. RIFM report No. 47046, 7 July [cited in Scognamiglio *et al.*, 2012].

RIFM (2005a). Research Institute for Fragrance Materials. Repeated insult patch test with benzyl alcohol. RIFM report No. 47873, 16 March [cited in Scognamiglio *et al.*, 2012].

RIFM (2005b). Research Institute for Fragrance Materials. Benzyl alcohol diluted with vehicle 1:3 ETOH:DEP: Local Lymph Node Assay. RIFM report No. 47376, January 20 [cited in Scognamiglio *et al.*, 2012].

RIFM (2009). Research Institute for Fragrance Materials. A 4-week inhalation toxicity study of aerosolized benzyl alcohol and benzoic acid in Sprague-Dawley rats. RIFM report No. 58285. 8 February [cited in Scognamiglio *et al.*, 2012 and Chemical Inspection & Regulation Service Limited *et al.*, 2017].

Roche BM, Vinci TM, Hawk MA, Hassler CR, Pressburger DT, Osheroff MR, Ritchie GD, Burback BL (2013). MMB4 DMS: cardiovascular and pulmonary effects on dogs and neurobehavioral effects on rats. International Journal of Toxicology 32(4 Suppl), 49S-58S [abstract only].

Sasaki YF, Sekihashi K, Izumiyama F, Nishidate E, Saga A, Ishida K and Tsuda S (2000). The Comet assay with multiple mouse organs: comparison of Comet assay results and carcinogenicity with 208 chemicals selected from the IARC Monographs and US NTP Carcinogenicity Database. CRC Critical Reviews in Toxicology 30, 629-799.

SCCS (2012). European Commission. Scientific Committee on Consumer Safety. Opinion on fragrance allergens in cosmetic products. Opinion adopted by the SCCS at its 15th plenary meeting of 26-27 June 2012. SCCS/1459/11. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf

SCENIHR (2016). Scientific Committee on Emerging and Newly Identified Health Risks. Final opinion on additives used in tobacco products (opinion 1). Tobacco Additives I. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_051.pdf

SCF (2002). European Commission. Scientific Committee on Food. Opinion of the Scientific Committee on Food on benzyl alcohol (expressed on 24 September 2002). SCF/CS/ADD/FLAV/78. Final, 17 Sept 2002. http://ec.europa.eu/food/fs/sc/scf/out138_en.pdf

(b) (4)

Scognamiglio J, Jones L, Vitale D, Letizia CS and Api AM (2012). Fragrance material review on benzyl alcohol. Food and Chemical Toxicology 50 (Suppl 2), S140-S160.

Smyth HF, Carpenter CP and Weil CS (1951). Range-finding toxicity data: List IV. Archives of Industrial Hygiene and Occupational Medicine 4, 119-122.

Taylor PM, Chengelis CP, Miller WR, Parker GA, Gleason TR and Cozzi E (2012). Evaluation of propofol containing 2% benzyl alcohol preservative in cats. Journal of Feline Medicine and Surgery 14, 516-526 [abstract only].

Treon JF and Stasik MJ (1983). Alcohols. In: Encyclopedia of occupational health and safety. Third revised ed., L. Parmeggiani, Ed. U.S. EPA, Washington, DC. 1, 109–112 [cited in US EPA, 2009].

US EPA (2009). US Environmental Protection Agency. Provisional peer-reviewed toxicity values for benzyl alcohol (CASRN 100-51-6). Final, 30 September 2009. http://hhpprtv.ornl.gov/issue_papers/Benzylalcohol.pdf

York RG, Bamwell P and Bailes W (1986). Screening of priority chemicals for reproductive hazards. Unpublished report (ETOX-85-1 002) [cited in US EPA, 2009].

(b) (4)

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