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Opinion

of the Scientific Committee on Food

on Benzyl alcohol

(expressed on 24 September 2002)

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: G-1 01/242
Telephone: direct line (+32-2) 29 84698, switchboard 299.11.11. Fax: (+32-2) 299.4891
Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels
http://europa.eu.int/comm/food/fs/sc/scf/index_en.html

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Terms of reference

The Committee is asked to evaluate the safety in use of benzyl alcohol as a carrier solvent for flavouring substances.

Background

Previous evaluations

Benzyl alcohol has been evaluated by the Scientific Committee for Food in 1981 (SCF, 1981). The Committee agreed on the following evaluation: *"The metabolism by man is well established. Although no specific toxicological studies are available it is acceptable to include benzyl alcohol in the group ADI of 5 mg/kg bw established for benzoic acid (representing total benzoates) by JECFA (1973). The Committee considers the use of this extraction solvent acceptable."*

The SCF classified benzyl alcohol for use in the field of food contact materials in list 1 (substances for which an ADI has been established) (SCF, 1986).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated benzyl compounds like benzyl alcohol, benzylacetate, benzaldehyde, and benzoic acid at several meetings, starting with benzoic acid at its sixth meeting (JECFA, 1962). An ADI for benzoic acid, estimated on the basis of the no-effect level in the rat, was established at 0-5 mg/kg bw.

JECFA evaluated benzyl alcohol and benzyl benzoate for use as carrier solvents at the 23rd meeting in 1979 (JECFA, 1980). It established a group ADI of 0-5 mg/kg bw for the benzyl/benzoic moiety. At its 41st meeting, JECFA recommended that a full review of these substances be conducted in order to determine whether additional studies would be required (JECFA,1993). In 1996, JECFA evaluated benzylacetate, benzyl alcohol, benzaldehyde, and benzoic acid and its salts. “The Committee was satisfied that the data reviewed on

compounds in this group are sufficient to demonstrate lack of carcinogenicity, developmental and reproductive potential. Consequently, it concluded that further studies were not required, and the group ADI of 0-5 mg/kg bw as benzoic acid equivalents was maintained" (JECFA, 1996).

JECFA evaluated benzyl alcohol and some other benzyl compounds at its 57th meeting in 2001 using the Procedure for the Safety Evaluation of Flavouring Agents. Based on current intakes as flavouring agents, JECFA concluded that there was "No safety concern". The existing specification of benzyl alcohol was revised (JECFA, 2002).

The Committee of Experts on Flavouring Substances of the Council of Europe classified benzyl alcohol in category A (flavouring substances which may be used in foodstuffs) based on an ADI of 0-5 mg/kg bw allocated by JECFA at its 23rd meeting in 1979 (CoE, 1992).

In the present evaluation, the SCF has been asked to evaluate a request from a petitioner (unpublished data, 2000 and 2002) for the use of benzyl alcohol as a carrier solvent for flavouring substances at levels up to 300 ppm in the final food as consumed. The description of the studies discussed below are drawn mainly from the JECFA monograph (JECFA, 1996).

Current regulations

Benzyl alcohol is included in the Community register of chemically defined flavouring substances laid down in Commission Decision 1999/217/EC (EC, 1999) and Commission Decision 2002/113/EC (EC, 2002).

Chemical characterisation

Name:	Benzyl alcohol
Synonyms:	Benzenemethanol, alpha-hydroxytoluene, phenol carbinol, phenyl carbinol, phenylmethanol, phenylmethyl alcohol
CAS No:	100-51-6
Other CAS No:	1336-27-2
	185532-71-2
FL No:	02.010

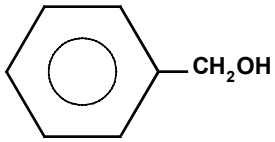
CoE No: 58

FEMA No: 2137

EINECS: 202-859-9

Molecular mass: 108.14

Structure:



Exposure

Food uses

Benzyl alcohol is a natural constituent of a number of plants. It occurs, for example, in some edible fruits (up to 5 mg/kg) and in green and black tea (1-30 and 1-15 mg/kg, respectively) (CoE, 1992). Benzyl alcohol is added as a flavouring substance to some foods and beverages at a level up to about 400 mg/kg (chewing gum 1254 mg/kg) (Fenaroli, 1994). The quantity which is requested to be used as a carrier solvent for flavouring substances to food and beverages is up to 300 mg/kg in the final food as consumed.

Non-Food uses

Benzyl alcohol is used as local anaesthetic, pharmaceutical aid, and in perfumery (MEDLINE, 2002). It is an indirect food additive for use as a component of resinous and polymeric coatings (HSDB, 2002). Benzyl alcohol is used in a wide variety of cosmetic formulations as a fragrance component, preservative, solvent, and viscosity-decreasing agent. In 1998, benzyl alcohol was reported by the US Food and Drug Administration to be used in 322 cosmetic formulations belonging to 43 cosmetic-product categories (CIR, 2001).

Hazard identification / characterisation

Absorption, distribution, metabolism and excretion

Benzyl alcohol and benzaldehyde were detected within 5 min in the plasma of CD-1 mice given single intraperitoneal doses of 700-1100 mg/kg bw benzyl alcohol in peanut oil. Prior administration of pyrazole, an inhibitor of alcohol dehydrogenase, resulted in increased plasma levels of benzyl alcohol (203 %), and prior administration of disulfiram, an inhibitor of aldehyde dehydrogenase, resulted in increased plasma levels of benzaldehyde (368 %) (McCloskey et al., 1986).

In humans and animals, benzyl alcohol is metabolised to benzoic acid, which after conjugation with glycine is excreted as hippuric acid in the urine. Formation of hippuric acid from benzoic acid is a saturable process in which the availability of glycine is the rate-limiting step. However, even with saturation of hippuric acid formation, clearance of compounds in the benzyl group is relatively rapid in most experimental species and in humans (JECFA, 1996).

In vitro studies on cellular and biochemical effects

Benzyl alcohol induced some cellular and biochemical effects as compiled by the Cosmetic Ingredient Review (CIR, 2001):

Benzyl alcohol is a membrane "fluidizer" that affects lipid bilayer structure (Ebihara et al., 1979). It has been demonstrated to act on membranes of erythrocytes (Burgen et al., 1970; Basse et al., 1992) and hepatocytes (Gordon et al., 1980).

Studies reported benzyl alcohol to increase activity of membrane-bound Ca^{2+}-dependent enzymes such as adenylate cyclase (Voorheis and Martin, 1982; Martin et al., 1985; Needham and Houslay, 1988) and thiol proteinase (Ahkong et al., 1980). Conversely, benzyl alcohol inhibited activities of various glycosyltransferases of the rat liver Golgi membrane (Mitranic et al., 1982). The activities of erythrocyte-bound *p*-nitrophenylphosphatase and acetylcholinesterase were increased at some concentrations of benzyl alcohol and inhibited by others (Tanaka, 1984). The effect on cell membranes was considered the mechanism by which benzyl alcohol inhibited lymphocyte-mediated cytolysis in vitro (Kemp and Berke, 1973).

Benzyl alcohol induced time-, dose-, and temperature-dependent hemolysis of erythrocytes in vitro. The critical hemolytic levels of benzyl alcohol to membranes were estimated to be about 500 nmoles/mg protein (about 54 microgram/mg protein) (Ohmiya and Nakai, 1978).

Acute toxicity

Acute toxicity in mice, rats and rabbits was moderate ranging from 1040 to 3200 mg/kg bw, when benzyl alcohol was given orally (Bayer AG, 1978; FEMA, 1984). In mice given benzyl alcohol intraperitoneally at doses of 500-1500 mg/kg bw, there was an initial acute phase with LD_{50} of 1000 mg/kg bw and a delayed lethal effect up to seven days after treatment with LD_{50} of 650 mg/kg bw (McCloskey et al., 1986). Single intravenous doses of 0.025-0.4 ml/kg bw resulted in clinical signs of tocixity at all doses except the lowest. Assessment of haemolytic and precipitation potential in blood samples from the mice indicated strong activity of benzyl alcohol at concentrations of 0.4-3.0 microl/ml (Montaguti et al., 1994).

Subacute / subchronic toxicity

Mice

Benzyl alcohol was administered in corn oil to groups of 5 male and 5 female B6C3F1 mice at doses of 0, 125, 250, 500, 1000, and 2000 mg/kg bw by gavage on five days a week for 12 doses over a 16-day period. All mice receiving 2000 mg/kg bw and one male and two females receiving 1000 mg/kg bw died before the end of the study. Clinical signs of toxicity occurred at the three highest doses. Mice at 1000 and 2000 mg/kg bw had blood in the urinary bladder at necropsy (NTP, 1989).

Benzyl alcohol was administered in corn oil to groups of 10 male and 10 female B6C3F1 mice at doses of 0, 50, 100, 200, 400, 800 mg/kg bw by gavage on five days a week for 13 weeks. Deaths were attributed by the study authors to the gavage procedure. The final mean body weight of males at 800 mg/kg bw was 5% lower than that of controls; the final mean body weight of female mice at this dose was 5% lower. Both male and female mice at the high dose showed staggering during the first and second weeks of the study. No treatment-related histopathological effects were observed (NTP, 1989).

Rats

Short-term intake of 2% benzyl alcohol in the drinking water resulted in an inhibition of hepatic alcohol dehydrogenase and mitochondrial aldehyde dehydrogenase isoenzyme activities in female rats. The effects were not noted in male rats (Messiha, 1991).

Compared to control rats, benzyl alcohol noncompetitively inhibited activity of hepatic alcohol dehydrogenase (L-ADH) of rats maintained for a short term on 5% ethanol (Messiha et al., 1992).

Benzyl alcohol was administered in corn oil to groups of 5 male and 5 female Fischer 344 rats at doses of 0, 125, 250, 500, 1000, and 2000 mg/kg bw by gavage on five days per week for 12 doses over a 16-day period. All rats receiving 2000 mg/kg bw and two males and three females receiving 1000 mg/kg bw died before the end of the study. The final body weights of males at 1000 mg/kg bw were 18% lower than those of controls, while the females at this dose had a body-weight decrement of < 5%. Lethargy was observed in rats at the two highest doses, which also had blood around the mouth and nose, subcutaneous haemorrhages, and blood in the urinary and gastrointestinal tracts (NTP, 1989).

When benzyl alcohol was administered in corn oil to groups of 10 male and 10 female Fischer 344 rats by gavage at doses of 0, 50, 100, 200, 400, 800 mg/kg bw on five days per week for 13 weeks, eight males and two females at 800 mg/kg bw, one female at 400 mg/kg bw, one male at 200 mg/kg bw and one female in the control group died after treatment. Four of the deaths in males and one in females at the high-dose group were attributed to gavage errors. At 800 mg/kg bw, signs of neurotoxicity were observed, and animals had blood around the mouth and nose. After 13 weeks, the body weights of males and females at the high dose were 7 and 5 % lower than those of the controls, and histopathological examination showed some treatment-related histopathological effects including necrosis of the dentate gyrus of the hippocampus, skeletal muscle necrosis, nephrosis of kidney, thymic congestion, haemorrhage, and athrophy (NTP, 1989).

Chronic toxicity / carcinogenicity

Benzyl alcohol was given to groups of 50 animals of each sex of B6C3F1 mice at a dose of 0, 100, or 200 mg/kg bw per day, and to Fischer 344/N rats at a dose of 0, 200, or 400 mg/kg bw per day in corn oil by gavage on five days a week for 103 weeks, respectively.

Dose-related negative trends were noted in the incidences of anterior pituitary gland neoplasms in female rats (control 29/50; low dose 17/47; high dose 9/49) and of Harderian gland adenomas in male mice (8/50; 3/50; 2/50). An increased incidence of hyperplasia of the forestomach epithelium was seen (not statistically significant) in male rats (0/48; 0/19, 4/50). An increased incidence of adenomas of the adrenal cortex noted in high-dose male mice (0/48; 0/44; 3/48) was within the historical range and not considered compound-related (NTP, 1989). According to the NTP investigators, there was no evidence of carcinogenic activity (NTP, 1989). However, reviewing the study, the EPA (1989) considered the increased incidence of adrenal cortex adenoma in high-dose male mice to be "equivocal evidence of carcinogenic activity rather than negative" (CIR, 2001).

The view of JECFA (1996) was that no adverse effects of benzyl alcohol were seen in rats and mice in the 2-year gavage studies performed by NTP.

Genotoxicity

Benzyl alcohol was reported to be negative in the Ames test with and without metabolic activation in several studies (Florin et al., 1980; Wiessler et al., 1983; Ishidate et al. 1984; Mortelmans et al., 1986; NTP, 1989; Zeiger, 1990). A positive result of a reverse mutation test in *B. subtilis* was reported by Yoo (1985).

Benzyl alcohol was found to be positive in mammalian cells in the mouse lymphoma thymidine kinase forward mutation assay without metabolic activation, whereas negative results were reported for tests with metabolic activation (S9) (McGregor et al., 1988; NTP, 1989). It induced chromosomal aberrations in CHO cells without S9, and was weakly positive in tests with S9 (NTP, 1989), while Anderson et al. (1990) observed positive results only with S9 at high concentrations. A negative result of a chromosomal aberration assay was reported by Ishidate et al. (1984). The induction of sister chromatid exchanges in CHO cells was found to be equivocal (NTP, 1989; Anderson et al., 1990). In an in vitro alkaline elution / rat hepatocyte assay, benzyl alcohol produced DNA double-strand breaks at cytotoxic concentrations (Storer et al., 1996).

In vivo, benzyl alcohol was reported to be negative in the micronucleus assay on mouse bone marrow cells (Hayashi et al., 1988), in an assay on replicative DNA synthesis in rats (Uno et al., 1994; Miyagawa et al., 1995), and in the sex-linked recessive lethal assay in Drosophila melanogaster (Foureman et al., 1994).

Developmental toxicity

In a study on mice, in which 50 female animals were given benzyl alcohol by gavage on days 6-15, the dose of 550 mg/kg bw (the predicted LD_{10}) had no significant effects on the development of CD-1 mice. The NOAEL was 550 mg/kg bw per day (York et al., 1986).

In a screening test on developmental toxicity looking at litter size, birth weight, and neonatal growth and survival as indices of potential developmental toxicity, benzyl alcohol was administered by gavage at a dose of 750 mg/kg bw per day to 50 mice on day 7-14 of gestation. Clinical signs of toxicity were reported in up to 20 mice during treatment. Nineteen animals of the treated group died, while none of controls died. Significant reductions in pup body weight and weight gain in conjunction with maternal toxicity were reported (US National Institute of Occupational Safety and Health, 1983; Hardin et al., 1987).

Human data

Some serious effects including central nervous system dysfunction, coma and death were observed in premature infants who had received benzyl alcohol in medications administered intravenously (Gershanik et al., 1982; Hiller et al., 1986; Benda et al., 1986; Jardine and Rogers, 1989). Death occurred at 6-46 days of age in infants who had received 99-234 mg/kg bw of benzyl alcohol, while a matched control group of infants who had received benzyl alcohol but did not develop the syndrome had received doses of 27-99 mg/kg bw (Gershanik et al., 1982).

Since the benzyl alcohol was administered acutely and intravenously in high doses, the effects observed in premature infants are considered irrelevant to the use of benzyl alcohol as a carrier solvent for flavouring substances at the intended use level.

Conclusions

The metabolism of benzyl alcohol to benzoic acid by man is well established. In special studies, biochemical effects have been investigated. The toxicity has been studied extensively, including acute, short-term and long-term toxicity, carcinogenicity, genotoxicity and developmental toxicity.

The Committee considers that the studies on carcinogenicity in rats and mice did not show compound-related adverse effects at dose levels up to 200 mg/kg bw in the mouse and up to 400 mg/kg in the rat, in both cases the highest dose levels tested. Data from sub-chronic studies on rats and/or mice show NOAELs of 400 mg/kg bw or more. Taking account the toxicity data and the fact that benzyl alcohol is metabolised via benzaldehyde to benzoic acid, the Committee confirms the inclusion of benzyl alcohol in the group ADI of 0-5 mg/kg bw for benzoic acid and benzoates, as agreed in the SCF opinion of 1981.

It should be noted that the total intake of benzyl alcohol and benzoic acid can result from different sources including the use of additives and flavourings as well as the natural occurrence in food. It is therefore possible that in some instances the intake of these substances may exceed the group ADI. Better data are required on use/residual levels following use of benzyl alcohol as carrier solvents in different food categories against the background of overall exposure in order to facilitate a more precise intake assessment.

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