The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BENZYL ALCOHOL

SUMMARY REPORT

1. Benzyl alcohol occurs naturally in a number of plants including raspberries and tea. It is an ingredient of several essential oils including clove, jasmin, hyacinth and ylang-ylang oils. In veterinary medicine it is widely used as an antimicrobial preservative and as a solubiliser. Benzyl alcohol is also used as an active ingredient in some teat dip and spray formulations where it is present at a concentration of approximately 4%, for the prevention of mastitis. Benzyl alcohol is an EU approved food additive where it is a component of synthetic flavourings. It is a constituent of some food packaging materials and is also used in cosmetics.

2. Benzyl alcohol is active against Gram positive bacteria and has some weak activity against gram negative bacteria, yeasts and moulds. Benzyl alcohol also has some mild local anaesthetic and anti-spasmodic properties. Slow intravenous injection of 1 ml/kg of 0.9% benzyl alcohol into dogs and monkeys did not affect blood pressure, heart rate, respiration, ECG traces, haematology or clinical chemistry values except for blood sugar changes in some dogs. The changes in blood sugar may have been due to other factors such as the fasting conditions.

3. In humans and animals, benzyl alcohol was readily absorbed from the gastro-intestinal tract. Percutaneous absorption was high following topical use. Rhesus monkeys absorbed 56-80% of a topical dose administered under occlusive conditions in 24 hours; absorption was less under unoccluded conditions due to evaporation. Benzyl alcohol rapidly disappeared from the injection site following intramuscular administration to rats; the disappearance half-life was estimated to be less than 10 minutes. Following oral administration to humans and animals, benzyl alcohol was rapidly metabolised to benzoic acid which was conjugated with glycine and excreted as hippuric acid in the urine. Subcutaneously injected benzyl alcohol was metabolised and excreted in the same way. Benzyl alcohol was an intermediate product in the metabolic pathway of benzyl acetate; the subsequent metabolism was identical to that of benzyl alcohol.

4. In premature human neonates, there was a greater accumulation of benzoic acid in the serum together with more unmetabolised benzyl alcohol and less hippuric acid in the urine, when compared with term neonates. This immaturity of the detoxification process was considered responsible for "gasping syndrome" in premature neonates (see paragraph 13).

5. Benzyl alcohol was of low acute toxicity in laboratory animals with acute oral LD_{50} values of 1040 mg/kg bw in the rabbit and 1230-3120 mg/kg bw in the rat. The acute intraperitoneal LD_{50} (4 hour observation) in both adult and neonatal CD-1 mice was 1000 mg/kg bw. The acute dermal LD_{50} was 2000 mg/kg bw in the rabbit. Benzyl alcohol was not irritating to rabbit skin in a 4-hour exposure experiment but was moderately irritating following 24 hours exposure. It was a moderate to severe eye irritant. In patch tests, it caused skin irritation in some human volunteers.

6. 16-day and 13-week repeat-dose studies were carried out in B6C3F1 mice and F344 rats by the US National Toxicology Program. Rats and mice given 800 mg/kg bw per day showed high mortality and clinical signs indicative of neurotoxicity. In rats, histopathological changes were observed at 800 mg/kg bw including necrosis of the dentate gyrus of the hippocampus, skeletal muscle necrosis, and kidney nephrosis. No pathological changes were seen in mice. Body weight gain was reduced in females (but not males) of both species given 200 mg/kg bw and above. There were no substance-related effects on rats or mice given 50 or 100 mg/kg bw per day for 13 weeks.

7. Oral administration of up to 550 mg/kg bw per day of benzyl alcohol to female CD-1 mice from days 6-15 of gestation had no effect on maternal bodyweight gain, gestation length, litter size, pup weight or post-natal survival. Higher dose levels caused maternal toxicity. In another study with the same strain of mouse, administration of 750 mg/kg bw per day to the dams caused one maternal death, reduced maternal bodyweight gain, reduced pup weight at birth and pup weight gain. There was no evidence of teratogenicity in either study.

8. Formulations containing benzyl alcohol were well tolerated in the target species. No signs of irritation were observed following application of a teat dip containing approximately 4% benzyl alcohol, to cow udders.

9. Benzyl alcohol was not mutagenic in several bacterial assays for gene mutation using *Salmonella typhimurium* and *Escherichia coli*. The results in rec. assays with *Bacillus subtilis* were equivocal with both positive and negative results reported by different authors using equivalent dose levels in different experiments. In a mouse lymphoma assay, negative results were obtained with metabolic activation but benzyl alcohol induced resistance to trifluorothymidine without metabolic activation at near lethal doses. *In vitro* cytogenetics assays gave conflicting results: with Chinese Hamster ovary (CHO) cells, positive results were obtained in the presence, but not the absence of metabolic activation and a negative result was obtained with Chinese Hamster lung fibroblasts. Weakly positive results were obtained in sister chromatid exchange assays with CHO cells. The positive results were observed only at high dose levels (≥4000 µg/ml benzyl alcohol) and were associated with toxicity.

10. Benzyl alcohol was not mutagenic in an *in vivo* micronucleus test in which mice were given up to 200 mg/kg bw by intraperitoneal injection.

11. Carcinogenicity studies were carried out in F344 rats and B6C3F1 mice as part of the US National Toxicology Program. The rats were given daily oral doses of 200 or 400 mg/kg bw per day in corn oil for 103 weeks. The mice were given doses of 100 or 200 mg/kg bw per day, also for 103 weeks. There was no evidence of carcinogenicity in either species.

12. The skin sensitising potential of benzyl alcohol was evaluated in the guinea pig. Positive results were obtained in the Open Epicutaneous Test and in an intradermal test with Freund's complete adjuvant, but not in the Maximization test. In humans, several cases of hypersensitivity reactions, especially to cosmetic products containing benzyl alcohol, have been reported.

13. Benzyl alcohol has been widely used in human medicine as an antimicrobial preservative and as a local anaesthetic and antipuritic. The "gasping syndrome" in premature human infants was attributed to the use of benzyl alcohol as a preservative in solutions which were previously used to flush umbilical catheters. The affected infants developed severe metabolic acidosis, gasping respiration, and blood abnormalities. Some infants had severe neurological deterioration and hepatic and renal failure resulting in death. Survivors had a significantly-increased incidence of cerebral palsy. It was estimated that the infants had received approximately 99 - 234 mg/kg bw per day of benzyl alcohol. The high concentrations of unmetabolised benzyl alcohol and relatively small amount of hippuric acid in the urine suggested that the immaturity of the metabolic detoxification process in premature neonates made them more sensitive to the toxic effects.

14. The WHO/FAO JECFA calculated an ADI of 0-5 mg/kg bw per day. This is a "group ADI" which covers benzoic acid, benzaldehyde, benzyl alcohol, benzyl acetate and benzoate salts. It was calculated from data relating to benzoic acid and was considered justified because of the "ample evidence for the *in vivo* oxidation of both benzyl alcohol and benzaldehyde to benzoic acid in man and rabbit." This ADI was adopted by the EU Scientific Committee for Food.

15. The theoretical maximum amount of benzyl alcohol to which consumers may be exposed was calculated for some formulations. The calculations took into account the maximum recommended dosage regimes and assumed immediate slaughter of the animal irrespective of whether withdrawal intervals had been set. The contribution of metabolism and excretion in the reduction of benzyl alcohol residues was not taken into account. The maximum calculated theoretical consumer intake from meat represents less than 10% of the above ADI. The rapid metabolism and excretion of benzyl alcohol ensures that consumer intake would be even lower providing an additional margin of safety.

16. When used as a teat dip, concentrations in the milk ranging from 7.6-120 µg/litre benzyl alcohol have been determined. When good husbandry practice was followed and the udder dry wiped before milking, mean residues in the milk were reported to be 21 µg/litre. Consumption of 1.5 litres of milk containing 120 µg benzyl alcohol would account for approximately 4% of the above ADI.

17. It is proposed to include Benzyl alcohol in Annex II of Council Regulation (EC) Nº 2377/90, for all food-producing species based on the following reasons:

    · the substance is a normal constituent of some plants such as tea and raspberries. It is an authorised EU food additive and is therefore a normal component of the diet of humans;

    · it is rapidly metabolised and excreted in most humans and animals.