



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HYDROXYBENZOIC ACID ESTERS AND THEIR SODIUM SALTS

SUMMARY REPORT

1. The p-hydroxybenzoic acid esters and salts include :

- butyl hydroxybenzoate
- sodium butyl and sodium benzyl hydroxybenzoate

These compounds are widely used in the pharmaceutical preparations and food industries as preservatives. The residues of these substances would not exceed 0.2 mg/kg bw, when the veterinary drugs are administered to the food producing animals.

2. The p-hydroxybenzoic acid and its esters possess antimicrobial properties which increase through the methyl to pentyl series. They are active against fungi, yeasts and Gram-positive bacteria but are less effective against Gram-negative bacteria. The effects of the esters being additive, mixtures of the esters are used to increase the quantity of bacteriostatic activity in solution.

3. The alkyl esters of p-hydroxybenzoic acid were readily absorbed following oral administration in dogs and rats.

These esters of hydroxybenzoic acid were rapidly metabolised by laboratory animals. After a single intravenous administration of 50 mg/kg bw methyl hydroxybenzoic acid to dogs, no ester form was measurable in plasma. In rat and dog, the major metabolites were the hydroxybenzoic acid and hydroxyhippuric acid, in both free and conjugated forms.

The hydroxybenzoate compounds were rapidly eliminated by urinary excretion. In the dog, 80-89% of the administered dose (50 mg/kg bw orally or intravenously) were excreted in the urine within the first 48 hours post-dosing.

4. The oral LD50 values were higher than 2000 mg/kg bw and could not be detected for the dog, mouse, rat and guinea pig while the intravenous LD50 values ranged from 170-180 mg/kg bw.

5. The administration of the methyl or propyl hydroxybenzoate at a concentration of 8% (correspondance in mg/kg bw was not reported) in the diet of rats for 96 weeks produced only an initial depression in growth rate. No other macroscopic or microscopic effects were noted. No effects were observed at the 2% incorporation level.

6. Sodium hydroxybenzoate was administered to pregnant mice by intramuscular injection at approximately 0.5 mg/g on either the ninth or twelfth day of gestation. Compared to controls, there were no effects on resorption and no gross or skeletal abnormalities.

7. Mice have been receive intravaginal administration of 0.1 ml of a 1% solution of methyl hydroxybenzoate in polyethylene glycol, twice daily for 18 months. There was no evidence of carcinogenicity and survival rates were comparable, or superior to those of the polyethylene glycol controls.

8. In human, the administration of 800 mg/kg bw of the propyl hydroxybenzoate for three days has been tolerated without adverse effect.

Of 100 patients with allergic contact dermatitis, 3 gave positive reactions to patch testing with a mixture of 3 hydroxybenzoates 5% in soft paraffin.

In man, the alkyl esters of p-hydroxybenzoic acid were rapidly absorbed, metabolised and eliminated by renal excretion.

9. Hydroxybenzoic acid compounds are natural components of many human foods. Concentrations up to 1000 mg/kg have been reported in some herbs and spices.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances into Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- alkyl p-hydroxybenzoates and their salts had a low order of toxicity when tested in mice, rats and dogs,
- hydroxybenzoic acid compounds are natural components of the diet,
- these compounds are rapidly metabolised and excreted.

The Committee considers that there is no need to establish an MRL for hydroxybenzoic acid esters and their sodium salts, and recommends their inclusion into Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
butyl p-hydroxybenzoate	All food producing species	
sodium butyl p-hydroxybenzoate	All food producing species	
sodium benzyl p-hydroxybenzoate	All food producing species	