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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

THIABENDAZOLE

SUMMARY REPORT (1)

1. Thibendazole is a benzimidazole anthelminic which is used in the treatment and control of gastro-intestinal mematodes and lung worms of sheep and goats and gastro-intestinal roundworms in cattle.

   In human medicine, the maximum recommended daily dosage of thiabendazole is 3g for patients weighing 60 kg. Reported adverse effects include hypersensitivity, CNS effects, cholestasis and parenchymal liver damage.

   Thiabendazole is also used as a pesticide (fungicide) on a wide range of fruit, vegetable and cereal crops. Its use as a post-harvest preservative on bananas, citrus and potatoes, in store, has the potential to lead to high residues in these commodities.

2. Thiabendazole is rapidly absorbed after oral administration and distributed throughout the body. It readily crosses the placental and blood/brain barriers. Thiabendazole and its metabolites are subsequently excreted mainly in the urine.

   The compound is of low acute toxicity. In 14-week repeat-dose sutides in rats, the no-effect levels were 25 mg/kg bw in the gavage study and 10 mg/kg bw in the dietary study based on thyroid and hepatocyte hyperplasia; the difference in no-effect levels was more a reflection of the different dose levels used in the studies than of greater toxicity following dietary administration.

   Although thiabendazole is known to be a spindle inhibitor, it was not mutagenic in bacterial assays. *in vitro* or *in vivo* chromosome aberration assays, in a mouse micronucleus test, or dominant lethal assays. There was no evidence of carcinogenicity in two rat chronic dietary studies nor in a two-year mouse study.

   Numerous reproductive toxicity studies have been carried out in various species but many of these were not to modern standards. In the mouse, thiabendazole was teratogenic at high dose levels producing malformations such as cleft palate at 7010 mg/kg bw per day and above. Lower doses caused foetotoxicity. In a well-conducted study in Sprague-Dawley rats, dose levels of 40 and 80 mg/kg bw per day caused decreases in average live foetal weights which were secondary to maternal toxicity. There was no evidence of maternal or foetotoxicity at 10 mg/kg bw.

3. Thiabendazole does not possess significant antimicrobial activity.

4. A provisional ADI of 0 - 0.05 mg/kg bw per day for thiabendazole was estimated by applying a safety factor of 200 to the no-effect level of 10 mg/kg bw per day for foetotoxicity in the Sprague-Dawley rat. The safety factor incorporated an additional factor of 2 for the temporary nature of the ADI. It is anticipated that a higher ADI may be set in due course, subject to satisfaction with the results of the further toxicity studies which are currently being carried out by industry.

5. Residues of thiabendazole and its metabolites were higher in liver and kidney than in muscle. On the basis of the information available, provisional MRLs of 0.1 mg/kg are proposed for the sum of thiabendazole and its major metabolite 5-hydroxythiabendazole in meat (muscle, liver and kidney) and milk. These MRLs are provisional due to the provisional nature of the ADI and because further data are required to identify a "target tissue" and "marker residue".

   The estimated total intake of thiabendazole from consumption of animal products containing residues of thiabendazole and other food commodities containing residues arising from the presticidal and preservative uses of the compound is calculated to be within the provisional ADI.

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6. HPLC analytical methods using UV or fluorimetric detection are available for determining residues of thiabendazole and its metabolites in milk and meat. Most methods do not distinguish between thiabendazole and 5-hydroxythiabendazole. The limit of determination of these methods is generally no higher than 0.1 mg/kg.

7. The following data are required before 31 December 1994 :

   - reports of the further toxicity studies which have been carried out and which are in progress;
   - further information on the residues of thiabendazole and its metabolites in tissues, identification of a "target" tissue and "marker residue";
   - a more sensitive analytical method for determining residues of thiabendazole and its metabolites.