REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF MADURAMICIN AMMONIUM IN FEEDINGSTUFFS FOR CHICKENS FOR FATTENING

Opinion expressed 27 April 1988

TERMS OF REFERENCE (October 1986)

The Scientific Committee for Animal Nutrition is requested to give an opinion on the following questions:

1. Has the use as coccidiostat of the antibiotic maduramicin ammonium (ammonium salt of polyether monocarboxylic acid) at the dosage proposed for chickens for fattening (see background) significant effects on the prevention of coccidiosis in this animal species?

2. Is this use safe for chicken?

3. Can it result in the development of resistance in bacteria to prophylactic or therapeutic preparations?

4. What is the metabolic rate of maduramicin in the chicken? Does the proposed use result in residues in animal tissues? If so, what are the qualitative and quantitative composition and persistence of these residues?

5. Do the toxicological studies allow to conclude that the proposed use does not present risks

   - for the consumer?
   - for the user?

6. What are the nature and the persistence of excreted products derived from maduramicin ammonium? Can these products be prejudicial to the environment?

7. In the light of the answers to the above questions, are the proposed conditions of use acceptable?

BACKGROUND

Maduramicin ammonium was the subject of an application for admission in Section D (Coccidiostats and other medicinal substances) of the Annex to Council Directive 70/524/EEC, of 23 November 1970, concerning additives in feedingstuffs(1) under the following conditions of use:

Species of animal : chickens for fattening
Use level : 5 mg/kg complete feedingstuff
Other provisions : use prohibited at least five days before slaughter.

OPINION OF THE COMMITTEE

1. Maduramicin ammonium is an ionophore consisting of 90% of the ammonium salt of a polyether monocarboxylic acid with an OCH_3 group at the C5 of the A ring (alpha-maduramicin) and 10% of the structurally similar compound with an -OH group instead of $-OCH_3$ at the C5 of the A ring (beta-maduramicin). The efficacy of maduramicin as a coccidiostat in chickens for fattening has been tested in battery chickens for fattening infected with four laboratory strains of Eimeria and in pen-raised chickens for fattening infected with six field strains of Eimeria. These trials established an effective but narrow dose range of 5-6 mg/kg complete feedingstuff as judged by improved weight gain, improved feed efficiency, reduced number of gut lesions and reduced mortality.

(1) O.J. No L 270 of 14.12.1970, p.1

In battery trials in six countries 5 mg/kg complete feedingstuff was effective in preventing clinical coccidiosis and was comparable to treatment with other ionophores. A similar series of pen-raised chickens for fattening in seven countries confirmed the efficacy of that dosage regime when judged by similar parameters. In trials under commercial conditions in seven countries involving 3,25 million chickens for fattening 5 mg/kg complete feedingstuff was efficacious while higher levels caused a reduction in body weight gain.

These findings suggest that maduramicin is effective for the prevention of clinical coccidiosis in chickens for fattening at a dose of 5 mg/kg complete feedingstuff.

2. Administration of maduramicin to chickens for fattening at doses as high as 15 mg/kg feedingstuff resulted in significant depression of body weight gain. Feed efficiency was reduced at doses from 8-15 mg/kg feedingstuff. No other treatment-related effects were noted except a slight reduction in lymphoid tissue of the bursa and thymus at high doses.

Maduramicin had no adverse effects at 5 mg/kg feed on turkey poults, guinea fowl, laying turkeys, fattening rabbits, horses, grower and finishing pigs, lactating cows and finishing steers. Maduramicin has no deleterious effect on carcase quality and flavour in chickens for fattening.

3. Maduramicin ammonium is an ionophore antibiotic with moderate activity against many Gram-positive bacteria, but with no activity against Gram-negative organisms. Although no in vitro studies on the development of resistance and cross resistance were carried out, the in vivo studies showed that stable resistance caused by chromosomal mutation in sensitive Gram-positive organisms does not develop, even though a transient loss in sensitivity was observed. Maduramicin does not cause the selection of transmissible resistance factors in indigenous faecal coliforms nor in experimentally introduced salmonella. No effect was observed on colonisation or shedding of salmonella in chickens.

The addition of maduramicin ammonium at the proposed dose of 5 mg/kg complete feedingstuff to the feed of chickens does not lead to the development of bacterial resistance to prophylactic or therapeutic preparations nor does it cause a persistence of Gram-negative bacteria in the gut of chickens.

4. The metabolism of maduramicin was studied using the compound labelled with 14-C in 7 well defined positions in the molecule. Rats metabolise alpha-maduramicin by O-demethylation at a site in the terminal G ring, the metabolite in the chicken being beta-maduramicin. The liver is the main site of metabolism in the rat and the other species. In the rat 96% of the radioactivity was extracted and consisted of 36% alpha-maduramicin and 64% metabolites.

Maduramicin and/or its metabolites are rapidly eliminated, more than 70% of the ingested radioactivity being recovered in the excreta within the first 48 hours and more than 93% within the first 5 days of withdrawal. No measurable radioactivity was found in the carcase after 8 days withdrawal. Repeated administration leads to a steady-state plasma level after 72h. Detailed tissue level kinetics

have not been determined. However at zero withdrawal time residues are found mainly in fat and skin (1,29 mg/kg tissue), liver (0,49 mg/kg tissue) and kidneys (0,13 mg/kg de tissue), with very little appearing in muscle (0,05 mg/kg tissue). These tissue levels decreased rapidly to the limit of detection (0,025 mg/kg) in muscle (1 day), but more slowly in kidneys (3 days), skin (4 days), liver (5 days) and fat (7 days). The residue half-life was 20-27 hours. Tissue residues in chickens fed 5 mg/kg feed for 29 to 44 days, are measured by RIA (detection limit 0,025 mg/kg), closely correlated with the radiochemical estimates but were generally somewhat lower. Overall no significant residues were detectable by RIA (Radioimmunoassay) after 5 days withdrawal.

Of the tissue metabolites in chickens dosed with 5,5 mg/kg 14-C maduramicin in feed for 7 days, 93-99% were extractable. Most was alpha-maduramicin, the balance being beta-maduramicin. No other metabolites were detected.

The antibiotic activity of the residues in tissues was not determined but in the fat it would be essentially that of alpha-maduramicin, the major component. Roasting of the carcase had no effect on tissue residue levels.

5. Maduramicin has been tested thoroughly in acute toxicity, 28-day, 90-day and 12-month studies, in carcinogenicity, chronic toxicity, reproductive function and teratogenicity studies in mice, rats, rabbits and dogs. Mutagenicity was examined both in in vitro and in vivo tests.

The alpha and beta components had a high acute oral toxicity in the mouse and rat and a high dermal toxicity in the rabbit. The subchronic studies in the rat and dog showed adverse effects on growth, the heart being the target organ in the rat (lowest effective dose 0,35 mg/kg body weight), the heart, skeletal muscle and the eye being target organs in the dog (lowest effective dose 0,45 mg/kg body weight). The rat reproductive studies showed marginal effects on pup weight, litter size and pup survival in the F2b generation at 0,15 mg/kg body weight. Maduramicin is not teratogenic or foetotoxic but 3 mg/kg body weight caused 100% maternal mortality. Maduramicin is not carcinogenic. The NEL is based on the long-term rat study, giving an estimated ADI of 0,001 mg/kg body weight. Maduramicin is not genotoxic except for equivocal results in one test for chromosomal aberrations in mammalian cells.

Alpha-maduramicin has a preferential affinity for monovalent cations as shown in ion displacement studies (Chao-Min liu et al., 1983). Tests in model systems for cardiovascular and central nervous system effects, because of the known pharmacological activities of ionophores, produced no significant effects. These pharmacological studies produced no evidence of myocardial damage in the rat and dog except for ECG changes in the dog at very high dose levels (1 mg/kg b.w.). Maduramicin has been shown to be incompatible with the therapeutic antibiotic tiamulin.

Although maduramicin is irritating to the skin and corrosive to the eye the method of preparation of the premix prevents any formation of dust containing maduramicin. The allergenic potential has not been examined.

On the basis of these findings the Committee concludes, that at the doses proposed for use in chickens there is no risk for the consumer nor for the user. Intake from residues up to 60 ug/person per day is acceptable on the basis of the ADI.

6. The half-life of maduramicin in stored chicken excreta, as determined by antibiotic activity measurements, is about 55 days depending on the temperature of storage. The concentration in the soil following standard agricultural practice of fertiliser usage is of the order of 2-6 ug/kg soil. Further maduramicin is rapidly degraded in the soil to a large number of polar breakdown products only 7% remaining as maduramicin. Considering these low levels it would be unrealistic to require the identification of the degradation products in the soil.

The toxicity of maduramicin for the Daphnia and fish is similar, the NEL being approximately 1 mg/l. Neither methanogenesis nor soil nitrification are inhibited by maduramicin in chicken excreta when these are used as fertiliser nor does it have any significant phytotoxicity.

In the opinion of the Committee the excreted products derived from maduramicin are not prejudicial to the environment.

7. In the light of the information supplied the Committee is of the opinion that maduramicin ammonium is acceptable without risk for use in the feedingstuff for chickens for fattening at a level of 5 mg/kg complete feedingstuff subject to a withdrawal period of 5 days before slaughter.

References : Dossiers supplied by Cyanamid
Liu, Chao-Min, Hermann, T.E., Downey, A., Prosser, B. La T., Schildknecht, E., Palleroni, N.J., Westley, J.W. and Miller, P.A., J. Antibiotics (1983), 36 (4), 343-350