REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF AVILAMYCIN IN FEEDINGSTUFFS FOR PIGS

Opinion expressed 27 April 1988

TERMS OF REFERENCE (July 1986)

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

1. Has the use of the antibiotic avilamycin (oligosaccharide) at the dosages proposed for feedingstuffs for pigs (see background) significant effects on the growth?

2. Is this use safe for the pig?

3. Can it result in the development of resistance in bacteria to prophylactic or therapeutic preparations, or exert an effect on the persistance of Gram-negative bacteria in the digestive tract of the pig?

4. What is the metabolic fate of avilamycin in the pig? Does the proposed use result in residues in animal tissues? If so, what is the qualitative and quantitative composition 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 persistance of excreted products derived from avilamycin? 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

Avilamycine was the subject of an application for admission in Annex II, Section A (Antibiotics), of Council Directive 70/524/EEC, of 23 November 1970, concerning additives in feedingstuffs [1] under the following conditions:

Species of animal : pigs
Dosages : - pigs up to 4 months : 40-80 mg/kg complete feedingstuff
- pigs of 4 - 6 months : 20-40 mg/kg compete feedingstuff

OPINION OF THE COMMITTEE

1. Avilamycine is an oligosaccharide which consists of 12 identified and a small number of unidentified factors, of which factor A represents about 60%, factor B about 7%, and factor D about 5%. The efficacy of avilamycin for promoting the growth of pigs has been tested in 21 trials conducted in Europe and in 11 trials performed in the USA. These trials involved a total of 2508 animals. During these trials several batches of product from two different manufacturers were used. The parameters considered were the daily increase in live weight and the indices of food consumption and daily ingestion of avilamycine.

The dose-response relationship was studied in a series of experiments consisting of 9 European trials with starter pigs with a live weight of 9 - 40 kg, 9 trials with pigs weighing 24 - 80 kg and using a

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

combination of the products of the two manufacturers, and three European bridging trials with the product of one manufacturer. Eight of the 11 US trials used one product and three the other product on pigs weighing between 23 and 70 kg.

The composition of the feeds was very variable and often incompletely recorded. The protein content was frequently either above or below the norm and the energy values were never indicated. Evaluation of the carcases was frequently absent and the experimental protocol not always optimal. Most of the European feeding regimes included 100 - 125 mg/kg copper as well as avilamycine thus delivering two growth factors to the animals. This was done because of the current practice of adding copper to pig feed but it led to a considerable spread of the results. No attempts were made to demonstrate efficacy under different feeding conditions, although a 6% increase in body weight was demonstrated under optimal feeding conditions. The product was tested at the following concentrations: 0, 10, 20, 40, 60 and 80 mg avilamycine/kg final feed.

Statistical treatment of the results using curvilinear regression methodology indicated that the optimum doses for fattening starter or grower pigs lay between 22 and 64 mg/kg feed. Doses of 40 mg/kg feed significantly improved the daily weight gain of starter pigs up to four months of age by about 5.6%. In grower pigs a significant improvement in weight gain was already noticeable at doses of 10 - 20 mg/kg feed. Higher doses did not appear to show any further significant improvement in weight gain. The food conversion index was already significantly improved by 10 mg/kg feed, higher doses giving no better results.

These findings suggest that avilamycin is effective for fattening pigs at doses of 20 - 40 mg/kg feed for pigs up to the age of four months and 10 - 20 mg/kg feed for pigs aged 4-6 months.

2. Avilamycine administration to pigs at doses up to 3000 mg/kg feed caused no treatment-related adverse effects. It improved body weight gain significantly. Avilamycin is not toxic to cattle or sheep. Feeding of avilamycin has no effect on the quality of the pig meat as determined by taste panel tests.

3. Avilamycine is an oligosaccharide consisting of several factors with a limited antibacterial spectrum. It is only effective against Gram-positive bacteria. In-vitro tests on various bacterial species showed only a slight reduction in sensitivity to avilamycin, Clostridia remaining fully sensitive. No correlation exists between a possible resistance to avilamycin and resistance to other therapeutically used antibiotics. Although high doses of avilamycin briefly increased the number of E. coli in the faeces, this effect disappeared after a few weeks. Salmonella-infected pigs showed no increased or prolonged faecal excretion of Salmonella when treated with avilamycin.

   The addition of avilamycine at the proposed doses to the feed of pigs 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 pigs.

4. The metabolic fate of avilamycin was studied using the compound uniformly labelled with 14-C on all constituent factors. Urinary

excretion was low (4.5%), most being excreted in the faeces (93.4%). There was only slight biliary excretion. Absorption was therefore minimal. Biotransformation yields two major metabolites of known structure. Excretion of avilamycin is very small, the major metabolites representing about 50% of the urinary and faecal excretion products.

Tissue residues are minute at zero withdrawal time, the maximum residues in the liver reaching 0.14 - 0.22 mg/kg tissue (limit of detection 0.012 - 0.017 mg/kg tissue). Residues in the kidneys were 0.10 mg/kg tissue, in the muscle 0.025 mg/kg tissue and there was slight accumulation in fat tissue. No residues with antibiotic activity were deteted in kidneys, muscle or fat by a radio-autographic method (limit of detection 50 ug/kg). No residues were detectable in muscle, liver, kidney and body fat after five days withdrawal. The residues are essentially inactive antimicrobially.

5. Avilamycin has been tested thoroughly in the mouse and rat in short-term, long-term, multigeneration-reproduction and teratology studies and in a relay toxicity study in rats without revealing any carcinogenic, mutagenic or reproductive effects. A 12-months study in dogs showed no significant toxic effects. However, doses of 3000 mg/kg feed of avilamycin activity, administered to rats in the multigeneration-reproduction study, caused borderline hepatic enlargement in some of the progeny in both sexes without any associated clinico-chemical or histological abnormalities. The substance is not genotoxic when examined in an adequate battery of mutagenicity tests. It has no allergenic potential but is slightly irritant to skin, eyes and the respiratory tract. The NEL is based on multigeneration-reproduction study. The ADI is estimated to be 0.15 mg/kg body weight avilamycin activity.

On the basis of these findings the Committee concludes, that at the doses proposed for use in pigs there is no risk for the consumer nor for the user.

6. Avilamycine has been studied extensively for persistence of excreted products in the environment. Only 5% of the excreted products are avilamycins, the remainder being hydrolysis products of which 50% are the two major metabolites. Avilamycin is not very stable in soil or water and is broken down within one day in sunlight. These factors suggest that it is unlikely to accumulate in the environment.

It is poorly soluble in water and has a low n-octanol/water partition coefficient suggesting little or no risk of avilamycin passing from soil to water or to any life forms on land and in water. Its toxicity to Daphnia, fish and earthworms is small.

The excreta of pigs given avilamycin do not affect methanogenesis or soil nitrification when used as manure nor do they have any deleterious effects on plant crops.

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

7. The chemical composition of avilamycin is controlled by HPLC and its potency is standardised microbiologically. The range of factors used in the efficacy trials is about the same as that in the present

production. For official control microbiological tests are recommended.

8. In the light of the information supplied, the Committee is of the opinion that-avilamycine may be used in the feedingstuff for pigs without risk at the following concentrations:

- pigs up to four months : 20 to 40 mg/kg complete feedingstuff
- pigs of 4 - 6 months : 10 to 20 mg/kg complete feedingstuff.

References : Dossier of Eli Lilly & Co