REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF NARASIN IN FEEDINGSTUFFS FOR CHICKENS

Opinion expressed 14 April 1982

TERMS OF REFERENCE (November 1980)

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

1. Does the use of coccidiostat Narasin in feedingstuffs for chicken under the proposed conditions of use (see Background), result in the presence of residues in animal products? If so, what is the nature and the amount of these residues? Could these residues be harmful to the consumer?

2. Could the use of this additive affect the development of resistance in bacteria?

3. Could the excreted products, derived from the additive, be prejudicial to the environment? If so, what is the nature of the risks?

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

BACKGROUND

Narasin was the subject of a submission for inclusion in Annex II, Section B, of Council Directive 70/524/EEC of 23 November 1970, concerning additives in feedingstuffs (1), under the following proposed conditions for use :

(1) OJ No L 270 of 14.12.1970, p. 1

Species of animal : chicken for fattening.
Minimum and maximum content in complete feedingstuffs : 60-80 ppm (mg/kg).

OPINION OF THE COMMITTEE

1. Narasin is a polyether antibiotic produced by deep culture fermentation of a strain of Streptomyces aureofaciens. Its structure has been elucidated (Berg and Hamill 1978) and shown to be a monobasic carboxylic acid, containing five cyclic ether rings.

In chicks given a single oral dose of ^{14}C Narasin, a mean recovery of radioactivity in the excreta of 99% (range 90-114%) was found within 2 days, of which 30% was unchanged ^{14}C Narasin. With the rat, 98.9% of total radioactivity was excreted in the faeces within 52 h following a single oral dose of ^{14}C Narasin (5% was unchanged Narasin), while the remainder was excreted in the urine. That absorption of the product from the digestive tract can take place is evidenced by the fact, that in rats with biliary cannulae 16% of an oral dose was excreted in bile within 24 h. Narasin is metabolised in both rat and chick to numerous metabolites. In rat faeces three of the most abundant comprise 4, 19 and 10% of total radioactivity: in chicken excreta equivalent values are 7, 4 and 3%. Six of the metabolites have been characterised by mass spectrometry, four being dihydroxynarasins and two trihydroxynarasins. Four or more of these metabolites are present in chicken liver. The rat produces the same metabolites as are found in chicken liver, and their presence has revealed no adverse effects during the subacute and chronic toxicity studies.

When Narasin was fed at 80 mg/kg complete feedingstuff, residues in chicken tissues following a one day withdrawal period ranged from 0.133 mg/kg (liver) to 0.084 mg/kg (skin) with none detectable in kidneys or lean tissue (limit of detection of the microbiological method : 0.005 mg/kg); after a three day withdrawal period there were no residues in kidney, lean tissue or fat, the amounts in liver and skin being respectively 0.044 mg/kg and 0.025 mg/kg. In further experiments total residues of Narasin plus metabolites, present in the edible tissue from a whole chicken, were, after a two day withdrawal period, estimated to be 0.006 mg (for 80 mg Narasin/kg complete feedingstuff) and 0.017 mg (for 100 mg Narasin/kg complete feedingstuff).

Acute toxicity studies show that for the chicken the LD_{50} value approximates to 50 mg/kg b.w., for mice and rats it lies in the range 15-20 mg/kg b.w., and for rabbits and dogs it is more than 10 mg/kg b.w. It is especially toxic to horses (LD_{50} 1 mg/kg b.w.). On the basis of a repeated dose study lasting 56 days, the no-effect level of Narasin for chickens was shown to be at least 80 mg Narasin/kg feed; at the higher levels tested, viz. 240 and 400 mg/kg, there were adverse effects on weight gain, feed comsumption and on various blood parameters. Two sub-chronic 90-day studies in mice showed no specific toxicity, with a no-effect level that appears to be higher than 10 mg/kg ration. The 90-days sub-chronic study in rats showed some haematological and biochemical changes which are difficult to interpret while the 2-year study revealed effects on body weight at all levels down to 7.5 mg/kg ration but no other significant findings. From the available studies the no-effect level for calculation of an ADI is 0.375 mg/kg b.w.

The use of Narasin under the proposed conditions does give rise to small amounts of residues. The Committee considers, however, that there will be no hazard to the consumer if a withdrawal period of at least 5 days before slaughter is imposed.

2. Narasin is inactive against gram-negative bacteria especially E. coli. In gram-positive bacteria (Streptococcus and Staphylococcus aureus) sensitivity to the antibiotic is occasionally very slightly decreased. None of the bacterial strains tested, even when they developed transient resistance to Narasin, showed resistance to a variety of clinical antibiotics tested. Hence there appears to be no need for concern over the possible development of bacterial resistance.

3. Narasin present in chicken litter does not degrade readily. After 18 months storage of chicken litter under field conditions, concentration of the product in the litter showed no change. However, in contrast, it appears to be readily degradable in soil. When Narasin was mixed with soil at 10 mg/kg, 90% degradation occurred within 22 days. Results of the same order have been obtained for poultry litter from birds fed narasin, which was incorporated in soil. Due to the rapid degradation of narasin in the soil nitrifying bacteria are not adversely affected.

Leaching of narasin from soil appears to be more dependant on soil pH than soil type, being significantly greater in basic soils (pH $\geqslant$ 7.7). Since narasin is virtually insoluble in water, it would appear that soil leachate carrying it into surface waters would not present any hazard to aquatic life. Narasin has a low toxicity for Daphnia magna (no-effect level : 4 mg/l at 24 h exposure, 2.3 mg/l at 48 h; LC_{50} greater than 16 mg/l at 24 h, 8.0 mg/l at 48 h) and fish (LC_{50} at 96 h : 1.4-2.0 mg/l for Salmo iridens; 1.0-1.4 mg/l for Lepomis macrochirus). At a concentration of 1 mg/l, narasin inhibited

N-fixation in the blue green algae Anabaena flos aquae and partially so in the heterotroph bacterium Azobacter chroococcum, although the growth of neither organism was affected.

No narasin-related phytotoxicity occurred in the 14 species of plants tested in soils treated with chicken litter from birds fed narasin.

These observations indicate that possible harm to the environment is unlikely.

4. In the light of the available facts, the Committee is of the opinion that the use of Narasin in feedingstuffs for chickens, at the proposed levels, could be admitted provisionally provided that a withdrawal period of at least 5 days before slaughter is imposed. A reassessment of this additive is envisaged when full data on the metabolism in chickens become available.

REFERENCES

Berg D.H. and Hamill R.L., 1978. J. Antibiot. 31, 1-6
Dossiers Lilly Research Centre Ltd.