REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITTION ON THE USE OF SALINOMYCIN IN FEEDINGSTUFFS

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 salinomycin sodium in animal feedingstuffs, 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 question, are the proposed conditions of use acceptable?

BACKGROUND

Salinomycin sodium was the subject of a submission for inclusion in Annex II of Council Directive 70/524/EEC of 23 November 1970, concerning additives in feedingstuffs (1), as a coccidiostat for fattening chickens and turkeys, and rabbits, and as a growth promoter (group of antibiotics)

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

for piglets, pigs, lambs and fattening cattle, under the following conditions :

	Minimum content ppm (mg/kg) of complete	Maximum content feedingstuffs
Chickens for fattening *	50	70
Turkeys for fattening *	20	30
Rabbits *	25	35
Piglets, up to 16 weeks	50	80
Pigs, up to 6 months	25	50
Lambs	10	30
Cattle for fattening	10	30

* Use prohibited at least five days before slaughter.

OPINION OF THE COMMITTEE

1. Salinomycin is a polyether antibiotic of known structure. It is a monobasic carboxylic acid containing five cyclic ether rings. Metabolism studies in mice, rats and chicken using oral doses of ^{14}C-labelled salinomycin showed that over 90% is excreted in the faeces within 48-72 hours, less than 5% in the urine and negligible amounts in the expired air. Small amounts of ^{14}C-salinomycin are found in the liver and bile after 48-72 hours. Salinomycin is rapidly metabolized in the gut and liver to numerous metabolites, some of which are 5, 15-dihydroxy derivatives. Metabolism is slowest in chicken, where ^{14}C-labelled residues in the liver amount to 0.1-0.4 mg/kg after 120 hours. In cattle, orally administered ^{14}C-salinomycin, 90.5% appears in the faeces, 1.4% in the urine, 0.6% in the

liver and 4.2% in all other tissues (at levels of < 0.1 mg/kg) after 4 days. Pigs excrete on average 83.5% in the faeces, 2.1% in the urine, with < 0.1 mg/kg in the liver and < 0.01 mg/kg in muscle, kidney and fat remaining after 4 days (limit of detection of radiochemical method 0.01 mg/kg). No data using ^{14}C-salinomycin are available on sheep.

Extensive residue studies in broilers, turkeys, rabbits and pigs showed no detectable residues after 24 hours withdrawal using a microbiological method (limit of detection 0.01 mg/kg). The exact chemical nature of most residues has not been established. Residues in the liver of sheep and cattle after 24 hours ranged from 0.06-0.17 mg/kg and had disappeared after 3-5 days (limit of detection by microbiological method 0.01 mg/kg). When fed erroneously to laying hens, dose-related residues appear in the yolk of eggs ranging from 0.2-0.3 mg/kg within 3 days and disappearing, if 5 days withdrawal is interposed.

Acute toxicity studies with dried mycelium, with the product without mycelium, or with pure substance in mice, rats, chicken, rabbits, dogs, pigs, bulls and horses showed oral LD_{50} values from 60-21 mg/kg b.w.; for mice, rats, chicken and rabbits the signs of toxicity being mostly neurological. Pigs, bulls and horses were increasingly sensitive in that order, toxic effects occuring mostly in the liver and myocardium. Subchronic studies were carried out in mice, rats, dogs and pigs. The target organs of toxicity were liver and spleen in mice, the nervous system in dogs and the liver in pigs.

Two year chronic studies were carried out in mice and rats and also a study over 2 1/2 years in rats using the mycelium. The no-effect levels ranged from 30-130 mg/kg diet. From the available studies an ADI of 0.05 mg/kg b.w. may be determined.

A one generation reproduction study in rats and embryotoxicity and teratogenicity studies in mice and rabbits revealed no adverse effects. Mutagenicity was absent when tested in a bacterial and two in vivo systems. Salinomycin had no effect on subsequent laying performance and hatchability of eggs when administered to young chicken for 16 weeks during rearing.

The use of salinomycin under the proposed conditions gives 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. Salinomycin is effective only against Gram-positive bacteria but no other microorganisms or helminths. No evidence for selection pressure or selection of enterococci with R-factors was found. No cross resistance to six other antibiotics used in human medicine was found. No resistance was induced in 10 different coccidia strains subjected to repeated passage. There appears to be no need for concern over the possible development of bacterial resistance.

3. Only about 1-5% of the microbiological activity in the feed appears in the broiler excreta because most metabolites are microbiologically inactive. The half-life of salinomycin in soil was 50 hours when measured microbiologically (limit of detection 0.01 mg/kg), only 1% remaining after 21 days. No data are available on leaching from soil or on the nature of the breakdown products in soil.

Salinomycin has a low toxicity for Daphnia (LC_{50} 24 hours: 4.3 mg/l) and fish (LD_{50} Idus idus 96 h: 30 mg/l). Salinomycin in the faeces of cattle reduced methane production by about 15% but in fresh pig manure it increased production by 5%. At a level of 8 mg/kg in soil nitrification was delayed but this level is about 1200 times the maximum possible concentration, if animal dung is used as fertiliser. Plant growth was slightly inhibited at doses of 12.5-200 mg/m^2 in a few crops only and no uptake in plants at 14 mg/kg soil was noted. These observations indicate that possible harm to the environment is unlikely.

4. In the light of the available evidence the Committee is of the opinion that the use of salinomycin in feedingstuffs for chickens, piglets, pigs and cattle, at the proposed levels, could be admitted provisionally provided a withdrawal period of at least 5 days before slaughter is imposed. A reassessment of this additive is envisaged when details of the metabolism become available.

REFERENCES

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