REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF NIFURSOL IN FEEDINGSTUFFS FOR TURKEYS

Opinion expressed 14 April 1982

TERMS OF REFERENCE (February 1978)

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

1. Does the use of nifursol as antihistomoniasis agent in feedingstuffs for turkeys, under the conditions of use authorized (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 excreted products, derived from the additive, be prejudicial to the environment? If so, what is the nature of the risks?

3. In the light of the answers to the above questions, should the conditions of use authorized for this additive be maintained or should they be modified?

BACKGROUND

In accordance with the provisions of Council Directive 70/524/EEC, of 23 November 1970, concerning additives in feedingstuffs (1), as last amended by the twentieth Commission Directive of 7 December 1977 (2), Member States are authorized to use nifursol by way of derogation up to 31 December 1978, under the following conditions set out in Annex II, Section B, of the Directive:

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(1) OJ No L 270, 14.12.1970, p. 1
(2) OJ No L 18, 24.01.1978, p. 7

Species of animal : turkeys.
Minimum and maximum content in complete feedingstuffs : 75 ppm (mg/kg).
Other provisions : use prohibited at least 5 days before slaughter.

It was proposed to authorize this use at Community level at dose-levels of 50-75 mg/kg complete feedingstuff.

OPINION OF THE COMMITTEE

1. Studies of the metabolism of nifursol [3,5-dinitro-(5-nitrofurfurylidene)salicylic acid hydrazide] in turkeys and rats, using molecules labelled with ^{14}C either uniformly in both aromatic rings or only in the furan moiety, indicate that the compound is excreted mainly via the bile of the faeces. The main absorption site is the jejunum, some 30-50% of the absorbed material entering the enterohepatic circulation. In rats 80-85% appears in the faeces and 11% in the urine within 24 hours, whilst turkeys excreted 86% in the same period. Rats eliminate nifursol completely after 96 hours, with 2% appearing as labelled $^{14}CO_2$ derived from the furan moiety. Turkeys excreted 96-99% after 96 hours.

   Complex schemes for the metabolism in the turkey and rat have been proposed and some of the individual ultimate metabolites have been identified. In turkeys they arise by hydrolysis of the azomethine bond and by reduction of the nitrogroup in the furan ring followed by oxidative ring scission while maintaining the azomethine bond. In the rat only the furan ring is opened after reduction and hydrolysis of the hydrazine-furan bond. The turkey and the rat have only 2 of the proposed metabolites in common. Conjugation in turkeys occurs with pyruvic and glucuronic acid, in rats with acetic acid.

Residues in turkey tissues were determined by HPLC using an electron capture detector specific for nifursol but not detecting any metabolites (limit of detection 10 µg/kg). If ^{14}C-labelled nifursol was used at the proposed concentration of 75 mg/kg feed in turkeys, then residues in skin, liver and kidneys ranged from 0.35-0.60 mg/kg, with most of the nifursol being excreted in the bile. Residues in muscle were $<$ 0.1 mg/kg independent of the length of administration or withdrawal period. After 5 days withdrawal from feed residues in all tissues were $<$ 0.1 mg/kg using ^{14}C-labelled material. No detectable residues of unchanged nifursol were found in liver, kidney, muscle and skin of birds treated without a withdrawal period using the HPLC method (limit detection 10 µg/kg).

Orally administered nifursol is virtually non-toxic to rats, chicken and dogs in acute tests. Short-term studies in rats, dogs and turkeys showed the dog to be the most sensitive species, causing hepatotoxicity at high dose levels. A chronic 118 weeks feeding study in rats revealed no carcinogenic but some hepatotoxic effects. A three generation reproduction study in rats showed no adverse effects on reproductive function. From these long-term studies a no-effect level of 400 mg/kg diet could be established to serve for the evaluation of an ADI.

The fertility and hatchability of eggs was not affected by 4 months administration of 75 mg nifursol/kg feed. No teratology or embryotoxicity studies were performed. Studies on mutagenicity in several Salmonella typhimurium strains were negative.

It would appear that the proposed use, which includes a 5 day withdrawal period, presents no risk to the consumer.

2. Nifursol has only weak antibacterial activity. The mean inhibitory concentrations for 12 species of soil microflora demonstrated that significant antibacterial activity was present only against B. subtilis. The level of nifursol in turkey excreta is well below the effective level against the most sensitive soil bacteria tested. The rapid degradation of nifursol in turkey excreta (20 mg/kg decomposing in 10 days) with a half-life of 8.4 days, together with the dilution when excreta are spread on soil, make any selective effects on soil microflora unlikely.

Studies with aquatic organisms, relevant to the assessment of environmental effects, showed that nifursol is only moderately toxic to Daphnia magna ($LC_{50} > 10$ mg/l) and Poecilia reticulata (LC_{50} 24-96 hours : 6-10 mg/l). Algae were not investigated specifically. No adverse effects on trout were noted. Nifursol is unstable when aqueous solutions are exposed to UV light, 82% being decomposed in 8 hours. Nifursol is rapidly decomposed in soil, its concentration falling to 50% in 3 days and complete decomposition occurring within 77 days. No more than 9% of nifursol in soil can be removed by leaching. The nature of the decomposition products in soil is not known.

The instablility of the compound in excreta, soil and aqueous solutions exposed to UV light makes it unlikely to become a hazard for the environment. The low antibacterial activity suggests no adverse effects from nifursol on soil microorganisms and makes it unnecessary to determine its effects on nitrifying and methanogenic bacteria.

3. In the light of the available information the Committee is of the opinion that the use of nifursol in feedingstuffs for turkeys, at use level of 50-75 mg/kg (ppm) should be maintained subject to a withdrawal period of not less than five days before slaughter.

REFERENCES

Dossiers Salsbury Laboratories.

Rijksinstituut voor de Volksgezondheid, Bilthoven, Nederland : Internal report.