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

Opinion expressed 8 July 1981

TERMS OF REFERENCE (July 1978)

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

1. Does the use of the growth promoter olaquindox in feedingstuffs for pigs, 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 use of this additive affect the development of resistance in bacteria?

3. Could this use be prejudical to agricultural workers or to the environment? If so, what is the nature of the risks?

4. 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 twenty-third Commission Directive of 23 June 1978 (2), Member States are authorized to use olaquindox, by way of derogation up to 31 December 1978, under the following conditions set out in Annex II, Section F, of the Directive:

Species of animal: pigs, up to four months.
Minimum and maximum content in complete feedingstuffs: 15-50 ppm (mg/kg); milk replacers: 50-100 ppm (mg/kg).
Other provisions: use prohibited for at least 4 weeks before slaughter. Mixing or simultaneous administration with an antibiotic prohibited.

OPINION OF THE COMMITTEE

1. When incorporated in feed for pigs, olaquindox /2-(N-2'-hydroxyethyl-carbonyl)-3-methylquinoxaline-1,4-dioxide/ is absorbed from the digestive tract. The residues resulting from the use of the normal dose-level (50 mg/kg complete feedingstuff) for periods of eight weeks and from higher levels (100 and 160 mg/kg complete feedingstuff) for 20 weeks were determined in liver, kidney, muscle, adipose tissue and serum. In no case did the residues exceed the lower limit of determination (0.1 mg/kg by microbiological or spectrophometric analysis) 48 hours after the withdrawal of the supplemented feedingstuff.

(1) OJ No L 270, 14.12.1970, p. 1
(2) OJ No L 198, 22.07.1978, p. 10

Investigations on the biotransformation using ^{14}C-labelled olaquindox showed that the residues consist of unchanged olaquindox and metabolites resulting from the reduction of the N=O radicals and from the oxydation of the alcohol group of the side chain. No trace of 2-carboxymethylaminocarbonyl-3-methylquinoxaline-1,4-dioxide was detected. Tissues taken 48 hours after oral administration of 2 mg labelled olaquindox/kg live weight contained residues of 0.01 to 0.07 mg/kg (by measurement of radioactivity expressed as olaquindox).

Olaquindox was investigated in short- and long-term toxicological studies in several species of laboratory animals. The levels without effect were evaluated at 1, 20 and 5 mg/kg live weight for rat, dog and monkey respectively. No teratogenic or carcinogenic effect was observed. A number of mutagenicity tests showed that the metabolite 2-carboxymethylaminocarbonyl-3-methylquinoxaline-1,4-dioxide, isolated from pig urine is mutagenic; the other metabolites are not mutagenic. The mutagenicity studies on olaquindox itself appear insufficient (Voogd et al., 1980). The Committee considers it necessary that extensive studies using a battery of tests covering not only bacterial test systems but also investigating other genetic endpoints in relation to chromosomal and DNA changes be carried out.

According to these data, residues resulting from the use of olaquindox in pig feed are below the acceptable limits and are no longer detectable after a four-week withdrawal period of the supplemented feedingstuff.

2. Olaquindox has antibacterial properties but does not lead to changes in the intestinal flora in pigs submitted to a diet containing up to 100 mg olaquindox/kg.

Investigations carried out over several years on more than 700 pigs showed that, at the normal level of use (50 mg/kg complete feeding-stuff), olaquindox does not lead to a selection of enterobacteriaceae carrying R-plasmids nor to a transfer of R-factors. It does not promote selection of intestinal bacteria resistant to tetracyclin, strepto- mycin, sulphafurazole, ampicillin or kanamycin nor does it favour the development of strains resistant to chloramphenicol. A slight redue- tion in sensitivity of E. coli strains to olaquindox and in their rate of excretion in faeces was observed after a few weeks of treatment (Gedek 1979 a,b). The use of olaquindox as feed additive is thus without consequences for the use of antibiotics (in particular chloramphenicol) in human or veterinary therapy.

3. The Committee considers that the chemical and physico-chemical specifications of olaquindox and its preparations, presented in the dossier examined, are satisfactory. The Committee is not aware of undesirable effects arising during the handling of the product or its preparations. In the present state of knowledge, there is no evidence to suggest that a risk may be encountered by agricultural workers.

Olaquindox and its metabolites are excreted essentially in the urine and, to a small extent, in the faeces during the 48 hours following the administration to pigs of the supplemented feedingstuff. The products excreted in urine consist mainly of unchanged olaquindox and a monoxy-reduction product and, in smaller proportion, of derivatives of 2-carboxymethylaminocarbonyl-3-methylquinoxaline among which small amounts of the 1,4-dioxide are present.

The kinetics of degradation of olaquindox have been determined by measuring the antibacterial activity (E. coli). This compound is stable in aqueous solution but breaks down rapidly under the action of light. In liquid manures, biodegradation is practically complete within two to three days; in soils, it reaches 87 to 99% within 10 days. These observations indicate that accumulation in the environment is unlikely.

Olaquindox has a low toxicity (lethal concentrations : 1-10 mg/l) for protozoa, algae, daphnids, carps and eels and is not phytotoxic.

4. In the light of these data, the Committee is of the opinion that the use of olaquindox in feedingstuffs for pigs could be maintained provisionally in the conditions presently authorized. However, a reassessment of this additive is needed. For this purpose, the mutagenicity studies required by the Committee (see point 1 above) should be available.

REFERENCES

Dossiers Bayer A.G.

Gedek B., 1979 (a). Study carried out over several years on the behaviour of E. Coli and gram-positive cocci in swine, poultry and calves in the presence of antibiotics (personal communication).

Gedek B., 1979 (b). Modern growth promoters and bacterial resistance. Proc. of the Round Table held in Milano, 11 October 1979, on Performance in Animal Production. Minerva Medica Ed. (Milano 1979), 277-294.

Voogd C.E., van der Stel J.J. and Jacobs J.J.J.A.A., 1980. The mutagenic action of quindoxin, carbadox, olaquindox and some other N-oxides on bacteria and other yeasts. Mutation Research 78, 233-242.