

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

Opinion expressed 6 July 1978

TERMS OF REFERENCE

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

1. Does the use of the growth promotor carbadox in feedingstuffs for pigs, under the conditions of use authorized by derogation (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 prejudicial to persons required to handle this product in industry and/or agriculture 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 already 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 carbadox, 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.

Maximum content in complete feedingstuffs : 50 ppm (mg/kg).

Other provisions : use prohibited for at least 4 weeks before slaughter.

Mixing or simultaneous administration with an antibiotic prohibited.

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

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

OPINION OF THE COMMITTEE

1. Carbadox (methyl-3-(2-quinoxalinylmethylene)-carbazate-N,N'-dioxide) is metabolized in pigs to quinoxaline-2-carboxylic acid and methylcarbazate with the intermediary formation of desoxycarbadox (methyl-3-(2-quinoxaline-methylene) carbazate). Carbadox and desoxycarbadox have a short life-time. After three weeks administration of 3.5 mg carbadox/kg body weight/day (= maximum authorized level) to pigs the residues in edible tissues are less than 5 µg/kg (limit of determination) six hours after withdrawal of the supplemented feedingstuff for carbadox, and 72 hours after withdrawal for desoxycarbadox.

Twenty-four hours after withdrawal, residues consisting essentially of quinoxaline-2-carboxylic acid and small amounts of methylcarbazate are less than 0.1 mg/kg in all tissues except the liver, where they reach 1.0 mg/kg. Their concentration in this organ decreases progressively, being 0.1 mg/kg after two weeks and 0.03 mg/kg (limit of determination) after four weeks. A four-week withdrawal period therefore suffices for elimination of the residues.

Carbadox and its metabolites have been investigated in short- and long-term toxicological studies in laboratory animals. Administration of carbadox for two years in the daily diet of rats produced toxic effects (nodular hepatoma) at doses above 2.5 mg/kg body weight. The compounds causing these effects have been shown to be carbadox and desoxycarbadox. The long-term administration of daily doses up to 50 mg/kg body weight of quinoxaline-2-carboxylic acid (main metabolite) or of 10 mg/kg body weight of methylcarbazate produced no adverse effects.

The induction of a variety of mutagenic effects in certain strains of microorganisms, *Drosophila* and mice appeared to be associated with chemicals having a quinoxaline-N,N'-dioxide structure. This property has not been observed with the metabolic products of carbadox and desoxycarbadox.

These results show that residues of carbadox can be considered to be of low toxicity as soon as the original compound and desoxycarbadox have disappeared, i.e. 72 hours after administration of the product.

Carbadox residues produced no adverse effects in relay toxicity studies carried out during two years over three generations in rats, and for 87 months in dogs. The test animals were fed during

these trials rations containing meat and/or liver from pigs which had received 200 mg carbadox/kg feedingstuff (four times the maximum authorized level) and had been slaughtered without any withdrawal period. In neither case were any harmful effects observed.

2. Although carbadox has antibacterial properties, it modifies only slightly the intestinal flora of animals. It does not induce the selection of enterobacteriaceae (E. coli or others) carrying R-plasmids nor does it cause a transfer of R-factors. Despite continuous use for several years in pigs, a decrease of transferable resistance to chemotherapeutics was observed in E. coli of the intestinal flora. This more sensitive flora tended to become dominant.

3. Carbadox with a chemical and physico-chemical specification considered satisfactory by the Committee is available commercially as apermix containing soya oil. This inert ingredient prevents the formation of dust during the preparation of the premix and the feedingstuff. Surveys conducted in factories indicate that these products may be handled safely. The risks to agricultural workers appear negligible if the feedingstuff is in pellet form.

61-72 % of the dose ingested by pigs is excreted in the urine and 2-10 % in the faeces during the 24 hours following administration. The total quantity excreted after 72 hours amounts to 85-90 %. The excreted products contain only traces of carbadox and desoxycarbadox. They consist essentially of quinoxaline-2-carboxylic acid and methylcarbazate either in their free or conjugated forms. These compounds are neither toxic nor mutagenic. They are polar compounds which, on the basis of present knowledge, do not appear to accumulate in the food chain or to pollute the environment.

4. In the light of the available data the Committee is of the opinion that the use of carbadox cannot lead to the presence of residues in animal products provided the conditions of use mentioned below are adhered to, nor that it is harmful to the environment or to persons required to handle the product in industry and/or agriculture.

#### Conditions of use

Feedingstuffs for pigs, up to the maximum age of four months.  
Maximum carbadox content : 50 mg/kg of complete feedingstuff.  
Presentation of the feedingstuff : pellets.  
Withdrawal period of the supplemented feedingstuff : at least four weeks before slaughter.

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