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

Opinion expressed 7 July 1982

TERMS OF REFERENCE (March 1981)

The Scientific Committee for Animal Nutrition is requested to give an opinion on the toxicity and the possible effects on health of the exposure to carbadox. The Commission considers it desirable that the following aspects especially be evaluated :

(a) carcinogenic potential of carbadox and its metabolites (dose/effect relationship, classification of the product according to the nature of the effects, etc.);

(b) risks inherent in exposure to carbadox dust under practical stock-farming conditions and opinion on the protective measures.

BACKGROUND

In its opinion expressed on 6 July 1978 (*), the Scientific Committee considered that carbadox can be used without risks for the health under determined conditions. Some arguments have been developed recently against this opinion, so that a further consultation of the Scientific Committee became necessary.

(*) Commission of the European Commuties. Reports of the Scientific Committee for Animal Nutrition, Second Series, EUR 6918 (1980), p. 7.

OPINION OF THE COMMITTEE

(a) Carbadox is structurally related to the know carcinogen 4-nitroquinoline-1-oxide. It is hepatotoxic causing nodular hepatic hyperplasia in a dose-related manner in chronic studies in rats down to a dose level of 2.5 mg/kg b.w./day. At the lowest dose level tested (1 mg/kg b.w./day) a lower incidence of hepatic nodular hyperplasia was seen when compared to controls. However, the number of animals in each group was too small to establish 1 mg Carbadox/kg b.w./day with certainty as the true no-adverse-effect level. The findings in two long-term feeding studies on rats point to carbadox being a hepatocarcinogen of low potency. These studies were, however, of inadequate design in the light of present-day guidelines. Hepatocellular carcinomas appeared only at the highest level tested (25 mg/kg b.w.). The compound has also been shown to be mutagenic in in vitro and in vivo tests. No evidence for toxicity or carcinogenicity was seen in a one-year study in guppies (Poecelia reticulata). Relay toxicity tests on rats extending over 3 generations and on dogs over 87 months showed no adverse effects.

The short-lived metabolite desoxycarbadox was a potent carcinogen in a fifteen months feeding study in rats with some evidence of a dose-response relationship. The metabolite quinoxaline-2-carboxylic acid, the compound persisting as residue in the liver of treated pigs, and detectable in the urine exposed indiduals, has been shown to be non-carcinogenic in an adequate 29 months study. The highest dose level studied was 100 mg/kg b.w. The other metabolite,

methylcarbazate, which appears temporarily in the urine of treated pigs, has also been found to be non-carcinogenic in a 2-year feeding study in rats. This study was, however, carried out on groups of only 24 males and females per dose level. Moreover, survival was comparatively poor. The highest dose level of methylcarbazate investigated was 10 mg/kg b.w./day, corresponding to a dose of $>$ 25 mg carbadox/kg b.w./day.

(b) It has been established that, following administration of carbadox, residues in food of animal origin are of low toxicity for the consumer once the original carbadox and its metabolite desoxycarbadox have been metabolised, i.e. 72 hours after administration of the product. The withdrawal period of at least 4 weeks before slaughter, imposed by the EEC regulation, therefore ensures the safety of the consumer, particularly in the light of the results of the relay toxicity tests.

With regard to the exposure to carbadox dust in handling premixes and feedingstuffs, the Committee expressed the view in its previous evaluation (Commission of the European Communities, EUR 6918) that carbadox was available commercially as a premix with a satisfactory physico-chemical specification. According to this specification the inert ingredient soya oil prevents the formation of dust during preparation of the premix and the feedingstuff. These products could therefore be handled safely and with negligible risks to agricultural workers, particularly if the feedingstuff was in pellet form.

Additional studies on agricultural workers and on pigs were undertaken at the request of the Committee with feedingstuffs containing

50 mg/kg feed of carbadox prepared from a 10% premix and used in meal form to obtain a maximum dust level in the ambient air during the preparation and distribution of pig feed. Dust inhalation was studied in animals and farm workers exposed for 15 days using test filters. The urine of both pigs and exposed farm workers was examined for the presence of the carbadox metabolite quinoxaline-2-carboxylic acid as evidence of systemic absorption.

The average inhalation exposure of farm workers was found to be 0.05 mg carbadox/kg bodyweight in 24 hours as measured by deposition on test filters. No quinoxaline-2-carboxylic acid was found in the urine of either exposed farm workers preparing and handling the feed or of treated pigs (limit of detection 10 ug/l).

These findings confirm the opinion of the Committee stated earlier, that the risk to health incurred by farm workers is negligible under practical conditions of preparation and distribution of animal feed containing carbadox, provided that defined specifications are being fulfilled. This opinion refers however to carbadox premixes, the documentation of which was available to the Committee, i.e. commercial premixes containing up to 10% active substance and specially formulated with ingredients preventing the formation of dust and fulfilling defined specifications. The evaluation of preparations containing carbadox and differing in specification would require that these products be tested in a manner similar to that described for the product used in the above investigations.

REFERENCES

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