

SECOND REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON  
THE USE OF SALINOMYCIN IN FEEDINGSTUFFS FOR CHICKENS

Opinion expressed 4 April 1984

TERMS OF REFERENCE (November 1980)

In reply to questions put by the Commission on the safety of use of salinomycin in feedingstuffs for chickens, the Committee expressed a favourable opinion on 14 April 1982 (\*) on the provisional use of the additive in feedingstuffs for chickens, piglets, pigs and fattening cattle, subject to a withdrawal period of five days before slaughter. It was agreed that the product should be reassessed when additional data on the nature of tissue metabolites in the various species were available.

In the light of the information that has since been received on the use of the additive for chickens it is possible to interpret the original data more accurately. Accordingly, the Committee's opinion is now as follows.

OPINION OF THE COMMITTEE

1. The metabolism of salinomycin has been studied in the chicken, using a molecule labelled with  $^{14}\text{C}$  at three specific sites, including one corresponding to the carboxylic function. After administration of single or multiple oral doses, most (up to 97%) of the radioactivity was recovered in the excreta within 72 hours. Almost all the activity was detected in the intestinal and caecal contents, showing that excretion via the urine is of limited significance.

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(\*) Reports of the Scientific Committee for Animal Nutrition, fourth series (1984), No EUR 8769, p. 36

Measurable quantities of radioactivity (14% of the ingested dose) were excreted over a 72 hours period in the bile, indicating that salinomycin is partially absorbed. However, the very low levels measured in the blood and their limited persistence therein (1 hour) indicated that the salinomycin that is absorbed returns mainly to the intestine via the bile after metabolism in the liver. A very low excretion of  $^{14}\text{CO}_2$  was observed.

Analysis of the excreted products showed the presence of a very small quantity of the unchanged antibiotic (< 1%) and a number of metabolites, of which the three main ones have been identified. One is a di-hydroxylated derivative and two are tri-hydroxylated, representing 11% and 28% respectively of the excreted radioactivity. Chromatographic analyses showed the presence of the same metabolites in the bile. It can be established from these data that salinomycin once absorbed is metabolized and that the metabolites are eliminated mainly via the bile and subsequently via the faeces. There was no qualitative or quantitative difference between males and females. Metabolites recovered from the excreta have a much lower antibiotic activity and acute toxicity (mouse) than salinomycin itself.

2. Following administration of salinomycin at the level of 66 g/ton of feedingstuff for 10 days and after a withdrawal period of 24 hours no antibiotic activity was detected in the chicken tissues (microbiological limit of detection, expressed as salinomycin : 0.01 mg/kg).

In another experiment covering 28 days of administration at dose-levels between 80 and 140 g/ton of feedingstuff, an antibiotic activity was measured after 17 hours withdrawal of salinomycin in the liver and kidneys (0.05 mg/kg, expressed as salinomycin) and subcutaneous fat (0.05 - 1 mg/kg, expressed as salinomycin). After 72 hours withdrawal, there was no more activity except in the liver of one animal where traces were detected. Under the same experimental conditions, the use of  $^{14}\text{C}$ -salinomycin showed measurable residual

radioactivity in the liver, kidneys, muscle and adipose tissue 120 hours after cessation of administration. In further investigations salinomycin was identified in the adipose tissue and the liver after a withdrawal period of 17 hours, together with labelled triglycerides. After longer withdrawal periods (72 and 120 h), the residual radioactivity in adipose tissue and skin was mostly present in the lipids and resulted from the incorporation of labelled carbon fragments arising from the salinomycin molecule. It is likely that the insoluble radioactive fraction simultaneously present in the liver and kidneys has a similar origin.

3. On the basis of the available data, the Committee is of the opinion that salinomycin can be used without risks in feedingstuffs for chickens at the level provisionally authorized (50 - 70 mg/kg) and with a withdrawal period of not less than five days before slaughter.

#### REFERENCES

Dossiers Hoechst A.G. (1983)