

**REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION  
ON THE USE OF HALOFUGINONE IN FEEDINGSTUFFS  
FOR CHICKENS REARED FOR LAYING  
(Terms of Reference: November 1991)**

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

1. Has the use as a coccidiostat of Halofuginone (dl-trans-7-bromo-6-chloro-3-(3-hydroxy-2-piperidyl)acetyl)-quinazoline-4-(3H)-one-hydrobromide) under the conditions proposed for its use as an additive for chickens reared for laying (see background) significant effects on the prevention of coccidiosis in this animal species?
2. Is this use safe for the chickens reared for laying?
3. Does the proposed use result in residues in the eggs? If so, what is the qualitative and quantitative composition of these residues?
4. Do the toxicology studies allow the conclusion that the proposed use does not present risks
  - for the consumer?
  - for the user?
5. In the light of the answers to the above questions, are the proposed conditions of use acceptable?

**BACKGROUND:**

In Accordance with the provisions of Council Directive 70/524/EEC of 23 November 1970 concerning additives in feedingstuffs<sup>1</sup>, as amended by Council Directive 84/587/EEC of 29 November 1984<sup>2</sup>, the use of Halofuginone (E 764) is authorized at Community level under the conditions set out as follows in Annex I, Section D (Coccidiostats and other medicinal substances) of Commission Directive 91/248/EEC<sup>3</sup>:

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<sup>1</sup> O.J. No L270 (14.12.70) p. 1

<sup>2</sup> O.J. No. L319 (08.12.84) p. 13

<sup>3</sup> O.J. No. L124 (18.05.91) p. 1

D. Coccidiostats and other medicinal substances				
Species or category of animal	Maximum age	Minimum content mg/kg of complete feedingstuff	Maximum content mg/kg of complete feedingstuff	Other provisions
Chickens for Fattening	-	2	3	Use prohibited at least 5 days before slaughter
Turkeys	12 weeks	2	3	Use prohibited at least 5 days before slaughter

The Scientific Committee for Animal Nutrition has expressed its favourable opinion in its reports of 25 April 1972<sup>4</sup>, 17 November 1982<sup>5</sup> and 8 February 1984<sup>6</sup>. An extension of the use of halofuginone has been requested in section D (Coccidiostats and other medicinal substances) of Council Directive 70/524/EEC<sup>1</sup> of 23 November 1970 concerning additives in feedingstuffs, under the following conditions of use:

D. Coccidiostats and other medicinal substances				
Species or category of animal	Maximum age	Minimum content mg/kg of complete feedingstuff	Maximum content mg/kg of complete feedingstuff	Other provisions
Chickens reared for Laying	12 weeks	2	3	Indicate in the instructions for use: "Dangerous for Ducks and Geese"

#### **OPINION OF THE COMMITTEE (14 January 1993):**

1. The efficacy of halofuginone against different *Eimeria* spp affecting the chicken is well documented and assessed over many years of field experience. In the absence of specific experiments carried out with pullets, but considering that the same strains affect both sexes and that the rearing conditions are strictly similar, it is

<sup>4</sup> Report of the Scientific Committee for Animal Nutrition on the use of Halofuginone in feedingstuffs for Chickens. In: **Reports of the Scientific Committee for Animal Nutrition, Second Series 1980**. Lux: Office for Official Publications of the EC, Report EUR 6918, p. 11-13, No. Catalogue CD-NK-80-002-EN-C

<sup>5</sup> Report of the Scientific Committee for Animal Nutrition on the use of Halofuginone in feedingstuffs for Turkeys. In: **Reports of the Scientific Committee for Animal Nutrition, Fourth Series 1984**. Lux: Office for Official Publications of the EC, Report EUR 8769, p. 94-97, No. Catalogue CD-NK-83-010-EN-C

<sup>6</sup> Third Report of the Scientific Committee for Animal Nutrition on the use of Halofuginone in feedingstuffs for Chickens. In: **Reports of the Scientific Committee for Animal Nutrition, Fifth Series 1986**. Luxembourg: Office for Official Publications of the EC, Report EUR 10410 EN, p. 6-7, No. Catalogue CD-NK-86-003-EN-C

considered that the data available concerning the male birds may be extended to the females.

A specific problem encountered with pullets for all coccidiostats is to develop a sufficient immunity during the dosing period to avoid the administration of the same or similar compound during the subsequent laying phase. Halofuginone exhibits, as do other coccidiostats used for pullets, a medium coccidiostatic activity suggesting that sufficient viable oocysts should remain to induce immunity and protect the future layers. However neither direct proof nor indirect proof, such as a challenge study, has been produced. Information should be required on this matter.

2. The oral LD50 is 15.7-19.7 mg/kg live weight, i.e. 50-60 times the dose proposed for use.

The consequences of the 3ppm treatment over a long period (19-20 weeks) on the following laying period have been evaluated (two studies). No effect has been observed in terms of feed consumption, weight gain and mortality of the birds, nor the number of eggs layed, their fertility and hatchability.

A tolerance study of different dosages (3, 9 and 12ppm) has shown a significant reduction of feed efficacy and pullet weight at 9ppm but a higher incidence at 15ppm. The number of eggs layed, their weight and shell thickness were reduced at 15ppm level, whereas their fertility and hatchability were not affected. No haematological damage was observed. The histopathological analysis of pullets receiving the 9 or 15ppm dosage indicates a higher incidence of mineralisation of renal tubules and ovaries; an occasional accumulation of lymphoid cells in the myocardium, and hyperplasia of lymphoid cells in the bursa of Fabricius, bone marrow and kidney.

3. The original data concerning the metabolic fate and residues of halofuginone in the chicken have been analyzed by the SCAN Committee, and the conclusions published in the SCAN Report Series EUR 6918 (1980). A major drawback is the lack of information on the metabolic pathways and the nature of the metabolites, namely those present as residues in the tissues and eggs apart from unchanged halofuginone.

The additional data supplied by the firm support the request to the American FDA to reconsider the tolerable residue in the liver of broilers. In fact these new data: 1) confirm that the liver is the target tissue and indicate that halofuginone is the major residue even when the halofuginone/ total metabolites ratio decreases over the withdrawal period, 2) indicate that the metabolic profiles are qualitatively similar in the chicken and mice, so validating the toxicological studies (the lowest NOEL was observed in the chronic toxicological studies carried out in mice).

A study was designed to provide data on residual concentrations of halofuginone in the first eggs produced by young laying hens, i.e. during the first two weeks of the laying period (21st and 22nd week of age), following oral treatment with 3ppm halofuginone during weeks 13 and 14 followed by <sup>14</sup>C-halofuginone at the same

dosage during weeks 15 and 16. The duration of the treatment period (4 weeks) was chosen so that the residues should reach steady state concentrations within this period. The results indicate that the total residual radioactivity in egg homogenate was below the limit of detection (0.0015 mg/kg).

4. If one takes into account that the species is the same, that the chickens are male and female birds, that the duration of the feed supplementation covers the same period of life and that the rearing conditions and dose applied are identical, it can be considered that the present application for pullets is already covered by the existing authorization for chickens. The only additional specific point of concern is the possible transfer of residues into and subsequent safety of the eggs. The lag of at least 4 weeks between the end of the supplementation and the onset of the laying period appears to be sufficient to ensure the absence of residues in eggs (less than 0.0015 mg/kg, limit of detection). Therefore it can be concluded that the use of halofuginone in pullets should not present any risk for the consumer.

The safety for the user has been already considered by the SCAN Committee in its former and favourable opinion (see above).

5. In the light of the above analysis and previous SCAN opinion it can be concluded that the conditions of use of halofuginone proposed for pullets are acceptable.

However, in reference to the Directive 87/153/EEC<sup>7</sup> certain insufficiencies have been noted, namely the absence of data concerning the metabolic fate of halofuginone in both the chicken and the pullet. This compound should be considered as a candidate for the general procedure of periodic re-examination of the additives.

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<sup>7</sup> O.J. No. L64 (07.03.87) p. 19