Report of the Scientific Committee for Animal Nutrition on the use of Nitrovin in feedingstuffs

Opinion expressed 29/30 November 1988

TERMS OF REFERENCE (November 1988)

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

- Does the use of nitrovin as a growth promoter under the conditions given in the background give rise to dangers for human or animal health, particularly mutagenic, teratogenic or cancerogenic effects or present undesirable effects on the environment?

BACKGROUND

In accordance with the provisions of Council Directive 70/524/EEC (1) of 23 November 1970, concerning additives in feedingstuffs, Member States are authorized to use, by way of derogation up to 30 June 1989, nitrovin as an additive in feedingstuffs for use as a growth promoter in chickens for fattening, other poultry, calves and pigs under the following conditions:

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

Additive	Species or category of animal	Maximum age	Min. content mg/kg of complete feedingstuffs	Max. content mg/kg of complete feedingstuffs	Other provisions
1. Growth-promoters					
Nitrovin					For all feedingstuffs mixing or simultaneous use with antibiotics prohibited
	Chickens for fattening	-	10	15	
	Turkeys	26 weeks	10	15	
	Other poultry except ducks, geese, laying hens, pigeons	16 weeks	10	15	
	Calves	6 month	20	40	
			40	80	Milk replacers only
	Piglets	10 weeks	10	25	
			20	30	Milk replacers only
	Pigs for fattening	6 month	5	15	

Nitrovin had been authorized, in Annex I of the 4th Commission Directive 74/38/EEC (2) amending the annexes to Council Directive 70/524/EEC (1) as a growth promoter for chickens for fattening and in Annex II for pigs, calves and turkeys. In 1976 the Annex II uses for pigs were transferred to Annex I (13th Commission Directive 76/13/EEC (3)).

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(2) OJ no. L 30, 17.12.1974, p. 21
(3) OJ no. L 4, 09.01.1976, p. 21

Subsequently evidence arose of an apparant lack of stability transferred back to Annex II (46th Commission Directive 84/349/EEC (4)), whilst further work relating to stability was carried out. This work showed that the apparent lack of stability was due to the unreliability of the method of analysis then being used. A satisfactory method has now been developed resolving this problem (Dossiers Orphahell).

More recently doubts have been raised by certain Member States, partly based on a IARC publication of 1983, concerning the safety of the substance, in particular carcinogenicity, mutagenicity, teratogenicity and hazards for the environment. Data not previously known to the Commission have now become available.

OPINION OF THE COMMITTEE

The SCAN was provided with comprehensive documentation on nitrovin (see annex). In evaluating this evidence the working group noted that the data on metabolism in rats, pigs and chickens (Dossier Cyanamide) were adequate. Nitrovin is poorly absorbed (max. 1%), most being excreted in the faeces.

The available short-term studies in rat, dog and pig (Dossier Cyanamide) showed some evidence of hepatotoxicity and adverse effects on the kidneys and intestinal tract. From these a no-effect level of about 12,5 mg/kg body weight could be estimated.

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(4) OJ. no. L 183, 11.07.1984, p. 15

Chronic studies were available in three species:

The two chronic studies in rats (Dossier Cyanamide) were negative with regard to carcinogenicity. Both were inadequate regarding the number of animals, the parameters investigated and the duration of the studies.

The chronic study in hamsters (Dossier Cyanamide) showed no evidence of carcinogenic activity.

Of three chronic studies in mice, the study in C 57 black mice (Dossier Cyanamide) showed no evidence of carcinogenicity. The other two studies (Dossier Cyanamide) were performed in a lung-adenoma susceptible strain. Both showed an increased response to nitrovin administration which was dose-related concerning frequency, size and malignancy of tumors, particularly in females. However, the results of investigations in these susceptible strains are difficult to interpret. A whole series of mutagenicity tests, in bacterial systems and a test for sex-linked recessive lethals in Drosophila were positive, being evidence of a genotoxic potential of nitrovin.

The SCAN is of the opinion that information on the following aspects is required to enable a full toxicological evaluation to be made:

1. in vivo mutagenicity tests, particularly for their chromosomal effects

2. adequate multigeneration-reproduction and teratogenicity studies

3. adequate investigations of environmental impact.

For evaluating potential hazards to the user, additional information is needed on dust formation and whether an antidust formulation can be provided.

To evaluate the hazards to the consumer a better analytical method for tissue residues with a sensitivity of 10 ppb or less is needed. The SCAN draws attention to the fact that the apparent no-effect level in the rat and dog study would allow the establishment of an acceptable daily intake (ADI) of approximately 125 ug/kg bw. This is very close to the limit of sensitivity of the presently available method of analysis. In order to determine whether the ADI is likely to be exceeded, a much more sensitive method of analysis is required. Furthermore additional residue studies using such a more sensitive method are required.

On the basis of the information hitherto available the SCAN is unable to give a final opinion on the hazard for humans and target species, particularly the carcinogenic, mutagenic and teratogenic potential of nitrovin and on the possible hazards to the environment. Nevertheless the Committee wishes to draw attention to the advice given on the Nitrofuranes published in 1979.

REFERENCES

Dossiers Cyanamide international corporation (1971-1976)
Dossiers Orphahell (1985-1987)
IARC - Monograph 31 (1983), Lyon Symposium
Reports of the Scientific Committee for Animal Nutrition, first series, Brussels 1979.