# REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF MONENSIN SODIUM AND FLAVOPHOSPHOLIPOL IN FEEDINGSTUFFS FOR FATTENING CATTLE

Opinion expressed 26 April and 11 July 1979

## 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 antibiotics monensin sodium and flavophospholipol in feedingstuffs for fattening cattle, 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 be harmful to the consumer ?

2. Could the excreted products, derived from these additives, be prejudicial to the environment ? If so, what is the nature of the risks ?

3. In the light of the answers to the above questions, should the conditions of use already authorized for these additives 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-fourth Commission Directive of 28 July 1978 (2), Member States are authorized to use flavophospholipol and monensin sodium by way of derogation up to 31 December 1978, under the following conditions set out in Annex II, Section A, of the Directive :

(1) OJ No L 270, 14.12.1970, p. 1
(2) OJ No L 247, 9.09.1978, p. 25

| Additif | Species of animal | Minimum content | Maximum content | Other provisions |
|---|---|---|---|---|
| | | ppm (mg/kg) of complete feedingstuffs | | |
| Flavophospholipol | Cattle for fattening | 5 | 15 | Maximum dose in the daily ration : 50 mg |
| Monensin sodium | Cattle for fattening | 10 | 40 | Maximum dose in the daily ration :<br>- Cattle from the commencement of rumination up to 250 kg : 125 mg<br>- Cattle of more than 250 kg and up to 450 kg : 250 mg<br>- Cattle of more than 450 kg : 360 mg<br>In addition to the labelling provisions referred to in Article 10, give the following instruction:<br>"Keep out of reach of equine species". |

A recent examination revealed a divergence between the maximum levels established respectively for the daily ration and the complete feedingstuff for flavophospholipol. Moreover, the relationship between the maximum doses of monensin sodium in the daily ration and the ranges of cattle body weight was not appropriate.

Considering the normal dose-levels of these additives in the daily ration, it was proposed

- to fix the minimum and maximum content for flavophospholipol in complete feedingstuffs at 2 and 5 mg/kg respectively,
- to maintain the minimum and maximum content (10 and 40 mg/kg) for monensin sodium in complete feedingstuffs,
- to delete for both products the provisions on maximum doses in the daily ration, because these additives are intended for supplementary feedingstuffs and because the conditions of use of these feeds are subject to the labelling provisions of Article 11 of the directive.

OPINION OF THE COMMITTEE

A. USE OF MONENSIN SODIUM

Opinion expressed 26 April 1979

1. Monensin is an antibiotic produced by Streptomyces cinnamonensis. The active ingredient of the marketed mycelian product is the sodium salt of monensin.

Monensin sodium is not absorbed in appreciable quantities from the digestive tract when incorporated in feed for fattening cattle according to the authorized conditions of use. No residues were detected in tissues and organs by microbiological analysis (limit of determination : 0.05 mg/kg). Traces of the product appeared in the liver of cattle receiving daily doses of 750 mg of the product (i.e. more than three times the maximum authorized level) for 106 days up to slaughter. These residues disappear when the treatment is stopped 48 hours before slaughter.

Investigations using 14C-labelled monensin sodium showed that, under normal conditions of use of the product (30-40 mg/kg of complete feedingstuff), residues were absent (limit of detection of radioactivity expressed as monensin sodium : 0.021 mg/kg) from the edible tissues and organs, except the liver. Residues in the liver varied with the animal from 0.21 to 0.59 mg/kg. Further investigation showed that these residues are comprised of 2-3 % of monensin sodium and a large number of metabolites resulting from demethylation, hydroxylation and/or decarboxylation of the product. The presence of monensin sodium and its metabolites in concentrations of 13-14 mg/kg in the bile suggests that this is the active route of elimination.

Monensin was investigated in short- and long-term toxicological studies, including carcinogenicity, mutagenicity, reproduction tests over several generations and tests on allergic effects. Short-term toxicological studies, relay toxicity in dogs and rats and tests on allergic effects were also performed on the mycelian product. No significant clinical, biochemical or histopathological alterations nor any carcinogenic, teratogenic, mutagenic or allergenic effects were observed.

The use of monensin sodium under the authorized conditions is therefore not prejudicial to the consumer.

2. Monensin is eliminated in ruminants for the most part unchanged in the faeces, the rest being in the form of microbiologically inactive metabolites. The active principle then decays by 30-40 % in faecal matter in 10 weeks, by more than 80 % in manure in 11 weeks and by more than 80 % in soil in two weeks.

Phytotoxicity studies were carried out on plants in the germinative and vegetative stages. Field trials were performed in soils fertilized with manure from cattle which had been fed rations containing monensin sodium. No phytotoxic effects were observed. Investigations on soil micro-organisms, including nitrogen fixers, did not show any interference by the product.

In the light of these data and because of the low solubility of monensin sodium in water, there is no reason to suspect a contamination of the environment under the authorized conditions of use.

3. After consideration of all available documentation, the Committee considers that the dose-levels authorized, i.e. 10-40 mg/kg of complete feedingstuff, should be maintained together with the instruction "keep out of reach of equine species".

In order to prevent incorrect use of monensin sodium in ruminant cattle receiving supplementary feedingstuffs, it is considered useful to establish a maximum daily dose per animal based on live weight. It is accepted that feed intake of ruminant cattle does not increase in direct proportion to body weight. This necessitates an adjustment of the amount of additive in the ration.

In view of the foregoing, the Committee is of the opinion that the maximum amount of monensin sodium in the daily ration should not exceed : 80 mg (constant value) + 60 mg/100 kg live weight. The values obtained according to this formula are as follows :

| Weight of the animal (kg) | Average daily consumption of feed (kg) | mg monensin sodium/head/day (80 mg + 60 mg/100 kg live weight) | ppm equivalent (mg monensin sodium/kg complete feedingstuff) |
|---|---|---|---|
| 100 | 3.4 | 140 | 41 |
| 150 | 4.4 | 170 | 39 |
| 200 | 5.6 | 200 | 36 |
| 250 | 6.7 | 230 | 34 |
| 300 | 7.6 | 260 | 34 |
| 350 | 8.3 | 290 | 35 |
| 400 | 9.0 | 320 | 36 |
| 450 | 9.6 | 350 | 36 |
| 500 | 10.4 | 380 | 37 |
| 550 | 10.5 | 410 | 39 |
| 600 | 10.9 | 440 | 40 |

The Committee therefore proposes to replace the maximum doses, at present laid down for the daily ration, by the following provision : "For ruminant cattle receiving supplementary feedingstuffs, the maximum dose in the daily ration shall be adjusted so as not to exceed 80 mg + 60 mg/100 kg live weight".

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## B. USE OF FLAVOPHOSPHOLIPOL

Opinion expressed 11 July 1979

1. Flavophospholipol is an antibiotic produced by Streptomyces bambergiensis. The marketed product is mycelian.

   Flavophospholipol is not absorbed in appreciable quantities from the digestive tract when incorporated in feed for fattening cattle according to the conditions of use authorized. No residues were detected in the tissues and organs by microbiological analysis (*). Flavophospholipol residues up to 1 mg/kg were found in the liver of cattle receiving 600 mg of the product daily for 140 days up to slaughter. No residues were found under the same experimental conditions with a dosage of 400 mg.

   Balance studies and investigations using 32P-labelled flavophospholipol showed that orally administered, the product is eliminated unchanged in the faeces without any metabolites being formed. The stability of the product is explaned by its resistance to the action of various enzymes.

   Short- and long-term toxicity studies were carried out on both the pure substance and the mycelian product. No significant clinical, biochemical or histopathological changes were observed nor any carcinogenic, teratogenic, mutagenic or allergenic effects. Pharmacological investigation of the mycelian product did not reveal any stimulant or depressing effect on the central nervous system nor any muscle-relaxing, analgesic, spasmolytic, pressor, gonadotrophic, glycaemic or neurotoxic effects. Flavophospholipol produced no clinical symptoms when administered to human volunteers. The use of flavophospholipol under the authorized conditions is therefore not prejudicial to the consumer.

2. Practically 100 % of the flavophospholipol contained in the ration of ruminants is eliminated unchanged in the faeces. The antibiotic activity of the compound reaching the soil with manure decreases steadily and in 5-6 weeks declines to 15 %. The decay of the antibiotic activity declines to 15 % after 7 days in the faeces of cattle which have been receiving feed supplemented with flavophospholipol for a long period. Flavophospholipol present in the soil is not absorbed by vegetation.

   In the light of these data and because of the low solubility of flavophospholipol in water there is no reason to suspect a contamination of the environment under the authorized conditions of use.

(*) Limit of determination :
Muscular tissue and organs : 0.2 - 0.5 mg/kg
Adipose tissue : 0.2 - 0.4 mg/kg
Blood : 0.1 mg/l

3. After consideration of all available documentation, particularly on the efficacy of the product, the Committee considers that the dose-levels authorized should be limited to 2-10 mg/kg of complete feedingstuff.

In order to prevent incorrect use of flavophospholipol in ruminant cattle receiving supplementary feedingstuffs, it is considered useful to establish a maximum daily dose per animal based on live weight. It is accepted that feed intake of ruminant cattle does not increase in direct proportion to body weight. This necessitates an adjustment of the amount of additive in the ration.

In view of the foregoing, the Committee is of the opinion that the maximum amount of flavophospholipol in the daily ration should not exceed : 25 mg (constant value) + 15 mg/100 kg live weight. The values obtained according to this formula are as follows :

| Weight of the animal (kg) | Average daily consumption of feed (kg) | mg flavophospholipol/ head/day (25 mg + 15mg/ 100 kg live weight) | ppm equivalent (mg flavophospholipol/kg complete feeding-stuff) |
|---|---|---|---|
| 100 | 3.4 | 40 | 11.7 |
| 150 | 4.4 | 47.5 | 10.8 |
| 200 | 5.6 | 55 | 9.8 |
| 250 | 6.7 | 62.5 | 9.3 |
| 300 | 7.6 | 70 | 9.2 |
| 350 | 8.3 | 77.5 | 9.3 |
| 400 | 9.0 | 85 | 9.4 |
| 450 | 9.6 | 92.5 | 9.6 |
| 500 | 10.4 | 100 | 9.6 |
| 550 | 10.5 | 107.5 | 10.2 |
| 600 | 10.9 | 115 | 10.5 |

The Committee therefore proposes to replace the maximum doses, at present laid down for the daily ration, by the following provision : "For ruminant cattle receiving supplementary feedingstuffs, the maximum dose in the daily ration shall be adjusted so as not to exceed 25 mg + 15 mg/100 kg live weight."

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