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Reports of the Scientific Committee for Animal Nutrition

1980

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C O N T E N T S

FOREWORD

The first series of reports of the Scientific Committee for Animal Nutrition was published in 1979 (1). This collection constitutes the second series and contains the Committee's opinions on the use of certain additives in feedingstuffs together with a chapter entitled "Guidelines for the Assessment of Additives in Feedingstuffs".

The opinions of the Committee relate to questions put to it by the Commission on the safety of certain additives used to promote growth in chickens, pigs and cattle for fattening, or to prevent coccidiosis in chickens. Since consideration was being given to authorization of these additives at Community level, it was important to ensure, on the basis of sound scientific advice, that they are safe to use under the conditions proposed.

The Commission also felt it would be useful to publish the guidelines, which had been approved by the Committee, on the contents of the dossiers required to assess substances for authorization as feedingstuffs additives. These guidelines, which are published in response to frequent requests for information, should help to achieve a more uniform implementation of Community provisions governing the authorization of feedingstuffs additives.

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(1) Set up by Commission Decision 76/791/EEC, 24 September 1976 (OJ L 279, 9.10.1976, p.35).
(2) Until expiry of his term of office on 23 September 1979
(3) Appointed on 7 September 1979
(4) Re-elected Chairman on 27 September 1979
(5) Re-elected Vice-Chairman on 27 September 1979
(6) Commission of the European Communities, Directorate-General for Agriculture.

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

Opinion expressed 6 July 1978

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 growth promotor carbadox in feedingstuffs for pigs, 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 residues be harmful to the consumer ?

2. Could the use of this additive affect the development of resistance in bacteria ?

3. Could this use be prejudicial to persons required to handle this product in industry and/or agriculture or to the environment ? If so, what is the nature of the risks ?

4. In the light of the answers to the above questions, should the conditions of use already authorized for this additive 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-third Commission Directive of 23 June 1978 (2), Member States are authorized to use carbadox, by way of derogation up to 31 December 1978, under the following conditions set out in Annex II, Section F, of the Directive :
Species of animal : pigs, up to four months.
Maximum content in complete feedingstuffs : 50 ppm (mg/kg).
Other provisions : use prohibited for at least 4 weeks before slaughter.
Mixing or simultaneous administration with an antibiotic prohibited.

(1) OJ No L 270, 14.12.1970, p. 1
(2) OJ No L 198, 22.07.1978, p. 10

OPINION OF THE COMMITTEE

1. Carbadox (methyl-3-(2-quinoxalinylmethylene)-carbazate-N,N'-dioxide) is metabolized in pigs to quinoxaline-2-carboxylic acid and methylcarbazate with the intermediary formation of desoxycarbadox (methyl-3-(2-quinoxaline-methylene) carbazate). Carbadox and desoxycarbadox have a short life-time. After three weeks administration of 3.5 mg carbadox/kg body weight/day (= maximum authorized level) to pigs the residues in edible tissues are less than 5 µg/kg (limit of determination) six hours after withdrawal of the supplemented feedingstuff for carbadox, and 72 hours after withdrawal for desoxycarbadox.

   Twenty-four hours after withdrawal, residues consisting essentially of quinoxaline-2-carboxylic acid and small amounts of methylcarbazate are less than 0.1 mg/kg in all tissues except the liver, where they reach 1.0 mg/kg. Their concentration in this organ decreases progessively, being 0.1 mg/kg after two weeks and 0.03 mg/kg (limit of determination) after four weeks. A four-week withdrawal period therefore suffices for elimination of the residues.

   Carbadox and its metabolites have been investigated in short- and long-term toxicological studies in laboratory animals. Administration of carbadox for two years in the daily diet of rats produced toxic effects (nodular hepatoma) at doses above 2.5 mg/kg body weight. The compounds causing these effects have been shown to be carbadox and desoxycarbadox. The long-term administration of daily doses up to 50 mg/kg body weight of quinoxaline-2-carboxylic acid (main metabolite) or of 10 mg/kg body weight of methylcarbazate produced no adverse effects.

   The induction of a variety of mutagenic effects in certain strains of microorganisms, Drosophila and mice appeared to be associated with chemicals having a quinoxaline-N,N'-dioxide structure. This property has not been observed with the metabolic products of carbadox and desoxycarbadox.

   These results show that residues of carbadox can be considered to be of low toxicity as soon as the original compound and desoxycarbadox have disappeared, i.e. 72 hours after administration of the product.

   Carbadox residues produced no adverse effects in relay toxicity studies carried out during two years over three generations in rats, and for 87 months in dogs. The test animals were fed during

these trials rations containing meat and/or liver from pigs which had received 200 mg carbadox/kg feedingstuff (four times the maximum authorized level) and had been slaughtered without any withdrawal period. In neither case were any harmful effects observed.

2. Although carbadox has antibacterial properties, it modifies only slightly the intestinal flora of animals. It does not induce the selection of enterobacteriaceae (E. coli or others) carrying R-plasmids nor does it cause a transfer of R-factors. Despite continuous use for several years in pigs, a decrease of transferable resistance to chemotherapeutics was observed in E. coli of the intestinal flora. This more sensitive flora tended to become dominant.

3. Carbadox with a chemical and physico-chemical specification considered satisfactory by the Committee is available commercially as a permix containing soya oil. This inert ingredient prevents the formation of dust during the preparation of the premix and the feedingstuff. Surveys conducted in factories indicate that these products may be handled safely. The risks to agricultural workers appear negligible if the feedingstuff is in pellet form.

   61-72 % of the dose ingested by pigs is excreted in the urine and 2-10 % in the faeces during the 24 hours following administration. The total quantity excreted after 72 hours amounts to 85-90 %. The excreted products contain only traces of carbadox and desoxycarbadox. They consist essentially of quinoxaline-2-carboxylic acid and methylcarbazate either in their free or conjugated forms. These compounds are neither toxic nor mutagenic. They are polar compounds which, on the basis of present knowledge, do not appear to accumulate in the food chain or to pollute the environment.

4. In the light of the available data the Committee is of the opinion that the use of carbadox cannot lead to the presence of residues in animal products provided the conditions of use mentioned below are adhered to, nor that it is harmful to the environment or to persons required to handle the product in industry and/or agriculture.

   Conditions of use

   Feedingstuffs for pigs, up to the maximum age of four months.
   Maximum carbadox content : 50 mg/kg of complete feedingstuff.
   Presentation of the feedingstuff : pellets.
   Withdrawal period of the supplemented feedingstuff : at least four weeks before slaughter.

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REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF HALOFUGINONE IN FEEDINGSTUFFS FOR CHICKEN

Opinion expressed 25 April 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 coccidiostat halofuginone in feedingstuffs for chicken, 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 residues be harmful to the consumer ?

2. Could the excreted products, derived from the additive, 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 this additive 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 twentieth Commission Directive of 7 December 1977 (2), Member States are authorized to use halofuginone, by way of derogation up to 31 December 1978, under the following conditions set out in Annex II, Section B, of the Directive :
Species of animal : Chicken for fattening.
Minimum and maximum content in complete feedingstuffs : 2 - 3 ppm (mg/kg)
Other provisions : use prohibited at least 5 days before slaughter.

(1) OJ No L 270, 14.12.1970, p. 1
(2) OJ No L 18, 24.01.1978, p. 7

OPINION OF THE COMMITTEE

1. Studies of the metabolism of halofuginone (dl-trans-7-bromo-6-chloro-[3-(3-hydroxy-2-piperidyl)acetonyl]-4(3H)-quinazolinone hydrobromid) in chicken, using compounds with the 14C-label incorporated either in the piperidine or the quinazolinone nucleus, show that the product does not undergo intensive metabolic degradation in animals. Residues in tissues and organs appear to consist mainly of halofuginone and non-polar metabolites containing the piperidine and quinazolinone nuclei.

   Residues in tissues and organs of chicken which had been fed for several weeks with a ration containing 3 mg halofuginone/kg feedingstuff (maximum authorized level) were determined by measurement of total radioactivity and by high-pressure liquid chromatography. Residues were negligible (less than 0.03 mg/kg) in muscle, skin and fatty tissue 24 hours after withdrawal of the supplemented feedingstuff. Small amounts (less than 0.06 mg/kg) were still present in the liver and kidney 5 days after withdrawal.

   Halofuginone was investigated in short- and long-term toxicological studies in laboratory animals. The Committee considered that certain observed effects, one of which was an increase in the incidence of lymphoreticular tumours in mice, required further investigation. The interpretation of these effects is difficult because of the use of animal strains with a tendency for developing similar tumours spontaneously and because studies on mutagenesis, histopathology and clinical chemistry were limited. The acquisition of more extensive data on these aspects is essential because of the low acceptable daily intake of the product for mice, rats and dogs, and because the metabolites are incompletely known.

2. Studies on the fate of halofuginone in chicken showed that, under the authorized conditions of use, about 80 % of the amount ingested appears in the excreta within the next 24 hours. Excretion continues for about a week. The presence of residues in bile indicates the existence of an enterohepatic cycle. The excreted products appear to be composed mainly of halofuginone and non-polar metabolites of similar structure.

   Tests performed on different types of soil showed that these products are strongly adsorbed, difficult to extract with water and resistant to biodegradation. Halofuginone is not phytotoxic

in tests carried out on tomato, cucumber, lettuce and tobacco crops.

These observations indicate that contamination of the environment is unlikely. However, additional data on biodegradation of excreted products and on their effects on soil microbiology and aquatic life are necessary in order to remove any uncertainties.

3. In the light of the available facts, the Committee is of the opinion that the use of halofuginone in feedingstuffs for chicken, at the levels presently authorized, could be maintained provisionally, provided a withdrawal period of at least 7 days before slaughter is imposed in order to assure the elimination of residues from liver and kidneys. A reassessment of this additive is needed, after a more detailed study of the long-term toxicity in rats and additional studies on the biodegradation of the residues excreted by chicken as well as the possible effects on soil micro-organisms and aquatic life have been carried out.

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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 : - Cattle from the commencement of rumination up to 250 kg : 125 mg - Cattle of more than 250 kg and up to 450 kg : 250 mg - Cattle of more than 450 kg : 360 mg In addition to the labelling provisions referred to in Article 10, give the following instruction: "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.

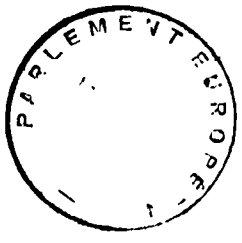
In the light of these data and because of the low solubility of monensin sodium in water, there is no reason to suspect a contamination of the environment under the authorized conditions of use.

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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REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF AVOPARCIN IN FEEDINGSTUFFS FOR CHICKEN AND PIGS

Opinion expressed 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 antibiotic avoparcin in feedingstuffs for chicken and pigs, 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 residues be harmful to the consumer ?

2. Could the use of this additive affect the development of resistance in bacteria ?

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

4. In the light of the answers to the above questions, should the conditions of use already authorized for this additive 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 twentieth Commission Directive of 7 December 1977 (2), Member States are authorized to use avoparcin, by way of derogation up to 31 December 1978, under the following conditions set out in Annex II, Section A, of the Directive :

Species of animal	Minimum content	Maximum content
	ppm (mg/kg) of complete feedingstuffs	
Chicken for fattening	7.5	15
Pigs, up to 10 weeks	10	40
Pigs, more than 10 weeks	5	20

(1) OJ No L 270, 14.12.1970, p. 1
(2) OJ No L 18, 24.01.1978, p. 7

OPINION OF THE COMMITTEE

1. Avoparcin is a glycopeptide antibiotic produced by Streptomyces candidus. The active substance of the mycelian product on the market is avoparcin lauryl sulphate.

   Radiotracer methodology sensitive to 0.05 mg/kg has been used to follow the routes and rates of excretion and the distribution in tissues of 14C-labelled avoparcin administered to rats and to broiler chicken. The radioactivity was quantitatively recovered in the excreta after a few days and there were no measurable residues in muscle, fat, liver and kidneys.

   Investigations on residues in tissues were also carried out in a number of experiments with chicken and pigs receiving avoparcin in their ration according to the conditions of use authorized and also at higher levels. There were no microbiologically detectable residues (limit of detection : 0.2 to 0.5 mg/kg, according to the substrate) nor any antibiotic activity in the muscle, fat, blood, liver, kidneys and skin at slaughter after withdrawal periods of 0, 1 and 3 days. The investigation of the muscle and liver by a gas-chromatographic method confirmed the absence of residues at the detection limit of 0.1 mg/kg.

   Avoparcin has been investigated in short- and long-term toxicity studies in laboratory animals. It had a low acute toxicity (oral LD50 for rat, mouse and chick exceeds 10 g/kg body weight). Long-term studies in rats fed diets containing various doses of the mycelian product did not show any significant dose-related differences from the control groups in the usual parameters nor was there any indication that avoparcin induces specific tumours. A three-generation study in rats showed decreased neonatal survival and lower body weights of the young only at the highest dose investigated (1600 mg avoparcin/kg feedingstuff). No abnormalities were observed in relay toxicity studies in rats fed for 90 days a diet containing 33 % of tissues from chicken reared for nine weeks on feed containing 500 mg avoparcin/kg.

2. Avoparcin is active in in vitro tests against gram-positive but not gram-negative bacteria and has been shown to have no significant influence on the flora of the small intestine of broiler chicken. Despite a slight development of resistance in vitro in strains of enterococci, there is no evidence that the use of avoparcin in the diet of pigs and chicken favours the selection of bacteria with stable resistance in Clostridium welchii, group D streptococci and nasal staphylococci. The development of

cross-resistance between avoparcin and a number of therapeutic antibiotics has been studied in pigs. There was no evidence that avoparcin, at levels of 20 to 200 ppm in the diet, induced the selection of bacteria resistant to avoparcin itself, or to any of the other therapeutic antibiotics tested.

3. The elimination of avoparcin lauryl sulphate in pig and chicken excreta and the stability of the excretion products in manure have been studied. The additive passes through the digestive tract of pigs mostly undegrated, but in chicken only about half of the antibiotic activity of the ingested dose appears in the excreta. Antibiotic activity appears to decline more rapidly in chicken excreta than in pig faeces. After storage at 24°C and 37°C the half life values of avoparcin (based on antibiotic activity) were respectively 9 and 4 days in chicken excreta and 22 and 15 days in pig faeces.
   Avoparcin breakdown products are strongly bound in the soil. Hence only very small amounts of the antibiotic and its residues are likely to enter the aquatic environment either by drainage or directly. The results of a study in an ecosystem model and a study of the bioaccumulation potential suggest that manuring with chicken excreta containing avoparcin will not result in the accumulation of avoparcin or related residues in components of the environment, only trace amounts being taken up by plants and animals. Avoparcin has no obvious phytotoxic effect on crop plants and weed species and is of low toxicity to aquatic organisms.

4. The Committee considered all available information, particularly the data showing that avoparcin has a low toxicity for mammals and aquatic life, that it is virtually not absorbed from the gastro-intestinal tract, and the absence of any evidence that its use in feedingstuffs could lead to the development of resistant or cross-resistant bacteria and thereby diminish the effectiveness of therapeutically used antibiotics. In the light of the above information, the Committee is of the opinion that the use of avoparcin in chicken for fattening, piglets and pigs, under the authorized conditions, is not prejudicial to the consumer nor to the environment and should be maintained.

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GUIDELINES FOR THE ASSESSMENT OF ADDITIVES IN FEEDINGSTUFFS

GENERAL ASPECTS

This document is intended as a guide for establishing dossiers on substances being submitted for authorization as additives in feedingstuffs. These dossiers should enable an assessment of the additives based on present state of knowledge and should ensure their compliance with the fundamental principles laid down for their admission, which are the subject of the provisions of Article 6(2) of Council Directive 70/524/EEC, of 23 November 1970, on additives in feedingstuffs (*).

For this purpose all the studies outlined in this document and schematized below (cf. Presentation of studies), may be required and, if necessary, additional information may be requested. However, no study which is obviously superfluous or inappropriate for an additive will be required.

As a general rule, all the information to establish the identity, physico-chemical properties, presentation, conditions of use, methods of determination and effectiveness of the additive, its balance, tolerance, biological and toxicological effects on target species must be provided, together with data on the effects on human health and the environment, which may result directly or indirectly from its use. The studies necessary for the evaluation of risks will depend essentially on the nature of the product and the circumstances of its use. In this respect, no strict rule is applicable. It is understood that additives intended exclusively for pet foods will not be subject to the same requirements as additives intended for feedingstuffs for productive livestock whose products are consumed by man or whose excrements could constitute a significant source of pollution for the environment.

A knowledge of the metabolism and fate of the additive in productive livestock is essential. In particular it will permit the determination of the extent of pharmacological and toxicological studies to be performed on laboratory animals in order to assess the risks for the consumer. However, this evaluation cannot be based solely on studies confined to determining the direct effects of the additives on laboratory animals. The latter do not provide specific information on the toxicity and bioavailability of residues resulting from the metabolism in the species for which the additive is intended.

These guidelines are applicable generally but require that the necessary documentation be adapted to each case. This documentation should include detailed reports, presented in the order and with the numbering proposed in these guidelines, and should be accompanied by a summary. The omission of any studies proposed in these guidelines should be justified. The publications quoted as references should be attached.

(*) OJ No L 270, 14.12.1970, p. 1

OBSERVATIONS

The term "additive", as used in this document, refers to the active substances in the state in which they will be incorporated in premixes and feedingstuffs. The evaluation of these additives will also take into consideration the preparations to be used in feedingstuffs and the possible use of the relevant active substances in human nutrition and human and veterinary therapy.

The guidelines will be up-dated as new scientific knowledge develops.

PRESENTATION OF STUDIES

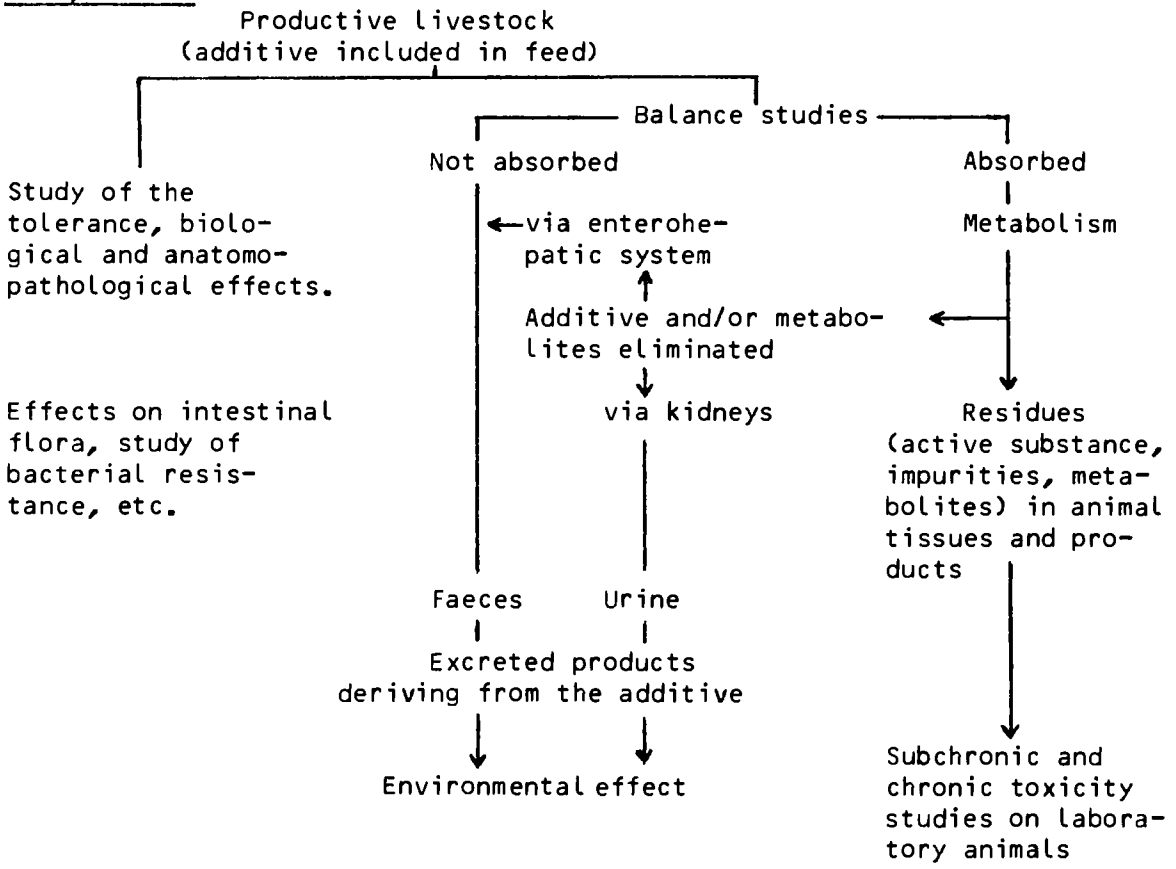
I. Identity, physico-chemical properties, presentation and conditions of use, methods of determination of the additive.

II. Studies concerning the effectiveness of the additive for the intended use.

III. Studies concerning the biological consequences of the use of the additive in feedingstuffs (for productive livestock, cf. scheme below).

IV. Other relevant studies.

Study scheme (*)



(*) Application of all or part of the scheme may be required, depending on the nature of the additive and the circumstances of its use.

SECTION I : IDENTITY, PHYSICO-CHEMICAL PROPERTIES, PRESENTATION AND CONDITIONS OF USE, METHODS OF DETERMINATION OF THE ADDITIVE.

1. IDENTITY

1.1. Chemical name of the additive, existing synonyms and abbreviations;

1.2. Molecular and structural formulae. If the active substance cannot be chemically defined or is a fermentation product, indicate empirical formula;

1.3. Degree of purity of the additive. Qualitative and quantitative data on any impurities present;

1.4. Manufacturing and purification processes, consistency of composition of the product in the course of production, methods used to check the consistency.

N.B. If the active substance is a mixture of two or more compounds, describe each compound separately and give their proportion in the mixture.

2. PHYSICO-CHEMICAL PROPERTIES

2.1. Physical properties of the additive (physical state, particle size, electrostatic properties, melting point, boiling point, decomposition temperature, density, vapour pressure, solubility in various solvents, UV and IR spectra, etc.);

2.2. Stability of the additive on exposure to atmospheric agents (light, temperature, moisture, etc.);

2.3. Stability of the additive in premixes and feedingstuffs during manufacture and storage. Incompatabilities with other components and possible decomposition products. Ability to obtain homogeneous mixtures at the proposed levels of incorporation in feedingstuffs.

3. PRESENTATION AND CONDITIONS OF USE

3.1. Proposed trade names for marketing the additive;

3.2. Proposed preparation for marketing the additive. Qualitative and quantitative composition of the premixes and their content of additive;

3.3. Intended use of the product in animal feed;

3.4. Proposed concentrations of the additive in feedingstuffs;

3.5. Other uses of the active substance in foodstuffs, human and veterinary therapy and the dosages to be applied. In each case list the trade names and indications for these uses.

4. METHODS OF DETERMINATION

4.1. Methods of analysis to determine the degree of purity of the additive, the nature and amount of impurities;

4.2. Qualitative and quantitative methods for the determination of the additive in premixes and feedingstuffs;

4.3. Qualitative and quantitative methods of analysis used to establish the balance sheet and the metabolism of the additive in livestock and its fate in the environment (determination of the active substance, its impurities and metabolites in organs and tissues, eggs, milk etc; determination of the nature of the excreted products, derived from the additive,

in excreta, manure, soil and water);

4.4. Qualitative and quantitative methods for the determination of residues in food (these methods should be specific and sensitive).

N.B. All the methods specified should be accompanied by information as to percentage recovery, specificity, sensitivity, possible interferences by other additives, limits of detection, margin of error. Reference standards of the additive, of the pure active substance and, if possible, of the main metabolites should be available.

SECTION II : STUDIES CONCERNING THE EFFECTIVENESS OF THE ADDITIVE FOR THE INTENDED USE

1. TECHNOLOGICAL AND ANIMAL PERFORMANCE STUDIES

1.1. Evidence of the effectiveness of the additive under the intended conditions of use

1.1.1. in technology, in comparison with reference feedingstuffs and, possibly, feedingstuffs containing additives of known effectiveness;

1.1.2. in animal production, in comparison with animals in control groups, and possibly, animals in groups receiving feedingstuffs containing additives of known effectiveness (effect on growth rate, feed conversion rate, morbidity, mortality, etc.).

1.2. Effect of the additive on nutritive, technological and organoleptic quality of carcasses, meat, offal, eggs, milk, etc.

2. EXPERIMENTAL CONDITIONS IN THE STUDIES ON ANIMAL PERFORMANCE

Give a detailed description of the tests performed and provide the following data :

2.1. Species, breed, age and sex of the animals, identification procedure;

2.2. Number of test and control groups; number of animals in each group (the number should be large enough for statistical analysis using suitable statistical parameters);

2.3. Dose-levels of the additive, percentage of the ingredients of the ration and detailed analysis thereof;

2.4. Location of each experiment, physiological and animal health conditions, rearing conditions (these should reflect those used in practice in the Community);

2.5. Date and exact duration of testing, date of examinations performed;

2.6. Adverse effects which occurred during the experiment and time of their appearance.

SECTION III : STUDIES CONCERNING THE BIOLOGICAL CONSEQUENCES OF THE USE OF THE ADDITIVE IN FEEDINGSTUFFS

The studies outlined in this section are intended to permit assessment of the safety in use of the additive in all the target species, and of the risks for man and the environment which could result directly or indirectly from this use. The data required may vary with the nature of the additive and the animal species concerned. A knowledge of the balance and fate of the additive will always be essential for determining the need for and the extent of the information required.

As a general rule, all the additives intended for feedingstuffs for productive livestock should be investigated to determine the nature of the excreted products, the fate of these products in manures, slurries, soils and water, and their effects on soil biology and aquatic life. For additives intended for feedingstuffs for livestock whose products are consumed by man, detailed studies are required on their metabolism (as indicated in the scheme outlined under "Presentation of studies") and on the residues in animal products (composition, persistence, pharmacological effects, subchronic and chronic toxic effects) in all cases where the balance studies indicate intestinal absorption. These studies should be performed on all animal species concerned under the practical conditions of use proposed for each additive.

1. STUDIES ON TARGET SPECIES

1.1. Study of the tolerance of the additive and of its biological, toxicological and anatomo-pathological effects. Determination of the safety coefficient (margin between the proposed maximum dose-level and that resulting in adverse effects);

1.2. Study of the balance of the additive (level of absorption, level of elimination in faeces, urine, etc.);

1.3. Study of the metabolism and pharmacokinetics of the additive (fate in the organism, absorption, distribution and elimination, etc.);

1.4. Study of the effects of the additive on microorganisms, in particular the microorganisms of the intestinal flora, and of the phenomena of bacterial resistance relating to the selection of bacteria with induced chromosomal parallel resistance to chemotherapeutics and R-plasmid carrying bacteria. Study of the effect of the additive on the colonization of pathogens in the intestinal tract.

2. STUDY OF THE RESIDUES IN ANIMAL PRODUCTS

2.1. Nature and concentration of the residues (active substance, impurities, metabolites) in tissues and organs, particularly in edible products (muscle, skin, liver, milk, eggs, etc.) after withdrawal of the supplemented feedingstuff;

2.2. Persistence, half-life value and kinetics of elimination of these residues. In some cases, studies on the effects of storage and cooking may be required.

3. STUDY OF EXCRETED PRODUCTS DERIVED FROM THE ADDITIVE

3.1. Nature and concentration of the excreted products, derived from the additive (active substance, metabolites), in urine and faeces;

3.2. Persistence, half-life value and kinetics of elimination of these products in manure, slurry, soil and water;

3.3. Their effects on soil biology, in particular on nitrifying bacteria, on plant growth and aquatic life;

3.4. Their effects on methane production.

4. PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES ON LABORATORY ANIMALS

These studies may be carried out on the additive, on its residues and derivatives of these residues in edible animal products, which are likely to be toxicologically significant. As far as possible, attempts should be made to select laboratory animals showing metabolic similarities to the target species for which the additive is intended.
The test substance should be administered daily and continuously in the diet in all oral subchronic and chronic tests.

4.1. Acute toxicity

Acute toxicity studies should be carried out in at least two animal species, one of which being a rodent (preferably the rat). The test substance should be administered orally, at several dose-levels, preferably in logarithmic progression, in order to establish the LD 50. Detailed observations should be given of the biological effects during a period up to two weeks after ingestion.

4.2. Mutagenicity tests

Investigations of potential mutagenicity, including *in vitro* screening tests using metabolic activation systems may contribute to the evaluation of the toxicity.

4.3. Pharmacological studies

Appropriate investigations should be made to reveal any pharmacological activities.

4.4. Subchronic toxicity (at least 90 days)

In general, these studies should be carried out on two animal species, one of which being a rodent. The test substance should be administered orally at a minimum of three dose-levels. These should be chosen so as to determine a no-effect level and also a level permitting the establishment of a dose-response relationship. The experimental groups should contain an adequate number of animals of each sex. A control group should always be included.

In certain cases, investigations extending over six months to two years in dogs or other non-rodents may be desirable to establish the variation in sensitivity of different animal species to the test substance.

All relevant biological data should be recorded at appropriate intervals, particularly data on growth rate, feed consumption, haematology, urine analysis, biochemical parameters, mortality, organ weights, gross pathology and histopathology of major organs and tissues. If there is any evidence of specific toxic effects, these should be investigated to elucidate their origin and mechanism.

The results should be presented in detail and, as far as possible, should include statistical assessment.

4.5. Chronic toxicity

In general, chronic toxicity studies should be carried out on two species of rodents. The substance should be administered orally in at least three dose-levels. Experiments should extend for a minimum of two years in the rat and 80 weeks in mice. The experimental groups should contain an adequate number of animals of each sex. A control group should always be included. The experiment, if continued beyond the minimum period, should be terminated when survival in any but the highest dose-level group has fallen to 20 %.

The biological examinations mentioned above (cf. item 4.4) should be carried out at appropriate intervals throughout the experiment and on the surviving animals at the end of the experiment. For assessing carcinogenicity, particular attention should be paid to the time of appearance, the histological types of any observed tumours and their incidence. In certain cases, it may be necessary to investigate the possibility of transplacental carcinogenicity.

Reproduction studies should extend over at least two filial generations and may be combined with embryotoxicity including teratogenicity studies. Particular attention should be paid to fertility, fecundity and observation on post-natal development of litters.

The results should be presented in detail and, as far as possible, should include statistical assessment.

4.6. Relay toxicity

In certain circumstances - in particular, where it is not possible to isolate or identify the metabolites of the additive, or in order to obtain indications on the bio-availability of the residues - a relay toxicity study of at least 90 days may be desirable in addition to the studies required as indicated under items 4.1 to 4.5.

In this test, rats or other laboratory animals should be fed the edible products of target species which have received the additive in their ration. The experimental animals should then be examined as indicated in 4.4 and 4.5.

N.B. Any further toxicity study providing additional information useful for the assessment of the test substance should be made available.

4.7. Experimental conditions

For all pharmacological and toxicological studies give a detailed description of the tests performed and provide the following data :

4.7.1. Species, breed, strain and sex of animals;

4.7.2. Number of test and control groups; number of animals in each group (the number should be large enough for statistical analysis using suitable statistical parameters);

4.7.3. Dose-levels of the test substance, percentage of the ingredients of the ration and detailed analysis thereof;

4.7.4. General rearing conditions throughout the period of testing;

4.7.5. Date and exact duration of testing; date of examinations performed;

4.7.6. Rate and timing of deaths for the various lots;

4.7.7. Pathological incidents which occured during the experiment and time of their appearance.

SECTION IV : OTHER RELEVANT STUDIES

Depending on the nature and the conditions of use of the additive, data on allergic effects, on irritation of the skin and mucous membranes of the eye, respiratory or digestive tract, and also tests on inhalation and percutaneous toxicity, using single and repeated doses, may be required to assess possible risks in handling premixes or supplemented feedingstuffs. If necessary the preventive measures and the means of protection to be applied should be indicated.

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The opinions of the Committee relate to questions put to it by the Commission on the safety of additives used to promote growth in chickens, pigs and cattle for fattening, or to prevent coccidiosis in chickens.

The 'Guidelines' are a document intended for establishing the contents of the dossiers required by the Committee to assess substances being submitted for authorization as feedingstuffs additives.

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