COMMISSION OF THE EUROPEAN COMMUNITIES

REPORTS
OF THE SCIENTIFIC COMMITTEE
FOR ANIMAL NUTRITION

First series

1979

COMMISSION OF THE EUROPEAN COMMUNITIES

REPORTS
OF THE SCIENTIFIC COMMITTEE
FOR ANIMAL NUTRITION

First series

Manuscript finished in December 1978

This publication is also available in

DA ISBN 92-825-1000-X
DE ISBN 92-825-1001-8
FR ISBN 92-825-1003-4
IT ISBN 92-825-1004-2
NL ISBN 92-825-1005-0

A bibliographical slip can be found at the end of this volume

Printed in Belgium

ISBN 92-825-1002-6 Catalogue number: CB-28-79-277-EN-C

FOREWORD

The Scientific Committee for Animal Nutrition was set up by Commission Decision 76/791/EEC of 24 September 1976 (OJ No L 279 of 9.10.1976, p. 35) in order to provide the Commission with informed opinions on matters relating to animal nutrition and stock farming and the effects of production techniques on food quality and the environment.

The Members of the Committee are independent persons, highly-qualified in the fields associated with animal nutrition, biology, pharmacology, toxicology, medicine, veterinary medicine and the environmental sciences. The Secretariat of the Committee is provided by the Commission's Directorate-General for Agriculture.

The Committee's first series of reports, published in this volume, includes opinions relating principally to the safe use of antibiotics, coccidiostats and other medicinal substances in animal feed for collective prophylaxis, and on the effects of the presence of certain contaminants in animal feed. Questions in this connection had arisen in the course of the Commission's work on the approximation of Member States' laws on additives and undesirable substances in feedingstuffs. The detailed opinions drawn up by the Committee have removed much of the uncertainty which threatened to hold up the preparation of proposals on the use of these substances in animal feed.

Composition of the Scientific Committee for Animal Nutrition

Professor D.G. Armstrong
Professor G. Ballarini (1)
Professor S. Dalgaard-Mikkelsen (1)
Professor R. Ferrando (2)
Professor B. Gedek
Professor K. Kaemmerer (3)
Professor D. Hoetzel (1)
Professor P. Lechat (1)
Professor S. Maletto (4)
Professor D.M. McAleese
Professor D. Mura
Professor W. Oyaert (5)
Doctor J. Pantaléon
Doctor E. Poulsen (6)
Doctor K.L. Robinson (7)
Professor M. Vanbelle (1)
Doctor G.J. van Esch
Professor J. Voets (†)

(1) Appointed on 6 September 1978
(2) Elected Vice-Chairman on 15 October 1976; Chairman on 23 September 1978
(3) Elected Chairman on 15 October 1976; resigned from the Chair and from the Committee on 7 June 1978
(4) Elected Vice-Chairman on 23 September 1978
(5) Resigned from Committee on 8 December 1978
(6) Resigned from Committee on 22 September 1977
(7) Elected Vice-Chairman on 15 October 1976

S U M M A R Y

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

Opinion expressed 5 October 1977

TERMS OF REFERENCE

The Scientific Committee for Animal Nutrition was requested to give an opinion on the following questions concerning furazolidone, nitrofurazone and bifuran (furazolidone + nitrofurazone):

1. Have carcinogenic or mutagenic effects been noted in experiments with these products ?
2. Does the use of these products as additives in feedingstuffs result in the presence of residues in products of animal origin ? If so, what are the nature and quantities of such residues ? Could these residues be harmful to the consumer ?
3. Are there any differences in purity of marketed products ?
4. Are data available to make it possible to establish that use of the products as coccidiostats is no longer economic in livestock production ?
5. In view of the answers to the abovementioned questions should
   - use of the products concerned as additives in feedingstuffs be prohibited in Member States ?
   - use be restricted to certain animal species under specific conditions ?

BACKGROUND

In accordance with the provisions of Council Directive 70/524/EEC (1), of 23 November 1970, concerning additives in feedingstuffs, as last amended by the nineteenth Commission Directive of 26 July 1977 (2), Member States are authorized to use, by way of derogation up to 31 December 1977, furazolidone, nitrofurazone and bifuran (furazolidone + nitrofurazone) as additives in feedingstuffs. These products are listed in Annex II, Section B, of the directive without specific conditions of use.

A recent examination of the use of these products has revealed numerous uncertainties as regards compliance with the fundamental principles governing Community approval of additives, as laid down in Article 6 of the Directive. The Commission, therefore, considered it as necessary to seek the Opinion of the Scientific Committee for Animal Nutrition on the unresolved questions relating to these products.

(1) OJ Nr L 270 of 14.12.1970, p. 1
(2) OJ nr L 207 of 13.8.1977, p. 53

OPINION OF THE COMMITTEE

The Committee has examined the available data on the use of furazolidone, nitrofurazone and bifuran in animal nutrition and has identified numerous gaps in knowledge concerning methods of analysis, metabolism, carcinogenecity and mutagenecity. The information on nitrofurazone and bifuran appeared particularly deficient. The replies to the Commission's questions are set out below :

1. Carcinogenic, mutagenic and teratogenic activity has been observed in laboratory animals. Additional data on these effects is necessary, particularly "dose/effect" relationships.
2. These products, whose molecules are unstable, give rise to residues which are difficult to assess qualitatively and quantitavely given the lack of specificity and sensitivity of the existing methods. It is likely that certain of the metabolites formed are not detected by analysis. It would be desirable to study the effects of these residues by the method of relay toxicity.
3. In addition to the substances originally authorized, products of various origins are being marketed without any guarantee as to purity criteria required by national pharmacopeas. These constitute a further risk factor. In this regard the Committee wishes, as a general rule, that marketed additives be warranted with respect to purity and amount of impurities.
4. It has been established that the nitrofurans concerned have favourable coccidiostatic effects in some instances.
5. In view of these considerations, the Committee feels that, in the absence of additional data, the use of furazolidone, nitrofurazone and bifuran as additives in feedingstuffs should be prohibited in the Community.

REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF NITROIMIDAZOLE DERIVATIVES IN FEEDINGSTUFFS

Opinion expressed 8 December 1977

Terms of reference

The Scientific Committee for Animal Nutrition was requested to give an opinion on the following questions concerning dimetridazole, ronidazole and ipronidazole :

1. Have carcinogenic or mutagenic effects been noted in experiments with these products ?
2. Does the use of these products as additives in feedingstuffs result in the presence of residues under the authorized conditions of use ? Could these residues be harmful to the consumer ?
3. In view of the answers to the abovementioned questions, should
   - use as additives in feedingstuffs of the products concerned or of some of them be prohibited in Member States ?
   - their conditions of use be modified ?

BACKGROUND

In accordance with the provisions of Council Directive 70/524/EEC (1), of 23 November 1970, concerning additives in feedingstuffs, as last amended by the nineteenth Commission Directive of 26 July 1977 (2), the use of dimetridazole is authorized at Community level under the following conditions set out in Annex I, Section D, of the Directive :

Species of animal : turkeys, guinea fowl.

Minimum and maximum content in complete feedingstuffs : 125 - 150 ppm (mg/kg).

Other provisions : use prohibited from laying age onwards and at least 3 days before slaughter respectively.

Furthermore, Member States are authorized to use, by way of derogation up to 31 December 1977, dimetridazole for animal species other than turkeys and guinea fowl, ronidazole and ipronidazole. These provisions are set out in Annex II, Section B, of the Directive without specific conditions of use for dimetridazole and ronidazole and under the following conditions for ipronidazole :

Species of animal : turkeys

Minimum and maximum content in complete feedingstuffs : 50 - 85 ppm (mg/kg).

Other provisions : use prohibited at least 5 days before slaughter.

(1) OJ No L 270 of 14.12.1970, p. 1
(2) OJ No L 207 of 13.8.1977, p. 53

In pursuance of this derogation, some Member States have authorized the use of dimetridazole in feedingstuffs for swine at levels of 100 to 150 ppm (mg/kg) with a withdrawal period varying between 3 to 5 days, the use of ronidazole in feedingstuffs for turkeys at levels of 50 to 60 ppm (mg/kg) and for swine at 30 to 90 ppm (mg/kg) with a withdrawal period varying between 3 to 5 days, and that of ipronidazole under the conditions laid down in the Directive.

A recent examination of these additives has revealed some uncertainties as regards the safety of their use in animal feeding. The Commission, therefore, considered it as necessary to seek the Opinion of the Scientific Committee for Animal Nutrition.

OPINION OF THE COMMITTEE

1. An increase in the number of benign and malignant mammary tumours and also mutagenic effects were observed in laboratory animals, in particular in rats, to which high doses of dimetridazole, ronidazole and ipronidazole were administered orally over their lifetime.

2. The sensitivity and specificity of analytical methods and also knowledge of the metabolism of these products enable a precise evaluation of their residues to be made. These are made up of the initial compound and oxidation products, which undergo rapid breakdown in animal products after withdrawal of the additive in the diet. Under the conditions of use at present authorized for these additives and, in particular, withdrawal periods varying between 3 to 5 days, it may be stated that, at the lower limit of analytical determination (0.002 mg/kg), there are no significant residues in the edible products (see Table in Annex). Possible traces in muscle or skin are broken down through cooking and during cold storage.

3. The Committee is of the opinion that there is no reason to prohibit the use of dimetridazole, ronidazole or ipronidazole as additives in feedingstuffs.

   Taking into account the similarity of their metabolism, the Committee considers however that withdrawal periods before slaughter should be standardized in order, with an additional safety factor, to ensure the absence of residues in products of animal origin. To this effect, a withdrawal period of at least 6 days is recommended for each of these additives.

   On this condition and account being taken of their efficacy for the various animal species, minimum and maximum dose-levels in mg/kg complete feedingstuffs should not exceed the following limits :

	Dimetridazole	Ronidazole	Ipronidazole
Feedingstuffs for turkeys	100-200	50-60	50-100
Feedingstuffs for guinea fowl	100-150	-	50-100
Feedingstuffs for swine	100-200	60-90	-

ANNEX

Comparison of data from rearing practice and the study of residues in meat derived from animals consuming nutritional doses of nitroimidazole derivatives

Additives	Practical conditions of use			Residues in meat(a)(b) (mg/kg)
	Species of animal	Dose-level (mg/kg feed)	Duration of use (weeks)	
Dimetridazole	Turkeys	100 - 200	12	<0.002
	Guinea fowl	125 - 150	10	<0.002
	Swine	100 - 150	16	<0.002
Ipronidazole	Turkeys	50 - 100	12	<0.002
	Guinea fowl	50 - 100	10	<0.002
Ronidazole	Turkeys	50 - 60	12	<0.002
	Swine	30 - 90	16	<0.002

(a) After a withdrawal period of 6 days

(b) Lower limit of analytical determination : 0.002 mg/kg.

REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE USE OF MACROLIDES AND RELATED PRODUCTS IN FEEDINGSTUFFS

Opinion expressed 8 December 1977

TERMS OF REFERENCE

The Scientific Committee for Animal Nutrition was requested to examine the problems of bacterial resistance raised by the use of macrolides and related products and to give an opinion on the following questions :

1. What are the possibilities of induction of resistances, cross-resistances or transfer of resistances which might result from the use as additives in feedingstuffs of the following antibiotics authorized by Community Directives :
   - oleandomycin
   - spiramycin
   - erythromycin
   - tylosin
   - lincomycin
   - virginiamycin ?

2. Is data available that makes it possible to establish that, under the conditions of use authorized by Community Directives, the use for nutritional purposes of one or several of these antibiotics is no longer of interest in livestock rearing ?

3. To what extent and for what purpose are these additives used in human or veterinary therapeutics ?

4. Is the use of these products for nutritional purposes likely to interfere with their application for therapeutic purposes ?

5. In view of the answers to the abovementioned questions, should :
   - use as additives in feedingstuffs of the products concerned or of some of them be prohibited in Member States ?
   - their conditions of use be modified ?

BACKGROUND

In accordance with the provisions of Council Directive 70/524/EEC (1), of 23 November 1970, concerning additives in feedingstuffs, as last amended by the twentieth Commission Directive of 7 December 1977 (2), the use of oleandomycin, spiramycin and virginiamycin is authorized at Community level under the following conditions set out in Annex I, Section A, of the Directive. In this regard, a derogation authorizing Denmark, Ireland and the United Kingdom to maintain in force until 31 December 1977 provisions of national law existing at the date of accession was granted according to the Acts of Accession of these countries to the European Community (3).

Additive	Species of animal	Maximum age	Minimum content	Maximum content
			ppm (mg/kg) of complete feedingstuffs	
Oleandomycin	Turkeys	26 weeks	2	10
	Other poultry, with the exception of ducks, geese, laying hens and pigeons	16 weeks	2	10
	Swine	6 months	2	10
Spiramycin	Turkeys	26 weeks	5	20
	Other poultry, with the exception of ducks, geese, laying hens and pigeons	16 weeks	5	20
	Swine, calves, lambs and kids	6 months	5	20 80 (*)
	Animals bred for fur		5	20
Virginiamycin	Turkeys	26 weeks	5	20
	Other poultry, with the exception of ducks, geese, laying hens and pigeons	16 weeks	5	20
	Swine	6 months	5	20
	Calves	6 months	5	20 80 (*)

(*) Milk replacers

(1) OJ No L 270 of 14.12.1970, p. 1
(2) OJ No L 18 of 24.1.1978, p. 7
(3) OJ No L 73 of 27.3.1972, p.136

Furthermore, Member States are authorized to use, by way of derogation up to 31 December 1978, erythromycin, tylosin, lincomycin, oleandomycin, spiramycin and virginiamycin under the following conditions set out in Annex II, Section A, of the Directive.

Additive	Species of animal	Maximum age	Minimum content	Maximum content
			ppm (mg/kg) of complete feedingstuffs	
Erythromycin	Chickens for fattening		5	20
	Swine		5	20
Tylosin	Swine	2 months	10	40
		2-6 months	5	20
Lincomycin	Poultry, with the exception of ducks, geese and laying hens	10 weeks	2	10
Oleandomycin	Poultry, with the exception of ducks and geese	4 weeks	> 10	25
	Swine	10 weeks	> 10	25
Spiramycin	Poultry, with the exception of ducks and geese	4 weeks	> 20	50
	Swine	10 weeks	> 20	50
	Calves, lambs and kids	16 weeks	> 20	50
	Animals bred for fur		> 20	50
Virginiamycin	Poultry, with the exception of ducks and geese	4 weeks	> 20	50
	Swine	10 weeks	> 20	50
	Calves	16 weeks	> 20	50

OPINION OF THE COMMITTEE

The Committee examined the specialized work on bacterial resistance in connection with macrolides and related products as also the recommendations from international organizations and regional advisory committees concerning the non-therapeutic use of antibiotics. In addition, twenty-five specialists in bacteriology, clinical microbiology, pharmacology, human and animal epidemiology and food hygiene had been consulted on the subject of the harmful effects for public health which might arise from the use of macrolides and related products in animal feeding.

Although knowledge of the phenomena of bacterial resistance and their consequences for the environment appeared to be incomplete, the Committee endeavoured to reply as completely as possible to the questions posed by the Commission.

1. All the macrolides and related products have analogous spectra of activity (*) and similar mechanisms of resistance.

   Studies carried out in vitro have shown that the majority of micro-organisms which are sensitive to these antibiotics may become resistant to them by spontaneous chromosomal mutation without previous contact with an antibiotic of the same group. The resistant strains have a prolonged reproduction time and an attenuated virulence. This type of resistance is very rare and not transferable.

   In addition, it has been established by studies on resistant strains isolated in hospitals that bacteria could develop two types of cross resistance to macrolides and related products, due to modification of the ribosomes. These types of resistance have been described as inducible and constitutive resistance.

   Inducible resistance has been observed solely with Staphylococcus aureus strains. It appears rapidly after contact of the micro-organism with very low doses of an inducer antibiotic and may affect simultaneously all the antibiotics of the same group. Among the macrolides and related products, erythromycin and oleandomycin have been shown to be powerful inducers. Lincomycin, tylosin, spiramycin and virginiamycin appear to be free from inducing properties. Inducible resistance is not stable. It disappears when the bacteria are subjected to prolonged culture without any contact with an antibiotic.

   Constitutive resistance has been observed essentially with saprophytic micro-organisms and certain pathogenic agents, particularly Staphylococcus aureus. It appears to result from heavy selection pressure (high dose) of one or other of the antibiotics of the group involved and affects simultaneously all the antibiotics of the same group. This resistance is stable and does not disappear spontaneously.

   A transfer of resistance to macrolides and related products may also occur between bacteria which are sensitive to these antibiotics. This has been shown to be a transduction phenomenon via bacteriophages and not one of conjugation.

   Up to now, these resistance phenomena have not appeared in bacteria representative of the intestinal flora of farm animals (enterococci, saprophytical staphylococci) when macrolides and related products were used at nutritional levels in feedingstuffs.

2. Available data show that these antibiotics, when used for nutritional purposes according to the conditions authorized by Community directives, contribute significantly to animal production by improving growth. The mode of action is through anabolic effects.

3. The use of macrolides and related products in human therapy varies considerably from one Member State to another. Erythromycin appears to have the widest application. This antibiotic is used for the treatment of infectious diseases due to Gram-positive bacteria, mycoplasma or Haemophilus influenza and also in cases of resistance of pathogenic agents to other antibiotics or of allergy to penicillin. Lincomycin is indicated for the treatment of diseases due to Bacteroides fragilis. In certain Member States, use is also made of oleandomycin in cases of resistance of pathogenic agents to other antibiotics or of allergy to penicillin, of spiramycin in stomatology and, on a very small scale, of virginiamycin. Only tylosin appears to have no medical use.

(*) This activity covers, with individual variations, essentially Gram-positive and-negative cocci, Gram-positive bacilli, actinomycetes, corynebacteria, certain representatives of the bacteroid family and mycoplasma. The enterobacteria are insensitive to them in vivo.

In addition, with the exception of virginiamycin, all the macrolides and related products involved have applications in veterinary therapy. Tylosin and spiramycin are used for the treatment of dysentry in pigs; tylosin and erythromycin for the treatment of mycoplasmic respiratory diseases in pigs, calves and poultry. Oleandomycin and lincomycin are used essentially for the treatment of localized infections, such as mammitis or external otitis; erythromycin is also used for these indications.

For the Community as a whole, the proportion of these antibiotics used in 1976 in therapy, expressed as % of the total therapeutic consumption of antibiotics, was as follows:

	Human therapy	Veterinary therapy
Tylosin	-	6
Virginiamycin	<1	-
Spiramycin	1	2
Oleandomycin	1-2	1
Lincomycin	2	1-2
Erythromycin	5	2-3

4. An exhaustive reply to the question raised would require the carrying out of systematic epidemiological studies on the transfer and behaviour of strains resistant to macrolides and related products in all the regions where these products are used therapeutically. Partial information available in this field together with knowledge gained about the mechanisms of resistance of certain micro-organisms to macrolides permits however some important conclusions to be drawn.

   According to enquiries made in the Federal Republic of Germany and in some other European countries during the period 1960-1975, the frequency of occurrence of strains of Staphylococcus aureus resistant to erythromycin isolated in hospitals, has remained constant or decreased slightly despite a marked increase in the use of macrolides in animal nutrition. On the other hand, a study performed in Japan has shown an increase in this resistance since 1965. It should be noted, however, that no information was available on the conditions of use of macrolides in Japan.

   According to various studies, staphylococci resistant to macrolides and related products do not produce any cross resistance with other antibiotics or chemotherapeutics. In addition, the transfer of resistance to these products with staphylococci does not involve direct contact (conjugation) but intermediate bacteriophages (transduction). This means that, unlike mechanisms specific to other antibiotics, the transfer of resistances is largely restricted. This phenomenon is confirmed by the high level of sensitivity to macrolides and related products at present found among pathogenic agents, particularly group A streptococci.

   Little is known about the development of resistance in other micro-organisms sensitive to macrolides (treponema, mycoplasma, bacteroides, haemophylus).

5. Whilst none of the data proved that the use of the antibiotics involved in animal nutrition has interfered with therapeutic uses, the Committee felt that, in the absence of more adequate information on the resistance phenomena, it would be desirable to adopt a cautious attitude and to take measures to avoid the build-up of resistant strains as far as possible.

   In view of the therapeutic uses of erythromycin and lincomycin and also of the inducible resistance properties inherent in erythromycin and oleandomycin, it is proposed that :

   - the use of spiramycin, tylosin and virginiamycin in animal nutrition be continued in accordance with the conditions of use already authorized for these products by Community Directives,
   - to ask the manufacturers of spiramycin, tylosin and virginiamycin to pursue research on the development of strains resistant to these products in order that the Committee can re-evaluate them in three years time.

FIRST REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE CONDITIONS OF USE OF CERTAIN ANTIBIOTICS IN FEEDINGSTUFFS

Opinion expressed 21 February 1978

TERMS OF REFERENCE

The Scientific Committee for Animal Nutrition was requested to examine the conditions of use of zinc bacitracin and flavophospholipol, authorized by Community Directives, and to give an opinion on the following questions.

A. Use of zinc bacitracin and flavophospholipol in feedingstuffs for laying hens

1. Has use of these antibiotics in feedingstuffs for laying hens a significant effect on egg production ?
2. If so, is it to be considered as a nutritional, prophylactic or therapeutic action at the dose levels authorized (15-100 ppm (mg/kg) in complete feedingstuffs for zinc bacitracin ; 2-5 ppm (mg/kg) for flavophospholipol) ?
3. Does the use of these antibiotics, under the conditions authorized, result in the presence of residues in eggs ? If so, what is the nature and the amount of these residues ?
4. In the light of the answers to the abovementioned questions and the requirements of Article 6(2) of Council Directive 70/524/EEC concerning additives in feedingstuffs (1), should
   - the use of zinc bacitracin and/or flavophospholipol in feedingstuffs for laying hens be prohibited in Member States ?
   - the permitted conditions of use be modified ?

B. Use of zinc bacitracin in feedingstuffs for young animals

1. Do increased nutritional effects, free of prophylactic or therapeutic effects, result from the addition to complete feedingstuffs of dose levels of zinc bacitracin higher than 20 ppm (mg/kg) and not exceeding 50 ppm (mg/kg) (with the exception of milk replacers where a maximum content of 80 ppm (mg/kg) is permitted), when feeding
   - poultry, excluding ducks and geese, up to the age of 4 weeks,
   - swine up to the age of 10 weeks,
   - calves, lambs and kids up to the age of 16 weeks,
   - animals bred for fur ?
2. Do these conditions of use result in the presence of residues in animal products ? If so, what is the nature and the amount of these residues ?

(1) OJ N° L 270 of 14.12.1970, p. 1

3. Can they give rise to problems of bacterial resistance ?

4. Are they acceptable for the environment ?

5. Would a modification of the conditions of use indicated under item 1 to increase up to 100 ppm (mg/kg) the maximum content of zinc bacitracin in complete feedingstuffs

   - for turkeys and chickens for fattening up to the age of 8 weeks,

   - for pullets up to point of laying,

   - for swine during the growing period

   result in a significant increase of nutritional effects, free of prophylactic or therapeutic effects, and/or result in modifying the answers to questions posed under items 2, 3 or 4 ?

6. In the light of the answers to the abovementioned questions and the requirements of Article 6(2) of Council Directive 70/524/EEC concerning additives in feedingstuffs (1), should

   6.1 conditions of use of zinc bacitracin indicated under item 1 for

   - poultry, excluding ducks and geese,

   - swine,

   - calves, lambs and kids,

   - animals bred for fur

   be maintained ?

   6.2 conditions of use for poultry, insofar as turkeys, chickens for fattening and pullets are concerned, and for swine be modified according to the conditions indicated under item 5 ?

BACKGROUND

In accordance with the provisions of Council Directive 70/524/EEC (1), of 23 November 1970, concerning additives in feedingstuffs, as last amended by the twenty first Commission Directive of 23 December 1977 (2), the use of zinc bacitracin and flavophospholipol is authorized at Community level under the following conditions set out in Annex I, Section A, of the Directive :

(1) OJ N° L 270 of 14.12.1970, p. 1
(2) OJ N° L 40 of 10. 2.1978, p. 19

Additive/Species of animal	Maximum age	Minimum content	Maximum content
		ppm (mg/kg) of complete feedingstuffs	
Zinc bacitracin			
Turkeys	26 weeks	5	20
Other poultry, with the exception of ducks, geese, laying hens and pigeons	16 weeks	5	20
Swine, calves, lambs and kids	6 months	5	20 80 (*)
Animals bred for fur	-	5	20
Flavophospholipol			
Turkeys	26 weeks	1	20
Other poultry, with the exception of ducks, geese, laying hens and pigeons	16 weeks	1	20
Swine	6 months	1 10 (*)	20 25 (*)
Calves	6 months	6 8 (*)	16 16 (*)
Animals bred for fur	-	2	4
(*) Milk replacers			

Furthermore, Member States are authorized to use, by way of derogation up to 31 December 1978,

- zinc bacitracin and flavophospholipol in feedingstuffs for laying hens,
- dose levels of zinc bacitracin exceeding the maximum permitted levels stated in Annex I,

under the following conditions stated in Annex II, Section A, of the Directive :

Additive/Species of animal	Maximum age	Minimum content	Maximum content
		ppm (mg/kg) of complete feedingstuffs	
Zinc bacitracin			
Laying hens		15	100
Poultry, with the exception of ducks, geese and laying hens	end of the 4th week	> 20	50
Swine	end of the 10th week	> 20	50
Calves, lambs and kids	end of the 16th week	> 20	50
Animals bred for fur	-	> 20	50
Flavophospholipol			
Laying hens		2	5
Cattle for fattening		5	15

Besides, the Commission was asked by a Member State to amend as follows the conditions of use of zinc bacitracin stated in Annex II, Section A :

Species of animal	Maximum age	Minimum content	Maximum content
		ppm (mg/kg) of complete feedingstuffs	
Turkeys, chickens for fattening	8 weeks	> 20	100
Pullets	point of laying	> 20	100
Other poultry	unchanged	unchanged	unchanged
Swine	growing period	> 20	100
Calves, lambs, kids, animals bred for fur	unchanged	unchanged	unchanged

OPINION OF THE COMMITTEE

A. Use of zinc bacitracin and flavophospholipol in feedingstuffs for laying hens

1. The addition of zinc bacitracin or flavophospholipol to feedingstuffs for laying hens can, under certain conditions, increase the output of eggs, particularly in the case of hens with a low level of egg production. It remains to be proved, however, that significant results are obtained from strains with high levels of production and that the use of zinc bacitracin in concentrations exceeding 80 mg/kg feedingstuff is justified. Nevertheless, it has been established that these additives have a favourable effect on the animal organism and that they reduce mortality.

2. At authorized dose-levels, both zinc bacitracin and flavophospholipol give improved utilization of dietary constituents and beneficial effects on the intestinal flora. For zinc bacitracin however, a concomitant bactericidal effect on some micro-organisms of the animal alimentary tract cannot be ruled out at concentrations higher than 80 mg/kg feedingstuff.

   These additives have a limited antibacterial spectrum with no systemic action and no known effects on specific diseases of laying hens.

3. Under the authorized conditions of use, zinc bacitracin and flavophospholipol are not absorbed in measurable amounts by the alimentary tract and, at the lower limit of analytical determination (*), no residues have been found in eggs.

4. The Committee is of the opinion that there is no reason to prohibit the use in Member States of zinc bacitracin and/or flavophospholipol in feedingstuffs for laying hens. However, for the reasons mentioned in points 1 and 2, it is recommended

   - that the maximum content of zinc bacitracin in complete feedingstuffs be limited to 80 mg/kg, and
   - that the manufacturers of these additives be required to continue to carry out studies with the view to determine both for flavophospholipol and zinc bacitracin the variation of egg production in relation to the dose-level of additive, the composition of the diet and the mode of feeding, the genetic quality of the breeds and strains of laying hens as well as the conditions under which they are reared. The results obtained should be presented with all details of the experimental procedures applied.

   A reassessment could subsequently be made in the light of the results of this work.

B. Use of zinc bacitracin in feedingstuffs for young animals

1. Improved growth can result when zinc bacitracin at levels between 20 and 50 mg/kg of complete feedingstuffs (or between 20 and 80 mg/kg in milk replacers) is given to :

   - poultry (excluding ducks and geese) up to the age of 4 weeks,
   - swine up to the age of 10 weeks,
   - calves, lambs and kids up to the age of 16 weeks,
   - animals bred for fur.

   This response to the antibiotic is considered to be nutritional and without prophylactic or therapeutic effects.

(*) zinc bacitracin : 0.1 mg/kg for egg yolk
0.05 mg/kg for albumen
flavophospholipol : 0.07 mg/kg for egg yolk
0.01 mg/kg for albumen

2. Zinc bacitracin is not absorbed in measurable quantities from the alimentary tract and, at the lower limit of analytical determination (0.05 - 0.1 mg/kg), no residues have been found in food products of animal origin when the antibiotic is given in feeding-stuffs at authorized levels.

3. At these levels there have been no indications of problems of bacterial resistances.

4. The use of zinc bacitracin at authorized levels is not considered detrimental to the environment. When excreted in animal faeces the product is degraded in dung and soil within a few weeks and, if much water is present, within a few days.

5. For

   - turkeys and chickens for fattening up to the age of 8 weeks,

   - pullets up to the point of laying,

   - swine during the growing period,

   experimental evidence is lacking that an increase of zinc bacitracin up to a level of 100 mg/kg in complete feedingstuffs results in a significant increase in nutritional effects. Furthermore, there is little information on the effects of these levels on the gut flora and on the bacterial resistances.

6. The Committee is of the opinion that the permitted conditions of use of zinc bacitracin indicated under item 1 should be maintained.

   An increase of the dose-levels, as indicated in the Commission's question N° B 5, could be envisaged only if statistically controlled data were available on the effects of these levels on

   - animal production, and

   - bacterial resistances after long-term feeding,

   as well as information on the degradation in dung and soil of the amounts excreted.

Use of zinc bacitracin and flavophospholipol in feedingstuffs for laying hens

Opinion expressed 11 October 1978

In its opinion expressed on 21 February 1978, the Committee, taking into account the available documentation, agreed that the use of flavophospholipol or zinc bacitracin in feedingstuffs for laying hens while producing zootechnic improvements did not result in hazards for the consumer.

However, it recommended

- that the maximum content of zinc bacitracin in complete feedingstuffs for laying hens be limited to 80 mg/kg, and
- that the manufacturers of these additives be required to furnish complementary information.

From this further information it appeared that, due to selection, use of hybrids, improvement in quality of rations and breeding techniques, there has been improvement in feed efficiency of laying hens associated with reduced feed intake. This phenomenon, which is independent of the effect of additives, results in a reduction of the amount of additives consumed with the ration.

In these conditions, the Committee is of the opinion that the use for laying hens of flavophospholipol to the extent of 2 to 5 mg/kg complete feedingstuffs or of zinc bacitracin to the extent of 15 to 100 mg/kg complete feedingstuffs is acceptable.

REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE EFFECTS OF NITRATES IN FEEDINGSTUFFS

Opinion expressed 19 April 1978

TERMS OF REFERENCE

The Scientific Committee for Animal Nutrition was requested to give an opinion on the following questions :

1. What are the normal contents of nitrates in milk, milk powder and powdered whey ?
2. What are the maximum intakes of nitrates acceptable for animal species, in particular, cattle ?
3. What are the levels of nitrates, nitrites and nitrosamines which could result in products of animal origin from absorption by animals of feedingstuffs containing normal and increased levels of nitrates ?
4. In the light of the answers to the abovementioned questions, should maximum contents be fixed for nitrates in
   - straight feedingstuffs and, in particular, milk powder and powdered whey ?
   - complete feedingstuffs and, in particular, milk feeds ?

BACKGROUND

As the presence of nitrates at dose-levels normally found in feedingstuffs was considered harmless to animals and, indirectly, to man, these products were not made subject to limitations in Council Directive 74/63/EEC of 17 December 1973 concerning the fixing of maximum permitted levels for undesirable substances and products in feedingstuffs (1).

In July and August 1976, one Member State, since it considered that nitrates were not free of health risks, took successively various measures intended to limit the nitrate content in whole milk, skimmed milk powder and powdered whey.

Since the decision must be taken at Community level whether these measures are justified or must be rescinded, the Commission deemed it necessary to ask the Scientific Committee for Animal Nutrition a series of questions, the answers of which it felt were essential to clarify the situation.

OPINION OF THE COMMITTEE

The Committee has examined the available information on nitrate toxicity and the presence of nitrates in animal feedingstuffs. It has observed numerous gaps in this documentation and felt that, in the absence of additional data, it was difficult to assess the risks resulting from the presence of nitrates in feedingstuffs and to answer the Commission's questions.

(1) OJ N° L 38 of 11.2.1974, p. 31

In order to obviate these difficulties, it appeared necessary to have available results of analytical checks carried out on milk products in the Member States and to pursue experimental studies on the effects of nitrates on piglets and calves. To this end, trials were undertaken at the end of 1976 in the departments of two Members of the Committee and also in the Netherlands at the Instituut voor Landbouwkundig Onderzoek van Biochemische Produkten (ILOB at Wageningen) and at the Laboratory of Chemical Analysis of Foodstuffs of the National Institute of Public Health at Bilthoven.

The Committee considered it essential to wait until these experiments were completed and full reports available before voicing its conclusions. The answers to the Commission's questions are given below.

1. According to results of checks performed in 1976 and 1977 in the Member States, the nitrate contents of milk products were in the following ranges :

   fresh milk : <0.1 - 3.1 mg NO_3^-/kg.

   skimmed milk powder : - normally : <10 - 50 mg NO_3^-/kg;
   - occasionally contents exceeding 50 mg/kg and reaching up to 440 mg/kg were noted.

   powdered whey : 20 - 2700 mg NO_3^-/kg with a maximum frequency occuring at 400 mg/kg.

   It should be noted that high concentrations of nitrates in powdered whey result, in general, from cheese-making processes using added nitrates. The presence of nitrates in concentrations above 50 mg NO_3^-/kg in skimmed milk powder can be considered indicative of poor quality resulting from faulty production or adulteration.

   Furthermore, the possibility cannot be ruled out that variations in the results from different sources are, to some extent, due to the various analytical techniques used.

2. The sensitivity of the animals to nitrates varies according to species, age, composition of ration and rearing conditions. Although the available information is not complete enough to permit an assessment of toxicity thresholds, it has been observed that most livestock animals tolerate high levels of nitrates, which may reach 5,000 mg NO_3^-/kg of dry matter in the case of green fodder.

   With regard to veal, trials conducted in France with two lots of 16 animals showed that a daily intake of nitrates of 50 to 60 mg NO_3^-/kg of ration for six weeks followed by 18 to 25 mg/kg of ration for ten weeks (the water for preparation of the ration having a content of 50 mg NO_3^-/kg) had no influence on growth pattern, biochemical parameters of the blood or hepatic reserve in vitamin A. Experiments in the Netherlands on 60 calves aged between 10 and 18 weeks confirmed the high tolerance of cattle to nitrates.

   Daily administration of nitrates for eight weeks at dose-levels of 400, 2,000, 5,000 and 10,000 mg NO_3^-/kg of milk replacer respectively had no effect on growth pattern, weight increase, food conversion rate, quality of carcass and biochemical parameters of the blood. Histopathological examination of the liver and the kidneys was negative. It was also established that the presence or absence of antibiotics in the ration had no influence on the results.

   Piglets alone appear to be sensitive under certain conditions. In experiments performed in Germany, it has been observed on new-born animals removed from the mother that daily intake of nitrates caused a slight increase in the methaemoglobin content of the blood where dose-levels exceeded 400 mg NO_3^-/kg of milk replacer ; the other biochemical or physiological parameters were unaffected. The phenomenon was however revealed to be reversible (the methaemoglobin content returning to normal after three to four weeks despite continuous administration of the nitrates) and had no effect on growth.

3. The normal contents of nitrates in milk were given under item 1. The nitrite contents appear generally less than 0.3 mg NO_2^-/kg of fresh milk and the N-nitrosamine contents below the detection limit (0.1 µg/kg of fresh milk).

   A significant increase in the nitrate content of milk appears only when high doses of nitrates are absorbed by the cow. Concentrations of 13 to 20 mg NO_3^-/kg have been recorded in fresh milk in cases where the quantity of nitrates absorbed had caused intoxication (dose-levels of the order to 600 mg NO_3^-/kg of live weight).

   At the end of the experiments conducted on calves in the Netherlands (see under item 2), the nitrate, nitrite and N-nitrosamine contents were determined in various tissues of the trial animals. The average nitrate contents were as follows :

NO_3^- content in the ration (mg/kg) / NO_3^- content in wet tissues (mg/kg)	18 (control)	400	2.000	5.000	10.000
Muscle	2	5	25	30	65
Liver	8	16	22	34	65
Kidney	4	13	44	92	182
Blood	2	11	53	115	245

   The nitrite contents (of the order of 1 mg NO_2^-/kg of wet tissue) appeared constant in all tissues and for all groups of animals and unconnected with the amounts of nitrates ingested.

   Determination of N-nitrosamines by highly specific methods showed the presence of traces of these products (always below 1 µg/kg of wet tissue) in the tissues of both the control and treated animals. As with nitrites there was no correlation with the amount of nitrates ingested.

4. According to present scientific knowledge, normal levels of nitrates found in feedingstuffs do not involve risks for animals.

   High levels of nitrates, which may reach 5,000 mg NO_3^-/kg of feedingstuff are generally well tolerated by livestock. Only piglets appear, under certain conditions, to be sensitive. In this regard, it has been observed that, in new-born piglets separated from their mothers, the administration of nitrates at dose-levels higher than 400 mg NO_3^-/kg of milk replacer resulted in a slight modification of the methaemoglobin content of the blood. This modification appeared, however, to be temporary (the methaemoglobin content reaching the normal level after three or four weeks, despite the continuous administration of nitrates in the ration) and without effect on the health of the animal.

   Moreover, on the basis of data available on calves, continuous administration of nitrates, even at high levels, does not result in the presence of nitrites or nitrosamines in animal products.

European Communities — Commission

Reports of the Scientific Committee for Animal Nutrition
First series

Luxembourg: Office for Official Publications of the European Communities

1979 — 32 p. — 21 x 29,7 cm

DA, DE, EN, FR, IT, NL

ISBN 92-825-1002-6

Catalogue number: CB-28-79-277-EN-C

BFR 55	DKR 9,70	DM 3,50	FF 8
LIT 1600	HFL 3,80	UKL 0.95	USD 1.85

The Committee's first series of reports, published in this volume, includes opinions relating principally to the safe use of antibiotics, coccidiostats and other medicinal substances in animal feed for collective prophylaxis, and on the effects of the presence of certain contaminants in animal feed. Questions in this connection had arisen in the course of the Commission's work on the approximation of Member States' laws on additives and undesirable substances in feedingstuffs. The detailed opinions drawn up by the Committee have removed much of the uncertainty which threatened to hold up the preparation of proposals on the use of these substances in animal feed.

Salgs- og abonnementskontorer · Vertriebsbüros · Sales Offices
Bureaux de vente · Uffici di vendita · Verkoopkantoren

Belgique - België

Moniteur belge — Belgisch Staatsblad

Rue de Louvain 40-42 —
Leuvensestraat 40-42
1000 Bruxelles — 1000 Brussel
Tél. 512 00 26
CCP 000-2005502-27
Postrekening 000-2005502-27

Sous-dépôts — Agentschappen:

Librairie européenne — Europese Boekhandel
Rue de la Loi 244 — Wetstraat 244
1040 Bruxelles — 1040 Brussel

CREDOC

Rue de la Montagne 34 - Bte 11 —
Bergstraat 34 - Bus 11
1000 Bruxelles — 1000 Brussel

Danmark

J.H. Schultz — Boghandel

Møntergade 19
1116 København K
Tlf. (01) 14 11 95
Girokonto 200 1195

Underagentur:

Europa Bøger
Gammel Torv 6
Postbox 137
1004 København K
Tlf. (01) 14 54 32

BR Deutschland

Verlag Bundesanzeiger

Breite Straße — Postfach 10 80 06
5000 Köln 1
Tel. (0221) 21 03 48
(Fernschreiber: Anzeiger Bonn
8 882 595)
Postscheckkonto 834 00 Köln

France

Service de vente en France des publications des Communautés européennes

Journal officiel

26, rue Desaix
75732 Paris Cedex 15
Tél. (1) 578 61 39 — CCP Paris 23-96

Sous-agent

D.E.P.P. — Maison de l'Europe
37, rue des Francs-Bourgeois
75004 Paris
Tél.: 887 96 50

Ireland

Government Publications

Sales Office
G.P.O. Arcade
Dublin 1

or by post from

Stationery Office

Beggar's Bush
Dublin 4
Tel. 68 84 33

Italia

Libreria dello Stato

Piazza G. Verdi 10
00198 Roma — Tel. (6) 8508
Telex 62008
CCP 1/2640

Agenzia

Via XX Settembre
(Palazzo Ministero del tesoro)
00187 Roma

Grand-Duché de Luxembourg

Office des publications officielles des Communautés européennes

5, rue du Commerce
Boîte postale 1003 — Luxembourg
Tél. 49 00 81 — CCP 19190-81
Compte courant bancaire:
BIL 8-109/6003/300

Nederland

Staatsdrukkerij- en uitgeverijbedrijf

Christoffel Plantijnstraat, 's-Gravenhage
Tel. (070) 62 45 51
Postgiro 42 53 00

United Kingdom

H.M. Stationery Office

P.O. Box 569
London SE1 9NH
Tel. (01) 928 69 77, ext. 365
National Giro Account 582-1002

United States of America

European Community Information Service

2100 M Street, N.W.
Suite 707
Washington, D.C. 20 037
Tel. (202) 862 95 00

Schweiz - Suisse - Svizzera

Librairie Payot

6, rue Grenus
1211 Genève
Tél. 31 89 50
CCP 12-236 Genève

Sverige

Librairie C.E. Fritze

2, Fredsgatan
Stockholm 16
Postgiro 193, Bankgiro 73/4015

España

Libreria Mundi-Prensa

Castelló 37
Madrid 1
Tel. 275 46 55

Andre lande · Andere Länder · Other countries · Autres pays · Altri paesi · Andere landen

Kontoret for De europæiske Fællesskabers officielle Publikationer · Amt für amtliche Veröffentlichungen der Europäischen Gemeinschaften · Office for Official Publications of the European Communities · Office des publications officielles des Communautés européennes · Ufficio delle pubblicazioni ufficiali delle Comunità europee · Bureau voor officiële publikaties der Europese Gemeenschappen

Luxembourg 5, rue du Commerce Boîte postale 1003 Tél. 49 00 81 · CCP 19 190-81 Compte courant bancaire BIL 8-109/6003/300

BFR 55 DKR 9,70 DM 3,50 FF 8 LIT 1600 HFL 3,80 UKL 0.95 USD 1.85

OFFICE FOR OFFICIAL PUBLICATIONS
OF THE EUROPEAN COMMUNITIES

ISBN 92-825-1002-6

Boîte postale 1003 — Luxembourg

Catalogue number: CB-28-79-277-EN-C