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.