



Report of the Scientific Committee for Animal Nutrition on the Efficacy and Risk for Users of the Therapeutic Macrolides Antibiotics Tylosin and Spiramycin Used as Feed Additives

(opinion expressed on 05 February 1998)

TERMS OF REFERENCE (June 1997, Reviewed 17/9/97)

The SCAN is requested to examine the scientific information provided by the Republic of Finland concerning the use of the macrolides tylosin and spiramycin as feed additives and express its opinion on the following question:

Should the use of tylosin and spiramycin for serious reasons concerning animal and public health be restricted to controlled veterinary therapeutic use?

BACKGROUND

While accessing to the European Union the Republic of Finland obtained a derogation enabling it to maintain the ban on its territory of the use of tylosin and spiramycin as feed additives. According to the Treaty of Accession, Finland was due to provide its request for adaptation of Community legislation before 31 December 1997, which should be accompanied by a detailed scientific statement of reasons for the additives in question.

The Republic of Finland has transmitted the information requested on 12 March 1997 and a decision concerning the Finnish request for prohibition shall be taken before 31 December 1997 in accordance with the procedure laid down in article 7 of Directive 70/524/EEC concerning additives in feedingstuffs.

According to this information, the use of tylosin and spiramycin must be restricted to controlled veterinary therapeutic use based on the following serious reasons concerning animal and human health. The reasons are the following:

- I. Tylosin and spiramycin are important veterinary drugs in Finland and are mainly used to treat bacterial diseases,
- II. The increased use of tylosin in swine and poultry production has resulted in a dramatic increase in the development of resistant bacteria, like antimicrobial resistance surveys conducted in Finland and Denmark in 1995-1996 in enterococci has revealed,
- III. there is scientific evidence that the use of tylosin results in the development of erythromycin (an important human drug) cross-resistance since the clinically most common resistance mechanisms within this macrolides, lincosamides and streptogramin B are similar and as cross resistance was very high between the macrolides antibiotics erythromycin, spiramycin and tylosin among the swine enterococcal isolates studied in the Finnish survey. Further research on the transfer of antimicrobial resistance factors is urgently needed,
- IV. this implies that the large-scale-use of tylosin and spiramycin and increased resistance causes a risk for treatment not only in veterinary medicine but may also cause a risk in human medicine.
- V. Since a continual discovery of effective antimicrobial agents for therapy cannot be expected in the near future, we must be able to manage with the antimicrobials available and therefore restrict the use of macrolides to therapeutic use only.
- VI. Whether tylosin in feed has a tendency to prolong the excretion of *Salmonella*, whether no investigations could be found on the excretion of *Salmonella* when macrolides are combined with coccidiostatics, whether according to

preliminary studies done at the National Veterinary and Food Research Institute spiramycin prolongs the excretion of *Yersinia enterocolitica* and whether the effect of tylosin and spiramycin on pathogens still needs further investigation.

- VII. hypersensitivity to tylosin and/or spiramycin, indicating a certain but not absolute cross-reactivity, has been reported, and both tylosin and spiramycin are thus capable of functioning as potent antigens and whether frequent use of macrolides in animal feed may therefore be regarded as an occupational hazard for farmers and other people in contact with this feed

OPINION OF THE COMMITTEE

1. Introduction

Finland has a derogation prohibiting the use of the macrolides spiramycin and tylosin as feed additives. In the EU, tylosin and spiramycin were approved as feed additives in 1970, tylosin for pigs and piglets and spiramycin also for poultry, calves, lambs, and fur animals. The substances have been shown to promote growth in animals.

According to the Treaty of accession to the European Union, Finland has submitted a report and supporting scientific documentation concerning the reasons for the ban of these macrolides as feed additives in its territory and why the use of tylosin and spiramycin must be restricted to controlled veterinary therapeutic use for reasons concerning animal and human health. The SCAN has been asked by the Commission to give an opinion on this position.

The Finnish submission consists of three parts. The first part provides information on the use of macrolides as feed additives and therapeutic agents in animals and humans, their mode of action and resistance mechanisms.

Throughout comparison is made with Denmark as an example of a country in which macrolides are used as feed additives and where data on use, resistance rate and consumption in veterinary and human medicine is available. The second part is a survey of antibiotic resistance in *Enterococcus faecalis*, *Enterococcus faecium* and *Escherichia coli* isolated from pigs and broilers in Finland. The third part consists of selected references.

The Finnish report asserts that :

- as the macrolide group mostly share the same resistance mechanisms there is a risk that the use of the feed additives tylosin and spiramycin could lead to cross-resistance to macrolides such as erythromycin used in humans;
- the conclusion of an American report on the potential hazard to human health from the use of feed additives meaning that the proposed hazards have neither been proven nor disproved does not mean that the proposed hazards do not exist;
- the research necessary to establish and measure a definite risk has not been conducted and indeed may not be possible (National Research Council, 1980).
- enterococci can easily acquire antibiotic resistance genes and lately they have become a serious cause of hospital infections, while only occasionally causing disease in animals;
- humans may be exposed to resistant enteric bacteria from animals via the food chain. Therefore potential environmental contamination with resistant strains, their effect on intestinal colonisation with enteric pathogens and the risk for allergic reactions should be regarded as a potential risk when approving the use of antimicrobials;
- considering the ecological aspects of the use of antimicrobials, the use of antimicrobials as feed additives, in human and in veterinary medicine should be considered as a whole.

Based on the following serious reasons concerning animal and human health the use of tylosin and spiramycin must be restricted to controlled veterinary therapeutic use:

- Tylosin and spiramycin are important veterinary drugs in Finland. They are mainly used in the treatment of swine dysentery and some infections caused by gram-positive organisms.
- The increased use of tylosin in swine and poultry production has resulted in a dramatic increase in the development of resistant bacteria. A comparison of antimicrobial resistance surveys conducted in Finland and

Denmark in 1995-1996 revealed startling differences. In Denmark, where tylosin is commonly used as feed additive, with a total use being 30 times greater than in Finland, the incidence of tylosin resistance in swine enterococci is 90-91%, whereas in Finland it is only 15%. The same applies for spiramycin: the incidence of spiramycin resistant enterococci in swine is 88-89% in Denmark but only 12-15% in swine in Finland.

- There is scientific evidence that the use of tylosin results in the development of erythromycin (an important human drug) cross-resistance, since the clinically most common resistance mechanisms within the MLS group (macrolides, lincosamides and streptogramin B) are similar. Cross-resistance was very high (90-100%) between the macrolide antibiotics erythromycin, spiramycin and tylosin among the swine enterococcal isolates studied in the Finnish survey. Further research on the transfer of antimicrobial resistance factors is urgently needed.
- This implies that the large-scale use of tylosin and spiramycin and increased resistance causes a risk for treatment not only in the veterinary medicine but may also cause a risk in human medicine.
- Since a continual discovery of effective antimicrobial agents for therapy cannot be expected in the near future, we must be able to manage with the antimicrobials currently available.

In analysing the Finnish submission SCAN considers and comments upon the preceding five claims in sequence and then moves to its response to question 92 of the Commission.

1.1. Tylosin and spiramycin are important veterinary drugs in Finland. They are mainly used in the treatment of swine dysentery and some infections caused by gram-positive organisms.

Consumption of macrolides

In 1994 and 1995, 14,8 and 13,7 tonnes, respectively, of feed additives with antimicrobial activity were used in Finland. In 1996 only carbadox, olaquinox, narasin, monensin and salinomycin were used as feed additives. In Denmark in 1995, 52.8 tonnes of macrolides (tylosin, 52.3 tonnes) were used as feed additives mostly in pigs (0.5 tonnes of spiramycin in broiler production) and 9.5 tonnes for therapy, whereas in Finland 0.74 tonnes (4.2% of the total consumption in animals) were used in animals and only for therapy.

Indications for macrolides in veterinary medicine

Tylosin is mainly used in the control of *Serpulina* infections in pigs in Finland.

Tylosin is also used to treat respiratory infections caused by *Pasteurella* species in pigs and cattle and *Mycoplasma* infections in pigs, although the activity of tylosin and spiramycin against these organisms is too low to ensure efficacy.

Tylosin may also be used to treat bovine mastitis caused by gram-positive cocci and foot-rot. The use of tylosin in cattle is very limited in Finland.

In other countries tylosin has been used in the control of *Mycoplasma* infections in poultry.

Spiramycin is used in Finland in the treatment of mastitis caused by penicillin-resistant staphylococci in cows and ewes.

In Finland, erythromycin is mainly reserved for use in human medicine. However erythromycin and another macrolide, oleandomycin, are used for intra-mammary treatment of mastitis in cattle. In other countries the use of erythromycin in veterinary medicine varies widely.

Reports on tylosin resistance in *Serpulina*

In *Serpulina hyodysenteriae*, the causative agent of swine dysentery, resistance to tylosin and lincomycin is remarkably common. In Finland, 53% to 86 % of clinical isolates depending on geographical origin were resistant to tylosin. It is presumed that the resistance is caused by the use of tylosin as therapeutic agent. Total cross-resistance between tylosin and lincomycin was demonstrated. In Denmark, with a much wider use of tylosin in pig farming, almost 100% of *Serpulina* isolates were resistant.

Comment (Minority opinion: One member of the Committee (Dr. Atte von Wright) does not agree with this

comment. According to Dr. von Wright "the report underestimates the clinical significance of macrolides in Finland".

Evidently in veterinary medicine macrolides are only used for therapy in Finland, however to a rather limited extent (possibly macrolides are of greater importance in other countries), as they constitute only about 4% of the total therapeutic use of antibiotics. Further, their importance in the treatment of swine dysentery seems to be decreasing all over the world, including Finland, Sweden and Denmark.

SCAN is surprised that the Finnish case for the reservation of tylosin for therapeutic use makes no reference to the related but more modern therapeutic tilmicosin.

Consumption and indications for macrolides in human medicine

In human medicine in Finland macrolides roughly account for about 10% of the total antibiotic consumption and erythromycin for about 30% of the macrolide consumption.

The most important indications, at least in Finland, for macrolides are respiratory infections. Four macrolides are in clinical use in Finland, namely erythromycin, azithromycin, clarithromycin and roxithromycin. Erythromycin is an important alternative for those allergic to penicillin and also for infections caused by anaerobic organisms. Erythromycin is the drug of choice for *Campylobacter* infections (when treatment is needed). Clarithromycin is a very important antibiotic in the eradication of *Helicobacter* in gastric ulcer patients.

In Finland a strong correlation between the consumption of erythromycin and development of resistance to erythromycin in group A streptococci has been demonstrated.

The high frequency of erythromycin-resistant streptococcal strains is of major clinical concern in Finland and it was found that the resistance decreased when the consumption decreased.

Comment:

The genetic background of the erythromycin resistance is not described but it is obvious that the erythromycin resistance was related to the consumption of erythromycin in the human population.

1.2. The increased use of tylosin in swine and poultry production has resulted in a dramatic increase in the development of resistant bacteria, as demonstrated by the antimicrobial resistance surveys in enterococci conducted in Finland and Denmark in 1995-1996.

The conclusion is based primarily on a comparison of results presented in part II of the report, Appendix, and results obtained in a Danish survey. In the Finnish study, a total of 204 enterococcal strains (*Ent.faecium* 44% and *Ent.faecalis* 56%) and 357 *E.coli* strains were isolated from faeces of slaughter pigs from 180 herds. Likewise a total of 542 enterococcal strains and 342 *E.coli* strains were collected from faeces (*Ent.faecium* 51% and *Ent.faecalis* 49%) and neck skin (*Ent.faecium* 36% and *Ent.faecalis* 64%) of slaughtered broiler chickens.

Enterococci only rarely cause disease in animals. However enterococci were investigated, since they are common commensals in the intestinal tract of humans and animals and acquire and transfer antibiotic resistance under experimental conditions. They may be regarded as indicator organisms to demonstrate the impact of an antibiotic selective pressure on the development of antibiotic resistance.

In Finland, 85% and 91% of enterococci of pig and broiler origin, respectively, were susceptible to tylosin. The corresponding figures for spiramycin were 86% and 91% , and for erythromycin 85% and 85%, thus implying that cross-resistance between these macrolides was high. There was not complete cross-resistance between the three macrolides, which was not to be expected.

No vancomycin-resistant enterococci were detected in the swine population, whereas 7% of broiler strains were vancomycin-resistant, 97% of which were identified as *Ent.faecium*. Avoparcin has not been used in pig production in

Finland and its use in broiler production was discontinued in 1995.

Comments:

The study is hampered by the way the results are presented. Preferably data on antimicrobial susceptibility should be presented as histograms of MIC (minimum inhibitory concentration) or at least as histograms of the inhibition zone diameters. MICs are presented only for tylosin. Furthermore it is stated that the results were interpreted according to the recommendations of NCCLS but that some limits were modified by the laboratory's own quality assurance. Which limits and why they were modified was not explained.

No evidence for increased use of tylosin and a related increase in antimicrobial resistance with time was presented.

Comparison of resistance in enterococci in Finland and Denmark.

In Finland 218 kg of tylosin were consumed by 2 million pigs in 1995 or 0.1 g per pig, whereas in Denmark 20 million pigs consumed at least 53 tonnes or 2.8 g per pig. In 1995, only about 10% of enterococci isolated from pigs in Denmark were susceptible to tylosin, whereas 41% of the broiler isolates were susceptible. The feed additive use of macrolides in Denmark accounted for 85% of the total use in Denmark. The comparison of the resistance rates and consumption figures between Finland and Denmark indicates that the continuous use of tylosin or spiramycin as feed additive to pigs and broilers in Denmark has led to a high prevalence of macrolide-resistant enterococcal strains. In Denmark resistance to lincomycin was about as common as macrolide resistance among porcine enterococci.

Comment:

Susceptibility to lincomycin or streptogramins was not investigated in Finland. Also the Danish figures are poorly presented. No MIC breakpoints or guidance as to how the MICs or zone diameters (mm) for the different antimicrobials were distributed are given. Further, due to different methodology and maybe different interpretation of the results, the Danish data are not directly comparable with the Finnish data, though it is stated in the report that they are comparable because the resistance rates of tetracycline and ampicillin for E.coli were approximately the same in the two countries.

Notwithstanding the insufficiencies associated with the above-mentioned studies, the results indicate and seem to justify the conclusion that the long-lasting and continuous wide use of tylosin and spiramycin as feed additives in pigs and broilers in Denmark is associated with a high prevalence of macrolide-resistant enterococci in the Danish pig and broiler populations as compared to the lower level of macrolide use and lower resistance rate levels in Finland.

The results were as expected as it is generally accepted that there is a correlation (not linear) between development of resistance and the amount of a particular antibiotic used over time.

1.3. There is scientific evidence that the use of tylosin results in the development of erythromycin (an important human drug) cross-resistance since the clinically most common resistance mechanisms within the macrolides, lincosamides and streptogramin B are similar and as cross-resistance was very high between the macrolide antibiotics erythromycin, spiramycin and tylosin among the swine enterococcal isolates studied in the Finnish survey. Further research on the transfer of antimicrobial resistance factors is urgently needed.

Structure and mechanisms of action of macrolides

As demonstrated in the Finnish study there was as expected a high degree of cross-resistance between spiramycin, tylosin and erythromycin. Their similar chemical nature and mode of action against bacteria are described. The macrolides form a group named the MLS antibiotics with the lincosamide (L) and the streptogramin B (S) antibiotics. MLS antibiotics are structurally distinct but have a similar mode of action by binding to the 50S ribosomal sub-unit.

Streptogramin antibiotics are composed of two elements, A and B, which act in synergy. All streptogramins in clinical use are composed of both the A and the B compounds. Three clinically important antibiotics belong to the streptogramin group, virginiamycin in veterinary medicine (approved as a feed additive in the EU), and in human medicine pristinamycin and the new combination dalfopristin/quinupristin.

Two antibiotics in human clinical use belong to the lincosamide group, lincomycin and clindamycin. MLS antibiotics have a similar antibacterial spectrum with a high activity against gram-positive and anaerobic bacteria and mostly low activity against gram-negative bacteria.

Mechanisms of MLS resistance

The three major resistance mechanisms and the genetic background of acquired MLS resistance are described and references given. The most important resistance mechanism is encoded for by erm (erythromycin ribosome methylase) genes causing modification of the target, the 50S sub-unit of the ribosome. Resistant isolates harbouring erm genes produce an enzyme that methylates the 23S rRNA. This form of resistance confers cross-resistance to macrolides, lincosamides and streptogramin B antibiotics. At least 30 erm- genes in different micro-organisms have been described. MLS resistance may be chromosomal or plasmid-borne, inducible (erythromycin-resistance) or constitutive (most other MLS antibiotics). Once induced, bacteria are resistant also to other macrolides, lincosamides and streptogramin B. Bacteria harbouring erm-genes may be phenotypically susceptible to spiramycin and tylosin but resistant to erythromycin. In general there is phenotypic cross-resistance between 14-membered (erythromycin) and 16-membered (tylosin and spiramycin) macrolides. The use of macrolides also increases resistance to lincosamides and streptogramins.

Comment:

The scientific data presented in the references given and the results presented in the appendix justify the conclusion that the use of tylosin is correlated with cross-resistance to erythromycin.

With regard to presumed cross-resistance to lincosamides and streptogramins one can only rely on data given in the references. No data on streptogramin or clindamycin resistance are presented in the Finnish survey.

However, from the literature it is apparent that macrolide resistance in enterococci often or mostly is encoded for by different erm-genes encoding resistance also to lincosamides and streptogramin B. The high MIC-values of tylosin-resistant enterococci reported in Finland indicate that the tylosin resistance is caused by acquisition of erm-genes.

However as stated in the report, in order to draw definitive conclusions on the character of macrolide resistance in enterococci and *Serpulina*, research on the genetic background of the macrolide-resistance and potential cross-resistance especially to streptogramins in these bacterial populations in pigs or poultry is necessary.

1.4. This implies that the large scale use of tylosin and spiramycin and increased resistance causes a risk for treatment not only in veterinary medicine but may also cause a risk in human medicine.

Evidence of the occurrence and transfer of macrolide resistance in animals and humans.

The genetic background of MLS and other antibiotic resistance is described and references cited. It is described how resistance genes may be disseminated i.e. via plasmids (conjugation and transduction), transposons, integrons, gene cassettes and also by transformation.

Comment:

It is obvious that enterococci carrying resistance plasmids and transposons with broad bacterial host range are common in the digestive tract of humans and animals. Conjugative plasmids and transposons encoding erythromycin resistance such as Tn 917 and Tn 1545 occur in *Ent. faecalis* and *Ent. faecium* isolated from both humans and different animal species. Transfer of MLS-resistance occurs by cell to cell contact. In *Ent. faecalis* erythromycin even induces transposition of Tn 917 together with MLS-resistance. DNA sequences hybridising with Tn 917 have been shown to be present in plasmids of enterococci isolated from human and animal origins in various geographical areas in the USA, indicating a wide distribution of Tn 917-like elements (Leclercq and Courvalin).

The conjugative transposon, Tn 1545, encoding for erythromycin, kanamycin and tetracycline resistance has been shown to be transferred to *Listeria monocytogenes* in the intestine of gnotobiotic mice. Furthermore, transfer of

vancomycin (*vanA*) and erythromycin resistance from *Ent. faecalis* to *Staphylococcus aureus* on the skin of mouse was detected when selecting for erythromycin-resistant recipients.

However, a possible co-transfer of macrolide and glycopeptide resistance in broiler enterococci was not investigated in the Finnish report, nor was there any experimental evidence establishing the transfer of macrolide resistance between bacteria of animals and man.

Does the increased macrolide resistance in animal bacteria cause a risk for increased resistance also in human medicine?

Resistance to macrolide antibiotics was much higher in Danish enterococcal isolates from broilers and pigs, where tylosin and spiramycin were widely used as feed additive, than in Finnish isolates, where tylosin or spiramycin are used only therapeutically. In Serpulina, resistance was frequent also in Finland but lower than in Denmark.

Comment:

Most probably the higher resistance rate in animal isolates in Denmark was the consequence of a much higher consumption of tylosin and considerably higher selective pressure of tylosin and spiramycin in Danish pig and broiler farming.

Whether this resistance is caused by clonal spread of resistant strains or by the spread of one or several different resistance genes within or between *Ent. faecium* and *Ent. faecalis* is not possible to elucidate in the Finnish submission, since no studies on the genetic background or transferability of the macrolide resistance are presented. From the literature it may be presumed that the spread of resistance was due to both clonal and horizontal spread of erythromycin resistance genes, since enterococci can exchange resistance genes, including macrolide resistance genes, not only with other enterococci but also with other bacterial genera. Since lincosamide and streptogramin resistance was not investigated in the report presented, that the erythromycin resistance was of the transferable MLS type can only be assumed.

Humans may be exposed to erythromycin-resistant enterococci from farmed animals via environmental sources or more likely via contaminated food, for example chickens. Erythromycin-resistant animal enterococci may colonise humans for a longer or shorter time period or they may transfer their macrolide-resistance genes to the resident bacterial flora of humans, either directly after ingestion or via gene exchange in the environment. However no figures to facilitate estimations on the frequencies of these transfers are presented.

The probability or risk for an increased macrolide resistance in human bacteria is of course higher the more resistant the ingested enterococci (or other bacterial species) are. The risk is also correlated to the total consumption of macrolides in humans and consequent selective pressure in the human bacterial population. Thus, the probability that resistant enterococci or *erm*-resistance genes will be transferred from animals to humans would be higher the higher the prevalence of resistant enterococci in animals is and the higher the consumption of macrolides is in the human population.

Moreover, gene transfer frequencies depend on bacterial species barriers and the character of the resistance genes, that is, for example, whether they are plasmid-borne, transposable, or more stably incorporated in the chromosome. The risks for gene transfer to human bacteria or colonisation of humans with macrolide-resistant strains are very difficult to quantify, if not impossible, even when the resistance genes are characterised as in the avoparcin safety evaluation, and no attempts to do so were presented in the report. With regard to the ability of animal enterococci to colonise the intestinal tract of humans, this was thoroughly analysed and discussed in the avoparcin opinion. No evidence of either occurrence was presented in the Finnish report.

Since there are no data presented on the transferability or genotype of the macrolide resistance in the report, a deeper discussion about the risks for increased resistance problems and consequent risks for therapy failures in humans caused by macrolide-resistant enterococci in farmed animals is not meaningful.

All the same, given the data in the report and all the literature published on the transferability and also the high

frequency of macrolide resistance in animal bacteria caused by the wide use of macrolides as feed additives, potential transfer of bacterial strains or resistance genes conferring macrolide-resistance from animals to man via the food chain or the environment constitute a hazard for increased macrolide-resistance in human bacteria.

However, macrolide resistance in enterococci does not present a clinical problem in human medicine, unless it is of the MLS-type (thus including the clinically important streptogramin B resistance) or unless it is transferred to human bacteria such as staphylococci or group A streptococci.

1.5. Since a continual discovery of effective antimicrobial agents for therapy cannot be expected in the near future, we must be able to manage with the antimicrobials available and therefore restrict the use of macrolides to therapeutic use only.

Comment:

Only one paragraph in the report deals with this issue and few references are given. As stated above macrolide resistance in animals and possibly also in human bacteria will probably decrease, provided the use of macrolides in animals is restricted to therapy.

Furthermore, new streptogramin antibiotics are presently introduced in human medicine for treating enterococcal infections. As macrolide-resistance is common in animal enterococcal isolates, streptogramin B-resistance might be common in animal enterococci. Since *Ent. faecalis* is intrinsically resistant to streptogramin A, animal macrolide-resistant enterococcal strains are probably to a great extent totally resistant to streptogramins A and B. The presence of such enterococci in the food chain must be considered as a threat to human health. However, these particular aspects regarding macrolide resistance and influence on streptogramin resistance are not investigated or analysed in the report.

Furthermore, references not cited in the Finnish document claim that several new antimicrobials are under development.

2. Whether tylosin in feed has a tendency to prolong the excretion of Salmonella, whether no investigations could be found on the excretion of salmonella when macrolides are combined with coccidiostats, whether according to preliminary studies done at the National Veterinary and Food Research Institute spiramycin prolongs the excretion of Yersinia enterocolitica and whether the effect of tylosin and spiramycin on pathogens still needs further investigation.

Colonisation of pathogens

Since macrolide antibiotics in general suppress the growth of gram-positive and anaerobic bacteria, a prolongation of the shedding of *Salmonella* or other gram-negative species as *Yersinia enterocolitica* in animals given these substances in the feed would be expected.

In one study referred to it was concluded that tylosin prolonged the persistence of *Salmonella typhimurium* both in the intestine and internal organs of broilers (Leuchtenberg) and in two other studies (Smith and Tucker) it was concluded that tylosin increased the number of *Salmonella typhimurium* excreted from broilers compared to control birds.

Comment:

The conclusions of the studies are based on rather small numbers of animals with highly variable results and also different design of experiments. Thus, while tylosin or other macrolides may prolong the persistence of *Salmonella* in infected animals, conclusive evidence for this has so far not been presented.

The existence of at least one GLP compliant study whose results oppose these conclusions is known.

As for prolonged excretion of *Yersinia enterocolitica* caused by exposure to spiramycin, no data are presented. Thus this issue can presently not be assessed.

3. Hypersensitivity to tylosin and/or spiramycin, indicating a certain but not absolute cross-reactivity, has been reported, and both tylosin and spiramycin are thus capable of functioning as potent antigens and whether frequent use of macrolides in animal feed may therefore be regarded as an occupational hazard for farmers and other people in contact with this field.

Allergic reactions

Five open literature reports are referred to where macrolides have caused contact dermatitis or asthma in pig farmers, feed plant workers, veterinarians and people working in the pharmaceutical industry. Airborne antigen is believed to be the cause of these reactions in humans.

Comment:

While the existence of hyper-sensitisation states is not surprising the evidence provided did not make an assessment of their overall severity or prevalence possible.

General Conclusion (Minority opinion: One member of the Committee (Dr. Atte von Wright) disagrees with this general conclusion and in particular with its second paragraph. He expressed the following: "the significance of a drug cannot be evaluated solely on the basis of the amounts used. In Finland tylosin is still effective in treatment of *Serpulina*-associated swine dysentery. A desire to keep the arsenal of clinically effective antibiotics as large as possible rather than to reduce it should be natural and understandable, and thus there are sufficient grounds to restrict the use of tylosin to controlled veterinary use. While admitting that risks of macrolides used as animal growth promoters to human chemotherapy are not rigorously proven in the data provided by Finland, I also find that intentional creation of antibiotic resistance gene pools is not a very responsible policy. The ability of bacteria to acquire genetic material under suitable selective conditions should not be dismissed lightly. For example, until recently, no natural antibiotic resistance plasmids were found in *Lactococcus*-bacteria associated with fermented dairy products. In 1990ies a strain has been isolated from natural sources containing a plasmid carrying a cassette of antibiotic resistance genes (streptomycin resistance, chloramphenicol resistance, tetracycline resistance, and a novel macrolide resistance system active in Gram negative organisms) apparently derived from staphylococci, enterococci, and *Listeria* (Perreten et al., 1997, Nature vol 389, 801-802)").

The only possible scientific justification for the Finnish case would be that the wider use of macrolides as feed additives in the long run would contribute to the overall selective pressure for resistant bacteria to a significantly larger extent than would result from the use of macrolides for veterinary therapy alone.

However, since tylosin is not a drug of first choice for veterinary use, increasing resistance to macrolides amongst livestock is not a major concern. The crux of the argument for a continuing ban lies therefore within the potential for increasing resistance to macrolides amongst the human flora. However, the laboratory data and the literature cited do not provide sufficient evidence that the use of macrolides as feed additives presents a significant risk to human or animal health. It is presumptuous to claim that any risk from allowing macrolides as feed additives have been proven.

In the absence of sufficient research data on the epidemiology and spread of macrolide resistance, both among farm animals and from them to man, there is no reason for a general ban on the use of macrolides as feed additives.

Answers to Commission question 92

1.1. For reasons of the quantities used and therapeutic indications mentioned, at least in Finland, the veterinary drugs tylosin and spiramycin are not of major importance in Finland. Therefore, this is no reason to restrict their use solely to the field of veterinary treatment.

1.2. No evidence of increased use of tylosin was presented neither was a time-dependent increase in resistance demonstrated.

- 1.3. Enterococci resistant to tylosin were nearly all simultaneously resistant to erythromycin. The design of the investigation was such that this correlation alone cannot be taken as definitive proof of simultaneous resistance also to lincosamides and streptogramin B. While the correlation between the presence of erythromycin and spiramycin resistance with resistance to tylosin is very close, this can not alone be used to substantiate cause and effect.
- 1.4. The possibility that an increase in the resistance pool poses risk to man has neither been proven nor disproved. While proof of the risk could be expected to be demonstrated, none was offered.
- 1.5. The Finnish claim that the arrival of novel antimicrobials is unlikely in the future is based on open literature references and is offered as an argument for the need to conserve existing agents. That argument is greatly weakened by the existence of other publications which identify several antimicrobials at various stages of development.
2. The evidence concerning prolonged excretion of pathogens, in particular salmonella, is weak and again contradicted by non-cited evidence.
3. Tylosin has been associated with episodes of hypersensitivity in man. However, no evidence establishes the magnitude of the risk to man, when compared with other allergic phenomena arising from animal feed components.