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SUMMARY - Antimicrobial growth promoters have become widely used in most EU countries and elsewhere. They act on micro-organisms within the intestine to increase growth and efficiency through permitting full use of dietary nutrients. The question of resulting antimicrobial resistance has been assessed at various points over the years. Such assessments have generally concluded that there were no demonstrable hazards to human health. However, concern has recently focused on resistance in *Enterococcus faecium* which sporadically causes disease in debilitated or immunosuppressed patients. In these patients, glycopeptides such as vancomycin are important, and the related feed additive compound avoparcin was suspended within the EU in April 1997, following evidence of resistance among isolates from animals, and fear that there might be a link with resistance in man. Avoparcin was suspended despite the SCAN Committee's conclusion (May 1996) that evidence was insufficient to warrant the move and is seen as an illustration of the "precautionary principle", which FEFANA believes should be replaced by a full risk analysis. Key information required for such an analysis includes knowledge of: (i) the incidence of resistance to feed additive compounds among *E. faecium* in EU countries; and (ii) the ease or difficulty with which resistance can pass from animals to man. A surveillance study is being carried out by the EU and the Feed Additive Industry, and studies are also underway to determine the transferablility of resistance factors. Recently, (1998) Denmark has suspended availability of virginiamycin, again based on the possibility that future related compounds may be useful in treatment of human infections. FEFANA believes that the "precautionary principle" should not be allowed to replace the need for a full evaluation of risks and benefits for any new or established technique, including the use of antibacterials as growth promoters. Research would be stifled, livelihoods damaged, and future food supplies curtailed.

Key words: Antimicrobial growth promoters, risk analysis, benefits, animal production.

RESUME - *"Bienfaits et risques microbiologiques des antibiotiques comme additifs alimentaires". Les promoteurs de croissance antimicrobiens ont atteint une large utilisation dans la plupart des pays de l'Union européenne et ailleurs. Ils agissent sur les micro-organismes de l'intestin afin d'augmenter la croissance et l'efficacité en permettant une utilisation pleine des nutriments des aliments. La question de la résistance antimicrobienne qui en résulte a été évaluée à plusieurs reprises avec les années. Ces évaluations ont généralement abouti à la conclusion qu'il n'y avait pas de risque prouvé pour la santé humaine. Cependant, les inquiétudes se sont récemment focalisées sur la résistance à* Enterococcus faecium *qui cause sporadiquement des maladies chez des personnes affaiblies ou immunodéficitaires. Chez ces personnes, des glycopeptides comme la vancomycine sont importants, et l'avoparcine, composé additif alimentaire apparenté, a été retiré au sein de l'Union européenne en avril 1997, suite à la démonstration de résistance dans des isolats d'animaux, et l'on craint qu'il puisse y avoir un lien avec la résistance chez l'homme. Ce retrait s'est fait malgré les conclusions du Comité SCAN (mai 1996) affirmant que les preuves étaient insuffisantes pour justifier cette action et ceci est vu comme une illustration du "principe de précaution", qui, selon la FEFANA, devrait être remplacé par une analyse complète des risques. L'information déterminante nécessaire à une telle analyse comprend la connaissance de : (i) l'incidence de la résistance parmi* E. faecium *aux composés additifs alimentaires dans les pays de l'Union européenne ; et (ii) la facilité ou difficulté avec laquelle la résistance peut passer des animaux à l'homme. Une étude de surveillance est menée par l'Union européenne et l'industrie des additifs alimentaires, et des études sont également en cours pour déterminer la transférabilité des facteurs de résistance. Récemment (1998), le Danemark a exclu la disponibilité de la virginiamycine, encore une fois en tenant compte de la possibilité que des composés futurs apparentés puissent être utiles dans le traitement d'infections humaines. La FEFANA estime que le "principe de précaution" ne devrait pas être autorisé à remplacer la nécessaire et complète évaluation des risques et bienfaits pour toute technique nouvelle ou déjà établie, y compris l'utilisation d'antibactériens comme promoteurs de croissance. Autrement la recherche sera étouffée, des emplois seront perdus, et des apports alimentaires futurs réduits.*

Mots-clés : *Promoteurs de croissance antimicrobiens, analyse des risques, bénéfices, production animale.*

Introduction

Since the discovery in 1949 (Stokstad *et al.*) that low concentrations of antibiotics could improve the growth performance of poultry, feed additive antibacterials have become widely used in agriculture. The original observation was on spent fermentation mash containing residues of chlortetracycline, but subsequently compounds have been specifically developed for the purpose.

Within the European Union feed additive antibacterials have been regulated under a series of Directives based on 70/524/EEC. The stringent requirements for registration of feed additives under the above Directive on antibacterial agents included requirements for safety evaluation such that, until recently, there has been little suggestion that there may be unacceptable hazards associated with their use.

The agents registered in the EU under Annexe I of Directive 70/534 EEC include avilamycin, bacictracin, carbadox, flavophosfolipol, monensin, olaquindox, salinomycin, spiramycin, tylosin and virginiamycin. These products are used in feed at low concentrations, and administered over a relatively long period. Most of the products used have an effect predominately against Gram positive organisms, and several modes of action have been proposed for their activity; however it is clear that these growth promoters have their effect through an antibacterial rather than a direct metabolic mechanism. This is illustrated by the reduced efficacy in germ free animals. Various mechanisms have been suggested for their mode of action:

Mode of action

(i) *Suppression of specific toxin-producing organisms.* Antibacterial agents may be controlling disease controlling organisms which have relatively subtle effects on the intestinal mucosa. A dramatic difference between the villus structure of germ free and conventional animals shows that the conventional mucosa suffers from a continual insult presumably caused by the bacterial flora. This causes the villus to be stunted and short in comparison with the germ free animal which has a much more slender and thin structure, making it more efficient for absorption. Moreover, the rate of migration of cells from the base to the tip of the villus is decreased in the germ free animal allowing more mature and more effective absorbing cells to arrive at the upper part of the structure. It has been suggested that the particular bacterial products which affects the mucosa adversely are ammonia and amines (Corpet, 1997).

(ii) *Sparing of feed nutrients.* The bacterial flora within the intestine consists of many million organisms per millilitre, and these will themselves constitute a metabolic drain on the animal's food intake. Control of the number of bacteria or of their metabolism, (particularly of urea and amino acids, Corpet 1997) by the antibacterial agent will reduce wasted consumption of nitrogen and energy, thus allowing more nutrients to be available for absorption by the host.

The net effect of the inclusion of antibacterial agents within the diet of growing animals is thus economically beneficial (Report, 1997).

Antibacterial agents are normally considered in a therapeutic context. However, when used for growth promotion any direct therapeutic benefit is specifically excluded by the governing EU Directive EC70/524. "At the level permitted, treatment or prevention of animal disease is excluded". This is because an antibiotic with a therapeutic benefit is registered as a prescription medicine and governed by appropriate other Directives.

Recent developments regarding feed additive antibacterials within the EU. Over the period of nearly 50 years during which time antibacterials have been used as feed additives, the effect on growth and productivity has been maintained despite their continued use. This contrasts with the therapeutic use of antibiotics, where continued use has in many cases led to clear loss of activity against the target organism, and therefore a loss of benefit from the use of the product.

Aspects of safety and consumer protection. The use of feed additive antibacterials, governed under the appropriate Directive within the EU, has led to safe and effective use over many years. This is supported by the absence of inherent toxicity in the compounds, and the fact that many of them are

poorly if at all absorbed from the intestine. In recent years, the question of resistance induction by the use of antibacterial agents as feed additives has become of much higher profile.

Enterococci. For many years, the gram positive enterococci were considered normal commensal inhabitants of the intestine, as indeed in most cases they remain. However, in certain immunocompromized patients, infections with *Enterococcus faecium* or *Enterococcus faecalis* can become life threatening. Where such infections occur, treatment is commonly with vancomycin. Vancomycin is a glycopeptide which is related structurally to avoparcin, which was widely used for growth promotion in pigs and poultry.

The use of avoparcin was found to be associated with reduced susceptibility of enterococci to avoparcin, and therefore to vancomycin. This in itself has no particular implication for animal health, since vancomycin is not used in treatment of animals. However, vancomycin resistant enterococci are found sporadically in European hospitals, and where they occur, such infections are difficult to treat. Vancomycin resistant enterococcal (VRE) infection is a more serious problem in the United States where VRE are much more common than they are in Europe, probably as a result of the widespread use of vancomycin in US hospitals (Schwartz, 1994).

The presence of vancomycin resistant enterococci in animals has given rise to the suggestion that this may be linked with the occurrence of vancomycin enterococci in man. In 1996, the EU Scientific Committee for Animal Nutrition (SCAN) considered the evidence on the influence of avoparcin resistance among enterococci in animals with vancomycin resistance among enterococci in man. In this discussion, it was notable and indeed this remains the case, that such resistance is much more common in the United States where avoparcin has *never* been used in animals. The SCAN Committee concluded that the data available then (and little has changed in the intervening period) was insufficient to support a direct link between avoparcin in animals and vancomycin resistance in man. However, they recommended that further work should be done on the question and that resistance surveillance should be undertaken.

Despite the SCAN Committee's conclusion, the EU reacted to the potential threat according to the "precautionary principle", and suspended the use of avoparcin from the 1st April 1997. The Directive requiring the suspension of avoparcin also required the industry to carry out surveillance of resistance among enterococci for all products used for growth promotion.

"The precautionary principle". Many events, occasions and experiences in every day life can represent a hazard, whether it be a hazard of crossing the road, driving a vehicle, or falling out of bed. For most situations, individual consciously or otherwise assesses the degree of risk associated with the hazard and acts accordingly. In aspects related to food, health and, in particular, pharmaceutical products, there has been an increasing tendency has been to expect zero risk. In reality of course, zero risk is an impossible aim, and zero tolerance of risk is what is implied by the application of the "precautionary principle". This results from the atmosphere engendered by Bovine Spongiform Encephalopathy (BSE) in Europe making rational decision making difficult. Nevertheless an appropriate process of risk analysis should be followed.

Risk analysis comprises of three elements, (North, 1995):

(i) Risk assessment, which is the process of estimating the probability of an adverse result from the factor under assessment -in this case the use of feed additives.

(ii) Risk management, is the process of identifying measures which can be applied to reduce the risk to an acceptable level and documenting the final decision.

(iii) Risk communication, is the process by which the result of risk assessment and risk management are communicated to decision-makers and to the public.

In a discussion of feed additives, risk assessment must fully analyse the potential impact, if any, on human health of the use of feed additive antibacterial agents. The risk management aspect will then incorporate a balance between any risks assessed to take place with the benefits and counter risks of reacting by banning such products. Thus in the case of feed additives, an assessment must be made of the implications for their suspension. There is a danger that Risk Management (i.e., identification of

measures) and Risk Communication (followed rapidly by action), will precede the Risk Assessment step. Such a sequence will be, by its nature, arbitrary and perhaps unnecessarily damaging. For instance, it was emphasized in the Report of the WHO on Medical Impact of Antimicobial in Food Animals (1997) that "the magnitude of the medical and public health impact of antimicrobial use in animals production is not known" yet recommendations were made on reduction or termination of the use of such agents. There were, however, recommendations that resistance monitoring should be considered a priority.

In October 1997, the World Health Organization organized a Conference to consider the "Medical Impact of the Use of Antibacterial Agents in Food Animals". The report of this conference included a recognition of the importance of antibacterial agents in animals, and the benefits from their use. However, it also recognized the concern that use of antimicrobials in animal production might have an impact on medical and public health, although it accepted that the magnitude of the impact of this use remained unknown. The recommendations were that antimicrobial feed additives should be phased out, particularly where they had any possible relation with resistance to compounds used in human health, that National practices on the use of antibacterial agents in animals should be reviewed, that resistance should be kept under surveillance, and that alternatives to growth promoters be actively considered.

Sweden

In 1986 it was decided by the Swedish Government at the instigation of farmers, that feed additive antibacterial agents should no longer be used without prescription, i.e., antibiotics should be used only for therapy and not for growth promotion. On joining the EU, Sweden was to continue the ban on the use of antibacterial feed additives during a period of four years. This period is shortly to end (Dec. 1998). The Swedish case for continued derogation (or extension of their approach to other EU countries) is described in the comprehensive Report (1997) "Antimicrobial Feed Additives" submitted to the EU in 1997. They concluded that the benefits of antimicrobial feed additives do not outweigh the risks of emergence of resistance, also taking into account considerations of welfare and animal health. However, the Report recognized the economic benefits of the use of feed additives, and was very open about the difficulties which are inherent in abolishing their use which were experienced (and generally overcome) in Sweden.

What would happen if antibacterial growth promoters were banned? If antibacterial growth promoters were to be banned, the impact would be considerable. Sweden represents a case study of the effects that could be predicted. Effects of this ban were considerable, particularly in the early years. These effects may be defined as follows:

(i) *Economic effects*. These are the predictable results of removing beneficial production support, which feed additive antibacterials represent. The cost benefit of the use of antibacterial agents varies, but types of benefits which can be expected.

(ii) *Effects of animal health*. Effects were more marked than might have been expected, since feed additive antibacterial agents are licensed on the assumption that they do not have effects on prophylaxis of animal disease. However, due to the direct antibacterial effect, or indirect effects on the host, it does appear that removal of feed additive antibacterial agents did result in health problems in chickens (necrotic enteritis) and in pigs (where post weaning mortality was found to increase). The ban of antibacterial agents in Sweden led to much effort and in the adjustment of diets and management techniques which have allowed Sweden to continue to maintain the ban, and indeed to recommend this approach to the rest of the EU. However, it should be noted that several points in Sweden are not directly applicable elsewhere in the EU:

- The intensity of animal product in Sweden (the distance between holdings) is almost certainly higher than elsewhere in the EU, and the intensity of production is within facilities is probably lower.
- Even after much care in changing rearing techniques and in dietary manipulation, in 1997 it was still accepted that zinc oxide was found very helpful in maintaining an acceptable incidence of post weaning diarrhoea in pigs. Unfortunately, high concentrations used

(greater than 2000 ppm) were above those generally acceptable elsewhere in the EU and had potential environmental side effects. For this reason they have recently been proscribed, and this may lead to further problems for the Swedish pig industry.

(iii) *Environmental effects.* It has been calculated that removal of feed additive antibacterial agents elsewhere in Europe will add very substantially to the environmental contamination following the increased number of animals necessary to produce the same amount of food (Vianne, 1997). It was calculated that for Germany, the national increase in pigs required to compensate for the loss of feed additive efficacy would be an extra 1.3 million pigs, to add to the 36.5 million which was the then output. Feed use would increase by nearly 1 million tonnes, with a resulting increase in 2.9 million cu m of slurry, and 22,000 tonnes of nitrate. Clearly, an additional pollution burden.

(iv) *Effects on antibiotic consumption.* It is quite possible that abolition of feed additive use would lead to an overall reduction in the overall use of antibacterial agents, although it must be recognized that feed additive use would to some extent, be replaced by increased use of therapeutic (prescribed) antibiotics. Interpretation of reductions claimed in Sweden are complicated by changes in national herd numbers, and substitution of more recent therapeutic compounds with a high potency, and therefore used at lower dosages in comparison with older less potent compounds such as oxytetracycline.

Conclusion

So in conclusion, the question of feed additive antibacterial agents used in animals remains contentious; the impact on human health has not been fully defined, and data are needed to properly evaluate the potential risk involved in their use. It is possible that proposals may be made for a total or a partial extension of the existing restrictions, and if such were to be implemented, these would have major effects on the economy of EU animal production. Moreover under World Trade Organization constraints, the ability to control imports from countries who will continue to use these products will be limited (Vianne, 1997).

Thus the European consumer may be exposed to low cost food produced without welfare or other constraints, and with potential hazards far beyond those minimal risks associated with feed additive antibacterials carefully used on the EU conditions. Meanwhile the EU producers would be under even greater pressure in a world market. The "precautionary principle" implies the by-passing or ignoring of science-based decision making. Such would have serious implications for the way in which new animal products could attract investment, and in the subsequent loss of benefits to producer and consumer alike.

Finally, it should be noted that any risk to human health through resistance induction in microorganisms is trivial in comparison with the very real problems of food poisoning following bacterial contamination food by bacterial pathogens. The removal of these by hygiene or other methods would remove the risk of food poisoning, and, incidentally, any risk of resistant bacteria being swallowed by consumers. It is interesting that the United States has recently licensed the use of irradiation for red meat (Feedstuffs, 1997), and there is little doubt that this and other, even simpler methods will become commonly used to decontaminate meat and meat products. Such approaches will allay any fears of antibiotic resistant bacteria in meat, as well as the far more pressing need to eliminate pathogenic organisms. This must surely be the way of the future.

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