THE CHALLENGE OF FINDING ALTERNATIVES TO ANTIBIOTICS GROWTH PROMOTERS

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Introduction–The ban of antibiotic growth promoters

The animal feed industry worldwide has been using antibiotics for over 50 years. To date antibiotics are used in farm animals at therapeutical levels to control actual disease and at subtherapeutical levels to promote growth and feed efficiency. However, more recently, the use and apparent over-use of antibiotics in animal feed as been widely discussed in the scientific literature, at scientific meetings and in the general press. The main concern is the emergence of a so-call superbug, an antibiotic resistant human pathogens, after the prolonged use of antibiotics in animal feed (22). The first step toward controlling the use of antibiotics as growth promoters was made by the Swann Committee in 1969 (29). This committee initiated restriction of the use of AGPs without veterinary prescriptions. As a result of increased pressure from consumer groups to further reduce AGP in animal feed, Sweden was the first country to implement a partial ban on the use of AGPs in farm animals in 1986. Sweden was joined by the European Union (EU), which placed a partial ban on the use of AGP in 1997 which will be replaced in 2006 by the general ban of all AGP (including ionophore anti-coccidials) in all animal feed. In the US one of the largest purchaser of meat, McDonalds Corp. has adopted a police that prohibits its supplier from using medically important antibiotics as growth promotants (18). Some group heavily criticize the total ban of AGP arguing that such a ban follows "precautionary principles" rather than scientific facts (28). Despite this, it appears to be inevitable that we will face a global ban on the use of antibiotics as growth promotants in the not too distant future. The animal industry will be forced to develop alternate strategies to maintain current standards of animal production, animal health and welfare. The objective of this paper is to discuss some of the challenges faced by the industry without AGP as well as some of the strategies which can replace AGP now and in the future.

The use of AGPs–Advantages and disadvantages

The use of antibiotics in animal feed has a wide range of benefits. Undoubtedly, AGP are an effective tool to improve growth performance in farm animals. In a review of over 12'000 studies Rosen, 1995 (25) concluded that antibiotics will improve growth and FCR in 72% of the time. However, the use of AGP has wider implications than just improving performance. AGP selectively modify the gut flora, suppress bacterial catabolism, reduce bacterial fermentation and reduce the intestinal wall thickness, all of which lead to increased health, increased nutrient availability for the animal and subsequently increased growth performance (3). Improved feed utilisation means that feed resources will last longer. This is of particular relevance when feed ingredients are limited due to extreme weather conditions and poor crop yield. The more efficient use of nutrients by the use of AGP results in a significant reduction of nutrients that are excreted into the environment (6). Furthermore, the selective use of AGP has a major impact on overall animal health and welfare. One of the main reasons AGP are still used at present is to protect animals against subclinical infections of such as clostridial infections (Necrotic enteritis), E. coli infections (post-weaning diarrhoea in piglets) or coccidial infections.

The biggest concern on the use of AGP is the occurrence of resistance to these AGP as well as the occurrence of resistance to antibiotics used in human medicine. There is considerable controversy between leading scientists as to whether the ban of AGP in feed is justified on the basis of increasing resistance. Veterinarians defend the use of AGP on the basis that there is no link between the use of AGP in feed and any resistance pattern in human medicine (7, 28). In addition, the ban of AGP, antibiotics that are generally not used to treat human diseases, has led to an increase in the use of therapeutical antibiotics that are also used to treat human disease. As a result there is now a trend of increased resistance to antibiotics used in hospitals of human pathogens such as *S. typhimurium*, *E. coli* or *C. jejuni* (8). There is also considerable doubt over whether a simple ban of AGP will reduce or eliminate resistance. A study at the University of Kentucky showed that even after the complete withdrawal of all antibiotics, population of antibiotic resistant bacteria can survive in a pig herd for decades (20). This is in direct contrast to the reports from Denmark. The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) has reported that after the ban of AGP in Denmark the occurrence of resistance to *E. faecium* has drop significantly (8). Possible the most direct link between the use of AGP and the increase resistance in a human pathogen is the occurrence of vancomycin resistance enterococci (VRE) in hospitals and in the general population (5, 24).

Despite this apparent controversy on the benefits of a total ban of AGP in animal feed it seems to be very unlikely that any banned antibiotic will be reintroduced. The challenge to the animal industry is therefore to find acceptable and effective alternative additives.

Manipulation of the intestinal microflora without AGPs

Antibiotic growth promoters work primarily by reducing the microbial load in the intestine. In the absence of a microflora the demands on nutrients to maintain intestinal tissue and the immune system is reduced, hence more nutrients are available for growth and production. It is known that germ-free animals have increased performance parameters compared to 'conventional' animals (19, 31). The key to a successful animal production without AGP is clearly controlling and maintaining a healthy and diverse gut microflora. Reports in the literature emphasis the fact that the incidence of clostridial infections is significantly higher in birds fed diets based on wheat, barley, oats or rye containing high levels of indigestible soluble NSP which leads to increased digesta viscosity and decreased digesta passage rate and nutrient digestibility (4). A highly viscous intestinal environment will increase the proliferation of facultative anaerobes like gram-positive cocci and enterobacteria (30). Larger amounts of undigested material in the small intestine together with a slower flow of digesta increases the chances of rapid bacterial colonisation. Pluske, 2001 (23) showed that the incidence of Porcine intestinal spirochaetosis (PIS), swine dysentery (SD) and post weaning diarrhoea is closely related to the amount of indigestible starch and non-starch polysaccharides in the diet and the proliferation of pathogenic bacteria in the intestine. Similarly the use of poorly digestible protein sources alters the microflora and creates favorable condition in the intestine for the proliferation of pathogens. The microflora population depends very much on the balance between communities of organisms and the diet composition as the source of available substrates for microorganisms. The colonisation of potential pathogen is greatly reduced in animals fed highly digestible and balanced diet according to their nutrient needs.

Knowing that specific feed ingredients can influence the intestinal microflora is a powerful tool to formulate feed rations without AGP. In additions, a number of possible feed supplements have been identified that specifically alter the intestinal microflora and eliminate potential pathogens. It has to be pointed out that most of these supplements possess a distinctly different mode of action to AGP, hence these become clear alternatives to AGP rather than merely replacement of the currently used AGP.

Alternative additives

The numbers of publications on the efficacy of possible alternatives has been steadily growing over the last years. The basic mode of action of these supplements can be divided into four basic groups with distinct strategies: 1) improvement of nutrient utilisation by the host (exogenous feed enzymes); 2) stimulation/modulation of the immune system (cytokins, vaccines, gluco-and mannanoligosaccharides (MOS); 3) stimulation or introduction of beneficial bacteria (probiotics or direct fed microbials, fructooligosaccharides (FOS)) and 4) direct reduction of pathogens (MOS, organic acids, botanicals and herbs, bacteriocins, antimicrobial peptides, bacteriophages). Within these general categories there are hundreds of commercial products available claiming to be as effective to improve growth performance and animal health. Rosen, 2004 (26) proposed a seven question test by which producers can assess the potential value of a potential alternative. Two of the central questions in this test are the number of feeding test conducted and the frequency of positive response. Many replacement products have only been recently developed and therefore have not been tested under a wide range of condition. Two of the potential replacements, which have been extensively tested under scientifically controlled feeding tests, include exogenous feed enzymes and mannan oligosaccharides (MOS).

Enzymes: Today the use of exogenous enzyme supplementation is almost standard in all pig and poultry feed. The efficacy of these enzymes to improve animal growth performance as been established in over 2500 publications (27). Inclusion of gylanases and phytases significantly improves nutrient availability by depolymerising indigestible feed ingredients such as phytate and soluble NSP. As a result nutrient digestibility by the host is significantly increased and bacterial population in the small intestine is reduced (2). Apajalahti, J, 2000 (1) suggested further that the depolymerisation of larger arabinoxylans in wheat with xylanase produced xylo-oligomers and xylose which could only be partially utilised by the microflora. Subsequently the total number of bacteria in the ileum was reduced by 60%. However, it as to be mentioned that the inclusion of exogenous enzymes are only useful if the diets contain the specific substrate for the enzyme to work on.

Oligosaccharides: Unlike exogenous enzymes mannan-oligosaccharides (MOS) have little influence on nutrient utilisation. The growth promoting effect of MOS is primarily based on inhibiting colonisation of pathogenic bacteria by blocking type-1 fimbriae on the bacteria surface (10) and the improvement in overall intestinal health by improving gut integrity and modulating the immune system (9, 11, 15). It has also been reported that MOS has a direct influence on nutrient utilisation in the intestine. Addition of MOS can improve specific population of microbes with enhance fibre fermentation capacity and reduce the population of microbes using starches and sugars (12, 16). The relationship between the specific modes of action of MOS (Bio-Mos®, Alltech Inc.) and the effects of animal growth performance and health under a range of conditions have clearly been establish in over 300 research trials and scientific publications and (13, 14, 17, 21).

Conclusions

Consumer demands and legislative pressure will dictate the future use of AGP worldwide. The challenge for producers is to find suitable, reliable and most importantly cost effective replacements for AGP for a sustainable and successful animal production in the future.

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