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Review

An update on alternatives to antimicrobial growth promoters for broilers

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ABSTRACT

Livestock performance and feed efficiency are closely interrelated with the qualitative and quantitative microbial load of the animal gut, the morphological structure of the intestinal wall and the activity of the immune system. Antimicrobial growth promoters have made a tremendous contribution to profitability in intensive husbandry, but as a consequence of the increasing concern about the potential for antibiotic resistant strains of bacteria, the European Commission decided to ban all commonly used feed antibiotics. There are a number of non-therapeutic alternatives, including enzymes, (in)organic acids, probiotics, prebiotics, etheric oils and immunostimulants. Their efficacy and mode of action are briefly described in this review.

Introduction

Antibiotics have been widely used in animal production for decades. Although some are used therapeutically to improve the health and well-being of animals, most were given for prophylactic purposes and to improve growth rate and feed conversion efficiency (as antimicrobial growth performance promoters, or AGPs). However, due to the emergence of microbes resistant to antibiotics which are used to treat human and animal infections, the European Commission (EC) decided to phase out, and ultimately ban (January 1st 2006), the marketing and use of antibiotics as growth promoters in feed (EC Regulation No. 1831/2003[1]). This political decision was taken by invoking the precautionary principle: '*Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*' (Principle 15 of the Rio Declaration, 1992[2]).

In other countries, such as the USA, consumer pressure is pushing the poultry industry to rear animals without AGPs (Dibner and Richards, 2005; Castanon, 2007). AGP removal has led to animal performance problems, feed conversion increases, and a rise in the incidence of certain animal diseases, such as (subclinical) necrotic enteritis (Wierup, 2001; Dibner and Richards, 2005). One disease syndrome that is clearly emerging in the EU broiler industry simultaneously with the ban of growth promoting antibiotics is often referred to as 'dysbacteriosis'. This is a poorly described condition of the gut and may be synonymous with conditions such as 'wet litter', 'small intestinal bacterial overgrowth', 'malabsorption', and 'feed passage syndrome'. The common clinical denominator is thinning and ballooning of the small intestine, increased water content of faeces and reduced digestibility of feed with indigested residues visible in the faeces.

The impact of phasing out animal growth promoters could be minimised provided that adequate attention is given to the implementation of alternative disease-prevention strategies and management factors, such as alternative husbandry practices in food animal production. Indeed, overall disease and performance problems have been rather limited, partly because ionophore anticoccidials are still available, therapeutic antibiotic use (e.g. macrolides and penicillins) has increased, and alternatives for AGPs have been empirically used such that those with the best effects on performance are currently used as feed additives.

Characteristics of good AGP alternatives

Ideally, alternatives to growth promoters should have the same beneficial effect as AGPs. It is however not totally clear how AGPs exert their beneficial action. The most well-known mechanism to

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[1] See: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0029:0043:EN:PDF.

[2] See: http://www.unep.org/Documents.Multilingual/Default.asp?DocumentID=78andArticleID=1163.

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be proposed is that AGPs have an antibacterial action that favours performance in different ways: (1) by reducing the incidence and severity of subclinical infections (George et al., 1982; Brennan et al., 2003); (2) by reducing the microbial use of nutrients (Snyder and Wostmann, 1987); (3) by improving absorption of nutrients because of thinning of the intestinal wall, and (4) by reducing the amount of growth-depressing metabolites produced by Gram-positive bacteria (Feighner and Dashkevicz, 1987; Knarreborg et al., 2004). The basis of this mechanistic explanation is that AGPs do not exert growth-promoting effects in germ-free animals (Coates et al., 1963).

Although certain authors reason that AGPs are used in sub-therapeutic or sub-minimum inhibitor concentration (MIC) doses and so any growth-inhibitory action is unclear (Niewold, 2007), clear shifts in the microbiota composition have been demonstrated when AGPs are added to broiler feed (Pedroso et al., 2006; Wise and Siragusa, 2007). Indeed, sub-MIC concentrations do not mean that growth-inhibition of certain bacterial species in the gut can be excluded but shifts in microbiota composition can, at least in theory, explain the effects of the AGPs. Furthermore, microbiota shifts can affect morphology of the gut wall and induce immune reactions that can have effects on energy expenses of the host (Humphrey and Klasing, 2003; Teirlynck et al., 2009).

Niewold (2007) hypothesised that AGPs may be growth permitting by inhibiting the production and excretion of cytokines by immune cells (macrophages), after AGPs accumulate in these cells. Cytokine release would then lead to an acute phase response leading to loss of appetite and muscle tissue catabolism (Niewold, 2007). Certainly inflammation leads to performance decreases (Humphrey and Klasing, 2003), but equally AGPs may act by shifting the microbiota composition towards one that is less capable of evoking an inflammatory response. AGPs could also simply lower the total microbial load, leading to less inflammation and lower energetic cost for the animal.

Whatever the mechanism of action of AGPs, the main characteristic of a good alternative from a practical point of view is that it must improve performance at least as well as AGPs. Based on the proposed mechanism of action of AGPs, both microbiota modulating and immunomodulatory compounds could have potential. There are many possible ways microbiota modulating compounds could influence the intestinal microbiota population without adding AGPs to the feed. The most obvious method is the use of therapeutic doses of antibiotics under prescription, a practice that will undoubtedly increase and (ironically) probably raise the likelihood of the emergence of resistant human pathogens.

None of the non-antibiotic AGP alternatives suggested below is likely to compensate fully for the loss of AGPs. It must be emphasised that some strategies will only help to compensate partially (but will not replace) AGPs, and will work through indirect mechanisms. The list is by no means exhaustive and there are also other products claiming to be of value in AGP-free diets.

Some alternatives for AGPs and their mode of action

Exogenous enzymes

Non-starch polysaccharides (NSPs) in animal feedstuffs are a complex group of components differing widely in chemical composition, physical properties and physiological activity, many of which have negative effects on growth and performance. NSPs include (hemi)celluloses, pectins and oligosaccharides as well as arabinoxylans and β-glucans (consisting of either a more soluble or a non-soluble fraction).

Different cereal types contain variable NSP levels with concomitant differences in chemical composition. For example, maize contains almost exclusively insoluble NSPs, whereas wheat and barley contain NSPs of which the ratio of soluble to insoluble is about 1/6. This ratio is about 3/4 in rye, making this cereal one with particularly high levels of soluble NSPs (Choct, 2002).

The mechanism by which NSPs exert their anti-nutritive effects is complex, but their viscous nature is considered a primary cause for their anti-nutritive effect in poultry. This is because the increased bulk and viscosity of the intestinal contents decrease the rate of diffusion of substrates and digestive enzymes and hinder their effective interaction at the mucosal surface (Choct et al., 1996). NSPs also induce thickening of the mucous layer on the intestinal mucosa (Hedemann et al., 2009) suggesting that the concentrations of soluble NSPs in wheat are inversely correlated with their metabolisable energy (MEn)-values in broiler chickens (Annison, 1991).

In addition to the direct effect of viscous NSPs on gut physiology and morphology, there appear to be some indirect effects that could have important implications for the efficient use of nutrients by the chicken (Dänicke et al., 1999). One such indirect effect may be related to stimulation of fermentation of NSPs by the gut microbiota, leading to volatile fatty acid production (VFA) in the small intestine. Under normal circumstances with low NSP-diets, facultative anaerobes predominate in the chicken small intestine and nearly strict anaerobes make-up the entire caecal microbiota (Salanitro et al., 1978; Lu et al., 2003; Bjerrum et al., 2006). On a NSP-rich diet, the VFA-concentration increases mainly in the distal ileal lumen due to excess fermentation combined with a proliferation of the fermentative microflora with a rather limited effect on the activity of the hindgut microbiota (Choct et al., 1996, 1999). Small intestinal fermentation indicates competition with the host for digestible nutrients. Enzyme-free diets containing soluble-NSP rich cereals (wheat) have been shown to induce lymphocyte infiltration in the gut wall and induce apoptosis of epithelial cells much more than cereals such as maize that have low levels of soluble NSPs (Teirlynck et al., 2009).

Negative effects of diets with high NSP levels can be partly counterbalanced by adding AGPs (Teirlynck et al., 2009). Without these, supplementing the NSP-rich diet with enzymes results in both a reduction in ileal VFA-concentration and an elevation in caecal VFA-concentration (Choct et al., 1996) as more 'low molecular weight' fermentable material is entering the caecum. Caecal fermentation suggests the conversion of indigestible compounds into readily absorbable VFAs.

Dietary NSP-enzymes work by reducing the viscosity of the digesta in the small intestine, so that digesta passage and nutrient digestion rate increase providing less substrate and less time for the fermentation organisms to proliferate. This may restore the normal and efficient endogenous enzymatic digestion of nutrients in the small intestine. The enzymes are partially counterbalancing the adverse effects of soluble NSP on performance (Bedford and Classen, 1992).

It is not possible to measure the relative contribution following improved nutrient utilisation or the 'selective' reduction in the microbial population (Smits and Annison, 1996). However, there is evidence that the consequence of a NSP-mediated reduced rate of digestion is much more radical in the presence of intestinal microbiota due to the degradation of both digestive enzymes and bile salts and colonisation of the absorptive surface area (Smits and Annison, 1996). In the absence of antimicrobial growth promoters (as in the European Union), there will be a greater response to enzymes, particularly in less well-digested diets (Elwinger and Teglöf, 1991). Furthermore, NSP degrading enzymes will also reduce the proliferation of pathogenic bacteria such as *Clostridium perfringens* (Jackson et al., 2003). These days all broiler feed contains enzymes such as xylanases and beta-glucanases that breakdown NSPs.