

ROLE OF GROWTH PROMOTANTS IN POULTRY AND SWINE FEED

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INTRODUCTION

Feed producers are faced with choosing from a myriad of growth promoting substances all claimed to improve performance and have some advantage over competitive products. In most cases, these products are "non-nutritional" and contain nothing that contributes directly toward meeting the animals requirement for nutrients. Yet, many have been confirmed to be highly cost-effective when added to feeds. The selection of a growth promotant must be based on safety and probability to give high economic returns. The most widely used are the antimicrobial agents, including antibiotics. In recent years, there has been a flurry of interest in the use of other non-nutritive substances such as acidifiers, probiotics, enzymes, herbal products, beta-agonists, microflora enhancers and immunomodulators. New entries into the market are common each year, as are new research reports on products and product combinations. The purpose of this paper is to present an overview on the use and mode of action of various growth promoting substances, give some perspectives that may assist in product selection based on safety and farm conditions, and discuss future directions.

ANTIBIOTICS AND ANTIMICROBIALS

Antibiotics are natural metabolites of fungi that inhibit the growth of bacteria. In 1949, Dr. Thomas Jukes stumbled on the curious observation that low level feeding of chlortetracycline to chicks or pigs improved growth and feed efficiency. Today, more than 50% of all antibiotics produced are used in animal feeds. While growth promotants inclusion rate in individual formulations has declined in recent years, the total amount used has increased with expansion of the feed industry. Antibiotics are used as growth promotants in all countries

except Sweden. Approvals vary from country to country, depending on safety concerns and funding for clinical research by drug companies. Currently, there are ten antibiotics approved for use as growth promotants within the U.S. These are Zn bacitracin, bacitracin methylene disalicylate, bambarmycins (flavomycin), chlortetracycline, lincomycin, oxytetra-cycline, penicillin, tylosin, tiamulin and virginiamycin. Antibiotics such as avoparcin, spiramycin, oleandomycin, bicozamycin, colistin, avilamycin and many others have approval in other countries. Table 1 gives a list of approved antibiotics for growth promotion. Table 2 classifies growth promoting antibiotics with respect to molecular type and spectrum of activity.

Antimicrobials refer to synthesized chemicals that inhibit microorganisms. They have similar properties as antibiotics. These include arsenicals such as arsanilic acid and roxarsone (3-nitro), and others such as carbadox, olaquinox, halquinol and copper sulfate. Most countries have banned sulfonamides and nitrofurans (furazolidone) as growth promotants because of problems with tissue residue and suspected carcinogenicity.

BENEFITS OF FEEDING ANTIMICROBIALS

The major benefit of feeding an antimicrobial is cost savings from improved feed conversion. Feed efficiency response is highest in fast growing genetically improved animals. There are also savings from faster growth, reduced mortality, greater resistance to disease challenge, improved pigmentation and improved manure or litter quality. Under normal practical conditions, savings

Table 1. Approved Antimicrobial Growth Promotants

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B=broiler L=layer S=swine

*From: Feed Additive Compendium, 1995
Brenninkmeijer, 1996*

Table 2. Antibiotic Type and Spectrum of Activity

Antibiotic	Activity	Type	Molecular Weight
Avoparcin	narrow g+	glycopeptide	1900
Bacitracin	narrow g+	polypeptide	1400
Chlortetracycline	wide	tetracycline	515
Colistin	narrow g-	polypeptide	1168
Flavomycin	narrow g+	glycophospholipid	1700
Lincomycin	narrow g+	lincosamide	461
Penicilin	narrow g+	b-lactam	589
Spiramycin	narrow g+	macrolide	884
Tylosin	intermediate	macrolide	916
Virginiamycin	narrow g+	peptolide	750

from improved FCR can be expected to return product cost between two and 12 fold.

A review of the literature on 12,153 feeding studies by Rosen (1996) has indicated that antimicrobial growth promotants give positive responses 72% of the time. The magnitude of response depends on animal management, disinfection procedures, age of the farm buildings and feed quality.

Results of recent practical feeding studies with virginiamycin and Zn bacitracin are given in Tables 3 and 4. Virginiamycin was tested in broilers during the hot summer months which had poultry litter added to the feed to simulate dirty conditions (Belay and Teeter, 1994). This study demonstrated a product cost:payback of around 1:10 using Asian feed costs. In another recent study con-

ducted in the Philippines, addition of Zn bacitracin gave a 2.5% improvement in FCR equivalent to a 1:6 product cost:payback (Mateo, 1996). Birds were grown on slatted floors in a several year old shed that had been disinfected prior to placement of chicks. Copper sulfate is an often overlooked but highly effective and economical growth promotant. Whereas the nutritional requirement for copper is ten to 20 ppm, growth promotion can be demonstrated between 125 to 250 ppm. Recent work reported by Dove (1995) has shown copper sulfate to improve fat digestibility in weanling pigs starting (Table 5). In diets containing 5% animal fat, 250 ppm copper improved ADG by 47% and FCR by 18%. The effect, however, was less pronounced when no fat was added to the diet. Copper sulfate can be used in both swine and broiler diets but should be

Table 3. Benefit of Virginiamycin in Broilers

Cost:payback = 1:10.6 assuming Virginiamycin-20 cost of US\$2.40/kg, feed cost of US\$340/MT and 7.5% improvement in FCR

Study conducted during summer; litter added to feed
From Belay and Teeter, 1994

Table 4. Benefit of Zn Bacitracin in Broilers

Cost:payback = 1:5.8 assuming Zn Bacitracin-11 cost of US\$3.20/kg, feed cost of US\$340/MT and 2.5% improvement in FCR

Study conducted on disinfected bamboo slats under Philippine conditions
From Mateo, 1996

Table 5. Effect of Copper and Fat on Young Pig Performance

	ADG	FCR
Copper - 15 ppm		
0% fat	333	1.226
5% fat	294	1.357
Copper - 250 ppm		
0% fat	359	1.264
5% fat	432	1.111
Probability of significant Fstatistic:		
Cu	.01	.01
Fat	NS	NS
Cu x Fat	.01	.01

6.8 kg, 26 days old starting

From: Dove, 1995 JAS 73:166-171

removed if signs of gizzard erosion or stomach ulceration develop.

MODE OF ACTION

Antimicrobial feed additives promote growth by altering the gut microflora to the benefit of intestinal tissue. Feeding of antibiotics to chicks has been clearly shown to improve performance, reduce ileal weight, and decrease the population of *Clostridium perfringens* across different diet types (Table 6: Stutz and Lawton, 1984). Various reports in the literature indicate that feeding of sub-therapeutic levels of antibiotics and antimicrobials result in:

- Suppression of bacteria responsible for mild but unrecognizable infections,
- Reduced production of growth depressing toxins from microflora,
- Lower nutrient use by microflora leaving more for the animal,
- Increased production of vitamins and other nutrients by microflora,
- A thinner gut wall capable of enhanced nutrient absorption,

- Lower production of ammonia in the gut which reduces turnover of mucosal cells and results in less energy consumption by the animal,

- Lower immune stress resulting in a shift of protein synthesis toward muscle and away from antibody production.

USE CONSIDERATIONS FOR GROWTH PROMOTANTS

Selecting which product to use often creates a dilemma for the feed producer. The decision should be based on known field problems and disease challenges at the farm level. Although used for promoting growth, many additives have additional benefits that justify their specific use over other products under certain conditions.

Post weaning scours

Broad spectrum antibiotics active against both gram negative (*E coli* and *Salmonella*) and gram positive (*Clostridia*) bacteria such as chlortetracycline or carbadox, are usually more effective than narrower spectrum agents such as penicillin and bacitracin.

Coccidiosis

Products including roxarsone (3-nitro), halquinol, carbadox and olaquinox potentiate the effect of anticoccidial drugs.

Table 6: Effect of Bacitracin and Diet Type on Performance and Intestinal Weight

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Malabsorption and necrotic enteritis

Because of their high impact against Clostridia species, avoparcin, Zn bacitracin and virginiamycin are the most effective products to use when challenge is high. Switching to one of these growth promotants if malabsorption syndrome is suspected may prevent the condition from progressing to necrotic enteritis. Halquinol is also useful as it has a wide spectrum of activity and slows peristalsis in the gut.

Improved pigmentation

Roxarsone and arsanilic acid are beneficial for improving pigmentation in poultry.

Respiratory disease and air sac infection

Chlortetracycline use may help prevent atrophic rhinitis in pigs, early mortality in chicks due to air sac infection and maintain egg production of breeders during times of respiratory stress. High doses above 50 ppm of chlortetracycline should not be fed to laying chickens.

Swine dysentery

Use of tiamulin may help control *Treponema hyodysenteriae*.

Mycoplasma

Tylosin and halquinol are useful to use as growth promotants where *Mycoplasma gallisepticum* may be a problem.

Litter and manure quality

Halquinol is particularly effective in reducing moisture content of manure and litter material as it is effective in reducing amoebas and other protozoans from the digestive system.

Mold contamination of feed

Copper sulfate, halquinol and natamycin are useful antifungal agents. Although these products will not destroy mycotoxins already present in raw materials, they will limit further growth of mold after feed mixing.

Crop mycosis

Copper sulfate, halquinol, and acidifiers are useful to control *Candida*.

Gizzard erosion

Avoparcin, flavomycin, colistin and bacitracin are recommended as they are low in irritation. Avoid copper sulfate, arsenicals, acidifiers, olaquinox and carbadox to prevent further irritation and limit endogenous acid production.

SAFETY

Since the mid-eighties, there has been much criticism and concern over the use of growth promoting substances in feed. Regulation has increased over time in most countries. Doses and specific products are now controlled. Use of drugs

important to human medicine are limited, as are those known to cause rapid development of resistance in bacteria. The U.S. Food and Drug Administration has recently classified growth promotants into two categories. "Category I" products require no withdrawal from feed when used at growth promotant levels and include bacitracin, bambarmycin (flavomycin), chlortetracycline, lincomycin, penicillin, tiamulin, tylosin, and virginiamycin. "Category II" products do require withdrawal and include arsanilic acid, roxarsone (3-nitro), carbadox and oxytetracycline.

Tissue residues

Guidelines developed in regions such as Japan, U.S., Australia or E.E.C. countries should be followed with respect to withdrawal of additives from feed before slaughter. Compounds such as β -agonists, gentian violet and nitrofurans (furazolidone) should never be used.

Environmental contamination

The use of any additive containing high levels or potentially toxic minerals such as copper, selenium or arsenic are a possible environmental hazard. These elements can accumulate in soil fertilized with manure and may find their way into crop products or pasture forages. Caution must be exercised as to where these manures are applied.

Bacterial resistance to antimicrobials

Use of antibiotics in feed does increase the number of antibiotic resistant organisms in animals. This resistance and reduced product efficacy to growth promotants is usually temporary and takes place slowly over a period of months. The process involves changes in populations and ecology of intestinal microflora. It is known that antibiotic resistance can be transferred from one bacterium to another. The ability of some bacteria to resist antibiotics is carried in nonchromosomal pieces of genetic material called plasmids. Transferable plasmids carrying the ability to resist antibiotics are called R-factors. Feed producers usually anticipate when bacterial populations are about to become resistant to a given growth promotant and switch products before efficacy is lost. Most producers change products two or three times per

year. Some will also change products during the growout period to avoid resistance. In the absence of the old antimicrobial, the bacteria revert back to their original energy conserving state and become sensitive to the new antimicrobial. Of the 12,153 published feeding studies with chickens and pigs covering the use of 14 antibacterial agents over 47 years, there is no evidence that products have lost effectiveness over time or have caused any long term changes in bacterial resistance (Rosen, 1996).

The medical profession and public however continue to be concerned that R-factors could be transferred from bacteria in antibiotic fed animals to pathogenic bacteria such as Salmonella in humans. Although theoretically possible, no unequivocal evidence has been found to indicate that sub-therapeutic use of antibiotics in animal feed has put human health at risk. Improved management such as "all-in, all-out" rearing of breeder flocks and adherence to other biosecurity measures will reduce the reliance on many therapeutic products that must be used at high doses. This would have a greater impact on prevention of resistance in bacteria than discontinuing the use of growth promotants.

PRESENT AND FUTURE DEVELOPMENTS

Alternative approaches are now being developed to find products that improve digestion or reduce the negative effects of certain bacteria and antigens in the gut. These products will gain popularity in the future if cost effectiveness can be demonstrated.

Acidifiers

Acids such as formic, fumaric, lactic, propionic, citric, sorbic and phosphoric have been studied for potential growth promoting properties. Ravidran and Kornegay (1993) reviewed the literature and came to the conclusion that although benefits were observed in many studies, results were inconsistent. Acidifiers may work by supplying energy to the animal or have a function similar to other antimicrobial substances. Acidi-

fier combinations and enterically protected acidifiers hold promise of more consistent performance. Food grade acidifiers are generally recognized as safe, do not require approval and have no concern over safety.

Probiotics

Products based on *Lactobacillus*, *Bacillus*, *Saccharomyces* and many other organisms are marketed for use as growth promotants. Their response has been somewhat inconsistent in the past possibly due to loss of viability in the feed or destruction during passage into the intestinal tract. Newer products and delivery systems are being developed to improve efficacy. Of particular interest is the concept of inoculating baby chicks in the hatchery with probiotics. A new product developed by the U.S.D.A. called CF-3 is based on a stable culture of 29 anaerobic bacteria. This product shows promise in protecting birds from *Salmonella* and may also promote growth (Burns, 1995).

Enzymes

Feed enzyme supplements are protein catalysts derived from various microorganisms that enhance digestion of feed ingredients. Enzymes enhance growth by degrading deleterious substances in the feed such as poorly digested polysaccharides or antigenic proteins. They also aid digestion of nutrients. The science of enzyme use in feed is developing rapidly with many successful products already developed.

Microflora enhancers

Fermentation residues containing *Aspergillus* meal and killed yeast have been used as growth promotants since the early 1980's. These products contain bacterial growth factors that stimulate growth of beneficial intestinal bacteria such as *Lactobacillus* in the gut of the animal. Many studies have reported effects similar to those observed with antibiotics.

Immunomodulators

These are compounds that modulate and/or selectively stimulate immune response. The idea is to prevent immune stress to antigens in the gut,

yet still allow immunity to develop when required. Certain polysaccharides such as glucans, peptidoglycans (muramyl peptide), mannan-oligosaccharides and fructo-oligosaccharides are currently being sold as immune stimulators. These products are derived from the cell walls of yeasts and other organisms such as *Brevibacterium lactofermentum*. Microbial glucans have linkages in the b-1,3 and b-1,6 positions unlike the b-1,4 linkages found in barley glucans. Peptidoglycan was found to enhance NO₂ release from macrophages thus enhancing viral and bacterial killing capacity. Both mannanoligosaccharides and yeast glucans have been reported to improve phagocytic function of neutrophils and monocytes. b-glucan has been found effective in enhancing performance and reducing piglet morbidity, mortality and diarrhea caused by *Streptococcus suis* (Dritz *et al.*, 1995). Trial work in broilers with mannanoligosaccharide has also shown significant improvement in performance (2.5% FCR) and reduced mortality (Macdonald, 1995). Conjugated linoleic acid (CLA) is a compound that has been recently shown to reduce negative effect of cytokines in animals undergoing immune stress. Growth depression of chicks from injection of *E. coli* endotoxin was eliminated with the addition of 0.5% CLA to feed (Cook *et al.*, 1993). The addition of CLA had no effect on immune response against sheep red blood cells indicating that immune stress may be reduced while still maintaining immune function.

Carotenoids

Growth promoting, immune stimulating and reproduction enhancing effects of carotenoids have been recently reported by several authors (Inborr and Foder, 1996; Chew, 1993; Cafantaris and Papadopoulos, 1995). Dietary inclusion of astaxanthin at two ppm has been reported to improve weight gain by 5% and FCR by 2% in 36 day old market broilers. Carotenoids have also been reported to stimulate phagocytic and bacteria killing ability of blood neutrophils and peritoneal macrophages. Beta carotene in combination with vitamin E, biotin, folic acid and vitamin C was shown to improve reproductive performance in swine by 0.5 piglets per sow per year.

Herbal products

Plant derived agents including saponins, alkaloids, esters, quinones, isobutylamides, phenol carboxylic acid esters and terpenoids are currently being studied for growth promoting and immune modulating effects (Hylands and Poulev, 1995). Herbal products used to promote growth in poultry are currently quite popular in India and China (Devegowda, 1996). In many cases, only the manufacturer knows the composition and potency of these products. Although marketed as "natural", some of these products may be highly pharmacologically active or even carcinogenic. As such, herbal products should be required to undergo the same scrutiny for efficacy and safety testing as other additives before being allowed to enter the human food chain.

Metabolic peptides

Peptides that regulate intestinal absorption are currently under intense study (Croom *et al.*, 1996). Agents such as epidermal growth factor and pancreatic polypeptide YY have been found to enhance glucose and amino acid absorption when applied into the lumen of the gut. These peptides appear to function by increasing the number of "nutrient transporters" present in mucosal cell membranes. If these substances can be produced at economical cost, and practical methods can be found to deliver them from feed to intestinal cells without destruction, they may represent a new class of safe and efficient growth promotants.

b-agonists

These compounds have been extensively studied for their ability to promote growth, enhance feed efficiency and repartition nutrients toward protein and away from fat synthesis. Compounds such as clenbuterol, cimaterol and ractopamine are norepinephrine analogs. These stimulate b-adrenergic receptors in tissue causing a host of different metabolic changes in animals. Such products are manufactured commercially for use in human medicines including bronchodilator sprays for asthmatics. None of these products have been approved in the U.S., Australia, Japan, or E.E.C. for use as feed additives because of concerns over

animal health and tissue residues. Commercial use has occurred in smaller and less regulated countries to the benefit of swine producers but not the meat consuming public.

SUMMARY

Antibiotics and other growth promoting antimicrobials have been used successfully in feed with economic benefit for over 45 years. These materials improve digestion of nutrients and increase resistance to disease. Commercial feed companies have many different products at their disposal. Selection should be based on safety and highest cost benefit ratio. This is often difficult to determine and may change depending on field conditions.

Concern over residues and the possibility of bacteria developing resistance to antibiotics has resulted in increased regulation being applied to the feed industry. This concern has created new opportunities for scientists to develop alternative non-antimicrobial growth promotants. Demonstration of performance and economic benefit in coming years will determine their success.

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