

## **Non-antimicrobial production enhancers**

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### **Introduction**

Since the 1940's, antibiotics have been fed to swine and other livestock as growth promoters, and have been shown to enhance animal performance. The level of performance improvement depends on management and housing conditions. As sanitation improves on the farm, there are smaller increases in performance response (19).

There is concern that feeding animals growth promoting antibiotics may lead to antibiotic resistant human and animal pathogens. If pigs are fed subtherapeutic levels of antibiotics for extended periods of time, the pig's intestinal bacteria can become resistant to the antibiotics used. At slaughter, these resistant bacteria may enter the human food chain and cause illness in humans. These infections may be more difficult to treat with antibiotics similar to those that were fed to the swine. Resistance in human infection has been attributed to the therapeutic use of antibiotics in humans, pets and livestock and to the use in livestock as growth promotants (87). In response to the concern over antibiotic resistance, the European Union has banned the use of many growth promotant antibiotics. The United States Food and Drug Administration has provided a guidance to industry to qualitatively assess risk of new and approved animal antimicrobials. Risk management strategies in the guidance include restrictions of certain uses such as long-term or group administration, as well as other risk management strategies, for antibiotics assessed to pose a risk to human health. For these reasons, there is a need to understand the potential uses of alternatives to growth promoting antibiotics, and understand their basis in science so that pork producers can make decisions based on objective information.

Antibiotics enhance performance by increasing growth, improving feed efficiency, altering intestinal bacteria and reducing incidence of disease. Alternatives to antibiotics must have some or all of these same characteristics, although they may use different modes of action. In this booklet, we will review the most common antibiotic alternatives, how they are presumed to work, and what is known about their effectiveness. The alternatives reviewed here include probiotics, prebiotics, organic acids, enzymes, herbs, immune modulators, and carnitine. There are other compounds that have been suggested as antibiotic alternatives, but they are not reviewed here.

We will discuss how these alternatives are presumed to work, and what is known about their effectiveness. The information presented comes from a review of the published literature cited at the end of this booklet. There may be other sources of additional information on these compounds. Completed Pork Checkoff funded research on alternatives is summarized by category. The summary results presented are from the research reports submitted by the investigator. These results were obtained under specific research conditions that may not duplicate conditions found in some commercial pork production facilities. For more information, the final project reports and lists of projects currently underway can be

found at [www.pork.org](http://www.pork.org). Because there is much to learn about the specific mode of action, and other contributing factors to the efficacy of many of these compounds, results on individual farms may vary. Producers should carefully consider the costs and benefits of using these compounds in their operations.

## Probiotics and Competitive Exclusion

The newborn pig's gastrointestinal tract is sterile. Beginning at birth and continuing to adulthood, the pig acquires "normal" intestinal bacteria. These bacteria can benefit the pig by providing nutrients for the animal, including vitamins, amino acids and volatile fatty acids (88, 105). The beneficial bacteria in the intestine can also prevent certain detrimental bacteria known as pathogens from causing disease. Disruptions in the normal intestinal microflora can occur, especially during times of stress or diet change. During these times, pigs are especially susceptible to disease caused by intestinal pathogens like *Salmonella* and enterotoxigenic *E. coli* (61). Infection by these pathogens can result in scours and long-term shedding in neonatal and weaned piglets (3). Feeding probiotics to pigs can help re-establish the normal intestinal microflora, benefiting the animal by providing it with nutrients and by lowering incidence of disease.

### Mode of action

Probiotics are live microbial feed supplements which benefit the pig by improving the balance of bacteria in the gut (15, 31). The most prevalent probiotics studied in swine diets include different species of *Lactobacillus*, *Bacillus*, and *Streptococcus*, the yeast *Saccharomyces cerevisiae*, and combinations of these organisms.

Another form of microbial supplementation are competitive exclusion cultures, which are a mixture of pathogen-free intestinal bacteria obtained from an adult animal of the same species. The use of probiotics and competitive exclusion cultures as an alternative to antibiotics takes advantage of the modes of action of normal intestinal bacteria, which include:

- Competing against pathogenic bacteria for nutrients in the gut
- Competing with pathogens for binding sites on the intestinal wall
- Producing compounds that are toxic to pathogens
- Stimulating the immune system so it is ready to fight invading pathogens

### Antimicrobial effects

While much of the data is variable, it appears that probiotics are most effective in preventing disease in pigs that are stressed by disease challenge or diet (particularly during the early post-weaning period), or are held in unsanitary conditions. Current data on the antimicrobial effects of probiotics and competitive exclusion cultures include the following:

- Competitive exclusion cultures have been shown to decrease the shedding and mortality associated with *Salmonella* (2, 30) and pathogenic *E. coli* (33) in newborn and early weaned pigs.
- Several reports have shown that feeding pigs probiotics containing bacteria that are normally found in the gut, like *Lactobacillus acidophilus* (50), *Bacillus* (53), *Bifidobacterium lactis* (91) and *Streptococcus faecium* protected suckling piglets against *E. coli* infection (100), diarrhea and death (49). However, others reported that feeding *Bacillus cereus*, *Lactobacillus* spp., and *Streptococcus faecium* did not prevent or reduce the symptoms of *E. coli* infection in weanling pigs (20).

### Animal Performance

While it is thought that feeding probiotics to pigs may improve animal performance and intestinal nutrient digestibility, reports are variable. This variability may be the result of varying conditions when probiotics are fed, as well as differences in activity between the species of bacteria that have been used. Research has demonstrated the following:

- The results of feeding pigs *Lactobacillus* spp. are inconsistent. Some reports show that feeding *Lactobacillus* improved growth performance in suckling pigs (1) weanling pigs (78, 1, 44) and grower pigs (5, 76), and decreased finishing costs by 17% (43). However, other studies have found no differences in growth performance of weanling pigs fed diets containing either *Lactobacillus* or low levels of antibiotics (38).
- The response to *Bacillus* supplementation has also been variable. Improvements in growth rate and

feed efficiency have been seen in weaned piglets (53) and grower pigs fed *Bacillus* spp. (95, 96). Also, improved Nitrogen (N) retention, but not apparent N digestibility was observed for growing pigs fed a *Bacillus* product (89). However, other reports show no effect on digestibility of Dry Matter, Neutral Detergent Fiber, Acid Detergent Fiber, N or N retention when pigs were fed probiotics containing *Bacillus* or *Lactobacillus* cultures (52, 35, 93).

- In one early study, addition of *Clostridium butyricum* to grower pig diets resulted in improved feed conversion (36).

## Pork Checkoff Funded Research on Probiotics and Competitive Exclusion

**Effect of Probiotics on Enteric Colibacillosis.** Ronald Moxley, University of Nebraska. Project #98-052. The feeding of probiotic bacteria did not reduce the severity or progression of diarrhea and other disease caused by enterotoxigenic *E. coli* (ETEC) in gnotobiotic piglets, nor did it significantly reduce the spread of ETEC from the intestine to the blood and other organs. Additional studies are needed to address the effects of probiotic bacteria inhibition to disease caused by ETEC in piglets.

**Effect of Oligosaccharides and Organic Salts on the Health and Performance of Growing-Finishing Pigs.** A. L. Sutton, J. A. Patterson, and D. T. Kelly, Purdue University. Project #99-219. In experiment 1, pigs receiving antibiotics demonstrated improved performance, while pigs receiving prebiotics or probiotics did not. In Experiment 2, both probiotics and prebiotics provided an improvement in performance over controls, but less than the group fed antibiotics in their diet. When pigs are growing close to their maximum potential, it is difficult to demonstrate effects of growth promotant antibiotics, or their alternatives, on animal performance. The general lack of a significant influence of the growth promoting antibiotics suggests that the animals were in good health and not stressed. Under these conditions the treatments containing the probiotic tended to give performance values between the control group and the group fed antibiotics in their diet.

**Applied Studies on Immune Stimulation by Lactobacilli for the Reduction of Human Foodborne *Salmonella* and Replacement of Subtherapeutic Antimicrobials.** D.L. Hank Harris and Christian Baum, Iowa State University. Project # 00-103. In two of six trials feeding live *Lactobacillus* yogurt cultures significantly reduced the levels of *Salmonella* in tonsil and fecal samples from swine.

**Effects of Competitive Exclusion on Post-Weaning *Escherichia coli* Infection.** Kenneth Genovese and David Nisbet, United States Department of Agriculture, College Station, Texas. Project #00-137. No mortality was observed in groups of pigs that received a low dose challenge with enterotoxigenic *E. coli* (ETEC), however the competitive exclusion (CE) treated group had fewer numbers of bacteria recovered following challenge. In the high dose challenge study, mortality was 14.3% in the untreated group, compared to 0% in the CE treated group. No differences in weight gain were observed in any of the trials. These studies demonstrate that CE may be an alternative, or possibly an adjunct prophylactic measure for the control of ETEC in weaned pigs.

**The Effects of Probiotics in the Health and Performance of Nursery Pigs Raised in Conventional or Antibiotic/Growth Promoter Free Farms.** Robert Morrison and Spiros Kritas, University of Minnesota. Project #02-197. Pigs receiving low doses of antibiotics throughout the nursery period were compared to pigs receiving probiotics with regard to their health status and performance. There were no statistically significant differences observed in average daily gain, average daily feed intake, feed conversion, feed cost, or mortality between pigs receiving antibiotics and those receiving probiotics. It was concluded that in high health status farms, probiotics may substitute for antibiotics given for prevention of disease.

**Evaluation of Antimicrobial Alternatives to Reduce the Development of Antibiotic Resistance.** Darryl Ragland, Purdue University. Project 02-084. Neither the probiotics or inorganic minerals improved growth rate or feed efficiency in comparison to the non-medicated control diet. Furthermore, the diet supplemented with antibiotics failed to support an increase in growth rate compared to the control diet. Results of this study concur with results of other studies where growth responses to non-antimicrobial feed additives tend to be variable, with improvements in feed intake and feed efficiency being observed more commonly.

## Prebiotics

Prebiotics are indigestible carbohydrates that can enhance animal performance by stimulating growth of beneficial intestinal bacteria. While there are many prebiotics available, common examples used in research or on farms include oligofructose, fructooligosaccharide (FOS) and inulin (75). Prebiotics can also be fed in combination with probiotics, as treatments known as “synbiotics”.

### Mode of action

Most prebiotics cannot be digested by the pig’s intestinal enzymes, but they can be fermented by the bacteria in the pig’s gut. As a readily available nutrient source, the prebiotics allow the normal gut bacteria to thrive in the intestinal tract, where they can help prevent disease and may even provide some nutrients for the host. Prebiotics may also selectively enhance beneficial bacterial populations, such as *Bifidobacteria* and *Lactobacilli*.

### Antimicrobial effects

Prebiotics are thought to decrease incidence of intestinal disease in swine, particularly in neonates and early weaned pigs. The data are variable, possibly because if the animal already has high concentrations of beneficial bacteria, prebiotics may have little effect on microbial numbers. Sanitation on the farm also contributes to the effect of prebiotics—if animals are stressed, prebiotics may have a greater effect.

- FOS has been shown to reduce *E. coli*-induced diarrhea and death in young piglets (85), as well as *Salmonella* shedding (55).
- Feeding pigs inulin, oligofructose (29), and a synbiotic containing oligofructose and *Lactobacillus* (65) increased numbers of normal intestinal bacteria.
- Supplementing swine diets with oligofructose reduced the severity and incidence of diarrhea, and increased the recovery of the normal intestinal bacteria (67).

### Performance effects

By improving the intestinal environment, prebiotics may also lead to improvements in pig performance. A number of studies have shown trends for improvements in growth performance in pigs fed prebiotics, with the greatest effects occurring during periods of stress.

- Feeding a synbiotic containing FOS and *Bifidobacterium longum* improved feed efficiency in early weaned pigs (28).
- Weanling pigs fed FOS or Carbadox had improved average daily gain (86).

## Pork Checkoff Funded Research on Prebiotics

**Effect of Oligosaccharides and Organic Salts on the Health and Performance of Growing-Finishing Pigs.** A. L. Sutton, J. A. Patterson, and D. T. Kelly, Purdue University. Project #99-219. In experiment 1, pigs receiving antibiotics in the feed demonstrated improved performance, while pigs receiving prebiotics or probiotics did not. In Experiment 2, both probiotics and prebiotics provided an improvement in performance over controls, but less than the antibiotic fed group. When pigs are growing close to their maximum potential, it is difficult to demonstrate effects of growth promotant antibiotics, or their alternatives, on animal performance. The general lack of a significant influence of the growth promoting antibiotics suggests that the animals were in good health and not stressed. Under these conditions the treatments containing either probiotic or prebiotic tended to give performance values between the control group and the antibiotic group.

**Dietary Manipulation as a Method of Modifying Intestinal Bacteria and Reducing the Need for Subtherapeutic Administration of Conventional Antibiotics.** Michael Howard, United States Department of Agriculture, Ames, IA. Project #01-060. Low level feeding of antibiotics did not dramatically improve pig performance in weaned pigs, while addition of short chain fructooligosaccharides did not enhance performance. Neither low level addition of antibiotic to the feed or lactic acid to the water of market weight hogs reduced *Salmonella* prevalence.

## Organic Acids

Organic acids are another class of compounds that have been suggested as potential alternatives to antibiotics. Common organic acids used in swine diets include formic, acetic, propionic, butyric, citric, malic and lactic acids. In the swine industry, organic acids are fed as both individual acids and blends of several acids. These have been used in swine diets for decades and not only can prevent the growth of mold in feed, but may also share many antimicrobial and performance benefits with antibiotics.

### Mode of action

Like antibiotics, organic acids have an antimicrobial activity. The acids can penetrate the bacterial cell wall and disrupt the normal actions of certain types of bacteria including *Salmonella* spp, *E. coli*, *Clostridia* spp, *Listeria* spp. and some coliforms. Therefore, reductions in numbers of some species of the normal intestinal bacteria as well as pathogenic bacteria can occur in animals fed organic acids. Organic acids are believed to improve overall performance by reducing microbial competition with the pig for nutrients, by lowering the risk of subclinical infections, reducing the intestinal immune response and by reducing the production of harmful bacterial compounds (22).

Organic acids also work in ways that are different to antibiotics. By reducing gut pH and stimulating digestive enzyme secretion, organic acids improve protein digestibility and may enhance overall feed digestion and utilization by the pig.

### Antimicrobial effects

Although much is known about how organic acids should affect the bacteria in the gut, research has shown that acidifiers have variable effects on intestinal microbes. Variations may be due to the use of different types and levels of organic acids, as well as feeding them with different diets.

- Feeding organic acids has reduced the coliform burden along the gastrointestinal tract (14, 90, 97, 8, 57) and reduced scouring and piglet mortality.
- Other studies have shown that organic acids have little effect on *E. coli* infection and incidence of scours, or on numbers of *Lactobacillus* spp., *E. coli* or *Clostridia* spp. in the intestine (82, 81).

### Performance effects

Organic acids have been shown to enhance performance in young swine, especially in early-weaned piglets. Numerous studies have demonstrated significant improvements in feed efficiency when piglets were fed formic, fumaric and citric acids, along with potassium diformate. Improvements in animal performance may be due to an increase in feed intake, possibly because some organic acids may improve diet palatability (74).

- Feeding formates or formic acid (92, 69, 22), fumaric acid and citric acid (77) improves the average daily gain and reduced feed efficiency of weaned piglets (74). Greater effects are seen during the growth of young pigs, rather than during the finishing phase of growth.
- Organic acids have been shown to improve digestibility and absorption of proteins, minerals and other nutrients in the diet (45, 47, 60, 77, 84).
- In grower pigs and sows, formic acid or formates were the most effective in improving average daily gain and feed: gain ratio, followed by fumaric acid (74).

## Pork Checkoff Funded Research on Organic Acids

Dietary Manipulation as a Method of Modifying Intestinal Bacteria and Reducing the Need for Subtherapeutic Administration of Conventional Antibiotics. Michael Howard, United States Department of Agriculture, Ames, IA. Project #01-060. Low level feeding of antibiotics did not dramatically improve pig performance in weaned pigs, while addition of short chain fructooligosaccharides did not enhance performance. Neither low level addition of antibiotic to the feed or lactic acid to the water of market weight hogs reduced *Salmonella* prevalence.

## Enzymes

Although pigs have many gastrointestinal enzymes to aid in feed digestion, there is a limit to what feed constituents they can digest. For example, newly weaned piglets have not developed all of the enzymes needed to digest plant-based feed, and adult animals often don't have all the enzymes needed to digest complex feed ingredients. Feeding dietary enzymes to pigs can help the animal break down components of its feed, allowing the pig to obtain energy from complex carbohydrates that would otherwise be indigestible. Administration of enzymes can also aid digestibility of phosphorus and protein in the diet. Research has shown variable animal response to enzyme additives. Variation may be due to differences in enzyme source, diet, enzyme interactions with dietary ingredients, age and health status of the animal (7).

## Phytase

A large portion of the phosphorus in swine feed is in a form called phytate that is poorly digested by swine. Feeding phytase enhances the digestibility of phosphorus in feed, which can reduce the need for dietary phosphorus supplements, and can reduce the amount of phosphorus excreted into the environment.

- Phytase has been found to increase weight gain and sometimes increase feed efficiency in pigs on several diets, including a barley-maize diet (32, 39), a corn-soybean diet (51, 83, 94), and a sorghum-soybean meal diet (68).
- Adding phytase to grain-oilseed meal diets improves the apparent digestibility and bioavailability of dietary phosphorus (54, 46, 17, 18, 99).
- Phytase's effect on digestibility of protein is variable. Some studies have shown that supplemental phytase improves apparent digestibility of protein in swine diets (59), but other studies show little or no effect of feeding phytase on protein digestibility (62, 106, 101, 99).

## Carbohydrate degrading enzymes

Enzymes that assist in carbohydrate degradation include amylase, glucanase, cellulase, xylanase and glucoamylase. These enzymes differ in their activity against specific feed ingredients, and tend to produce variable animal performance results.

- Feeding a mixture of cellulase, xylanase, glucanase, amylase and pectinase improved nutrient utilization and performance of growing pigs fed hulless barley (4).
- Addition of amylase, glucanase and glucoamylase to a barley diet improved feed conversion and reduced incidence of diarrhea in newly-weaned pigs (42). Other research demonstrated no growth improvement in weanling pigs on a wheat based diet fed enzymes to degrade starch, proteins, fiber or fat (66).

## Herbs

Herbs have been used for treatment and prevention of disease in humans and animals for centuries. Research has shown that some herbs perform better than others as additives for swine diets. This discussion will focus on garlic, oregano and other herbs studied in swine diets.

## Mode of action

Some natural remedies contain compounds that can have antiviral or antibacterial effects on pathogens, and antidiarrheal effects on pigs, perhaps by enhancing the immune response. Herbs may also improve feed intake by enhancing diet palatability.

## Antidiarrheal and performance effects

- Oregano and Aromex (a mixture of essential oils, spices and herbs) increased growth and reduced diarrhea in pigs (58).
- Feeding a mixture of great nettle, garlic, and wheat grass improved growth and feed efficiency in growing pigs (34).
- Feeding garlic to weanling pigs had no positive influence on weight gain, feed intake and feed efficiency (40, 41).
- Dietary *Sarcandra glabra* extract increased feed intake and weight gain, and improved feed conversion in weaning piglets (12).

## Immune Modulators

In recent decades, weaning age of piglets in U.S. swine operations has been reduced, resulting in weanling pigs with less developed immune and digestive systems (10). Feeding immune modulators to piglets may enhance the action of the immune system, and may promote disease resistance during the vulnerable weaning periods. Compounds suggested to function as immune modulators include spray-dried plasma, egg yolk antibodies, conjugated linoleic acid (CLA) and other compounds.

### Mode of action

Spray-dried plasma may improve postweaning growth and performance by several methods, including improved diet palatability (27), prevention of pathogens binding to the intestine, or by providing immunity against disease (13).

Egg yolk antibodies against swine disease organisms can be created by immunizing hens, which produce eggs containing antibodies to pig diseases. These antibodies may reduce the incidence of disease in pigs by preventing attachment of pathogens to the intestine.

CLA is a mixture of isomers of linoleic acid. It is a compound that occurs naturally in animals, and can be found in milk fat and meat. When fed as a dietary additive, CLA is believed to enhance the immune system, improve animal performance and carcass characteristics, and can act as an anticarcinogen. CLA can enhance certain components of the immune system, which may aid in disease prevention (6) and allow more nutrients to be allocated for growth. Like many other antibiotic alternatives, CLA is believed to be most effective when animals are under stress.

### Spray-dried plasma

Like many other antibiotic alternatives, the response to spray-dried plasma is greater when animals are housed in less sanitary conditions (13), and if the young pigs have weakened immune systems (11).

- Feeding piglets SDP at weaning can significantly improve growth and feed intake (13, 21, 37).
- Feeding spray-dried plasma may prevent pathogen attachment to the intestine and has been shown to decrease mortality in pigs challenged with *E. coli* (9).
- Spray-dried plasma may provide immune protection to the pig, which allows nutrients to be used for growth rather than for immune system activation during mild infections (10).

### Egg-yolk antibodies

Freeze-dried eggs or egg yolks containing antibodies to several common swine diseases are available, including antibodies to several strains of *E. coli* and *Salmonella*.

- Studies have shown that feeding chicken egg-yolk antibodies to early-weaned piglets reduces incidence of diarrhea and mortality, and improves animal performance (73, 48, 56).
- Data concerning the role of egg-yolk antibodies in inhibition of disease has been variable. One study found that feeding piglets egg-yolk antibodies did not reduce *Salmonella* colonization or shedding (55). This variability may result from the antibodies being altered in the harsh environment of the digestive tract before they are activated against pathogens.

### Conjugated linoleic acid

- Feeding pigs CLA tends to increase white blood cell counts (16) with the greatest increases occurring in specific populations of lymphocytes occurring after 42 days of CLA supplementation (6).
- CLA has been demonstrated to improve feed efficiency (24) and gain in growing-finishing pigs (98). However, the data are variable, as other studies have found little improvement in growth performance, feed intake and feed efficiency in weanling pigs fed CLA (102, 25, 26, 104). Variations in response may be due to differences in dietary concentrations of CLA, feeding duration, and environmental conditions and health status of the pigs.
- Feeding CLA to pigs can improve carcass characteristics by increasing lean muscle mass and decreasing subcutaneous carcass fat (23, 98).

## Pork Checkoff Funded Research on Immune Modulators

**Immunomodulatory and Growth Effects of the Seaweed *Ascophyllum nodosum* in Pigs.** J. Ernest Minton, Kansas State University. Project #00-063. Results suggested little beneficial effect of dietary *Ascophyllum nodosum* on growth performance or immune response in the presence or absence of *Salmonella typhimurium* challenge.

**Conjugated Linoleic Acid: A Dietary Immune Modulator that Decreases Intestinal Inflammation.** Josep Bassaganya-Riera, Iowa State University. Project #01-134. Supplementaion of conjugated linoleic acid (CLA) in the diet prior to the induction of colitis decreased mucosal damage, maintained immune profiles resembling those of the non-infected pigs, and attenuated growth suppression. The suppressed susceptibility to inflammation and maintained growth performance following the infection in CLA-fed pigs resulted in a positive economic value for health.

## Carnitine

Carnitine is a naturally occurring compound found in the muscle tissue of humans and other mammals. It is normally synthesized in the body from amino acids, but young piglets may lack the special enzymes needed for this process. Carnitine is known to have very important metabolic functions in mammals, such as improving the utilization of dietary fat. Current research suggests that adding carnitine to swine diets may result in improved animal performance and carcass characteristics.

## Mode of action

Producers commonly supplement the diet of weanling pigs with fat sources to increase the energy density of the diet in an effort to diminish the post-weaning growth lag. Although naturally occurring carnitine can help pigs utilize the fat in their diets, young pigs have very low levels of carnitine just after weaning. For this reason, researchers hypothesize that supplementing pigs with carnitine during the weaning period may help the animals reap more benefits from their high energy diets (79). The greatest growth response to supplemental L-carnitine occurs approximately 10 days post-weaning (80).

## Performance effects

- Weanling piglets supplemented with L-carnitine grew faster and had increased feed intake and improved average daily gain (64, 103).
- Feeding carnitine to growing pigs can result in greater lean muscle deposition and reduced backfat thickness (63, 72, 70).
- Dietary carnitine improves performance and reduces carcass lipid accretion in early weaned piglets (71).

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