# Effects of Immune Activation on Metabolism and Nutrition of Pigs

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## Take-Home Message

Nutrition and immune function are inextricably linked, and only through a better understanding of their reciprocal relationship can we hope to develop novel approaches to improve health and productivity of livestock species. Activation of the immune system elicits a cascade of metabolic, neuroendocrine, and behavioral events that have direct implications on feeding behavior and rates of lean tissue accretion. Nutritional intervention may constitute a cost-effective means by which to alter immune function, including the incidence, severity, and duration of sickness.

## Immunological Stress Responses

Immunological stress is characterized by a reduction in voluntary feed intake and animal productivity (i.e., growth), which is largely due to a repartitioning of nutrients away from skeletal muscle accretion and toward metabolic responses that support the immune system (Johnson, 1997; Klasing and Johnstone, 1991; Spurlock, 1997). Early evidence that immune activation negatively affects protein accretion rates of livestock species was provided through an elegant series of experiments in broiler chicks, where 70% of the reduction in body weight gain was linked directly to reduced feed intake (Klasing, 1984; Klasing and Barnes, 1988; Klasing et al., 1987). Similar conclusions can be drawn from studies conducted in an applied swine production setting when comparing high and low health status situations. When no vaccines or antibiotics were administered and the facility remained in a 'dirty' state, pigs exhibited a decreased rate in whole body protein accretion, which translated into a 20% reduction in the dietary lysine requirement (expressed as % of diet) and a 40% reduction in daily lysine intake (Williams et al., 1997). Obviously, these findings translate into increased costs and lost profits for livestock producers.

A substantial body of evidence suggests the collective set of metabolic, neuroendocrine, and behavioral events that occur during immunological stress is largely driven by the production and release of specialized proteins known as cytokines, including tumor necrosis factor-alpha (TNFα), interleukin (IL) 1-beta (IL-1β), and IL-6. When an animal's innate immune system is activated through recognition of a pathogen, proinflammatory cytokines are produced acutely by peripheral leukocytes (e.g., monocytes and macrophages). These cytokines also serve as a major route to transmit information to the brain that an infection has occurred. More complex routes of peripheral-to-central communication are also known to exist, and the reader is encouraged to peruse seminal reviews that have been written on the subject (Blalock, 1994; Quan and Banks, 2007). Whether produced by peripheral leukocytes or by resident microglial cells directly in the central nervous, proinflammatory cytokines have a profound ability to induce central adaptive responses designed to restore homeorhesis and get the animal back to a 'healthy' phenotype following an infection.

Collectively referred to as 'sickness behavior', the non-specific symptoms of an activated immune system include fever, fatigue, disruption of sleep patterns, social isolation, decreased

feed and water intake, and body weight loss (Kelley et al., 2003). Whereas the obvious phenotypic signs of infection may be evident to a livestock producer, it is the underlying metabolic shifts that are most important to understand. A major reprioritization of nutrients occurs during an acute infection, with maintenance of the immune system becoming a higher priority than growth, and this translates into a reduced availability of dietary nutrients for muscle protein accretion. Importantly, cytokines can independently and simultaneously affect both synthesis and degradation of protein in tissues, and thus, cytokines are responsible for adjusting animal growth rates based on the level of immunological challenge. Also important is the fact that proinflammatory cytokines are manifest in both central and peripheral compartments, and these effects are what ultimately drive the phenotypic responses observed during sickness. For example, the febrile response harnesses metabolic inefficiency to produce heat by increasing the metabolic rate 13% for every degree Celsius increase in core body temperature (Kluger, 1991). Additionally, the production of cytokines and development of immune cells require significant nutrient resources, most notably in the form of amino acids, to allow the animal to mount an effective immune response. The consequence of nutrient repartitioning as a result of immune activation is that dietary nutrient requirements and efficiency of utilization are altered, and this has direct implications for animal nutritionists.

From a livestock production perspective, a drastic decrease in voluntary feed intake and loss of body weight, especially of skeletal muscle mass, are particularly important consequences of immunologic stress. Acute immune activation results in increased whole-body protein turnover, with a decreased rate of protein synthesis and increased rate of protein degradation, but responses differ by peripheral tissue. Considering skeletal muscle represents 40-45% of body mass, this tissue represents the largest labile pool of amino acids. Dietary amino acid requirements are decreased in immunologically-challenged animals, suggesting that decreased muscle accretion and an overall slower growth rate spare essential amino acids for use in anabolic processes that occur primarily in the liver and immune cells. In essence, protein degradation of skeletal muscle during innate immune activation increases the supply of amino acids for acute phase protein synthesis in the liver (Spurlock, 1997). It has been estimated that contributions of the liver to whole body protein synthesis increase from 15% to 33% during acute immune stimulation (Breuille et al., 1998), as accompanied by increased hepatic uptake of amino acids (Humphrey and Klasing, 2005). The combination of reduced feed intake, increased hepatic acute phase protein synthesis, and disparity in amino acid composition between skeletal muscle and acute phase proteins ultimately results in greater body protein losses in immunologically-challenged animals than can be explained by reduced feed intake alone (Reeds et al., 1994). Considering amino acids in excess of physiological requirements cannot be stored, greater rates of amino acid oxidation are also evident during immune activation.

Quantitation of amino acid requirements for development, maintenance, and use of the immune system clearly shows the greatest quantitative need is for acute phase protein synthesis and activation of oxidative defenses (Klasing and Calvert, 1999). Using a direct approach, work with broiler chicks suggested that development and maintenance of immune function accounts for no more than 2% of the total lysine requirement, while use of lysine during an acute infection may consume 7-10% of the total requirement as part of liver hypertrophy and production of acute phase proteins (Klasing, 2007). Considering acute phase protein synthesis accounts for a significant proportion of total body protein synthesis during peak sickness, identification of amino acids that are enriched in these specialized proteins may help to guide nutritional strategies. Work by Reeds et al. (1994) suggested that acute phase proteins contained increased concentrations of aromatic amino acids (i.e., phenylalanine, tyrosine, and tryptophan) relative to skeletal muscle composition. Moreover, nearly all acute phase proteins are glycosylated and enriched in threonine, serine, aspartate, and asparagine, and cysteine may play a particularly important role as the limiting nutrient for synthesis of glutathione, a primary

antioxidant, during infection (Breuille et al., 2006). It should be noted that attempts to alter the immune response via supplementation of individual amino acids have largely been unsuccessful, but investigations into supplementation of amino acids combinations to immunologically-challenged animals are needed.

Finding ways to manage both the magnitude and duration of an acute inflammatory response is key to maximizing productive performance and profitability. However, eliminating the proinflammatory response altogether is not feasible due to its integral role in host immune defenses. Complicating the matter further is evidence that genetic selection for growth potential may negatively affect the ability for animals to cope with an infection. By selecting for optimal production traits (e.g., lean tissue accretion), livestock species may have also been inadvertently selected to be more susceptible to pathogens (i.e., reduced immune robustness) or less able to maintain performance after infection (Clapperton et al., 2008; Flori et al., 2011; Qureshi and Havenstein, 1994). As sub-therapeutic antibiotic use is phased-out of disease preventative strategies, it may be necessary to alter genetic selection techniques to consider immune robustness along with production traits in production livestock species. From a nutritional perspective, however, there remain a number of mechanisms whereby nutrient intake can influence immunity and susceptibility to infectious diseases.

As we gain a better understanding of how nutrition can play an immunomodulatory role, it is important to keep in mind that developing robust immunity is key. In general, managing sick animals should include delivery of nutrient profiles that support an appropriate level of immune reactivity while minimizing growth depression, and this must occur concomitantly with a reduction in voluntary feed intake. Evidence suggests certain nutrients can directly alter leukocyte proliferation rates, magnitude of cytokine production, differentiation of leukocyte populations, and even protect against cellular damage resulting from activated leukocytes (Klasing and Leshchinsky, 1999). Nutrients that fall into this category include polyunsaturated fatty acids, carotenoids and other specialized plant extracts, as well as vitamins A, D, and E. Antioxidant nutrients are also able to modulate immune function, due in part to their ability to protect against immunopathology via quenching of free radicals produced by leukocytes. Nutritional strategies designed to improve outcomes in animals experiencing immunological stress have often focused on feeding individual nutrients, but this is often met with highly variable responses. Further studies on how ingestion of specific nutrient(s) and bioactive compound(s) by pigs experiencing acute immune activation are warranted.

**Soybean Meal and the Viral Immune Response in Weanling Pigs**

Porcine reproductive and respiratory syndrome (PRRS), caused by the PRRS virus (PRRSV), is the most prevalent swine disease globally (Lunney et al., 2010), accounting for annual losses upwards of $665 million for US swine producers (Holtkamp et al., 2012; Neumann et al., 2005). Despite increased research focus and improved biosecurity measures, PRRS continues to pose a substantial financial burden for US swine producers. In parallel with pharmaceutical developments, there exists an impetus to better manage PRRSV-infected pigs, and nutrition may play an important role in this effort. Soybean meal (SBM) is the primary dietary source of crude protein and amino acids for swine in the US, and in addition to providing these nutrients, soybean feedstuffs also contain the isoflavones genistein, daidzein, and glycitein. Importantly, these plant-derived compounds are considered to have a range of biological activities, including antiviral effects, when included in an animal's diet (Andres et al., 2009). Greiner et al. (2001a, b) evaluated graded concentrations of purified genistein and daidzein in diets of pigs infected with PRRSV, and determined that while daidzein had minimal impact on immune function or growth of PRRSV-infected pigs, genistein at 200-400 mg/kg of diet elicited positive immunomodulatory effects and improved body weight gain. Thus, our laboratory sought to evaluate the effects of

SBM inclusion, which would concurrently increase both dietary crude protein and isoflavone concentrations, on immune and growth responses of pigs acutely infected with PRRSV.

Four experimental treatments included a 2×2 factorial arrangement of 2 dietary SBM concentrations, 17.5% (LSBM) and 29% (HSBM), and 2 levels of PRRSV infection, uninfected (sham) and PRRSV-infected. Weanling pigs (32 barrows and 32 gilts, 21 days of age, 7.14 ± 0.54 kg) were individually housed in disease containment chambers. Pigs were provided a common diet for 1 week before being allotted to 4 treatment groups with 16 replicate pigs per group. Pigs received experimental diets for 1 week before administration of either a sham inoculation (sterile PBS) or a $1\times10^5$ 50% tissue culture infective dose of PRRSV at 35 days of age (0 days post-inoculation, DPI). Growth performance was recorded weekly, and rectal temperatures were measured daily beginning on 0 DPI. Blood was collected on 0, 3, 7 and 14 DPI for determination of differential complete blood cell counts, serum PRRSV load, and haptoglobin and cytokine concentrations.

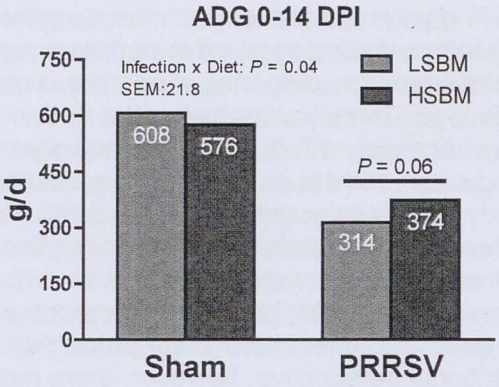


**Figure 1**. Average daily body weight gain of weanling pigs fed diets containing low (LSBM) or high (HSBM) concentrations of dietary soybean meal during the 14-day infective period.

As a reliable measure of successful immune stimulation, PRRSV-infected pigs exhibited a mild febrile response, with increased ($P < 0.01$) rectal temperatures 0 to 14 DPI, but there was no influence of dietary SBM concentration on this response ($P > 0.05$). In the PRRSV-infected group, pigs fed HSBM tended to have improved ADG ($P = 0.06$; **Figure 1**) and G:F ($P = 0.09$) compared with pigs fed LSBM. No effects of dietary SBM concentration on leukocyte measurements were observed within the PRRSV-infected group at any time point. Serum PRRSV load of PRRSV-infected pigs was lower ($P < 0.05$; **Figure 2**) in pigs fed HSBM compared with pigs fed LSBM at 14 DPI, but no differences were observed at 3 or 7 DPI; this suggests that pigs receiving HSBM may have had an improved ability to eliminate the virus during the initial stages of recovery. Serum haptoglobin and tumor necrosis factor-α concentrations of PRRSV-infected pigs were greater ($P < 0.05$) at 3 and 14 DPI, respectively, in pigs fed LSBM compared with pigs fed HSBM; again, this indicates the potential for mild viral protective effects of SBM. Overall, it appears that the immunological stress elicited by PRRSV infection was decreased in pigs fed HSBM compared with pigs fed LSBM, which may have

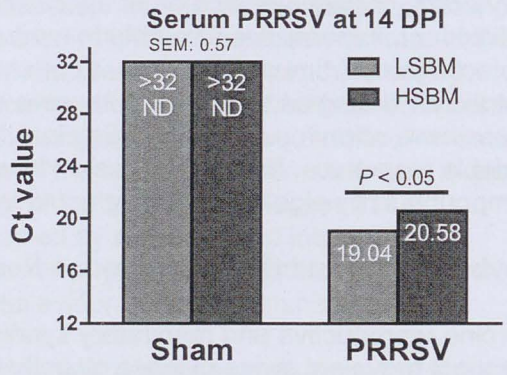


**Figure 2**. Serum PRRSV loads [expressed as raw cycle threshold (Ct) values] at 14 days post-inoculation (DPI) from pigs fed diets containing low (LSBM) or high (HSBM) concentrations of dietary soybean meal. *Note that a higher Ct value represents fewer PRRS viral particles being detected.* ND = not detectable.

contributed to the tendency for improved ADG and feed efficiency of the HSBM-fed pigs during the 14 day infection period.

Considering the anti-inflammatory effects observed as a result of increased SBM concentration, one is left wondering about the mechanism of action, and we have focused our attention on both soy-derived bioactive compounds and greater CP delivered by the HSBM diet. Soybeans and soybean-derived feedstuffs are the richest sources of the isoflavones genistein, daidzein, and glycitein (Wang and Murphy, 1994), which are reported to exert both anti-inflammatory and anti-viral activity through various mechanisms. A plethora of *in vitro* studies indicate that genistein may potentially inhibit virus-cell binding and entry, virus replication, viral protein translation, and viral envelope formation of a multitude of viruses (Andres et al., 2009). In our study, dietary genistein concentration of the LSBM diet (369 mg/kg) was within the range (200-400 mg/kg) suggested by Greiner et al. (2001b) to have potential immunomodulatory and growth-enhancing effects on PRSSV-infected pigs, while genistein concentration of the HSBM diet (638 mg/kg) exceeded this range. Bioavailability of isoflavones is certainly influenced by the feed matrix (Cassidy et al., 2006), so it is entirely possible that the isoflavones contributed by SBM in the current study were less bioavailable than those provided in a supplemental, purified form by Greiner et al. (2001a, b). Further investigations to identify the mechanism by which SBM reduces immunological stress in PRSSV-infected weanling pigs are warranted.

**Acute Enterotoxigenic *E. Coli* Infection in Weanling Pigs**

Post-weaning diarrhea remains an important cause of mortality and morbidity in pigs weaned in the US swine industry, and enterotoxigenic *Escherichia coli* (ETEC) is a major cause of this illness. Whereas etiology of disease caused by ETEC is complex, it is strongly associated with structural and functional changes that occur in the intestine (Nagy and Fekete, 2005), and likely the immune system (Raetz and Whitfield, 2002), of newly-weaned pigs. Toxins produced by ETEC strains that ultimately lead to diarrhea include heat labile enterotoxin (LT), heat stable enterotoxin types A (STa) and B (STb), and Shiga toxin type 2e (Stx2e) (Imberechts et al., 1997; Wilson and Francis, 1986). Pathogenic *E. coli* are categorized by 5 antigenically-distinct adhesins, all of which are fimbriae (also known as pili); F4 (K88), F5 (K99), F41, and F6 (987P) all mediate adhesion in neonatal piglets, while F18 is a common cause of post-weaning colibacillosis. Receptors for F18 fimbriae are not expressed in neonatal piglets, but are expressed in sufficient numbers to cause illness around the time of weaning (Nagy et al., 1992). Pathogenesis of ETEC begins with fimbriae-mediated adherence to specialized receptors located on microvilli of enterocytes, followed by colonization and production of enterotoxins, which subsequently elicit excessive secretion of fluids and electrolytes into the intestinal lumen.

Approaches to control post-weaning ETEC diarrhea through improvements in management and environmental conditions, including prophylactic antibiotic use, have been largely ineffective. However, the requisite adherence of ETEC to mucosal receptors prior to colonization may allow for nutritional interventions to serve as alternative or complementary approaches to reducing incidence or severity of ETEC infection in weanling pigs. In our laboratory, we use an acute model of infection by orally-inoculating newly-weaned pigs with an F18-fimbriated ETEC isolated from a field disease outbreak (isolate number UI-VDL 05–27242). In brief, pigs are administered a $10^{10}$ CFU/3 mL dose of ETEC once-daily for 3 consecutive days to cause mild-to-moderate pathogenesis. Peak sickness in this model generally occurs 3-5 days after the initial ETEC inoculation, with symptoms subsiding or completely absent at 11 DPI. Over the 11-day infective period, pigs generally experience a 35-40% decrease in average daily body weight gain and a concomitant increase in total leukocytes of nearly 40%. Moreover, both diarrhea score and frequency are increased in ETEC-inoculated pigs relative to sham-inoculated control animals.

Likely owing to a variety of mechanisms, research using this acute ETEC model has suggested that both hydrated aluminosilicates (i.e., dietary clays) (Almeida et al., 2013; Song et al., 2012) and purified plant extracts (Liu et al., 2013) are able to attenuate clinical symptoms in weaned pigs. Presumably, the dietary clay substrates are able to absorb and inactivate enterotoxins, or perhaps inhibit the growth of pathogenic *E. coli*, and secondary plant metabolites are able to directly or indirectly elicit immunomodulatory effects in pigs. Considering the incidence of F18 ETEC is quite high not only in weanling pigs, but in human populations as well, there is great interest in identifying whether additional nutritional technologies can alleviate untoward effects of this type of infection. Gaining a more thorough understanding of the molecular mechanisms by which ETEC interacts with the host may provide meaningful insights to help combat this disease through dietary intervention.

**References**


Almeida, J. A. et al. 2013. Escherichia coli challenge and one type of smectite alter intestinal barrier of pigs. Journal of animal science and biotechnology 4: 52.

Andres, A., S. M. Donovan, and M. S. Kuhlenschmidt. 2009. Soy isoflavones and virus infections. J. Nutr. Biochem. 20: 563-569.

Blalock, J. E. 1994. The syntax of immune-neuroendocrine communication. Immunol. Today 15: 504-511.

Breuille, D. et al. 1998. Sustained modifications of protein metabolism in various tissues in a rat model of long-lasting sepsis. Clin. Sci. (Lond.) 94: 413-423.

Breuille, D. et al. 2006. Beneficial effect of amino acid supplementation, especially cysteine, on body nitrogen economy in septic rats. Clin. Nutr. 25: 634-642.

Cassidy, A. et al. 2006. Factors affecting the bioavailability of soy isoflavones in humans after ingestion of physiologically relevant levels from different soy foods. J. Nutr. 136: 45-51.

Clapperton, M., E. J. Glass, and S. C. Bishop. 2008. Pig peripheral blood mononuclear leucocyte subsets are heritable and genetically correlated with performance. Animal : an international journal of animal bioscience 2: 1575-1584.

Flori, L. et al. 2011. Immunity traits in pigs: substantial genetic variation and limited covariation. PLoS ONE 6: e22717.

Greiner, L. L., T. S. Stahly, and T. J. Stabel. 2001a. The effect of dietary soy daidzein on pig growth and viral replication during a viral challenge. J. Anim. Sci. 79: 3113-3119.

Greiner, L. L., T. S. Stahly, and T. J. Stabel. 2001b. The effect of dietary soy genistein on pig growth and viral replication during a viral challenge. J. Anim. Sci. 79: 1272-1279.

Holtkamp, D. J., H. Lin, C. Wang, and A. M. O'Connor. 2012. Identifying questions in the American Association of Swine Veterinarian's PRRS risk assessment survey that are important for retrospectively classifying swine herds according to whether they reported clinical PRRS outbreaks in the previous 3 years. Prev. Vet. Med. 106: 42-52.

Humphrey, B. D., and K. C. Klasing. 2005. The acute phase response alters cationic amino acid transporter expression in growing chickens (Gallus gallus domesticus). Comp. Biochem. Physiol. A Mol. Integr. Physiol. 142: 485-494.

Imberechts, H., H. U. Bertschinger, B. Nagy, P. Deprez, and P. Pohl. 1997. Fimbrial colonisation factors F18ab and F18ac of Escherichia coli isolated from pigs with postweaning diarrhea and edema disease. Adv. Exp. Med. Biol. 412: 175-183.

Johnson, R. W. 1997. Inhibition of growth by pro-inflammatory cytokines: an integrated view. J. Anim. Sci. 75: 1244-1255.

Kelley, K. W. et al. 2003. Cytokine-induced sickness behavior. Brain Behav. Immun. 17 Suppl 1: S112-118.

Klasing, K. C. 1984. Effect of inflammatory agents and interleukin 1 on iron and zinc metabolism. Am. J. Physiol. 247: R901-904.

Klasing, K. C. 2007. Nutrition and the immune system. Br. Poult. Sci. 48: 525-537.

Klasing, K. C., and D. M. Barnes. 1988. Decreased amino acid requirements of growing chicks due to immunologic stress. J. Nutr. 118: 1158-1164.

Klasing, K. C., and C. C. Calvert. 1999. The care and feeding of an immune system: an analysis of lysine needs. In: G. E. Lobley, A. White and J. C. MacRae (eds.) Proceedings of the VIIIth International Symposium on Protein Metabolism and Nutrition. p 253-264. Wageningen Press, Wageningen, Netherlands.

Klasing, K. C., and B. J. Johnstone. 1991. Monokines in growth and development. Poult. Sci. 70: 1781-1789.

Klasing, K. C., D. E. Laurin, R. K. Peng, and D. M. Fry. 1987. Immunologically mediated growth depression in chicks: influence of feed intake, corticosterone and interleukin-1. J. Nutr. 117: 1629-1637.

Klasing, K. C., and T. V. Leshchinsky. 1999. Interactions between nutrition and immunity. In: M. E. Gershwin, J. B. Berman and C. L. Keen (eds.) Nutrition and Immunology: Principles and Practice. p 363-373. Humana Press, Totowa, NJ.

Kluger, M. J. 1991. Fever: role of pyrogens and cryogens. Physiol. Rev. 71: 93-127.

Liu, Y. et al. 2013. Dietary plant extracts alleviate diarrhea and alter immune responses of weaned pigs experimentally infected with a pathogenic Escherichia coli. J. Anim. Sci. 91: 5294-5306.

Lunney, J. K., D. A. Benfield, and R. R. Rowland. 2010. Porcine reproductive and respiratory syndrome virus: an update on an emerging and re-emerging viral disease of swine. Virus Res. 154: 1-6.

Nagy, B., T. A. Casey, S. C. Whipp, and H. W. Moon. 1992. Susceptibility of porcine intestine to pilus-mediated adhesion by some isolates of piliated enterotoxigenic Escherichia coli increases with age. Infect. Immun. 60: 1285-1294.

Nagy, B., and P. Z. Fekete. 2005. Enterotoxigenic Escherichia coli in veterinary medicine. Int. J. Med. Microbiol. 295: 443-454.

Neumann, E. J. et al. 2005. Assessment of the economic impact of porcine reproductive and respiratory syndrome on swine production in the United States. J. Am. Vet. Med. Assoc. 227: 385-392.

Quan, N., and W. A. Banks. 2007. Brain-immune communication pathways. Brain Behav. Immun. 21: 727-735.

Qureshi, M. A., and G. B. Havenstein. 1994. A comparison of the immune performance of a 1991 commercial broiler with a 1957 randombred strain when fed "typical" 1957 and 1991 broiler diets. Poult. Sci. 73: 1805-1812.

Raetz, C. R., and C. Whitfield. 2002. Lipopolysaccharide endotoxins. Annu. Rev. Biochem. 71: 635-700.

Reeds, P. J., C. R. Fjeld, and F. Jahoor. 1994. Do the differences between the amino acid compositions of acute-phase and muscle proteins have a bearing on nitrogen loss in traumatic states? J. Nutr. 124: 906-910.

Song, M. et al. 2012. Dietary clays alleviate diarrhea of weaned pigs. J. Anim. Sci. 90: 345-360.

Spurlock, M. E. 1997. Regulation of metabolism and growth during immune challenge: an overview of cytokine function. J. Anim. Sci. 75: 1773-1783.

Wang, H., and P. A. Murphy. 1994. Isoflavone Content in Commercial Soybean Foods. J. Agric. Food Chem. 42: 1666-1673.

Williams, N. H., T. S. Stahly, and D. R. Zimmerman. 1997. Effect of chronic immune system activation on the rate, efficiency, and composition of growth and lysine needs of pigs fed from 6 to 27 kg. J. Anim. Sci. 75: 2463-2471.

Wilson, R. A., and D. H. Francis. 1986. Fimbriae and enterotoxins associated with Escherichia coli serogroups isolated from pigs with colibacillosis. Am. J. Vet. Res. 47: 213-217.

## *Notes*


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