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Environmental, Human and Target Animal Safety Issues of Animal Growth Promotants

What is an animal growth promotant? This is a collective term not restricted to products of biotechnology which includes a number of different strategies to increase the rate and efficiency of animal product formation (eggs, meat, milk and wool). The following is offered as a contemporary definition as viewed by those involved in animal production research: Growth promotants—strategies to increase the rate and efficiency of animal product formation with improved composition and desirability by the consuming public, free from harmful residues and environmentally neutral. Unfortunately a very negative perception exists, particularly with reference to somatotropin, and this negativism is due to misinformation widely distributed in the popular press. Granted, anabolic steroids are considered a growth promotant; however, anabolic steroids are not restricted to diethylstilbesterol (DES). In fact, DES is now removed from use in production agriculture Strategies to use naturally occurring compounds and mimics in low supplemental levels have been developed to meet the above definition.

As an attempt to clarify the public perception of what constitutes a growth promotant, the following classification is offered:

Metabolic modifiers
—* beta andregenec agonists;
—* somatotropin
—* transgene manipulations
—anabolic (steroid-like mimics) implants
—enhancer of futile energy cycles
—* immunomodulation

Extrasomatic Modifiers
—antibiotics and probiotics
—anticoccidiostats
—anthelmintics.
Management Strategies
—restricted feeding
— compensatory growth
— rearing the intact male
—forage feeding systems.

Strategies vary with livestock species, clearly global geography and conditions of local legislation, as apparent in the U.S. Again, public perception is that growth promotants are used by the agricultural sector to the advantage of the livestock producer with blatant disregard for public welfare and the environment. Bringing a compound from the laboratory bench to the marketplace involves the approval of a very intricate mechanism of "checks and balances".

CHECKS AND BALANCES

During the initial research and development phase of a compound, the first check would fall to the ethics of the investigator. After initial discovery, questions are considered such as: Are the undesirable side effects noted in the use of the compound in the target species? Does the compound demonstrate selectivity with respect to the endpoint desired? Can the results be replicated at other locations? Is the compound worthy of commercialization? Amazingly, few compounds survive beyond the initial discovery stage and most are dropped.

Scientists, either in the public or private research sector, operate by stringent rules and regulations. These include institutional research, animal care committees that review experimental protocols for compliance to formal and informal guidelines, as established by fund granting agencies such as the U.S. Department of Agriculture (USDA) and the National Institutes of Health (NIH), and professional peer review of results submitted for publication. Due to recognized deficiencies in some environments, most research institutions in the U.S. are striving for uniformity by adopting standards such as those proposed by the American Association of Laboratory Animal Science.

('designates developments collectively referenced as "biotechnology" advances. At present none are approved beyond use in a research environment or in controlled field tests.)

Following the discovery phase, a compound may survive into the marketing phase, and checks and balances at this stage are more familiar to the public. As pertinent to animal agriculture, The Center for Veterinary Medicine of the Food and Drug Administration (FDA) has the primary responsibility for the new drug application review process. The Food Safety Inspection Service (FSIS) would have jurisdiction for the introduction of transgenic products into the food chain. The Animal and Plant Health Inspection Service (APHIS) regulates, in part, the use of animal biologies, transportation of transgenic products and surveillance monitoring. Approximately 14 Federal agencies interact and regulate the marketing and use of agricultural chemicals.

Public watchdog organizations operate at both the discovery and marketing phases of a compound. These include consumer and environmental activist groups which pose queries often resulting in legitimate research investigations. Other activist organizations raise issues concerning the ethics of animal research. This offers yet another level of "checks and balances". Unfortunately, an impasse is often encountered, because despite all attempts to recognize and improve animal welfare considerations, those involved in animal production find the issue of "animal rights" contrary to desires or "rights" of mankind.

EXAMPLE: PORCINE SOMATOTROPIN

To address the topic of animal growth promotants, porcine somatotropin (PST) was selected. Investigational PST is a mimic of the 191 amino acid protein naturally secreted by the anterior pituitary and is primarily involved with nitrogen metabolism and long bone growth. Porcine somatotropin is produced by recombinant DNA technology and is available in considerable quantities for research purposes through several companies seeking registration approval. The impetus to examine PST efficacy relates to a very specific problem of the pork industry. Biomedical recommendation has advised the public to reduce the intake of animal fat, particularly saturated fatty acids, to reduce the risk of developing coronary artery disease. Pork is commonly believed to be a fatty meat and therefore some regard it as unhealthful. In part, this may explain why per capita pork consumption has remained static for about 20 years. As part of a larger issue, recommendations to re-duce human lipid consumption from the current figure of 38 percent of total caloric intake to 30 percent will require the composition of meat to be altered dramatically. Growth promotants, specifically those which alter nutrient partitioning exemplified by PST, may provide livestock agriculture the means to adjust commodity production to benefit pub-

lie health. Animal product consumption provides the human population with a large portion of high quality protein and several important vitamins and minerals; therefore, lowering the contribution fat intake derived from animal products is a worthy undertaking.

Based on several dozen research reports, PST can reliably improve the rate of body weight gain by approximately 10-15 percent in growing hogs, reduce the quantity of feed required per unit of body weight gain by 25 percent, increase edible meat yield by 5-10 percent and reduce fat deposition of hogs by 40-80 percent, depending on the dosage. Voluntary feed intake has consistently been reported to be reduced by 10 percent as a result of PST treatment. These effects are consistent with the classification of PST as a nutrient partitioning agent and are not magic. Mechanistically PST is altering intermediary metabolism such that the hog is metabolically much younger. The carcass composition changes desired by the consumer are realized by improved production efficiency; therefore, producer adoption should occur quickly. Rather than create a pharmacolic milieu to alter growth patterns, PST represents a biological strategy permitting the animal to more fully express the genetic potential for lean tissue growth.

ENVIRONMENTAL SAFETY

The current decade was viewed as one of concern and action with respect to environmental quality. Some countries in Europe have enacted legislation in an attempt to minimize the environmental impact of technological advances. The Netherlands serves as an example. A country approximately the size of the state of New Jersey has a human population of 14 million and a swine population of 20 million. This livestock population requires 102,000 tons of nitrogen for feed purposes per year. Currently, standards have been established to impose an environmental impact tax on nitrogen and phosphorous as pollutants. Based only on the improvement in feed conversion efficiency, PST would reduce nitrogen pollution by approximately 3,600 tons annually. Phosphorous loss to the environment would decrease by a similar magnitude, but other strategies such as the use of phytase in the feed may be of greater consequence. In itself, PST would not correct all issues associated with environmental quality, but as part of a larger integrated strategy this growth promotant may contribute to the improvement of the environment. Intensive animal production management systems as found in The Netherlands, Iowa and Illinois could benefit indirectly from this technological advancements

HUMAN SAFETY

Somatotropins are extremely species-specific and follow a phylogenic hierarchy of biological activity such that PST would not have biological activity in the human, whereas human somatotropin would be active in hogs. Residues of the peptide, should they exist, would be denatured during the cooking process of treated pork and further degradation would occur in the digestive tract of humans. These factors all contribute to the conclusion that PST as a residue would not pose a threat to the human population. However, the perception of biologically active residue(s) persists.

Based on research data reviewed in several manuscripts, increased levels of PST resulting from treatment is cleared from the circulation in 15 hours following administration. Using validated assay methods, PST has not been detected in the meat of treated animals. Treatment of young growing hogs enhances rate and efficiency of body weight gain. Furthermore, withdrawal from treatment does not result in a decompensation of beneficial effects; therefore, a sustained beneficial effect can be realized long after treatment withdrawal. This would permit a lengthy withdrawal period prior to the marketing of treated pork should regulatory approval mandate.

On the proactive side, cardiovascular disease is the leading cause of mortality in industrialized societies and the biomedical community has concluded that this mortality is largely caused by the consumption of saturated fats in excess quantities mainly from animal products. Use of PST would allow the production of extremely lean animals and trimmed pork as a commodity would be approximately five percent lipid. Intramuscular lipid concentration of fresh pork is small compared to other meats. By substantially reducing the lipid content of pork, PST may reverse the public image of pork as a fatty and, therefore, unhealthful product.

TARGET ANIMAL SAFETY

An inherent joint problem in swine which relates to stiffness and feet and leg problems is known as osteochondrosis. Porcine somatotropin, possibly by accelerating rate of growth, was associated with an increase in the incidence of this problem in early experiments. Subsequently, adjustment of the dietary calcium and phosphorous concentration has greatly reduced this problem.

Unlike the dairy animal treated with bovine somatotropin (BST), hogs treated with PST have a narrow window of response, or dose res-

ponse range. This means that there is approximately a fivefold difference between the dosage required for biological effect and the dosage for maximum effect without adverse effect of appetite. This will require prudent use by producers and recognition that "more is not better".

As a consequence of the increased lean body mass, heat production resulting from basal metabolism increases 17 percent. This may require greater ventilation rates, particularly in warmer production environments.

Pale-soft-exudative pork is a meat quality problem of the pork industry which is associated with a lethal genetic disorder known as porcine stress syndrome. Treatment of hogs with PST results in a paler pork as judged from instrumental appraisal. Whether this is a true form of pale-soft-exudative pork is debatable. No indication of porcine stress syndrome resulting from the use of PST has been noted. A slight decrease of meat tenderness reported as a result of PST could relate to the mechanism of action; animals are physiologically less mature.

Some critics have implied that growth promotants, particularly PST and BST, will compromise the immunocompetence of the treated animal. Few studies have addressed this issue, but one report found PST to increase macrophage function such that immune system function would be enhanced. Theoretically this would decrease the risk of disease in treated hogs.

The major deterrent to the adoption of PST at present is the development and refinement of a drug delivery system. Ideally, this delivery device would be implantable with the capability of delivering the peptide for a 30 day period in a pulsatile manner, cycling every 24 hours. This is a major bioengineering challenge which is actively being investigated by several companies.

CONCLUSION

PST, as well as BST, is not a doomsday technology designed to create meat animals of monstrous proportions. Agricultural research efforts are not directed at an increase of livestock population numbers. The objective of somatotropin as a technological advancement is to improve the quality of the meat product so that consumer acceptability is improved and simultaneously improves production efficiency. PST clearly meets these objectives.