Session 2.I

Animal production and meat quality

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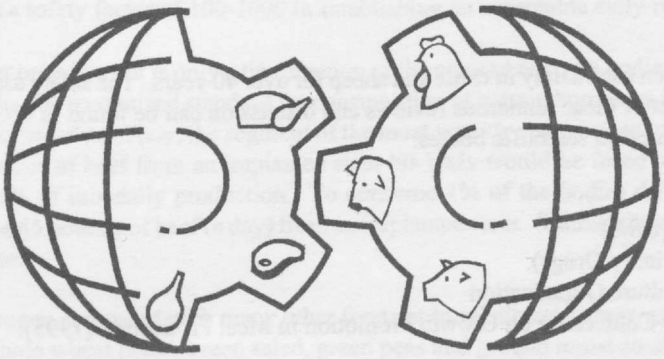

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USE OF GROWTH PROMOTERS IN FUTURE PRODUCTION: ONE POINT OF VIEW

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Background.

Hormone implants and antimicrobials have been used for decades in livestock production. However, concerns have arisen about their safety in relation to the human population. Selected countries have decided to ban their use in relation to growth promotion. However, other countries contend these bans are being used as artificial trade barriers. The scientific and government entities from various countries have come to different conclusion on the available data.

Objective.

To provide and update on the current use and justification of growth promotants and provide information on the status of current and future regulatory proposals.

Hormone Implant Safety.

Growth promoting implants have been used for over forty years (Preston, 1999). Perhaps the most recent and comprehensive review of the applied and carcass effects of growth promoting implants in beef cattle was published by Oklahoma State University (Owens et al., 1997). Implants improve growth rate (+10 to 30%), feed efficiency (+5 to 15%) and carcass leanness (+5 to 8%) of cattle. Implants remain the most cost effective method of reducing cost of production, keeping beef competitive with pork and poultry. There is much previous scientific evidence showing that beef from cattle implanted with approved hormone implants is safe.

Five hormones have been approved for use in implants.

Estrogen, testosterone and progesterone are hormones which occur naturally in humans, animals and some plants. Estrogen is produced primarily by the follicle on the ovary. Relatively small amounts of estrogen are produced by the testicles and adrenal glands. The placenta (fetal membrane) of a pregnant cow produces relatively large amounts of estrogen. Testosterone is mainly produced by the testicles with small amounts produced by the adrenal glands and ovaries. Progesterone is produced primarily by the ovary, placenta in the pregnant cow, and to a lesser extent by the adrenal glands and testicles.

The Codex Alimentarius Commission, a joint body of the UN Food and Agriculture Organization and the World Health Organization, is the international standard setting organization for food residues. They concluded that it was not necessary to establish maximum residue levels (MRLs) for estrogen, testosterone, and progesterone, because they are naturally occurring at varying levels in food producing animals and there is no practical way to test whether an animal has been implanted with these hormones.

Two synthetic compounds, zeranol and trenbolone acetate have been approved for use in implants. Zeranol a product of *Fusarium spp.* fungus. It is nonsteroidal semisynthetic agent with some estrogenic properties. Trenbolone acetate is a synthetic steroid with androgenic activity.

The Joint Expert Committee on Food Additives (JECFA) is an international committee that established maximum residue levels (MRLs) in food for drugs and other food additives. JECFA has established MRLs for the synthetic hormones used in implants based on research trials.

Implant Safety Studies.

Implant products have been used safely in cattle and sheep for over 40 years. The safety aspects of implants have been reviewed and discussed many times. A list of those numerous reviews and discussion can be found in Preston (1999). The safety of hormone implants has been studied by numerous scientific bodies:

World Health Organization
Food and Drug Administration (USA)
Health Canada (Bureau of Veterinary Drugs).
United Nations Food and Agriculture Organization
European Community Scientific Conference on Growth Promotion in Meat Production (1995).

Human safety of implant products properly used in beef production has been confirmed by these scientific bodies. The industry perhaps needs to be more proactive in response to questions of hormone safety.

Even if there is an eventual approval of movement of beef from North America into Europe, enough consumers in the European Union (EU) have been sensitized to the issue that beef produced with the use of hormones in growing/finishing may not find a ready market present with EU consumers (Smith et al., 1997). The current approved method for selling beef to the EU is to sell beef produced without use of the growth promotants.

Residue Levels.

The Codex Alimentarious Commission plays a role in establishing international standards for veterinary drug residues in food. The specific mission of the Codex program is to protect consumers and facilitate trade (Orr, 1999). The objectives of the Codex program are to develop and harmonize food standards between member nations so that non-tariff trade barrier are either minimized or eliminated. The Codex program is sponsored by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) with over 150 countries participating. The Codex Alimentarious Food Standard Program has no regulatory enforcement powers - it is merely a science-based international government standard-setting body. Countries that accept Codex standards must enforce them and agree to allow trade of products meeting the accepted Codex standards. Codex committees, such as the Codex Alimentarious Commission joint FAO/WHO Expert Committee on Food Additives (JECFA), are independent expert groups which deal with specific commodity issues or general health and safety matters related to food. The JECFA focus on the scientific evaluation of a veterinary drug and does not consider government policies and politics. JECFA recommends an acceptable daily intake (ADI) and a maximum residue limit (MRL) for a veterinary drug residue in a specific food commodity.

The fifty-second meeting of the Codex Alimentarius Commission Joint FAO/WHO Expert Committee on Food Additives (JECFA), held in Rome on February 2-11, 1999, recommended acceptable daily intakes (ADI) for the three additives (estradiol-17*b*, progesterone and testosterone). Maximum residue limits (MRL) were not specified. This means that the available data on the identity and concentration of residues of the veterinary drug in animal tissues indicate a wide margin of safety for consumption of residues in food when the drug is used according to good practices in the use of veterinary drugs. The committee concluded that at present the drug residues do not present a health concern and do not pose any health risk to humans (JECFA, 1999).

Under a section of the WTO rules known as the Sanitary and Phytosanitary (SPS) Agreement, a country is entitled to restrict imports if they feel the product compromises human, animal or plant health. But there is a fine line between protection and protectionism, and it is tempting for local producers to keep out foreign competition by invoking food safety or environmental concerns (The Economist, 2000). The exporting country can dispute the claim, and if a WTO panel rules that the restrictions are not scientifically justified the importing country may face trade sanctions.

But what if the science is in dispute? The EU's scientific advisory body on the this issue claims that some of the hormones could cause cancer in consumers, whereas scientists at Codex Alimentarious say the levels found in American beef are safe.

Hormone Levels.

The acceptable daily human intake (ADI) for a hormone is based on the no hormone effect level (NHEL). The ADI is the amount of a food additive, on a body weight basis, that can be consumed daily over a lifetime without appreciable health risk. Carcinogenic effects and the effect on the fetus during pregnancy are included in the health risks.

The approval process for any hormone requires the determination of the NHEL in several animal species (Lone, 1997). The NHEL in the most sensitive species is then divided by 100 to give an acceptable human daily intake (ADI) per unit of body weight. Average daily intake of animal tissues by humans multiplied times any residue found in these animal tissues following implantation provides a potential daily intake (PDI). An implant product will not be approved if the PDI exceeds the ADI. For example with tenbolone acetate, depending on the metabolite, the ADI is 46 to 1193 times the PDI proving a very wide safety margin (Preston, 1999). Endogenous production in humans of natural hormones used in implants greatly exceeds any potential intake from beef produced using implants (Preston, 1997). JEFCA normally uses a safety factor of 100-1000 in establishing an acceptable daily intake.

The amount of extra natural hormones in meat is only a tiny fraction of the amount our own bodies produced in a day. Although there is no MRL for the natural hormones, the recognized standard for consumption of natural hormones is that is should not exceed 1% of the bodies own daily production. The prepubertal boy, the segment of the most sensitive to estrogen, produced 41,500 nanograms of estrogen per day. If he consumed 4 ounces of beef from an implanted steer his body would be faced with metabolizing an extra 1.6 nanograms (Table 1) estrogen or .0004% of this daily production. To consume 1% of the bodies daily production of estrogen the prepubertal body would have to consume 65 pounds of beef (a day) from an implanted steer. Similar situations apply to the other natural hormones, testosterone and progesterone.

Beef is not a great source of estrogen compared with many other foods or in relation to human estrogen production (Anderson, 1991. In a meal of mashed potatoes, whole wheat bread, green salad, green peas and ground round steak from estrogen-treated cattle, the food that would contain by far the least estrogenic potency is the ground beef steak.

Implant Release Rates.

The highest level of residues from implants are found at the implant site. The implant is placed in a inedible portion of the animal, the middle third of the ear. The ear is removed on the killing room floor prior to skinning the carcass preventing the ear from ever entering food for human consumption.

Implants are designed to release hormones slowly over an extended period of time. The peak release occurs between day 2 and day 15 following implantation. During the peak release period, tissue hormone levels do not exceed established maximum residue levels in edible tissues. The body has the ability to excrete and the metabolism systems that break down any excess hormone that is absorbed from an implant. The hormones used in implants have low oral activity. It is estimate that only 10% of the hormone is absorbed when the hormone used in implants are fed, the rest is broken down by the bodies digestive system.

Regulatory Implant Bans.

At the time of the EU ban a European Economic Community scientific committee, chaired by Eric Lamming of Great Britain, was meeting to study the safety of growth promotants. According to Dr. Lamming, "the EU ban was instituted in spite of scientific evidence, as political solution to problems of food surpluses generated by the EU's Common Agricultural Policy (CAP)." The 1995 European Agricultural Commission Scientific Conference on Growth Promotion in Meat Products concluded that based on the "data available it seems most unlikely or even impossible that the residues following the use of these compounds according to good agricultural practice will ever exceed the set tolerance levels", similar to a previous conclusion (Lamming, 1987).

Antibiotic/Antimicrobial Use for Growth Promotion.

Antibiotic and antimicrobial are often used interchangeably. There is a difference, however, Antibiotics are a class of pharmaceuticals which are substances produced by microbes. Antimicrobials are essentially the same as antibiotics but also include substances of synthetic origin.

Globally, public health officials are concerned about the emergence of antimicrobial resistance in hospitals acquired bacterial infections. It is generally thought that this increase in resistance is the result of over-reliance on the use of antimicrobials in human medicine, failure to adhere to prescriptions for the full duration, and the increased clustering of people in places such as hospitals and day care centers. Canadians have taken action in managing Canada's antibiotic resistant bacteria problem by improving their use of antibiotics (Reid, 2000). Physicians and patients have adjusted their habits with regard to prescribing or using antibiotics during the past three years.

Resistance means that the bacteria no longer responds to the antibiotic treatment. Susceptibility is a term for describing how sensitive bacteria are in responding to treatment with antibiotics. A lot of what people call resistant really means less susceptible (CAHI-ICSA).

Antimicrobial resistance can occur 3 ways:

1. In any groups of bacteria, there are some individual bacteria that are naturally stronger than others and these stronger bacteria can survive antimicrobial treatment and reproduce more of their kind.

2. A small percentage of bacteria may be naturally resistant to certain antimicrobials, and

3. antimicrobial resistance can be transferred from one type of bacteria to another through genetic material called plasmids.

Antimicrobial residues are trace amounts of an antimicrobial remaining in meat after processing or in milk. Various regulatory agencies have established levels of antimicrobial residues that are deemed safe and may legally be in the edible tissues of the animal at the time of processing or in the milk. Antimicrobial residues and antimicrobial resistance are often confused but are not related according to the Canadian Animal Health Institute (CAHI-ICSA). When talking about the transfer of antimicrobial resistance from animals to humans, scientists are referring to the transfer of resistant bacteria, not trace levels of antimicrobials.

Resistance could, theoretically, spread from livestock to humans in several ways:

1. Through direct contact with livestock-carrying-resistant bacteria

2. Through consuming vegetables contaminated by manure from livestock-carrying-resistant bacteria

3. By consuming meat contaminated with resistant bacteria (from livestock) during processing.

Current Antimicrobial Livestock Uses.

The results of an Animal Health Institute survey on U.S. antibiotics used in animals indicate that the majority of antibiotics are used to treat and prevent human disease (Savage, 2000). The Centers for Disease Control and Prevention estimate that more than 50 million pounds of antibiotic are produced in the Unites States each year. According to the Animal Health Institute survey, 17.8 million pounds (36 percent) are used in animals. Of the total used in animals, 14.7 million pounds (83 percent) are used for prevention and treatment of disease. Of all antibiotic uses, only 3.1 million pounds (6.1 percent) are used for growth promotion.

Of the 17.8 million pounds used in animals, the antibiotics identified in the survey were 1.6 percent aminoglycosides, 0.12 percent fluoroquinolones, 3.75 percent penicillins, 2.0 percent sulfoamindes, 16.4 percent tetracyclines, 40.3 percent ionophores/arsenicals (unique dru products developed and used only for animal production), and 35.8 percent other antibiotics which included cephalosporins, macrolides, lincoasamides, polypeptides and streptogramins.

The 17.8 million pounds of antibiotics used in animals in the U.S. includes both farm animals and companion animals. There are more than 115 million dogs and cats, and more than 6.9 million horses, 7.5 billion chickens, 292 million turkeys, 109 million cattle, 92 million pigs and 7 million sheep in the United States.

Where do we go from here?

Fifteen years ago Sweden, now just recently Denmark, banned subtherapeutic (routine) use of feed additives for growth promotion. Use of several feed grade medications have been suspended in the European Union, citing the "precautionary principle." Will the Swedish model work in the Unites States and other larger livestock operations? The average farrow-to-finish operations in Sweden is 50 sows. Although using antibiotics for growth promotion isn't allowed, they can be used in feed therapeutically. That means they are used at high levels, short term.

The Centers for Disease Control and Prevention (CDC) maintains that based on scientific evidence, steps are needed now to decrease the use of antibiotics in livestock, especially as growth promoters. However, the United States Department of Agriculture says that more research is needed before decisions are made regarding restrictions on antibiotic use in food animals. Department officials argue that antibiotic use prevents serious disease outbreaks among farm animals. In the same vein, the Animal Health Institute, which represents feed-additive manufactures, maintains that there is little evidence linking antibiotic use in agriculture to increased antibiotic resistance in humans.

Current U.S. regulations for approval and use of antimicrobials in agriculture are focused on residue avoidance and not on antimicrobial resistance. However, the United States Food and Drug Administration has proposed a framework to evaluate existing and new feed additives or antimicrobials for their contribution to antibiotic resistance and potential effect on public health.

Some U.S. industry observers feel that the new FDA proposals could do more harm than good (Vansickle, 2000). according to Paul Sunberg, DVM assistant vice president, Veterinary Issues, National Pork Producers Council, It will severely limit availability of antimicrobials to animal agriculture both new and previously approved products." Dr. Sunberg went on to state, " It's possible we could be marketing animals that aren't as healthy, posing a greater food safety risk. The potential for antibiotic-resistant bacteria could even be heightened because producers and veterinarians would be forced to rely on a narrow supply of products."

Dr. Otto Radostits, from the Western College of Veterinary Medicine at the University of Saskatchewan, wrote in a summary of the 1999 "Managing Antimicrobial Resistance" Conference, held in Toronto (CAHI-ICSA, 1999). With the exception of a few enteric bacterial species, antimicrobial resistance is not a problem in food animal veterinary medicine. The standards used to determine susceptibility and resistance of human and animal bacterial pathogens vary from country to country and confound interpretation of the problem.

A panel was convened by the National Research Council and the Institute of Medicine in Washington, D.C. George Bran, a veterinarian at Iowa State University observed, the extent to which agriculture use is diminishing antibiotics' utility in fighting human disease "has not yet been quantified with hard data." It remains unclear whether the documented cases reflect a widespread problem or just a few outbreaks, he says. Indeed, the new report concludes that antibiotic use in livestock "does not appear to constitute an immediate public-health concern, " but it cautions, "additional data might alter this conclusion."

Recent articles have implied that the use of antimicrobials in agriculture are contributing the resistance or susceptibility challenges (Khachatourians, 1999 Raloff, 1999 and Wegener, 1999). In the European Union, some governments have already banned many growth-promotants in livestock. For example, a European product called avoparcin was shown to increase the number of bacteria on a farm where animals were resistant to vancomycin, a closely related antibiotic important in human medicine. Avoparcin was subsequently banned. However, this approach alone may not be sufficient because antibiotics used in humans is recognized as a major contributor to the problem.

The development of antibiotic resistant bacteria is not a problem with the use of some antimicrobials. Ionophores (such as monensin sodium) and antimicrobials which do not select for transferable resistance (such as bacitracin and bambermycins) could be used for growth promotion.

What are farmers and veterinarians doing about the issue of antimicrobial resistance in farm animals where antimicrobials are used for growth promotion? Gilbert Hollis, University of Illinois Extension Swine Specialist and a conference organizer on livestock antibiotic use stated, "We believe that U.S. livestock producers should begin to consider the what-ifs in regards to antibiotic use."

Quality assurance programs, developed by livestock and poultry producers with help from the animal health products industry, promote proper and effective use of all animal health products, including antimicrobials. These programs stress the importance of a

strong working relationship between producers and their veterinarians. They also teach efficient management practices and emphasize proper drug use as a way of improving the safety of the food supply.

Given the current climate of antibiotics and agriculture, will drug companies continue to produce new antibiotics for animal use? Some firms are a making investments in novel ways to kill bacteria without resistance occurring. We may also need to look at alternative management systems. A seaweed extract may boost immune systems. The use of "all in - all out" versus continuing to add and remove animals from a building may assist in controlling diseases. Preliminary work with natural rumen proteins may be a source of disease defense. Transgenic animals could be developed with increased disease resistance. However, what will be the response of growth and feed efficiency with more disease resistant animals?

Conclusions.

Currently, hormone implants are used in many parts of the world. While bans are in place in some countries, they have not drastically affected beef production in countries using such implants. We will continue to use antimicrobials but their use for growth promotion will be at least much more regulated. We have 5 billion people on Earth, and, we expect to have another 5 billion people in the early part of the 21st century. Efficient methods of agriculture production will need to be utilized to feed this human population.

Pertinent Literature.

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Table 1. Amount of Estrogen*

Estrogen contained in 4 ounces (113.4 grams of:	Amount(nanograms)
Beef from non-implanted steer, raw	1.2
Beef from implanted steer, raw	1.6
Beef from non-pregnant heifer, raw	1.5
Beef from pregnant heifer, raw	24-63
Cabbage, raw	2700
Peas, raw	454
Wheat germ	453
Milk	14.7
Estrogen produced per day by:	
Children	
Boys	41,500
Girls	54,000
Adolescent Females	93,000
Men	136,000
Non-pregnant women	192,000-1,190,000
Pregnant women	4,000,000-64,000,000

*Source, Food Safety and Inspection Service, of the US Department of Agriculture.