Benefits and risks of growth promoters in animal production

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Abstract
Producers use growth promoters to increase growth rates and improve overall efficiency and product quality. Various compounds have been tried for growth promotion, including hormones and antimicrobial agents. Natural hormones such as estradiol (estrogen), progesterone and testosterone or synthetic hormones such as zeranol, melengestrol acetate and trenbolone acetate are widely used as growth promoters in animals. The non-therapeutic use of wide spectrum of antimicrobial agents including ionophores is a common practice in improving animal production. There is substantial recent evidence that residues of hormones in meat and meat products of treated animals may pose a risk to the consumers. The adverse effects of hormones include developmental, neurobiological, genotoxic and carcinogenic effects. Several European countries have restricted or banned the use of antibiotics as growth promoters because of the possible risks of future drug resistance in human following exposure to small doses of antibiotics in animal products. Due to the various risks of antimicrobial agents and hormones, new alternative additives were suggested which may include microbial cultures (probiotics) that are now used in ruminants to manipulate certain biochemical events and the microbial composition of the rumen and prebiotic molecules such as oligosaccharides and lectins. Pre- and probiotics do not exclude each other’s function and can or must be used simultaneously in order to obtain a powerful synergistic effects.

Key words: Growth promoters, antibiotics, antimicrobials, probiotics, probiotics and ionophore.

Introduction
Since the dawn of recorded time, it has been the dream of animal nutritionists to manipulate and improve the efficiency of animal performance and production. Initial attempts to achieve this goal were by dietary manipulation, but during the last decades a number of active compounds have been discovered that when fed, can achieve some or all of the above objectives and hence improve efficiency of production in animals.

The Animal Health Institute of America has estimated that, without the use of growth promoting antibiotics, the USA would require an additional 452 million chickens, 23 million more cattle and 12 million more pigs to reach the levels of production attained by the current practices. Major advancements in improving efficiency of animal production will require increased knowledge of factors regulating metabolism and utilization of nutrients. The growth promoter effect of antimicrobial drugs was discovered in the 1940’s, when it was observed that animals fed dried mycelia of Streptomyces aureofaciens containing chlortetracycline residues improved their growth. The mechanism of action of antibiotics as growth promoters is related to interactions with intestinal microbial population.

The United States Food and Drug Administration approved the use of antibiotics as animal additives without veterinary prescription in 1951. Also in the 1950’s and 1960’s each European state approved its own national regulations about the use of antibiotics in animal feeds.

The mechanisms of growth promotion are still not exactly known. Results of experiments with germ-free chickens seemed to indicate that the action of the growth promoters is mediated by their antibacterial effect. Four hypotheses have been proposed to explain their action: (i) nutrients may be protected against bacterial destruction; (ii) absorption of nutrients may improve because of a thinning of the small intestinal barrier; (iii) the antibiotics may decrease the production of toxins by intestinal bacteria; and (iv) there may be a reduction in the incidence of sub clinical intestinal infections.

Besides antimicrobial agents, hormones are extensively used for growth promotion because one of the major factors controlling the deposition of protein in an animal is the activity of the hormones circulating in its blood. Many of the anabolic hormones interact with each other, e.g. growth hormone and insulin, and there is evidence for a direct interaction between catabolic and anabolic hormones, e.g. testosterone and glucocorticoids. Exogenously administered hormone-like substances can have marked effects on animal growth.

Hormones as outlined in various symposia are specific substances or growth factors that alter growth rate or body composition. Endogenous (e.g. insulin, somatotropin, IGF-I and IGF-11) and exogenous hormones promote translation, transcription and amino acid uptake. It is well known that hormones have defined roles in homeostasis within the body including regulation of energy, mineral or water balance and protein, lipid or carbohydrate metabolism. Therefore, it is important to investigate the role of hormones as growth promoters.

Because of the possible risks of antimicrobial drugs and
hormones, new additives were suggested which may include microbial cultures (probiotics) and pre-biotic molecules such as oligosaccharides and lectins. In the former case, an attempt is made at preventing intestinal pathogens from settling down, by administering microorganisms which can colonize the digestive tract and leave out all dangerous bacteria.

**Hormones**

Hormones have been developed for a number of purposes, including treatment of hormonal disorders in people, and also for promotion of unnaturally fast growth in farm animals. The natural hormones estradiol (estrogen), progesterone and testosterone and their synthetic alternatives zeranol, melengestrol acetate and trenbolone acetate have been approved by the VDD for use in Canadian beef production and in other countries.

Mode of action of growth promoting hormones is to 1) help to improve meat quality by decreasing the deposition of fat, producing the lean meat that consumers desire; 2) increase feed efficiency, thereby allowing more growth with less feed; 3) increase lactation period in cows when injected with bovine growth hormone (rBGH). This hormone interacts with other hormones in cows’ bodies to increase the amount of milk they produce. 4) Growth promoting hormones enhance endogenous estrogen production and growth.

**How growth hormones boost production:** Milk experts found that an estimated increase of about 12 per cent in the US milk supply was recorded after application of growth promoter hormones. However, it is argued that the US did not need higher milk supply. It is said that since the 1950’s, America’s dairies have consistently produced more milk than the nation could consume, the surplus being bought up every year by the Federal Government to prevent the price from plummeting, however, this is a disputed issue. Beef producers inject their cattle with growth hormones because this improves meat quality by increasing the development of lean meat and decreasing fat content and reducing costs for producers thereby reducing the price of meat and meat products for consumers. With the animal growing larger and quicker on less feed, producers have lower feed costs and therefore lower inventory costs.

**How are growth hormones used:** The US FDA approved six hormone growth promotants (HGP) including three naturally occurring hormones - oestradiol, progesterone and testosterone - and three synthetically prepared hormones - zeranol, trenbolone and melengestrol. These are implanted or injected into cattle in various stages of maturity. The FDA, however, does not permit injecting calves with these hormones. The male hormone testosterone and its synthetic equivalent trenbolone acetate and the female hormone progesterone including three synthetic derivatives zeranol, 17-β-oestradiol and melengestrol acetate (MGA) are either implanted or injected into the cows. Melengestrol is a feed additive and is not injected, but added to the feedstock. Hormones are also said to help the animal improve its nutrient absorption. This translates into feedstock needed for the animal to reach its finish weight (market weight).

One of the most well-known and controversial hormones used in farming is recombinant bovine growth hormone (rBGH), which is genetically engineered and injected into dairy cattle. Scientists have linked excess hormones to cancer.

Melengestrol acetate was the most widely used growth-promoting agent that is fed to heifers during the finishing period. Melengestrol acetate is a progestin that enhances endogenous estrogen production and growth. Busby and Loy found that feedlots that fed MGA to heifers had lower death loss (3.8 vs. 6.2%) than those that did not. These findings suggest that some growth-promoting products may be more appropriate for use in feedlot cattle in the winter, whereas others may be more effective in the summer.

Perrett reported that feeding melengestrol acetate (MGA) to feedlot heifer calves in western Canada resulted in significantly (P≤0.05) improved average daily gain, feed conversion and carcass quality grade and lower rates of initial undifferentiated fever treatment and bovine respiratory disease mortality. However, heifers fed MGA had less desirable (P≤0.05) carcass yield grade. Growth-promoting implants have been used for well over 30 years to improve feed efficiency and growth rate. The majority of the implants used today have estrogenic, androgenic or a combination of estrogenic and androgenic activity. Estrogenic implants increase thyroid gland activity and DMU that would be an asset under cold environmental conditions. Hunter and Vercoe concluded that trenbolone acetate decreases maintenance energy requirements, which may be an asset under hot environmental conditions by decreasing overall metabolic heat load.

The effect of estrogenic implants on mature weight seems contradictory. In a study lasting 486 days, repeated implants of an estrogenic substance (diethylstilbestrol) increased mature size of steers by 15% . Estrogens presumably act through enhancing secretion of growth hormone which should increase mature size. An increase in mature size automatically reduces fat content and increases growth rate at a specified weight as has been observed typically with estrogen administration. In contrast, by hastening closure of the growth plate and increasing ossification, estrogens should limit mature size. This could explain the smaller stature of females of many species. Field et al. found that closure in lambs occurred so late that mature size of lambs was not altered by estrogenic implants.

**Risk of using growth promoting hormones:** Gronner criticized the use of hormones such as steroid hormones, beta-agonists and somatotropins as growth promoters because their use may result in animal health and welfare risks and raise ethical questions. He suggested that the choice to use hormones as growth promoters should not be left to self-regulation based on self-interest and/or be made subject to international trade agreements governed by economic considerations only. In the production of food the price for the protection of the environment and the animals ought to be paid. It is time to make future oriented choices.

The use of six growth hormones 17β-oestradiol, progesterone, testosterone, zeranol, trenbolone and melengestrol acetate (MGA) for growth promotion in cattle poses a risk to the consumers but with different levels of conclusive evidence. This is the main finding of the Scientific Committee for Veterinary Measures relating to Public Health which has unanimously adopted an opinion on potential risks to human health from hormone residues in meat and meat products. The adverse effects include developmental, neurobiological, genotoxic and carcinogenic effects. These
effects can be attributed to either the parent compound or the metabolites.  

There is substantial recent evidence that the natural hormone 17β-oestradiol has to be considered as a complete carcinogen 23. It exerts both tumor initiating and tumor promoting effects. Estrogens bind to the estrogen receptor (ER) and subsequently stimulate cancer cell growth by transcriptional regulation of genes involved in cell proliferation 24. Cancers linked to the presence of estrogen include breast, endometrial and ovarian cancer 25.

**Antimicrobial Agents**

The term “antimicrobial growth promoter” is used to describe any medicine that destroys or inhibits microbes and is administered at a low, sub therapeutic dose. The use of antimicrobial for growth promotion has arisen with the intensification of livestock farming. Infectious agents reduce the yield of farmed food animals and, to control these, the administration of sub-therapeutic antibiotics and antimicrobial agents has been shown to be effective.

The non-therapeutic use of antibiotics has the following aims: prophylactic purposes in young animals, to reduce the enteric diseases whose onset is favoured by incomplete development of the immune system during the first weeks of life; and in adult animals, to prevent the onset of feed-induced pathologies (acidosis in steers). Supplementing animal feed with antimicrobial agents to enhance growth has been common practice for more than 50 years and is estimated to constitute more than half the total antimicrobial use worldwide 26. The potential public health consequences of this use have been debated; however, until recently, clear evidence of a health risk was not available. Several classes of antibiotics, including glycolipids (bambermycin), polypeptides (bacitracin), ionophores (salinomycin) and β-lactams (penicillin), are used for growth promotion and prevention of infectious diseases 27, 28. Butaye et al. 27 outlined the growth-promoting antibiotics allowed for use in the EC, both past and present (Table 1).

**Mode of action of antimicrobial growth promoters:** The mechanism by which antimicrobial growth promoters (AGPs) work is not clear. AGPs reduce normal intestinal flora (which compete with the host for nutrients) and harmful gut bacteria (which may reduce performance by causing subclinical disease). The effect on growth may be due to a combination of both fewer normal intestinal flora and fewer harmful bacteria. The class of antimicrobial drugs used and the animal species involved may determine the relative importance of each mechanism 29.

These antimicrobials improve feed conversion and body weight gain presumably by altering the composition and activities of microflora in the gut 30. Since the early 50’s antibiotics are used as additives promoting performance in animal nutrition, considerable improvements have been obtained in production.

The quantity used in feed varies with each antimicrobial agent. In the European Union (EU), avoparcin 20 and 40 mg/kg was approved for different age groups of pigs and chickens; the concentration is often referred to as “sub therapeutic”. The resulting concentration in the gastrointestinal tract of the animal is sufficient to inhibit the susceptible bacteria and markedly affect the composition of the bacterial gut flora 29.

This practice may modify the intestinal flora and create a selective pressure in favor of resistant bacteria 28, 31. Antimicrobials have also proved to be important for sustainable livestock production and for the control of animal infections that could be passed onto humans.

**Ionophore antibiotics:** In 1968, the generic term ionophores was used for the first time to refer to all carboxylic polyethers that fit the classical definition of antibiotics 32. In animals the ionophores are used mainly for growth promotion and as coccidiostats in the prevention of coccidiosis 32- 33.

Since the mid-1970’s ionophores have been extensively used to manipulate rumen fermentation, to improve the efficiency of feed utilization, and to increase weight gain of growing ruminants 36, 37. Most ionophore antibiotics are produced by Streptomyces spp. 38. Along with the natural products of microorganisms, several chemically modified ionophores exist.

**Table 1. Growth-promoting antibiotics allowed for use in the EC, both past and present.**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Banned since</th>
<th>Antibiotic group</th>
<th>Related therapeutics</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bambermycin</td>
<td>Glycolipid</td>
<td></td>
<td></td>
<td>Inhibition of cell wall synthesis</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>1999</td>
<td>Cyclic peptide</td>
<td>Bacitracin</td>
<td>Inhibition of cell wall synthesis</td>
</tr>
<tr>
<td>Monensin</td>
<td>Ionophore</td>
<td></td>
<td></td>
<td>Disintegration of cell membrane</td>
</tr>
<tr>
<td>Salinomycin</td>
<td>Ionophore</td>
<td></td>
<td></td>
<td>Disintegration of cell membrane</td>
</tr>
<tr>
<td>Virginiamycin</td>
<td>1999</td>
<td>Streptogramin</td>
<td>Quinupristin/dalfopristin</td>
<td>Inhibition of protein synthesis</td>
</tr>
<tr>
<td>Tylosin</td>
<td>1999</td>
<td>Macrolide</td>
<td>Erythromycin and others</td>
<td>Inhibition of protein synthesis</td>
</tr>
<tr>
<td>Spiramycin</td>
<td>1999</td>
<td>Macrolide</td>
<td>Erythromycin and others</td>
<td>Inhibition of protein synthesis</td>
</tr>
<tr>
<td>Avilamycin</td>
<td>Orthosomycin</td>
<td></td>
<td>Everninomycin</td>
<td>Inhibition of protein synthesis</td>
</tr>
<tr>
<td>Avoparcin</td>
<td>1997</td>
<td>Glycopeptide</td>
<td>Vancomycin, teicoplanin</td>
<td>Inhibition of cell wall synthesis</td>
</tr>
<tr>
<td>Aracin</td>
<td>1997</td>
<td>Glycopeptide</td>
<td>Vancomycin, teicoplanin</td>
<td>Inhibition of cell wall synthesis</td>
</tr>
<tr>
<td>Efrotomycin</td>
<td>Elflamycin</td>
<td></td>
<td></td>
<td>Inhibition of protein synthesis</td>
</tr>
<tr>
<td>Olaquindox</td>
<td>1999</td>
<td>Quinoxaline</td>
<td></td>
<td>Inhibition of DNA synthesis</td>
</tr>
<tr>
<td>Carboxox</td>
<td>1999</td>
<td>Quinoxaline</td>
<td></td>
<td>Inhibition of DNA synthesis</td>
</tr>
</tbody>
</table>
Examples of ionophores that either are used commercially or have been investigated for use in growing animals are monensin, lasalocid, tetronasin, salinomycin, lysocellin, narasin, nigericin, laiddomycin and valnemycin.

There are three major areas of animal metabolism that can contribute to or account for improvement of efficiency of production by ionophores: 1) increased efficiency of energy metabolism in the rumen and(or) animal; 2) improved nitrogen metabolism in the rumen and(or) animal and 3) retardation of feedlot disorders, especially lactic acidosis (chronic) and bloat. The most consistent observation upon ionophore feeding is the increased molar proportion of propionic acid. This acid improves efficiency of production in ruminants 39. Ionophores improve and increase efficiency in a number of different ways.

In cattle, methane can represent as much as a 12% loss of feed energy 47. Ionophores can decrease this loss by as much as 30% 48. Ionophores also increase the VFA propionate and decrease the VFA acetate 49. Propionate is commonly known as the best VFA acetate 39. Propionate has the highest ability to be utilized from feed energy for productive purposes 40. One study indicated that incorporating ionophore in the diet of steers resulted in a 76% increase in propionate production, a 16% decrease in acetate production and a 14% decrease in butyrate production 41. Such shifts in rumen fermentation should enhance the overall productive efficiency of ruminants 42.

Ionophores decrease protein deamination in the rumen. This increases the effectiveness of bypass protein in cattle. Bypass protein has been demonstrated to increase from 22 to 55% in various experiments 39. Bypass protein is protein that is not broken down in the rumen but instead is digested in the ileum of the small intestines. The basic effect of ionophores is to alter the flow of cations across cell membranes 43. This leads to a reduction in Gram-positive bacteria 44. Gram-positive bacteria are known as the cause of bloat and other digestive problems associated with high carbohydrate diets.

Ionophores decrease dietary problems from high carbohydrate diets 45. Ionophores are able to improve feed conversions and enable cattle to get more metabolizable energy from feed; 20% more metabolizable energy was available when ionophores were used in the diet 39. One study indicates ionophores feed in combination with fat supplementation caused increased lipid flow to the small intestines. The basic effect of ionophores is to alter the flow of cations across cell membranes 43. This leads to a reduction in Gram-positive bacteria 44. Gram-positive bacteria are known as the cause of bloat and other digestive problems associated with high carbohydrate diets.

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Dose</th>
<th>Ketone bodies</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Canada</td>
<td>36</td>
<td>16 ppm</td>
<td>\textbackslash{}Total Ketones &amp; \textbackslash{}BHB(S) only for 33 ppm</td>
<td>NS</td>
</tr>
<tr>
<td>1993</td>
<td>S. Africa</td>
<td>60</td>
<td>10 ppm</td>
<td>BHB (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>1993</td>
<td>U. S.</td>
<td>47</td>
<td>150 mg</td>
<td>\textbackslash{}BHB (S) only for 300 and 450 mg</td>
<td>NR</td>
</tr>
<tr>
<td>1994</td>
<td>Australia</td>
<td>16</td>
<td>CRC</td>
<td>\textbackslash{}BHB (S)</td>
<td>\textbackslash{}(Trend)</td>
</tr>
<tr>
<td>1996</td>
<td>Zealand</td>
<td>120</td>
<td>CRC</td>
<td>BHB (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>1997</td>
<td>U.K.</td>
<td>300</td>
<td>mg</td>
<td>\textbackslash{}BHB (S)</td>
<td>NR</td>
</tr>
<tr>
<td>1997</td>
<td>Australia</td>
<td>24</td>
<td>CRC</td>
<td>\textbackslash{}BHB (S)</td>
<td>\textbackslash{}(S) Preecalcing</td>
</tr>
<tr>
<td>1997</td>
<td>Canada</td>
<td>1010</td>
<td>CRC</td>
<td>\textbackslash{}BHB (S), Milk ketones (S)</td>
<td>\textbackslash{}(S)</td>
</tr>
<tr>
<td>1997</td>
<td>Canada</td>
<td>52</td>
<td>CRC</td>
<td>\textbackslash{}BHB (S)</td>
<td>\textbackslash{}(S)</td>
</tr>
<tr>
<td>1998</td>
<td>Netherlands</td>
<td>80</td>
<td>300 mg</td>
<td>\textbackslash{}BHB (S), \textbackslash{}ACAC (S)</td>
<td>\textbackslash{}(S)</td>
</tr>
</tbody>
</table>

\(N\) = number of animals in the study. Dose mg = mg/cow/day, CRC = controlled release capsule (335 mg/cow/day). ppm = concentration in mg/kg of total feed. \(\text{A sub sample from each herd was evaluated, NS = not statistically significant, S = statistically significant (P < 0.05), NR = Not reported, BHB = beta-hydroxybutyrate, ACAC = acetoacetate.}

### Risks of antimicrobial growth promoters

The use of growth-promoters is largely a problem of intensive farming methods and the problems caused by their use are largely those of developed rather than developing countries in response to the emergence of antibiotic resistance.

Currently, there is controversy surrounding the use of growth promoters for animals destined for meat production, as overuse of any antibiotic over a period of time may lead to the local bacterial populations becoming resistant to the antibiotic. This is it not an invariable rule: \textit{Streptococcus pyogenes} remains sensitive to penicillins after over sixty years of clinical use but such examples are, however, very rare. Undoubtedly, the medical exploitation of antimicrobial chemotherapy, particularly to treat human infections, has imposed an enormous selection pressure on formerly sensitive bacteria to acquire genetic elements that code for resistance to antibiotics.

It should be noticed that antimicrobial agents should not be used for growth promotion if they are used in human therapeutics or are known to select for cross-resistance to antimicrobial drugs used in human medicine 49. Antimicrobial agents are too valuable to be used as a tool in animal production because any antimicrobial drug may be useful for human therapy in the future even if not used therapeutically today. Adherence to the World Health Organization recommendations 48 will ensure a systematic approach toward replacing antimicrobial growth promoters with safer non-antimicrobial drug alternatives. The EU countries entered this process in December 1998 when four growth promoters (tylosin, spiramycin, bacitracin and virginiamycin) were banned because of their structural relatedness to therapeutic antimicrobial drugs used for humans 49.

However, concerns about using antibiotics in livestock are growing. In 1995, the WHO set up a special working group to assess this problem. More recently, the treatment of enteric diseases in children living in developing countries was found to be increasingly difficult, due to the spreading of resistance to antibiotics among the human intestinal pathogens. The magnitude of the medical and public health impact of antimicrobial use in food animal production is not known. It is unrefuted that the use...
of antimicrobials leads to the selection of resistant bacteria and that the scope of the emerging problem depends, among other things, on duration of exposure to and concentration of the antimicrobial. Residues of antimicrobial agents in food of animal origin in excess of the agreed acceptable minimum residue levels (MRLs) may contribute to generation of resistance in bacteria in humans. However, the current evidence suggests that the risk is low. Of more concern may be that such residues could indicate inappropriate use of antimicrobials by producer. The medical consequences of resistance acquisition in bacteria of animal origin are of concern to the public several European countries have restricted or banned the use of antibiotics as growth promoters 59.

**Risks of ionophores growth promoters:** Generally, ionophores have been found safe and effective in the target animals receiving recommended dosage levels 57, 58. However, toxic syndromes can result from over dosage and misuse situations. The use of ionophores as coccidiostats and growth promotants has resulted in the occurrence of toxicoses in target and nontarget species. Clinical and pathologic effects of ionophore poisoning are caused by bioactivity and damage to excitable tissues such as cardiac muscle, skeletal muscle, smooth muscle and the nervous system. Ionophore toxicoses are often related to errors in feed mixing, so the practitioner should give primary importance to the removal of suspect feeds and testing to confirm excessive exposure.

Care must be exercised in the diagnosis of ionophore toxicoses since clinical signs and lesions are not pathognomic. Ionophores toxicity was reported in cattle 52, horses 53, ostriches 54 and camels 55. However, camels were found to be particularly sensitive to ionophores compared with other animals. Toxic effects of ionophores are directed mainly against skeletal and/or cardiac muscle as a result of disturbances in muscle cell calcium homeostasis followed by increased intracellular Na+ concentration. Equines are much more susceptible to cardiac muscle damage than other species and the effects are reported to be persistent. Ionophores should not be used in birds laying eggs for human consumption due to the potential for residues to enter the food chain and the possibility of human toxicity. Ionophores are not used in human medicine due to their potent cardiovascular effects. Toxicity values of three important ionophores are presented in Table 3.

**Table 3.** Reported toxicity of ionophores (LD50 mg/kg of body weight).

<table>
<thead>
<tr>
<th>Ionophore</th>
<th>Horse</th>
<th>Cattle</th>
<th>Sheep</th>
<th>Chicken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monensin</td>
<td>2 - 3</td>
<td>20 - 80</td>
<td>12</td>
<td>200</td>
</tr>
<tr>
<td>Salinomycin</td>
<td>0.6</td>
<td>n/a</td>
<td>n/a</td>
<td>44.3</td>
</tr>
<tr>
<td>Lasalocid</td>
<td>21.5</td>
<td>50 - 150</td>
<td>75 – 350</td>
<td>71.5</td>
</tr>
</tbody>
</table>

Source: American Board of Veterinary Toxicologists (www.abvt.org/isonp.html).

At present, there is no antidote or treatment for toxicoses induced by the ionophores. Judicious use, avoidance of overdosing and adherence to species recommendation will help prevent the occurrence of adverse effects associated with this class of compounds.

**Probiotics as Growth Promoters**

Probiotics are live microorganisms capable of inducing a beneficial effect on the balance of microorganisms in the digestive tract 60. With the appearance of the first problems related to the use of antibiotics, the possibility of using probiotics as growth promoters began to be seriously considered for 84 scientific purposes 57, 58. With Directive 93/113, the EU acknowledged the validity of this category of products as “additives”, in that they improve the production performance and the quality of products of animal origin.

One of the most important advantages of such additives is the absence of undesired antibiotics residues in meat, milk and eggs. A first tentative list of products authorized in the different EU countries is reported in 1996. These products are capable of favouring the development of useful microorganisms and affecting the adhesion of undesired or pathogenic microorganisms to the gut walls 59. It is not only a matter of mechanically controlling the competition between microorganisms, shifting it towards those that are regarded as useful. It is rather a question of acting on the metabolism of microorganisms and of the gut wall, in order to control the metabolic activity of the digestive tract as a whole. It is therefore necessary to act nutritionally on the digestive tract microorganisms by way of increasing the useful microorganisms, perhaps via their exogenous supply, at the same time providing the compounds which may favour competition with the undesired microorganisms and positively control metabolism. Delzenne and Roberfroid 60 provided the scientific background for the characterization of such feedstuffs as prebiotics in the sense of “indigestible dietary ingredients which positively affect the host by beneficially and selectively stimulating the growth and/or activity of a limited number of bacteria”. Prebiotics act by stimulating the microorganisms which are present in the intestinal tract and not by integrating them, as is the case for probiotics 61. Pre- and probiotics do not exclude each other’s function and can or must be used simultaneously in order to obtain a powerful synergistic effect 62.

Probiotics are now used in ruminants to manipulate certain biochemical events and the microbial composition of the rumen. It was found that feeding steers with rations added with cells from *S. cerevisiae* reduces the production of lactate and stabilizes the pH. This is may be due to a stimulating action on the bacteria which use lactic acid, e.g. *Selenomonas ruminantium* 63 or *Megasphaera elsdenii* 64. It was also found that stabilization of ruminal pH improves production performance by stimulating *S. ruminantium* 63. An increase in the use of lactate in *S. ruminantium* can be obtained by using products based on *Aspergillus oryzae* 65.

**Chemical Probiosis**

Several molecules may play a pre-biotic role without using the energy and protein sources in the same fashion as microorganisms and have different needs for micronutrients and vitamins compared with microorganisms. These molecules include fructo-oligosaccharides (FOS), gluco-oligosaccharides (GOS), manno-oligosaccharides (MOS), galacto-oligosaccharides (GAS) and xylo-oligosaccharides (XOS). They may be derived from plant origin (FOS and galacto-oligosaccharides), from enzymatic polysaccharide hydrolysis (FOS and XOS) or be re-synthesized *de novo* (FOS, GOS, GAS). They promote the development of certain microbial groups; in fact it is therefore possible to stimulate the growth of special microbial species through the supply of certain substrates.

In ruminants, interesting results were obtained, both *in vivo* and *in vitro*, with the use of peptides 66 or amino acids and organic
Acids As the main category of probiotics, oligosaccharides have attracted a great deal of commercial attention; several types are currently produced and used as “additives” for breeding animals: Their limited inclusion in the diet (usually 0.1-0.3%) may improve weight gain, the feed conversion ratio and the health status. The size of such effects, however, is affected by numerous factors such as the type of “additive”, the age of the animals, the species and the breeding conditions. In the field of monogastric nutrition, the use of fructo-oligosaccharides (FOS) gave good results in rabbits.

Conclusions
Antimicrobial agents and hormones are potent growth promoters provided that the target animals receive recommended dosage levels and side effects, especially antibiotic resistance, are avoided by using growth promoter antibiotics not designed for human use. However, different approaches for the use of pro- and prebiotics have been suggested and promising non-risky application is achieved. Their inclusion in feedstuffs should designed so as to feature a pharmacological characteristic that enhance the immunity of the animal and to help in minimizing the use of the conventional antibiotics in prevention and treatment of diseases of domestic animals.

Future developments for ruminants include 1) manipulation of rumen fermentation by non-conventional rumen-protected oligosaccharides (fructans and mananns) to modulate the microbial population and activity in the rumen; 2) increased competitiveness between genetically modified ruminal microorganisms; 3) controlling the gut environment to favour the growth of important microorganisms which are usually present in small number and their oral administration; 4) animal breeding and selection programs; 5) administration of trace elements like Cu, Zn and Se that may act as immuno stimulants and antioxidants.

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