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Current situation and future perspectives of the use of antibiotics as growth promoters

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SUMMARY - Antibiotics are used for three major purposes in domestic animals: therapy, to treat an identified illness; prophylaxis, to prevent illness in advance; and performance enhancement, to increase feed conversion, growth rate or yield. It would be assumed that the antibiotics change the balance of the intestinal flora in a way that promote the animal growth. It is likely that the growth promoting effect of the antibiotic is associated with its inhibitory effect on intestinal microbes. The antibacterial feed additives, through their antimicrobial effects, will alleviate immune system challenges from the intestinal tract on the immune system. Although, it is often assumed that resistance observed in animal bacteria is entirely a result of the use of therapeuticals, it was suggested that the feeding of antibiotics for growth promotion purposes was also contributory. This will be of significance only if the organisms themselves are pathogens, if the resistance is transmissible *in vivo* to pathogens and if there is cross-resistance with therapeutic antibiotics resulting in a disease which may became more difficult to treat. It is recommended that antibiotics for nutritional use should be restricted to those which are of economic value to livestock production, have little or no implication as therapeutic agents in man or animals, and which do not impair the efficacy of therapeutic antibiotics through the development of resistant organisms. In the European Union, the legal use of antibiotic or chemotherapeutic (synthetically produced substances) feed additives requires an approval by a Community procedure as layed down in the Council Directive 70/524/EEC and its amendments. This Council Directive has been modified by the Council Directive 96/51/EEC (5th amendment of the EU Council Directive 70/524/EEC). The approved additives are classified as follows: Annex A (Part A including antibiotics, coccidiostats and other medicinal substances, growth promoters; and Part B including trace elements: copper, selenium, vitamins, provitamins and well-defined substances with similar effects); Annex B (Chapters I and II, additives linked to a person responsible for putting them into circulation, inserted in Annex I before 1-1-88 and after 31-12-87; Chapter III, additives linked to a person responsible for marketing, inserted in Annex II before 1-4-98); Annex C (Part I, additives subject to authorization linked to the person responsible for putting them into circulation, antibiotics, coccidiostats and other medicinal substances and growth promoters; Part II, other additives). The Council 87/153/EEC and Commission 94/40/EC Directives fixing guidelines for the assessment of additives, the Section IV outlines that if the active substance possesses antimicrobial activity at feed concentration level, the MIC should be determined in various pathogenic and non-pathogenic, Gram-negative and Gram-positive, endogenous and exogenous bacteria relevant to the target species as well as it will provide studies on the cross-resistance to therapeutic antibiotics. The last draft of amending the Council Directive 87/153/EEC states that the environmental studies are intended to permit the assessment of the risk. In the near future, it will also be necessary to perform residue studies for the antimicrobial feed additives including kinetics of marker residues in target tissues for setting the withdrawal periods on the basis of the MRLs.

Key words: Antimicrobial feed additives, microbiological risk, residues and environmental assessment.

RESUME - *"Situation actuelle et perspectives futures pour l'utilisation d'antibiotiques comme promoteurs de croissance". Les antibiotiques sont utilisés chez les animaux domestiques principalement avec trois propos : thérapeutique, pour traiter une maladie connue, prophylactique, pour prévenir une maladie en avance, et productif, pour augmenter l'amélioration du taux de croissance en production animale. Par rapport à cette dernière propriété, on peut présumer que les antibiotiques changent l'équilibre de la flore intestinale de façon que la croissance de l'animal se voie favorisée. Il semble que cet effet de l'antibiotique promoteur de la croissance est associé avec son effet inhibiteur sur les bactéries intestinales. L'effet antimicrobien des additifs antibiotiques va pallier les réponses immunitaires du tractus intestinal. Bien que le plus souvent on a assumé que les résistances bactériennes observées chez les animaux sont le résultat de l'utilisation des antibiotiques thérapeutiques, on a suggéré que les additifs antibiotiques comme promoteurs de la croissance pourraient aussi être responsables de ces résistances. Ceci peut être significatif si les microorganismes sont pathogènes, si la résistance est transmissible* in vivo *à d'autres pathogènes et s'il existe une résistance croissée avec d'autres antibiotiques thérapeutiques ce qui ferait qu'une maladie soit plus difficile de traiter. On recommande que les antibiotiques d'emploi nutritionnel soient restreints à ceux qui sont économiques en production animale, ceux qui sont peu ou non impliqués comme produits thérapeutiques chez l'homme ou l'animal, et ceux qui ne nuissent pas l'efficacité*

des antibiotiques thérapeutiques par le développement d'organismes résistants. Dans l'Union Européenne, l'emploi légal des additifs dans l'alimentation des animaux, soit antibiotiques ou chimiothérapeutiques (substances synthétiques), requiert une approbation par un procédé Communitaire selon la Directive du Conseil 70/524/CEE et ses modifications. Cette Directive du Conseil a été modifiée par la Directive du Conseil 96/51/CE (5ème modification de la Directive du Conseil EU 70/524/CEE). Les additives approuvés se classent comme : Annèxe A (Partie A, qui inclue : antibiotiques, coccidiostatiques et autres substances médicamenteuses and facteurs de croissance ; et Partie B, qui inclue les oligo-éléments : cuivre, selenium, vitamines, provitamines et substances à effet analogue chimiquement bien définies) ; Annèxe B (Chapitres I et II, additifs liés à un responsable de la mise en circulation inscrits a l'annexe I avant le 1-1-88 et après 31-12-87 ; Chapitre III, additifs liés à un responsable de la mise en circulation inscrits à l'annexe II avant le 1-4-98) ; Annèxe C (Partie I, additifs faisant l'objet d'une autorisation liée au responsable de la mise en circulation : antibiotiques, coccidiostatiques et autres substances médicamenteuses and facteurs de croissance ; Partie II, autres additifs). Les lignes directrices fixées par les Directives du Conseil 87/153/CEE et de la Commission 94/40/CE pour l'évaluation de la sécurité des additifs, le chapitre IV remarque que si la substance possède activité antimicrobienne à la concentration inclue dans l'aliment, on devra déterminer les CMI sur les bactéries pathogènes et non pathogènes, gram-négatives et gram-positives, endogènes et exogènes, d'importance pour les animaux cibles ainsi qu'il faudra proportionner des études de résistance croissée aux antibiotiques thérapeutiques. Le dernier projet de modification de la Directive du Conseil 87/153/CEE établit que les études sur l'environnement sont convenables puisqu'ils permettent l'évaluation du risque. Prochainement, il faudra aussi réaliser des études de résidus pour les additifs dans l'alimentation des animaux qui incluront la cinétique du résidu marqueur dans les tissus cibles en fixant les delais d'attente selon les LMR.

Mots-clés : *Antimicrobiens dans l'alimentation des animaux, risque, microbiologique, résidues et évaluation sur l'environnement.*

Antibacterial growth-promoter feed additives

Antibiotics are chemical substances produced by various species of micro-organisms (bacteria, fungi, actinomycetes) which kill or inhibit the growth of a microorganisms. Antibiotics also occur in nature as metabolites of certain moulds and bacteria.

The word "antibiotic" has tended to became synonymous with antibacterial or antimicrobial. This is unfortunate because many antibiotics, as well as having direct effect at a cellular level on the host animal, also have activity against a variety of other living organisms (i.e., virus, fungi, helminths, protozoa). Antibiotics differ markedly in physical, chemical, and pharmacological properties, antibacterial spectra, and mechanism of action.

During the latter part of the nineteenth century and the earlier years of the twentieth century, several antimicrobial substances were demonstrated in bacterial cultures, and some were even tested clinically but discarded because they proved to be highly toxic. The modern era of chemotherapy of infection started with the clinical use of sulphanilamide in 1936. The golden age of antimicrobial therapy began with the production of penicillin in 1941, when this compound was mass-produced and it was possible to initiate an limited clinical trial. In this year Florey and his associates opened the way for the practical use of penicillin which was discovered by Fleming in 1928. Three years latter, in 1944, Waksman discovered streptomycin from actinomyces in soil. Thus, the era of antibiotics began.

Antibiotics are used for three major purposes in domestic animals: (i) therapy, to treat an identified illness; (ii) prophylaxis, to prevent illness in advance; and (iii) performance enhancement, to increase feed conversion, growth rate or yield. The growth-promoting properties of antimicrobials for farm animals were discovered in the late 1940s. In 1950, Stockestad, in the United States, confirmed that the growth of animals, such as piglets and chiks, was promoted when a small amount of an antibiotic was supplemented in the feed. At this time, the mechanism of growth promotion was not clearly understood. However, taking into account that the antibiotics have to be taken orally to be effective, and that the growth promoting antibiotics do not exert a favourable influence in the germ-free animals (Coates *et al.*, 1963), it would be assumed that the antibiotics would change the balance of the intestinal flora in a way that promote the animal growth.

The use of antibiotics in feedingstuffs was increased in line with the development of the intensive animal production. The practice of feeding subtherapeutic doses of antibiotics was readily adopted

and antibacterial feed additives soon became an integrated part of the systems developed in the animal industry. Of special interest is the usage of a convenient method for administering the pharmacologically active substance to large numbers of intensively raised animals to ensure that each animal receives an appropriate oral dose.

Antibiotics are now commonly included in the feed of chickens, turkeys, pigs, veals, cattle, and fur-bearing animals. For growth promoting purposes, they are included in the feed at low levels where they also improve the rate of live weight gain and the efficiency of feed utilization. For therapeutic purposes, they are used in feed usually at higher levels for their antibacterial, antifungal, anthelmintic, or antiprotozoal effects. The use of growth promoters in feeds for growth enhancement can give improvements in daily weight gain and feed conversion efficiency of the order of 3-5% in broilers, 4-5% in pigs and veal calves and as much as 10% in beef cattle. The main advantages to producers from regular use of the growth promoters may be: economic benefits, greater uniformity of growth, stabilization of gut flora, and maintenance of the animal health in the face of environmental stress (to this extent they are acting prophylactically, i.e., reduction in morbility).

In the European Union, the legal use of antibiotic or chemotherapeutic (synthetically produced substances) feed additives requires an approval by a Community procedure as layed down in the Council Directive 70/524/EEC and its amendments. Feed additives are included into Annex I of this Directive can be used in all Member States according to the provisions outlined. Additives included in Annex II may be the subject of national provisional authorizations. For inclusion into Annex I, available data on efficacy and safety have to be evaluated by different independent and official scientific boards of the EU. Only those substances which have been proved being efficient in growth-enhancing and being safe for the consumers of food of animal origin, for the target animals, for the workers handling the feed additives and for the environment will be approved under Annex I. This Council Directive has been modified by the Council Directive 96/51/EEC (5th amendment of the EU Council Directive 70/524/EEC). The approved additives are classified as follows: Annex A (Part A including antibiotics, coccidiostats and other medicinal substances, growth promoters; and Part B including trace elements: copper and selenium and vitamins, provitamins and well-defined substances with similar effects: vitamins A and D); Annex B (Chapter I, additives linked to a person responsible for putting them into circulation, inserted in Annex I before 1 January 1988; Chapter II, additives linked to a person responsible for putting them into circulation, inserted in Annex I after 31 December 1987; Chapter III, additives linked to a person responsible for marketing, inserted in Annex II before 1 April 1998); Annex C (Part I, additives subject to authorization linked to the person responsible for putting them into circulation, antibiotics, coccidiostats and other medicinal substances and growth promoters; Part II, other additives: antioxidant substances, flavouring and appetizing substances, emulsifying and stabilizing agents, thickeners and gelling agents, colorants, including pigments, preservatives, vitamins, provitamins and chemically well-defined substances having similar effect, trace elements, binders, anti-caking agents and coagulants, acidity regulators, enzymes, and micro-organisms).

Antibacterial growth-promoting feed additives approved in the European Union

The antibacterial growth promoter feed additives which are approved in the EU according the EC Directives are the following: ardacin, avilamycin, bacitracin, flavophospholipol, monensin, salinomycin, spiramycin, tylosin, virginiamycin, carbadox and olaquindox.

The antibacterial growth promoters are belonging to several groups of antibiotics not being structurally related and exerting their antibacterial activity by different mechanisms either by disturbing the bacterial cation homeostasis or by inhibiting the formation of an intact bacterial wall or inhibiting the bacterial synthesis of proteins or DNA (Table 1). Except the quinoxalines, these substances have a narrow antimicrobial spectrum restricted to Gram-positive bacteria. Furthermore, the ionophores possess an antiprotozoal effect leading to their additional use as coccidiostatic feed additives mainly in poultry. The growth-promoting effect of the antibiotics, and the synthetic products carbadox and olaquindox, is supposed to be primarily caused by a stabilization of the intestinal microflora improving the feed conversion and reducing the formation of toxins (Hendrickx *et al.*, 1982).