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THE PUBLIC HEALTH ASPECTS OF THE USE OF ANTIBIOTICS IN FOOD AND FEEDSTUFFS

Report of an Expert Committee

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EXPERT COMMITTEE ON
PUBLIC HEALTH ASPECTS OF THE USE OF ANTIBIOTICS
IN FOOD AND FEEDSTUFFS

Geneva, 11-17 December 1962

Members : *

Dr W. T. C. Berry, Senior Medical Officer, Ministry of Health, London, England

Dr C. G. Durbin, Veterinary Medical Director, Division of Veterinary Medicine, Bureau of Medicine, Food and Drug Administration, Washington, D.C., USA

Professor R. Ferrando, Director, Veterinary College of Alfort (Seine), France (*Vice-Chairman*)

Professor L. P. Garrod, Radlett, Herts. ; formerly Director, Department of Bacteriology, St Bartholomew's Hospital, London, England (*Chairman*)

Professor H. S. Goldberg, Department of Microbiology, School of Medicine, University of Missouri, Columbia, Mo., USA (*Rapporteur*)

Dr A. Manten, Head, Antibiotics Department, National Institute of Public Health, Utrecht, Netherlands

Professor A. C. Sarkisov, Head, Antibiotics Laboratory, All-Union Institute for Experimental Veterinary Medicine, Moscow, USSR

Representative of the Food and Agriculture Organization :

Dr G. Kapsiotis, Food Technologist, Food Science and Technology Branch, Nutrition Division, FAO, Rome, Italy

Secretariat :

Dr C. Agthe, Scientist, Nutrition/Food Additives, WHO, Geneva (*Secretary*)

Dr M. G. Allmark, Head, Section of Pharmacology and Toxicology, Food and Drug Directorate, Ottawa, Canada (*Consultant*)

Dr Ella M. Barnes, Principal Scientific Officer, Microbiology Section, Low Temperature Research Station, Cambridge, England (*Consultant*)

Dr E. H. Kampelmacher, Head, Laboratory for Zoonoses, National Institute of Public Health, Utrecht, Netherlands (*Consultant*)

Dr J. Tiews, Institute for Animal Physiology and Nutrition, University of Munich, Germany (*Consultant*)

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* Unable to attend : Professor J. Brüggemann, Institute for Animal Physiology and Nutrition, University of Munich, Germany.

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Report of an Expert Committee

INTRODUCTION

The WHO Expert Committee on the Public Health Aspect of the Use of Antibiotics in Food and Feedstuffs met in Geneva from 11 to 17 December 1962, and was opened by Dr P. Dorolle, Deputy Director-General, on behalf of the Director-General. Professor L. P. Garrod and Professor R. Ferrando were unanimously elected Chairman and Vice-Chairman respectively. Professor H. S. Goldberg agreed to act as Rapporteur.

As a result of the recommendations of the Joint FAO/WHO Conference on Food Additives held in September 1955 [1] six Joint FAO/WHO Expert Committees on Food Additives have met and issued the following reports: "General Principles Governing the Use of Food Additives: First Report",[2] " Procedures for the Testing of Intentional Food Additives to Establish their Safety for Use: Second Report ",[3] " Specifications for Identity and Purity of Food Additives (Antimicrobial Preservatives and Antioxidants): Third Report ",[4] "Specifications for Identity and Purity of Food Additives (Food Colours): Fourth Report ",[5] "Evaluation of the Carcinogenic Hazards of Food Additives: Fifth Report ",[6] and "Evaluation of the Toxicity of a Number of Antimicrobials and Antioxidants: Sixth Report ".[7]

The present Committee was convened on recommendations made in the sixth report of the Joint FAO/WHO Expert Committee on Food Additives, its terms of reference being to discuss the public health problems that may arise in connexion with the increasing use of antibiotics in animal feeds, for food preservation, and in plant disease control.

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[1] *FAO Nutrition Meetings Report Series*, 1956, No. 11; *Wld Hlth Org. techn. Rep. Ser.*, 1956, **107**.

[2] *FAO Nutrition Meetings Report Series*, 1957, No. 15; *Wld Hlth Org. techn. Rep. Ser.*, 1957, **129**.

[3] *FAO Nutrition Meetings Report Series*, 1958, No. 17; *Wld Hlth Org. techn. Rep. Ser.*, 1958, **144**

[4] Unpublished working document WHO/Food Add./15.

[5] Unpublished working document WHO/Food Add./17.

[6] *FAO Nutrition Meetings Report Series*, 1961, No. 29; *Wld Hlth Org. techn. Rep. Ser.*, 1961, **220**.

[7] *FAO Nutrition Meetings Report Series*, 1962, No. 31; *Wld Hlth Org. techn. Rep. Ser.*, 1962, **228**.

1. SCOPE OF THE PROBLEM

The addition of selected antibiotics to feeds has been shown to be effective in promoting the growth of livestock and this use is well documented in published reports from all over the world. Most livestock can achieve maximum weight in shorter time and at less cost when specific amounts of antibiotics have been incorporated in their diet.

In addition, benefits have been achieved in the preservation of certain processed and fresh foods by the utilization of antibiotics for the extension of shelf and storage life.

In spite of these well-defined non-medical uses of antibiotics, these procedures have not been universally adopted. Various investigators, regulatory agencies and governments have expressed concern about potential hazards to the public health. Over the years, various food additives have presented health threats and given cause to regret their use. It is therefore most important to examine carefully the effects of the use of antibiotics in food preservation and animal feedstuffs. With one-fifth of the world's food supply lost to spoilage and large numbers of the world's population currently underfed, it is clearly the duty of food producers to take advantage of all technological advances for increasing the food supply. On the other hand, they must be fully aware of the possible hazards, such as antibiotic hypersensitivity, toxicity and the production of bacterial resistance.

To examine this subject properly, it is necessary to study each antibiotic or antibiotic group separately and to relate its chemical, physical and biological properties to the food or feedstuff in which it has found an important application.

For the purposes of this report, an " antibiotic " is defined as a chemical compound produced by micro-organisms, capable of inhibiting other micro-organisms in minute concentrations. It is to be clearly distinguished from synthetic substances used for similar purposes.

2. CURRENT STATUS OF ANTIBIOTICS IN FOODS AND FEEDSTUFFS

2.1 Animal feeds

It is generally held that certain antibiotics are capable of stimulating the growth rate of a variety of livestock and of several kinds of fur-bearing animals. As a result, it is a widespread practice in many parts of the world to feed animals on antibiotic-containing rations. However, differences of opinion seem to exist as to which antibiotics are the most useful and at what levels they are to be used.

Further, the mechanism of this effect is not at present clearly understood.

2.1.1 *Animal species*

It appears to be generally accepted that the following animals benefit most from antibiotic feeding: poultry—with the exception of ducks and geese—swine, calves, beef cattle, lambs and fur-bearing animals such as mink. Antibiotic feeding is usually limited to young animals, and many authorities advocate restricting its use to the early period of growth.

2.1.2 *Antibiotics used*

The most frequently used antibiotics for the purpose of animal growth stimulation are penicillin, chlortetracycline and oxytetracycline. Although these three antibiotics are used to a much greater extent than all others combined, some use is also made of bacitracin, erythromycin, oleandomycin, spiramycin, streptomycin and tylosin.

2.1.3 *Antibiotic levels in feed*

In the early 1950's the antibiotic levels used in feeds varied from 5-15 p.p.m. Since then the tendency has been to increase the level of antibiotics. Levels of 100-200 p.p.m. and even higher are reported in the literature and appear better suited to the prevention or treatment of infection than to the purpose of growth promotion.

2.1.4 *Tissue residues from antibiotics in feed*

Feeding of growth-promoting levels of antibiotics of the order of 20 p.p.m. does not result in detectable antibiotics in meat. However, as feeding levels reach 100-200 p.p.m. the antibiotic may become detectable in the tissues.

2.2 Antibiotic residues in milk

When antibiotics are administered parenterally in full therapeutic doses some excretion occurs in the milk. A much more important cause of the presence of antibiotics in cow's milk is intramammary injection via the teat canal for the treatment of mastitis. Quantities of the order of 0.15-0.3 g are injected into each affected quarter. Although some part of this dose is absorbed much of it escapes later in the milk in diminishing amounts. The duration of this excretion varies with the nature of the preparation : watery suspensions may be almost wholly excreted in 48 hours, whereas if oily suspensions are used the antibiotic may still be present in the milk after 96 hours. The number of such treatments varies from 1 to 3 at intervals of 1-2 days.

Benzyl penicillin in the form of the procaine compound is the antibiotic most commonly used, although with the present diminution in the frequency of streptococcal mastitis and an increase in the staphylococcal form—usually a penicillin-resistant strain—this treatment is losing some of its former effect. Other antibiotics administered in the same way are tetracyclines, chloramphenicol, mixtures of penicillin and streptomycin, bacitracin, colistin, neomycin, polymyxin B, and mixtures of the last four substances.

The undesirable effects of the presence of penicillin in milk are solely of an allergic nature. In the previously sensitized person, the consumption of milk containing even very small quantities of the antibiotic causes an unpleasant urticarial reaction; more serious reactions appear to be uncommon, but their possibility cannot be excluded. It has also been suggested that the consumption of such milk may actually cause sensitization, but this has not been proved.

Small amounts of chlortetracycline or oxytetracycline consumed occasionally are innocuous so far as is known. Streptomycin may cause sensitization, however, and a sensitized person might react to milk containing it. Chloramphenicol is in a different category because it is alone among the major antibiotics in being capable of exerting a fatal toxic effect when given in normal therapeutic doses. It is not known why a small proportion of treated patients suffer this damage to the bone marrow, but it has been suggested that one factor may be " sensitization " by previous exposure. Such exposure may result from the consumption of small quantities in milk. It is impossible to disprove this, and the presence of chloramphenicol must therefore be regarded as potentially highly dangerous, calling for exceptional measures (see section 4.3.3, page 21).

2.3 Food preservation with antibiotics

There is ample evidence of the efficacity of selected antibiotics in increasing the shelf or storage life of several kinds of processed and fresh foods. However, these procedures have not, as yet, been adopted widely because of the potential public health hazards.

2.3.1 *Antibiotics used*

At the present time the antibiotics permitted for use in food preservation in certain countries include chlortetracycline, oxytetracycline, nisin and nystatin.

2.3.2 *Foods preserved with antibiotics*

The two most important foods preserved in this way are fish and poultry, for which tetracyclines are used. The method of application to poultry is by immersing them in slush ice containing the antibiotic. Antibiotics may be applied to fish from the ice in the ship's hold, the antibiotic being released as the ice melts; tetracyclines may be applied to fish fillets by dipping them in a solution of the antibiotic. A few countries have permitted the surface treatment of beef carcasses combined with injection of the antibiotic into the carcass immediately prior to slaughter. Whales can be preserved either by injecting them intraperitoneally with antibiotic solutions after killing or by incorporating an antibiotic in the head of the harpoon. In the latter case, the antibiotic spreads through the whale's flesh during the time between harpooning and death.

Of less importance are the use of nisin in processed cheese and to control thermophilic spore-producing bacteria in certain canned foods in which the hazard of botulism either does not arise because of acid pH or has been eliminated by the application of sufficient heat. In some parts of the world nystatin is applied to the skin of bananas to control moulds. All these uses are permitted in some countries but not in others.

2.3.3 *Antibiotic residues in foods*

Some of the above-mentioned uses result in antibiotic residues on the food. The chlortetracycline or oxytetracycline residue on poultry, however, is rarely higher than 7 p.p.m. and the antibiotic is degraded during cooking. In fish and sea-food these antibiotics achieve levels of 5-10 p.p.m., but most of the activity is destroyed during cooking processes. The amounts remaining after cooking are calculated to be < 1.0 p.p.m.

Nisin is also found in detectable quantities in cheeses and some canned foods which have been processed with this antibiotic. The levels are less than 20 units/g (1 unit = approx. 1/40 of a microgram). Nystatin may be found in traces on the skin of treated bananas but does not penetrate to the fruit.

2.4 Antibiotics in plant disease control

Laboratory and field experiments have established the effectiveness of certain antibiotics in the treatment of some bacterial and mycotic diseases of plants.

2.4.1 *Plants treated with antibiotics*

Among the plants treated with antibiotics for the purpose of controlling microbial disease are apples, beans, celery, cucumber, hops, pears, peppers, lettuce, potatoes, sesame, tomatoes, walnuts and cherries.

2.4.2 *Antibiotics used*

Streptomycin is the antibiotic most often used to control bacterial disease of plants. In some formulations it is supplemented by a smaller amount of oxytetracycline. The ratio in this instance is streptomycin 15 parts to oxytetracycline 1.5 parts.

Mycotic disease of lettuce is controlled with griseofulvin, and cherry leaf spot, another fungal disease, with cycloheximide.

2.4.3 *Residues*

The manner of application of these antibiotics to plants is such that no residue results on the part of the plant that is to become food. All treatments are applied before fruit is matured or to vegetables in an early stage of growth or only to plant beds for preventive purposes.

3. POSSIBLE HAZARDS

3.1 Toxicity

The outstanding difference between most antibiotics and other preservatives is their much greater specificity ; the medically useful antibiotics are typically of low toxicity for man, but highly toxic (or inhibitory) to micro-organisms. Additional advantages are that they may be largely destroyed during cooking (tetracyclines) or digestion (nisin). It follows that the conventional method of assessing the safety of preservatives, by comparing the amounts likely to be consumed with the amounts likely to produce harmful effects, is often inapplicable since no antibiotics are ingested. The likely residues in cooked fish are less than 1 p.p.m. ; a consumption of 300 g of fish daily would provide less than 0.3 mg, which is negligible in comparison with the amounts that have been fed to adults and children for medical and other reasons, and, on an even more extensive scale, to experimental animals. There are no data on the amounts of raw treated fish that might be eaten by individuals throughout the world, but again, the amounts of chlortetracycline and oxytetracycline likely to be consumed are negligible in relation to the amounts required to produce toxic symptoms. Though the degradation products of chlortetracycline and oxytetracycline have not been as fully investigated, some studies have been done on iso-chlortetracycline, one of these degradation products, and the amounts likely to be ingested are insignificant in comparison with the amounts fed to experimental animals without harm.

As regards the therapeutic or prophylactic use of other antibiotics, assuming that appropriate measures are taken to regulate the amounts of antibiotics present in animals at slaughter, and in milk, the amounts consumed should also be negligible.

In short, the Committee was unable to discern any hazard of simple toxicity to man resulting from the use of antibiotics in animal feeds, in the treatment of animals, or as preservatives in food, with the possible exception of chloramphenicol residues in milk, a subject dealt with elsewhere in this report.

3.2 Hypersensitivity

The nature of this hazard is theoretically twofold: individuals not previously sensitized might become so, or persons previously sensitized as a result, for example, of medical treatment with an antibiotic might develop reactions of hypersensitivity. Some antibiotics, such as nisin, are not used medically, but where an antibiotic is widely used in medicine, the occurrence of reactions in persons already sensitized is more likely, particularly as such persons sometimes react to very small doses.

The persons theoretically at risk fall into two main groups: those who apply the antibiotics, such as farmworkers, and those who consume traces in food. The exposure incurred by the farmer is likely to be substantially greater than that of the consumer.

Of the antibiotics used both in medicine and for feeds or as preservatives, penicillin, streptomycin and, to a lesser degree, oleandomycin, neomycin and novobiocin, appear from experience to be more likely than the others to lead to hypersensitivity. Thus, the traces of penicillin present in bulked milk have incontestably caused skin reactions in persons already sensitized through medical use. The possibility of streptomycin causing reactions was investigated in farmworkers using streptomycin sprays and dusts, but the results were entirely negative. This investigation did not, of course, exclude the possibility that reactions might occur in previously sensitized farmworkers using sprays or animal feeds containing streptomycin, but the members of the Committee were unaware of any instance in which this has occurred.

Of the medically important antibiotics, only chlortetracycline and oxytetracycline are in use as preservatives. Sensitization to tetracyclines is so rare that there have been few suitable subjects for investigation. However, insofar as tests have been done, they suggest very strongly that the consumption of tetracyclines used as preservatives involves no risk of allergic effect.

3.3 Bacterial resistance in relation to antibiotics in animal feedstuffs and food preservation

When considering the problem of bacterial resistance to antibiotics, a distinction should be made between (1) natural resistance and (2) acquired resistance.

3.3.1 *Natural resistance*

Many different types of bacteria are normally present in the intestinal flora of animals and a very varied microflora is also concerned in food spoilage. Amongst the many micro-organisms present, there are generally some species that are naturally resistant to a particular antibiotic. Contact with the antibiotic will inevitably lead to the selective multiplication of these resistant species.

3.3.2 *Acquired resistance*

A strain originally susceptible to a certain drug may lose this property on continued exposure to the drug. Two theories have been advanced to account for acquired drug resistance.

The *mutation theory* assumes that during multiplication of normally drug-sensitive micro-organisms small numbers of drug-resistant variants are formed by a process of spontaneous mutation. These variants occur in any sizeable population of micro-organisms even before any drug is introduced. However, the resistance does not become manifest until the population is brought into contact with some antibacterial substance. This does not affect the resistant mutants, but eliminates all drug-sensitive bacteria. In a suitable medium the survivors can multiply selectively and so give rise to a resistant culture.

The *adaptation theory* assumes that drug-resistance is due to a physiological adaptation (training) and therefore has a non-genetic cytoplasmic basis. This theory, however, is not widely accepted as having general applicability.

Accepting that the mutation theory provides a satisfactory explanation for the origin of microbial drug resistance, it is evident that resistance is not likely to occur (*a*) if the number of organisms involved is so small as practically to exclude the possibility of any resistant mutants being present, or (*b*) if there is no possibility of a selective multiplication of the mutants.

(*a*) As a rule, populations of yeasts, moulds, and protozoa are small in comparison with those of bacteria. Consequently, there is less chance of the former organisms developing resistance. However, bacterial populations (e.g., in the intestines of animals) are usually large, so that here the first condition for the occurrence of resistance, namely the presence of drug-fast mutants, is nearly always fulfilled.

(*b*) Three factors may affect the possibility of selective multiplication of mutants :

(*i*) Selective multiplication of resistant mutants will not occur if the concentration of an antibiotic is so low as not to inhibit the great majority of sensitive organisms occurring in any bacterial population. Consequently, sub-inhibitory concentrations of antibiotics do not induce resistance.

(ii) On the other hand, levels corresponding to the minimum inhibitory concentration or just exceeding these are, theoretically, most likely to cause resistance. At these levels, all sensitive bacteria are prevented from multiplying, whereas all drug-resistant mutants remain unaffected and are therefore able to take part in the formation of a resistant population.

(iii) Concentrations far exceeding the minimum inhibitory concentration may partially or completely inhibit the resistant mutants as well as the sensitive bacteria. As a result, there is less chance of a resistant population emerging.

In the case of penicillin and many other antibiotics, development of resistance usually occurs slowly and in a stepwise manner (*multi-step resistance*). With streptomycin and some other substances, resistance may develop more rapidly (*one-step resistance*).

3.3.3 *Bacterial resistance arising from the presence of antibiotics in feeds*

It has been stated in the above theoretical consideration that the emergence of resistance largely depends (*a*) on the concentration of the antibiotics to which the bacteria are exposed and (*b*) on the type of drug that is used.

An additional factor in the development of resistance in practice is the time during which the bacteria are in contact with the drug. Generally speaking, long-term antibiotic feeding increases the chance of resistance developing.

(*a*) Animal experiments as well as practical experience show that low dosages of antibiotics in the feed (20 p.p.m. or lower) are not frequently associated with rapid emergence of resistance of the intestinal microflora. If, in the long run, resistance occurs, it mostly tends to disappear on withdrawing the drug from the feed. When larger dosages are used, resistance increases and becomes less likely to disappear on withdrawing the drug.

(*b*) Of the drugs in common use in feeding practices, streptomycin has a higher tendency to cause resistance than penicillin and tetracyclines. The use of penicillin, on the other hand, does not usually result in the development of acquired resistance, but rather in the selection of naturally resistant strains, as occurs, for example, with penicillinase-producing strains of *Staphylococcus aureus*. Addition of tetracyclines to animal feeds may, in the long run, cause resistance of the intestinal flora, although cases have also been found where no resistance emerged. As far as can be ascertained, it is not known whether the feeding of other antibiotics induces resistance, nor is there any information about this phenomenon when a combination of antibiotics (e.g., penicillin and streptomycin) is used.

As the antibiotics mentioned act exclusively on bacteria, there is no need to consider the possibility of emergence of resistance in disease agents such as viruses, protozoa, moulds and yeasts. In view of the very low concentrations of antibiotics appearing in the blood and organs of animals receiving low levels of drugs in their feeds, it is unlikely that pathogens causing systemic infections would become resistant. Therefore, a number of pathogenic organisms, including *Brucella* and *B. anthracis*, may be safely excluded from the list of dangerous organisms that might develop resistance.

Organisms deserving special attention are *Staph. aureus* and some genera of the family of the Enterobacteriaceae, including *Salmonella* and *Escherichia*. In one country it has been found that long-term low-level antibiotic feeding may lead to the appearance of resistant strains of *Staph. aureus*, the resistant bacteria also spreading to the men attending the animals. However, this finding did not appear to be associated with an increase in the carrier rate for resistant strains in the human population of rural districts, so that its significance remains uncertain.

Antibiotic feeding may also give rise to resistance in animal intestinal bacteria as, for example, *Clostridium welchii* and *Streptococcus faecalis*. The public health significance of this is probably small.

The ingestion of low levels of antibiotics may cause resistance in *Escherichia coli*. In so far as is known at the present time, serological types that cause disease in pigs or other animals differ from those pathogenic for man.

The intestinal bacterial flora of animals may occasionally include *Salmonella* species. Experience in some countries has shown that especially *Salmonella typhimurium*, by far the commonest species among the *Salmonella*, readily becomes tetracycline resistant. The highest percentages of resistant strains have been found in organisms isolated from chickens and dairy calves. In one country, it was recently observed that in dairy calves receiving 80 to 100 p.p.m. of tetracycline in their milk diet, *Salm. typhimurium* rapidly developed resistance. In fact, the majority of strains isolated from these animals were found to be tetracycline resistant.

It is evident that the acquisition of drug resistance in *Salmonella* is undesirable from a public health point of view. On the other hand, the public health menace involved should not be exaggerated, as in the treatment of salmonellosis in man the tetracyclines are not generally regarded as the drugs of choice.

3.3.4 *Resistant bacteria in food preservation*

The problem of resistant bacteria in food preservation may be considered firstly in relation to food stored continually under refrigeration throughout processing, distribution and in the home until eaten, and secondly in relation to food stored for some or all of the time at temperatures above 15°C.

(1) *Storage under refrigeration*

(*a*) *Fresh meat, fish and poultry*. When meat, fish or poultry is treated with an antibiotic and stored at refrigeration temperatures, i.e., below 5°C, any pathogens present will be unable to multiply, whether they are resistant or sensitive to the antibiotic being used. The usefulness of the treatment will, however, depend on the proportion of resistant low-temperature spoilage organisms transferred from the environment.

Whether resistant strains of such organisms occur naturally or develop in the presence of the antibiotic, in a processing plant where the equipment is not sterilized after use, the resistant strains will gradually predominate with a consequent loss of effectiveness of the antibiotic. This has already been found with psychrophilic spoilage organisms like the pseudomonads which multiply in the slush ice tanks in the poultry plants. It is feared that it may also happen in the holds of trawlers and in the boxes used for carrying fish and also in slaughter-houses where antibiotics are used.

Thus, at refrigeration temperatures there is no hazard of food poisoning, but there is a real possibility of spoilage from resistant bacteria, yeasts and moulds.

(2) *Storage at ambient temperatures (above 15°C)*

(*a*) *Fresh meat, fish and poultry*. There may be a risk from pathogens when antibiotics are used to prolong the storage life of food stored without refrigeration. Although many pathogens, including staphylococci, may from time to time contaminate meat, fish or poultry, the principal danger, particularly with fresh meat and poultry, is from salmonellae and clostridia which generally originate in the gut of the animals concerned. So far, chlortetracycline and oxytetracycline have been used extensively only with fish and poultry which is stored under refrigeration. Thus, only a limited amount of experimental data is available regarding the behaviour of any pathogens that may be present on antibiotic-treated food stored at temperatures above 15°C.

Salmonellae. The salmonellae, in particular *Salm. typhimurium*, are responsible for a considerable proportion of the food poisoning outbreaks in many countries. It has been shown that a hazard exists when resistant salmonellae are present on chlortetracycline-treated chicken carcasses stored at 15°C or at higher temperatures. The effect of the chlortetracycline was to delay growth of the spoilage flora, so that whilst the chicken was still acceptable to the consumer, the numbers of resistant salmonellae on a contaminated carcass increased from less than 50/sq. cm. to about 10 000/sq. cm. A similar problem might occur with meat animals (beef, pork and lamb) if resistant salmonellae were present in or on a carcass that had been treated with one of the tetracycline compounds by injection or spraying.

Clostridia. When assessing possible dangers from the growth of *Cl. botulinum* or *Cl. welchii* in meat, fish or poultry, it is essential to take into consideration the eating habits of the populations concerned. Very few people eat raw poultry, but in many countries raw fish and raw meat are eaten, whilst in certain places raw putrefying fish or meat is considered a delicacy. These practices are a known cause of botulism.

When an antibiotic is used under conditions where the clostridia can multiply, as, for instance, in deep muscle tissue held at ambient temperatures, the safety of the treatment will depend on the sensitivity of the organisms present. Fortunately, most of the evidence suggests that the majority of *Cl. botulinum* strains are sensitive to the levels of chlortetracycline or oxytetracycline likely be used, but the number of strains tested so far is very small and there is variation between strains.

Cl. welchii strains form an integral part of the intestinal flora of most food animals and, together with other clostridia and streptococci, are frequently the cause of deep spoilage in mammalian carcasses (whales, cattle, pigs, etc.) held for too long at warm temperatures. Certain of the strains have also been shown to cause food poisoning. The injection of low concentrations of chlortetracycline or oxytetracycline immediately before slaughter, or infusion into the carcass at slaughter, has been shown to delay the growth of clostridia, particularly in beef carcasses. Chlortetracycline and oxytetracycline have also been shown to delay clostridial spoilage in whales.

So far, most of the experiments using the tetracycline derivatives for meat preservation have been carried out with animals that have not been fed on the same antibiotic. Resistant strains of *Cl. welchii* have been obtained following the use of low levels of the tetracycline compounds in feed supplements, and under these circumstances the level used in meat preservation would probably not have the same inhibitory effect on the clostridia present.

Staphylococci. Most cases of food poisoning by staphylococci are due to contamination of the food during and after processing by the food handler. The resistance of the staphylococci to the antibiotics used medicinally is well known and the dangers of their multiplication in foods containing low levels of antibiotic have now been demonstrated in the case of milk products prepared from milk from cows treated for mastitis. However, it is not anticipated that antibiotic treatment of fish, meat or poultry would increase the danger of staphylococcal food poisoning.

The role of the intestinal flora in spoilage. Although the faecal organisms are not generally concerned in spoilage at refrigeration temperatures, at higher temperatures they may constitute the major spoilage organisms present, particularly if slaughtering is carried out under insanitary processing conditions. Thus, a resistant faecal flora would nullify the usefulness of an antibiotic for prolonging the storage life of the meat or poultry.

(*b*) *Processed foods*. In order to prolong their storage life, most perishable foods such as meat, fish, poultry, vegetables, milk, etc. may be given some form of processing. Unless absolute sterility is obtained, such procedures necessarily lead to the selection of specific groups of organisms which are able to survive the processing and cause spoilage. In cases such as these, it is possible to consider particular antibiotics for the control of these organisms, taking into account such conditions as the pH of the food and the salt concentration which may affect the activity of the antibiotic.

With processed foods, the type of processing adopted generally limits the growth of pathogenic organisms, but where there is still a possible risk, as for example from the growth of pathogenic clostridia, it is necessary to decide whether the use of an antibiotic, such as one of the tetracyclines, or nisin, will increase or decrease this risk. This will depend on the sensitivity of the pathogens concerned.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 General

Although it is obvious from what has gone before that there are limitations to the non-medical use of antibiotics discussed in this report, the Committee is confident that if these uses are intelligently exploited, the advantages to the consumer are great and the hazards few or non-existent. The approach should, however, be careful and deliberate, in order that predictions of usefulness and safety based on theory can be confirmed stage by stage by practical experience. Although the Committee's concern has been primarily with the public health aspects of the non-medical uses of antibiotics, this stage by stage approach may well be in the interests also of the health of the animals. At each stage the amounts of antibiotics used and the residues left should not be higher than are necessary to achieve the desired results under conditions of good animal husbandry and good technology.

4.2 Feed supplements

The Committee recognizes the value and consequent wide use of antibiotics as growth-promoting agents. The economic advantages obtained in animal production from this use of certain antibiotics in feed are undeniable.

Although it seems most desirable that antibiotics other than those of medical value should be used for growth promotion, the Committee accepts that such antibiotics as penicillin, chlortetracycline and oxytetracycline cannot be dispensed with at the present time for this purpose. More recently antibiotics such as bacitracin, erythromycin, oleandomycin, spiramycin, and tylosin have been used with success. Before other antibiotics are added to this list, their effectiveness and possible public health hazards must be carefully evaluated.

Since streptomycin does not offer significant advantages over those obtainable with the antibiotics listed above, but may in fact cause rapid emergence of resistant bacteria, the Committee does not recommend the use of streptomycin alone as a growth-promoting agent in animal husbandry.

It is the opinion of the Committee that, for the purpose of growth promotion, the concentration of antibiotic used either singly or in combination, need not exceed 20 p.p.m. of the animal's total feed intake (calculated on a dry matter basis). The lowest effective level of the antibiotic is to be preferred.

Since antibiotics are effective only in the early growing period, the addition of antibiotics to the feed should be confined roughly to the following age-periods for the various animal species :

poultry, with exception of ducks and geese	8-10 weeks
swine	4-6 months
calves	3 months
beef cattle	18 months
lambs	2 months
fur-bearing animals	2-3 months

Since it is not practical in modern animal husbandry to raise motherless calves and piglets without the aid of antibiotics, in some countries amounts of 50-80 mg of antibiotic per calf and 30 mg of antibiotic per piglet or lamb are fed daily in various milk-replacement formulas, but only during the suckling period. This exceeds the maximum level of 20 p.p.m. recommended above, but the Committee recognizes the necessity for this practice.

Under certain other circumstances, the use of levels higher than 20 p.p.m. of antibiotics in the ration may also be justified, but it must be recognized that these higher levels serve to prevent or treat infection rather than to promote growth, and levels that exceed 100 p.p.m. in the feed intake should only be administered on the recommendation of qualified veterinary personnel.

The antibiotic level in protein and mineral concentrates in countries where the agricultural system necessitates their use (e.g., where pigs are fed on potatoes) should be such that the concentration of antibiotic in the total feed intake does not exceed 20 p.p.m.

Concentrates containing very high levels of antibiotics should not be available to farms (see section 4.3) partly because they may be ineffective or even dangerous unless proper mixing facilities are available (which is rarely the case except on large farms or feed-manufacturing plants) and partly because their possession enables the farmer to add any level he likes to his feed without veterinary advice.

4.2.1 *Labelling*

The Committee strongly recommends that the labels on all feeds containing antibiotics should list : the specific antibiotic(s) present and the quantity, the purpose for which the feed is intended, and directions for proper storage and use of the feed ; if the antibiotic is of limited stability, an expiration date should also be given.

4.2.2 *Analytical control*

In order to ensure that the antibiotic in the feed is homogeneously distributed and in the correct concentration, the Committee strongly recommends analytical control of antibiotic-containing feeds.

4.2.3 *Residues*

The amounts of antibiotics recommended in this report for growth promotion do not leave residues in meat. This is also true for the higher levels recommended for raising motherless calves, lambs and piglets. If the antibiotic exceeds 100 p.p.m. in the ration, however, its administration should be discontinued a sufficient length of time before slaughter to allow the drug to clear from the edible tissues.

4.2.4 *Bacterial resistance*

This is dealt with in section 3.3.3 of this report.

4.3 Veterinary therapy

The use of antibiotics is often necessary in the control of animal disease. The range of antibiotics used is greater than in the case of animal nutrition and food preservation ; also, although the dose may vary widely, it is greater for any given antibiotic and, as a result, significant levels of the antibiotic may be detected in blood and tissue during treatment.

Antibiotics may be administered either parenterally or orally, and oral administration includes their incorporation in the animal's feed (medicated feed). Thus, rations containing 100-500 p.p.m. of antibiotic(s) are often used. As mentioned under section 4.2, such rations should only be administered under veterinary supervision. To this end, the Committee recommends that legislation should be introduced to govern the supply of preparations for veterinary use in countries where appropriate regulations do not already exist.

Analytical data, supported by clinical experience, show that the elimination of antibiotics from animal tissues is rapid and there is no tendency for accumulation. Nevertheless, in order to ensure that there are no residues of antibiotics in human food derived from treated animals, the Committee recommends that there should be an interval between the last treatment and the time of slaughter sufficient for the elimination of the antibiotic.

While, under most circumstances, an interval of 48 hours is sufficient, this may not be the case with all preparations and the manufacturer should state on the label the interval that is required.

4.3.1 *Emergency slaughter*

It sometimes happens that an animal has to be slaughtered while it is still under treatment with antibiotics. The Committee recommends that in countries where the human consumption of this meat is permitted after bacteriological examination the veterinary surgeon should provide a certificate with full details of treatment; but this should not exempt the meat inspection authorities from their responsibility for ensuring that the meat is safe.

There are circumstances under which small residues of certain antibiotics have been regarded as safe. The amounts of antibiotic(s) that are acceptable will vary according to circumstances, including subsequent handling and processing of the carcass (for example, in the USA, in pork and poultry meat that is subsequently to be cooked, levels of up to 4 p.p.m. of chlortetracycline have been found).

4.3.2 *Eggs of poultry treated with antibiotics*

The Committee recommends that eggs of poultry receiving therapeutic amounts of antibiotics should not be sold for human consumption.

4.3.3 *Antibiotics in milk from mastitis treatment*

The aim should be to ensure that no milk containing any antibiotic reaches the market. Milk from penicillin-treated cows should be withheld from human consumption for a period after the last treatment; the duration of this period depends on the nature of the preparation used, but should preferably be at least 72 hours. If a long-acting preparation is used, this period needs to be longer; if possible, such preparations should only be used in "dry" cows. The label on the container should state the period during which milk should be withheld from sale after its use; the veterinary profession can help by emphasizing to the farmer the necessity for this precaution.

The enforcement of this requirement seems only possible by imposing penalties on the farmer who markets milk in which antibiotic can be detected. The use of " markers " by which recent intramammary treatment can be immediately detected has not so far been found practicable.

A similar form of control is to be advised for other antibiotics, with the exception of chloramphenicol. The possible dangers associated with the use of chloramphenicol are such that in the Committee's view its employment for treating bovine mastitis should be strongly discouraged.

4.4 Food preservation

The antibiotics that have so far found commercial application in delaying spoilage in fresh foods are chlortetracycline and oxytetracycline. In general, they are used in conjunction with refrigeration.

At temperatures above 5°C, the usefulness of the tetracyclines may be reduced by the growth of resistant pathogens, in particular, salmonellae and clostridia. Under these circumstances, there could be a public health hazard. The likelihood of producing resistant strains will be increased by the use of the same antibiotic in the feedstuffs and the hazard correspondingly aggravated. Therefore, it is recommended that where it is proposed to use an antibiotic for the preservation of food to be stored at ambient temperatures, the same antibiotic should not be used as a growth supplement in the feedstuffs of the animal during life.

4.4.1 *Fish*

For a number of years, the tetracyclines have been used successfully in several countries for fish preservation by incorporating about 5 p.p.m. in the ice used for holding fish in the trawlers, and 10 p.p.m. in the dips for fish fillets. No ill effect on human health have been observed following these uses. However, it is not known how efficient these antibiotics would be when used in other parts of the world where the types of fish as well as the spoilage flora may be different. For this reason, before introducing the application of the antibiotics into a new area, careful trials should be conducted.

4.4.2 *Poultry*

For the preservation of poultry, the chlortetracycline or oxytetracycline is incorporated at 10 p.p.m. in the ice slush used for cooling the eviscerated carcasses. This treatment has proved successful in countries with good refrigeration facilities throughout processing and distribution and in the home. No ill effects on human health have been reported. With chickens stored at 15°C or higher temperatures, there is a possible hazard from the growth of resistant *Salmonellae*. Further tests should be carried out before recommending treatment under such conditions.

4.4.3 *Meat*

So far, the tetracyclines have not found such a wide application in the treatment of meat. It has been shown, however, that at refrigeration temperatures, surface spoilage can be delayed considerably, particularly when these antibiotics are combined with an antifungal antibiotic such as nystatin.

The internal spoilage of beef carcasses held without refrigeration can be delayed by the injection of chlortetracycline or oxytetracycline immediately before slaughter to give an overall level of 1-2 p.p.m. antibiotic in the tissue. Surface spoilage is controlled at the same time by an antibiotic spray. Whilst realizing that there is no substitute for good refrigeration, the Committee would like to draw attention to this application of antibiotics, particularly for use in places where adequate refrigeration is not yet available. It recommends that field trials should be carried out to determine whether there is any danger from pathogens that may be in or on the carcass.

5. PROPOSALS FOR FURTHER RESEARCH

The Committee believes that further study of the following subjects is desirable.

5.1 The mode of action of low-level feeding of antibiotics

It is astonishing that, in spite of the vast economic importance of low-level feeding in promoting growth and improving utilization of feeds, the mode of action is not yet really understood, although it has been under extensive study for at least 12 years. Any final explanation must account for the fact that the antibiotics chiefly used, penicillin and the tetracyclines, have different antimicrobial spectra and behave differently as regards absorption and distribution. Growth-promoting effects have also been claimed for a variety of other antibiotics. If these effects are produced by an action on the flora of the lower alimentary tract, the complexity of this flora and the enormous labour involved in studying it quantitatively may account for the failure to elucidate the problem up till now. In the present state of knowledge, low-level feeding is little more than empirical. If it could be placed on a rational basis, it could be better directed, probably with an improvement in results and economy in material.

5.2 The effects of antibiotics on the intestinal flora of animals

The study of changes in the intestinal flora following the administration of antibiotics to animals may not only throw light on the mode of action of low-level feeding but also has another object. Some concern has been expressed about the possible ultimate effects of administering, even in small doses, drugs that have so powerful an antibacterial action, possibly resulting in some permanent change in the intestinal microflora of animals. It has, for example, been suggested that it might result in an increase in the intestinal *Salmonella* carrier rate.

Information is also needed on the effect of antibiotic feeding on the susceptibility of the animal to intercurrent intestinal infection. It has also to be remembered that antibiotic feeding may cause a thinning of the intestinal wall, which, if associated with increased permeability, might result in more ready dissemination of pathogenic bacteria to other parts of the body.

5.3 The masking of infection at slaughter

If therapeutic doses of antibiotics have been administered to an animal shortly before slaughter, they may delay the growth of the causative bacteria (e.g., *B. anthracis*, *Salmonella*) in culture. This possibility requires further elucidation.

5.4 Transmission of antibiotic-resistant bacteria from animals to man

It is known that the antibiotic treatment of bovine mastitis and high-level (perhaps also low-level) feeding to animals leads to the appearance of resistant staphylococci and Enterobacteriaceae (including pathogenic species, such as those of *Salmonella*). It is not known to what extent these resistant organisms are creating problems in human therapy. Any evidence of transmission to man on an increasing scale, resulting from a greater prevalence of *Salmonella* infections or carrier states in pigs and cattle, would demand serious investigation.

5.5 Preservation of meat in hot countries

Reference has already been made to the need for information about the possibilities of preserving meat at high ambient temperatures by administering an antibiotic before slaughter or by perfusing the carcass after it. It is necessary to know the length of time that this procedure remains effective, and when spoilage does occur what bacteria will cause it. It is particularly important to know whether variations in the animal gut microflora in different countries will affect the rate at which spoilage occurs.

Above all, it must be known whether the antibiotic concentrations attained can always be depended upon to inhibit the growth of *Cl. botulinum*.

In some hot countries, meat is dried or powdered. It is advisable to know what antibiotic residues may occur in such products.

5.6 Preservation of fish

It is known that the spoilage flora of fish from tropical waters is different from that in northern latitudes. The effect of the tetracyclines on these fish merits further investigation to determine the best types of fish for treatment and the best methods of applying the antibiotic.

Fish are sometimes salted or otherwise treated to prevent decomposition and subsequently eaten uncooked. It is desirable to know what concentration of an antibiotic used for initial preservation may be contained in such fish at the time of consumption.

5.7 The merits of antibiotic combinations

Much is known about the nature of the combined action of certain mixtures of antibiotics in human medicine. Such data refer, however, to the action of relatively high concentrations, and it seems unwise to apply them in the present context. It would be of advantage to know whether combinations have any advantage (1) in deterring the development of resistance in spoilage bacteria, (2) in enhancing the general preservative effect.

5.8 Residual antibiotics in canned foods

The addition of nisin to canned foods is permitted in some countries, and that of tylosin has been proposed. The general question of the suitability of (preferably non-medical) antibiotics for this kind of use deserves consideration. For this purpose, information is required on the possible deleterious effects of consuming small amounts of these antibiotics, of which there must be residues in the canned product. It seems unlikely that changes in the intestinal flora would be caused, but this and other possibilities need to be examined. It is worthy of note in this connexion that this is a field in which there is no adequate substitute for experimentation in the human subject, a procedure which appears amply justified when the risks are almost non-existent.

5.9 New antibiotics as preservatives

The Committee believes that research might profitably be directed to the discovery or identification of further antibiotics not required for medical purposes, but suitable for use in food preservation.

5.10 Application to fruit and vegetables

Any extension of use for the control of plant disease will demand studies of (1) the possible effects of contact with the antibiotic on the operator, and (2) the occurrence of residues in the product as marketed.

5.11 Assay techniques

Although good methods exist for the assay of antibiotics in such materials as food and animal tissues, endeavours should be made to improve their simplicity, sensitivity and accuracy. Methods for assaying the degradation products of antibiotics are less well developed and deserve further study.

6. SPECIAL NEEDS IN DEVELOPING TROPICAL COUNTRIES

A hot climate and the lack of refrigeration facilities render perishable foods subject to rapid spoilage and this is particularly true of three important protein-containing foods — milk, fish and meat.

Milk. Although milk could certainly be kept longer in a satisfactory condition during transport from farm to dairy plant by the addition of an antibiotic, to adopt this practice at present seems undesirable because its ultimate consequences cannot be foreseen. This subject is further discussed in the second report of the joint FAO/WHO Expert Committee on Milk Hygiene.[1]

Fish. The preservation of fish in ice containing one of the tetracyclines is particularly indicated in hot climates, but this presents certain difficulties, as referred to in section 5.6.

Meat. The rapid spoilage of meat in hot climates might be averted if an antibiotic could be used as a preservative. Such use might also permit cattle or other animals to be slaughtered nearer home, instead of, as at present, being driven to slaughter over great distances, with consequent serious loss of weight. A tetracycline should serve the purpose best and should be injected intravenously before slaughter, or used to perfuse the carcass after it. No information is available, however, on how much benefit would accrue from this, i.e., how long at a given temperature the meat would remain in good condition, or what kind of spoilage would eventually follow. This is a matter calling for further investigation. The maximum concentration of tetracyclines found in carcasses after the intravenous injection of 10 p.p.m. before slaughter was 7 p.p.m. On

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1960, **197**.

general principles, the sale of meat containing throughout its substance such a high tetracycline concentration is to be discouraged, although thorough cooking would denature most of this. There are no data to indicate that residues higher than those defined as permissible elsewhere in this report (see section 4.4.3) would have serious detrimental consequences, and the theoretical disadvantages must be weighed against the substantial benefits in nutrition that might accrue from the use of tetracycline as a preservative.

The Committee emphasizes :

1. That further study is necessary before it can be concluded that these methods will give satisfactory results.

2. That their application should be regarded only as an exceptional and temporary measure pending the eventual provision of adequate cold storage facilities.

7. RECOMMENDATIONS

1. The Committee recommends that WHO and FAO should encourage research and training so that any non-medical application of antibiotics in developing countries may be carried out without hazard to public health. It will of course be necessary to undertake preliminary surveys, field studies and microbiological investigations in order to assess what are the possibilities for the non-medical use of antibiotics in such countries, and what might be the health hazards involved.

2. The Committee recommends that in view of research currently under way and of investigations anticipated a further meeting, or meetings, be held when appropriate for the purpose of studying developments.

3. The Committee requests governments to take cognizance of the recommendations in this report and recommends that, where necessary, legislation be enacted to control the non-medical use of antibiotics.

Annex 1

SUMMARY OF ANTIBIOTICS IN ANIMAL FEEDS IN DIFFERENT COUNTRIES *

Country	Antibiotics permitted	Dose permitted (dry matter feed intake)	Animal species
Argentina	Penicillin Oxytetracycline Chlortetracycline Tetracycline	Low levels for growth promotion (penicillin 5 p.p.m., tetracycline 10 p.p.m.). For medicated feeds, 10–15 times the low-level amounts	Poultry, swine
Austria	Penicillin Oxytetracycline Chlortetracycline	10–20 p.p.m. 30 p.p.m.	Adult swine, poultry Piglets up to 8–10 weeks
	Oxytetracycline Chlortetracycline	60 p.p.m.	Calves
Australia	Penicillin Oxytetracycline Chlortetracycline	Low levels for growth promotion	Swine, poultry
Belgium	Penicillin Oxytetracycline Chlortetracycline Bacitracin	20–50 p.p.m.	Swine, poultry, calves
Canada	Penicillin Streptomycin Oxytetracycline Chlortetracycline	2–50 p.p.m. in low-level feeds: 100–400 p.p.m. in disease-preventing feeds	Poultry, swine, calves, cattle, fur-bearing animals
Denmark	Penicillin Oxytetracycline Chlortetracycline	10–20 p.p.m. 100 p.p.m.	Swine, poultry, cattle Piglets, calves
France	Penicillin Oxytetracycline Chlortetracycline Bacitracin	up to 50 p.p.m. for growth promotion	Poultry (with the exception of ducks and geese), calves, pigs, fur-bearing animals
	Oleandomycin [a] Neomycin [a] Erythromycin [a] Spiromycin [a] Hygromycin [a]	50 p.p.m. (milk replacement) up to 20 p.p.m.	Calves, piglets

[a] Provisionally permitted for 1 year, but permission will be renewed for yearly periods,

* The information given in this table is valid for the period up to the end of 1961.

Annex 1 *(continued)*

Country	Antibiotics permitted	Dose permitted (dry matter feed intake)	Animal species
Germany	Penicillin Oxytetracycline Chlortetracycline Bacitracin Oleandomycin	10–20 p.p.m. up to 100 p.p.m.	Poultry, swine, calves Piglets, broilers, calves
Great Britain	Penicillin Oxytetracycline Chlortetracycline	up to 100 p.p.m.	Only for growing pigs and poultry
Hungary	Oxytetracycline	10–15 p.p.m.	Chickens, piglets
Ireland	Antibiotics may be added to feeds without restriction		
Israel	Penicillin Oxytetracycline Chlortetracycline Bacitracin	4–10 p.p.m.	Poultry
	Oxytetracycline Chlortetracycline	50–80 p.p.m.	Calves
Italy	Penicillin Streptomycin Oxytetracycline Chlortetracycline Bacitracin	Amount not restricted	Poultry, swine, calves
Japan	Penicillin Streptomycin Oxytetracycline Chlortetracycline Bacitracin	Amount not restricted	Poultry, swine, calves
Kenya	Oxytetracycline Chlortetracycline	7.5 p.p.m. 10 p.p.m. 75 p.p.m.	Poultry Pigs Calves
Netherlands	Penicillin Oxytetracycline Chlortetracycline Bacitracin	10 p.p.m. up to 100 p.p.m.	Poultry Calves
	Penicillin Oxytetracycline Chlortetracycline	10 p.p.m. up to 50 p.p.m.	Swine Piglets
New Zealand	Penicillin Oxytetracycline Chlortetracycline	Only pre-mixes may be obtained (5 g per lb of meal or grain base). Limited use of low-level feeds.	

Annex 1 *(continued)*

Country	Antibiotics permitted	Dose permitted (dry matter feed intake)	Animal species
Norway	Penicillin, Oxytetracycline	15 p.p.m.	Poultry, swine, calves, fur-bearing animals
	Chlortetracycline, Bacitracin	50 p.p.m.	Calves, piglets
South Africa	Penicillin, Streptomycin, Oxytetracycline, Chlortetracycline	10–15 p.p.m.	Poultry, swine
	High-level feeds can be obtained on veterinary prescription		
Spain	Penicillin	4–10 p.p.m.	Poultry, swine, calves
	Oxytetracycline	7–50 p.p.m.	
	Chlortetracycline	10–50 p.p.m.	
	Bacitracin	5–10 p.p.m.	
Sweden	Penicillin, Oxytetracycline, Chlortetracycline	Amount not restricted	Poultry, swine, calves
Switzerland	Penicillin	5–10 p.p.m.	Poultry, swine, calves
	Oxytetracycline, Chlortetracycline	10–20 p.p.m.	
United States of America	Penicillin, Streptomycin, Dihydrostreptomycin, Oxytetracycline, Chlortetracycline, Bacitracin, Oleandomycin, Erythromycin, Tylosin	For growth promotion: max. 50 p.p.m. In disease-preventing feeds: 100–2000 p.p.m.	Poultry, swine, calves, cattle
USSR	Penicillin, Oxytetracycline, Chlortetracycline	15–20 p.p.m.	Poultry, swine, calves,[a] fur-bearing animals

[a] Use restricted.

Annex 2

SUMMARY OF FOOD PRESERVATION BY ANTIBIOTICS IN DIFFERENT COUNTRIES *

Country	Antibiotics permitted	Tolerance permitted	Used for
Argentina	Chlortetracycline, Oxytetracycline	5–10 p.p.m.	Meat, poultry, fish
Canada	Chlortetracycline, Oxytetracycline	7 p.p.m.	Poultry
		5 p.p.m.	Fish preservation in ice
		10 p.p.m.	Fresh fillets in dipping tanks
Great Britain	Chlortetracycline [a], Oxytetracycline [a]	5 p.p.m.	Raw fish
	Nisin [a]	No limit	Cheeses and certain canned goods
	Nystatin	On the skin but not in the flesh	Bananas
Japan	Chlortetracycline, Oxytetracycline	5 p.p.m.	Fish preservation in ice; fish for fish pasta; salmon for canning
Norway	Chlortetracycline, Oxytetracycline	250 p.p.m.	Slaughterhouse offals for minks in the warm weather period
USA	Chlortetracycline, Oxytetracycline	5 p.p.m.	Fish preservation in ice; preservation of shrimps and scallops
	Chlortetracycline, Oxytetracycline	7 p.p.m.	Poultry preservation in slush-ice tanks
USSR	Chlortetracycline [b]	5 p.p.m.	Codfish preservation in ice and for transport

[a] The use of these antibiotics for the purposes and in the amount stated is a proposal only, made by the Antibiotic Panel of the Ministry of Health.

[b] This is only for a provisional period of 2 years, beginning in 1960.

* The information given in this table is valid for the period up to the end of 1961.

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