Chapter I

SUMMARY

GLOSSARY

E. coli: A species of gram-negative bacteria constituting the greater part of the intestinal flora of man and other animals and occasionally pathogenic for man.

Enteric: Of or relating to the intestines.

Feed efficiency: The use of certain drugs which results in animals gaining more weight than animals not given such drugs for the same amount of feed consumed.

Genotoxic: A toxic effect on the chromosomes—for example, mutation. In the context of cancer-causing agents, the hypothesis is that the agent acts directly on the chromosomes to cause cancer.

Gram-negative or gram-positive: A method of identifying bacteria, related to the color they retain in the gram's method of staining for microscopic examination. Bacteria are usually identified as being either gram-negative or gram-positive.

H. influenza: A species of gram-negative bacteria that may cause meningitis in infants and young children related to a respiratory tract infection.

N. **gonorrhea:** A species of gram-negative bacteria that is the specific causative agent of gonorrhea.

Nongenotoxic: In the context of cancer-causing agents, the hypothesis is that the agent acts indirectly to cause cancer. For example, the agent may enhance or promote the ability of a genotoxic agent to cause cancer but cannot cause cancer by itself.

Nonpathogen: An agent not usually capable of causing disease.

$1/10^6$ extra lifetime risk of cancer: A method of quantifying risk to humans from exposure (e.g., ingestion) to a specified amount of a cancer-causing substance over a lifetime for regulatory purposes. It is derived from extrapolation of cancer rates in laboratory animals (e.g., rats) exposed to the substance over their lifetimes. For example, if a daily dose of x over the animals' lifetimes leads to a cancer rate of 1/100 in the experimental animals, the extrapolation model might be used to predict what daily dose over the human lifetime would lead to a cancer rate of $1/10^6$. Alternatively, the model might be used to predict what the cancer rate would be in humans for the average daily lifetime consumption of the carcinogenic substance by humans.

Pathogen: An agent, such as a bacterium or virus, capable of causing disease.

Salmonella: Any of a genus of gram-negative bacteria that are pathogenic for man and other warm-blooded animals, usually causing intestinal disease such as food poisoning.

Subtherapeutic: The use of drugs where the doses given are less than that which would be used if disease were present. In the context of the use of antibiotics in animal feeds, these uses include prevention of disease and the weight-promotion and feed-efficiency effects of certain antibiotics.

Therapeutic: Treatment of known disease with drug doses that are high enough to eradicate or control the disease agent.

Weight promotion: The use of certain drugs which results in animals growing faster than animals not given such drugs over the same time period and for the same amount of feed consumed.

SUMMARY

INTRODUCTION

Over the past three decades drugs have been used increasingly in the rearing of animals for human consumption. The drugs can be administered via drinking water or feed, they can be injected, or pellets can be inserted under the animal's skin. This is done for five reasons:

1, As nutritional supplementation such as vitamins and minerals are given,
2. For treating disease,
3. For preventing disease,
4. For increasing weight gain,
5. For improving feed efficiency.

More than 40 percent of the antibacterials* produced in the United States are used as animal feed additives and for other nonhuman purposes, Nearly 100 percent of poultry, 90 percent of swine and veal calves, and 60 percent of cattle receive antibacterial feed supplementation. About 70 percent of U.S. beef by carcass weight comes from cattle that have received weight-promoting feed supplement tion.

This widespread use of drugs in livestock production has led to increasing concern over potential adverse effects on human health for two reasons:

1. Many of the same antibacterial are used both in human therapy and in animal feeds. The use of these drugs as feed additives contributes to a growing pool of drug-resistant bacteria, Physicians are now reporting reduced effectiveness of these same drugs in treating human disease. Some bacteria are resistant to several antibacterial; others require higher doses to control or kill them. Research findings point to animal feeds as a contributory source of many of these drug-resistant bacteria.
2 Residues of other drugs found in animal products such as meat and eggs are potentially carcinogenic and may be passed on to consumers.

There is much disagreement among scientists as to the validity of many of the findings and the weight that should be attributed to them when considering a ban or restrictions on the use of these drugs. The two main areas of dispute are:

1. What the effects are on human morbidity and mortality,
2. What tradeoffs there should properly be between risks and benefits.

Therefore, at the request of the Chairman of the Senate Committee on Agriculture, Nutrition, and Forestry, the Office of Technology Assessment (OTA) undertook an assessment of the use of drugs as feed additives in livestock and poultry production, with particular emphasis on the following concerns:

- The benefits to livestock producers from the use of each category of drugs used as feed additives,
- The established or potential risks from the use of each category of drugs,
- The available alternatives to the continued use of each category of drugs,
- The acceptable risks in the use of each category of drugs,
- The options available to Congress to improve regulation of drugs used in livestock feeds.

*The term "anti ibacterial " includes antibiotics and chemicals with similar action, Other technical terms a re defined i n t h eglossa r v.

This report summarizes the evidence on risks and benefits and the relevant regulatory and public-policy background against which this assessment takes place. Since the use of drugs in animal feeds either as nutritional supplements or for therapeutic purposes is relatively noncontroversial, this report focuses on the addition of low levels of antibacterial to feeds and on diethylstilbestrol (DES), a synthetic estrogenic hormone which is a proven human carcinogen. DES pellets are implanted under the skin or added to the diet to increase feed efficiency and promote growth in beef cattle.

Since estimates on risks and benefits of supplemental drugs in animal production are based on numerous complex factors, no one set of figures can confidently be used in any quantitative estimates of risks versus benefits. This difficulty in assigning precise figures has contributed greatly to the complexity of the debate over the safety of drugs in animal feeds.

HOW THE DRUGS ARE USED

Doses lower than the usual therapeutic level are given to poultry, cattle, swine, and calves to promote weight gain, to prevent disease, and to increase feed efficiency, thus increasing the meat yield per pound of feed used. The drugs most often used are: tetracyclines, penicillins, sulfas, nitrofurans, and DES. DES is different from other drugs used in animal feeds, as it is not an antibacterial but rather a synthetic estrogen.

It is not known precisely how the antibacterials work to increase weight gain and feed efficiency. At least three modes of action have been postulated, but there is still disagreement among scientists on this point:

1. **A Nutrient-Sparing Effect** in which the drugs reduce the animal's dietary requirements either by stimulating the growth of beneficial organisms that synthesize vitamins and other essential nutrients or by depressing the organisms that compete with the host animal for nutrients, or by increasing the capacity of the animal's intestinal tract to absorb nutrients.
2. **A Metabolic Effect** in which the antibacterial directly affects the rate or pattern of metabolic processes in the animal.
3. **A Disease-Control Effect** in which the drugs suppress those organisms that cause disease in animals of such a low level that symptoms are not apparent but the animal's weight gain is reduced.

It is thought that the disease-control effect is the most responsible for growth promotion. It has been demonstrated that the degree of response to antibacterial feed supplements is inversely related to the general well-being of the experimental animals. Healthy, well-nourished animals do not respond to antibacterials when housed in carefully cleaned and disinfected quarters that have not previously housed other animals. While such a level of sanitation is usually not practical for the large-scale animal producer, it does suggest that it is through the prevention of diseases that drugs promote growth.

When FDA approves a use of an antibacterial for a purpose other than the treatment of disease, the Agency specifies whether the drug is approved for growth promotion, feed efficiency, or disease prevention. However, these are somewhat artificial distinctions, since it is impossible to point to growth promotion or increased feed efficiency or disease control as being responsible for the improved product yield. It is possible that the effect is a result of all three. Furthermore, a completed feed mix may well contain drugs approved for all three uses anyway.

The safety debate arises from the widespread continuous use of antibacterial. The deleterious effects of the drugs appear regardless of the uses for which they are approved. Thus the actions of the drugs are so overlapping that distinctions based on intended purpose are irrelevant insofar as safety is concerned.

BENEFITS

The benefits of using antibacterial in animal feeds are:

. The prevention of disease,
• The promotion of growth, and
• The improvement of feed efficiency.

The evidence points to the disease-prevention effect as being primarily responsible for increased weight gain.

While increased weight gain resulting from low doses of antibacterial and DES is not in dispute, the amount of gain is. Even though drugs may increase weight gain by only a few percentage points, the absolute increase is large because of the size of the livestock market.

Present levels of livestock production do not depend specifically on the use of DES and the addition of low levels of tetracycline, penicillins, sulfa, and nitrofurans to feeds because substitute drugs are available. In addition, if adopted, the current Food and Drug Administration (FDA) proposal to restrict but not totally ban the most widely used antibiotic, tetracycline, could mitigate the impact of banning or restricting other drugs used for this purpose,

The economic consequences of such decisions, however, are a separate matter because marginal increases or decreases in production may make the critical difference in the profitability of the livestock industry, Economic dislocations within subsectors of the livestock market could be significant over the short term. Such economic effects are often raised in objections to proposed changes in regulations, but present statutory authority limits FDA's decisionary basis to scientific evidence of effectiveness and safety. Although under present law FDA does consider the practicality of achieving the desired result of regulatory changes, FDA does not explicitly consider the economic consequences of these changes. When FDA's proposed regulations have been successfully challenged, it has usually been on the grounds that FDA's procedures, rather than the substance of the law, were faulty.

There may soon be an opportunity to observe whether or not the banning of antibacterials will result in significant changes in production. FDA has withdrawn approval of one of the four nitrofurans, an antibacterial originally approved for food animal use, and will soon enter hearings on the remaining approvals. One of these, furazolidone, is the most widely used. Predictions point to no effect on beef and pork production but to significant short-term effects on poultry production. (See tables 23 and 24,) Penicillin and tetracycline are also widely used in poultry, and their uses overlap extensively with the nitrofurans. (See tables 1, 2, 4, 5, and 9.) Even if penicillin were banned subsequently, tetracycline would remain available, since FDA's proposal would allow its continued use if alternatives were unavailable. If these antibacterial cannot replace nitrofurans, effects should be observed immediately.

RISKS FROM CONTINUED USE OF THE DRUGS

The risks from the use of antibacterial in animal feeds stem from an increase in bacterial resistance to the drugs. Drug-sensitive bacteria are killed or inhibited by the drug, allowing resistant bacteria, which have adapted to the presence of the drug, to grow in their place, While drug-resistant variants exist even in the absence of antibacterial, they do not generally flourish unless a change in their environment favors their survival. When antibacterial are given, the drug-resistant bacteria are the fittest to survive in their presence, and they soon become the majority,

Genes for antibiotic resistance as well as its transfer are carried on structures called plasmids, which are bits of DNA that function independently of the organism's main genetic apparatus. Plasmids can transfer resistance

between bacteria of the same or of different species. Thus harmless resident bacteria, such as E. *coli*, which are present in the intestines of humans and animals, can become resistant in the presence of the drugs and can then transfer their resistance to a still sensitive strain of a more virulent pathogen such as Salmonella. The result of such a transfer would be a strain of Salmonella that was resistant to one or more antibacterial. The resident bacteria in the intestines of animals and humans receiving antibacterial are soon replaced with resistant resident bacteria and thus serve as a reservoir for the spread of plasmid-mediated resistance to antibacterial.

While research attention was originally focused on the transfer of drug resistance from E. *coli* to other intestinal microorganisms, principally Salmonella, it is now evident that the spread is wider. There is now strong evidence that similar transfers occur between *H. influenza* and *N.* gonorrhea and resistant *E. coli*. Thus the risks are no longer restricted to people who may have picked up Salmonella directly from animals or their edible products.

N. gonorrhea and *H. influenza* are harbored by humans. For these bacteria to have acquired plasmids for the transfer of resistance means that the plasmids are traveling in a wider radius than was originally predicted. For instance, identical plasmids have been isolated in parts of the world as distant as England and Vietnam,

In a sampling of *E. coli* from a freshwater river system and within the saltwater bay into which it emptied, it was found that nearly all the freshwater sites and about half the saltwater sites sampled contained resistant coliforms. Twenty percent of the strains contained resistance plasmids carrying multiple drug resistance transferable to sensitive E. *coli* and to *S. typhimurium* and S. *dysenteriae* (the bacteria which cause typhoid and dysentery).

Furthermore, plasmids are now carrying genes for resistance to more than one drug. Whereas formerly this was rare, it is now common, if not usual, for bacteria to be resistant to several drugs at a time. It is now necessary for physicians to run sensitivity tests to determine alternative drugs to which a given strain of bacteria is still sensitive. Certain strains of gonorrhea and typhoid, among others, have proven more difficult to treat than formerly as a result of resistance to the standard drug of choice.

The extent of the decrement in performance of antibacterial used in treating human and animal disease is still relatively unknown, The relationship between decreased sensitivity and decreased effectiveness in treating disease is complicated because many variables such as species, general health, and numbers of invading bacteria influence whether known pathogenic bacteria will cause observable disease and whether a specific drug will make the difference in outcome when disease does occur, This is particularly true for Salmonella, the bacteria on which much attention has been focused, However, FDA estimated that in 27 percent of the Salmonella cases treated each year, the first antibacterial chosen for treatment proved to be ineffective because the disease was caused by antibacterial-resistant bacteria.

Another risk from the use of antibacterial feed additives is that it eventually compromises therapeutic and prophylactic effects of the same drugs. Even though stopping the use of an antibacterial can be expected to result in the loss of dominance of resistant bacterial strains, these strains can persist in diminished but significant numbers. If growth promotion and feed efficiency are closely dependent on disease prevention, the effectiveness of supplemental antibacterial feeding will decline.

Noncarcinogenic drug residues pose little direct risk to consumers if tolerances are adequately established and the residues are below tolerance levels. But the sulfamethazine findings discussed in this report indicate that the majority of concentrations of residues above allowable limits results from the unintended cross-contamination of feeds during mixing. This may be occurring particularly with penicillin and tetracycline, since they are widely used and mixing is not limited to certified feed mills or done under a veterinarian's prescription, Cross-contamination

would increase the risk of plasmid-mediated drug resistance because such cross-contamination would mean that the extent of supplemental feeding of antibacterial is even higher than that of recognized, approved uses, Because tissue residues in general may not be good indicators of cross-contamination, the extent of cross-contamination needs to be monitored directly.

The risk from resistant plasmids of animal origin is not quantifiable even by the rough estimates made for Salmonella infections. The majority of resistance in human bacterial populations is probably caused by widespread use of antibacterial in humans (some of which are unnecessary), but the enormous pool of R-plasmids that now exists in animals, together with the ability of an R-plasmid to be promiscuously transferred among bacterial species, must be regarded as a threat to the therapeutic value of antibacterial in the treatment of both human and animal diseases.

CARCINOGENIC DRUG RESIDUES

DES and the nitrofurans pose risks because they are carcinogenic and may leave residues in animal products such as meat and eggs. The effort to determine carcinogenic risks from drug residue is complicated by two factors:

1, The difficulty of extrapolating data obtained from animal experiments to man, and
2. Analytical problems in measuring a "no residue' level.

Although carcinogenesis in laboratory animals is accepted as proof of a probable carcinogenic effect in humans, extrapolation techniques to determine the amount of cancers expected in humans are still embryonic in nature and subject to validation on a case-by-case basis. To conduct the tests using doses comparable to that ingested by humans would require a far larger sample—hundreds of thousands as opposed to hundreds—of animals, Therefore, tests are conducted with much larger doses and the results extrapolated back down.

Because of the increasing sensitivity of newer assay methods to smaller amounts of residue, FDA is attempting to define "no residue' on the basis of a "practical threshold"—i.e., that threshold below which the risk of cancer is statistically negligible rather than on the basis of absolute zero residue. Otherwise, standards must be revised with the appearance of each new assay method that can detect the presence of a minute level which the previous method was not quite sensitive enough to detect. Accordingly, FDA proposes to define "no residue" as the quantity leading to an extra risk of 1 in 1 million ($1/10^6$) of developing cancer over a lifetime of exposure,

Furazolidone is assumed to cause cancer by heritable damage to the genetic system of the host cells that eventually leads to tumor formation. Thus there is probably no level at which it is absolutely safe. Using a model which assumes that there is no safe threshold to extrapolate from animal data to humans, an extra risk of l/l 0^6 from furazolidone can be correlated to furazolidone residue levels in foods consumed by humans. Assuming that foods contain at least as much furazolidone as would be detected by FDA's proposed quantitative assay standards for furazolidone and using average consumption figures, the risks to humans from ingestion of foods containing furazolidone residues are less than the $1/10^6$ lifetime exposure risk. Using the high consumption population as the group at risk, the risk may approach $1/10^6$.

DES, a female hormone, has been associated with cancer in the daughters of women who took the hormone during pregnancy. In contrast to furazolidone, there is evidence that DES's carcinogenic action is through promoting the effect of substances that can produce cancer directly. This would mean that its carcinogenic action is caused not by heritable genetic damage but more likely by its estrogenic action. It is therefore likely that a threshold exists below which DES content

will not be sufficient to cause tumors. Using an extrapolation model for estimating risks that assumes such a threshold, the tissue level obtained falls in the approximate range FDA has set as associated with the "no residue" level. Obviously, such a measurement is not absolute, but rather is relative to risk. If, on the other hand, no threshold is assumed and if any level is considered carcinogenic, different extrapolation models would be used and would predict for the same tissue levels of DES risks from 10 to 100 times the $1/10^6$ lifetime exposure risk associated with the "practical threshold" level. However, at present, there is no assay method presently approved that is sensitive enough to measure DES at these levels.

ASSESSING AND QUANTIFYING RISKS AND BENEFITS

Risk-benefit assessments, in view of the kinds of evidence on benefits and risks reviewed in this report, are not only difficult to conduct but also difficult to use in making regulatory decisions or in revising the underlying statutory authorities.

The risks and benefits of drugs used to increase food animal production share some common attributes: (I) laboratory evidence provides scientific support for the identified benefits and risks; (z) effects expected in actual use can be shown in selected experiments, but it is often unclear whether the precise biochemical and or metabolic processes observed in the laboratory setting are responsible; and (3) quantification of the effects, whether it be extra pounds of meat or extra cases of cancer produced, are too imprecise to yield reliable figures, although such figures are useful for predicting the general magnitude of the expected effects. Such quantitative estimates of risks or benefits often are made with a degree of precision that is justified only within the statistical boundaries of a particular experiment. Once removed from the structured experimental setting, these numbers retain an aura of legitimacy that may not be warranted. This is not only true for the kinds of simple calculations included in this report for the risk from Salmonella infections or the risk of cancer from DES or furazolidone but also for the expected effectiveness of the drugs discussed in this report. Typically, the experiments that quantify the effect of antibacterial or DES on weight gain and feed efficiency measure these effects up to a hundredth of a percent (0.0001). Yet the gain is on the order of grams per day for small animals such as chickens or turkeys and fractions of a pound per day for large animals such as pigs and cattle.

Even if precise measurements could be validly obtained, they would still be of limited use in addressing policy issues because these risks and benefits cannot be approached through a simple balance-sheet type of assessment. No common denominator is generally acceptable for comparing human illness and death with pounds of meat. Rather than using monetary values as a common denominator, opposing advocates usually seek to make their case or ridicule their opponents in the most exaggerated terms. For example, one advocate might say that if one life is saved, that is worth whatever it costs in decreased meat production, and Americans eat too much meat anyway. The other advocate might seek to dismiss the risk of getting cancer from a certain product by saying that it is equal to drinking 800 12-ounce cans of diet soda daily over a lifetime. Such tactics clearly do not address the issue of risks versus benefits.

CURRENT REGULATORY POLICY

Present Federal regulation of animal drugs is based on evidence of effectiveness and safety.

- Animal drugs, as in the case of human drugs, must be shown to be both effective and safe.
- Residues in food, such as animal drugs in meat, must only be shown to be safe.
- Food-additive regulation is focused on safety. However, food additives also must be shown to have the intended effect or to be reasonably expected to become a component or affect the characteristics of food.
- The statutes and the implementing regulations set criteria for demonstrating effectiveness and safety that are independent of each other. There are no explicit guidelines for determining when the evidence on either effectiveness or safety overrides the evidence on the other.
- If a food additive is found to be carcinogenic, it must be banned regardless of how little is present in the food,
- Drugs may be carcinogenic and their use still allowed if effectiveness overrides the risks,
- When an animal-derived food product may contain residues of a carcinogenic substance (e. g., an animal drug), the law provides some leeway in determining an adequate assay procedure to demonstrate "no residue. " FDA has attempted to define "no residue" in terms of acceptable risk as extrapolated from animal experiment data, It is an attempt to define safety in practical instead of absolute terms, since definitions in absolute terms must continually be revised as newer assay methods are able to measure smaller and smaller residues of less than one part per billion,

FINDINGS AND CONCLUSIONS

1. **Drugs in animal feed are targeted for multiple purposes—40 percent of all antibacterials produced are used for animal feed.**
   - Drugs are added to livestock feeds for nutritional supplementation, treatment of disease, prevention of disease, weight promotion, and feed efficiency.
   - In addition to their use for therapeutic purposes, antibacterial are used to prevent disease by eliminating the carrier status of animals and egg-transmitted infections or by suppressing infections in the very young bird or animal.
   - Low concentrations of antibacterial also are commonly approved to hasten weight gain and to increase the amount of weight gained per unit of feed.
   - It is not clear whether these weight-promotion and feed-efficiency effects are separate from or dependent on the disease-prevention effect. Commonly, however, one concentration of an antibacterial is approved only for disease prevention, while another concentration of the same antibacterial is approved only for weight promotion and feed efficiency.
   - Feed premixes often contain a combination of antibacterials, and these premixes may be approved for some or all uses. For example, one combination approved for swine feeds contains procaine penicillin, chlortetracycline, and sulfamethazine for disease treatment, disease prevention, growth promotion, and feed efficiency.
   - Other drugs, including DES for beef cattle, also are used in feed or administered through subcutaneous implants for weight promotion and feed efficiency,
2. **Because of the attendant risks, regulatory attention has focused on the addition of low levels of antibacterial in animal feeds and on DES, a proven human carcinogen.**

- The continuous use of low-level antibacterials as feed supplements produces drug-resistant bacteria that may cause disease in animals and humans and transfer drug resistance to other bacteria. The use of one antibacterial may result in the transfer of genes carrying resistance to several other antibacterials as well,
  - —Development and interchange of resistance have been confined largely to gram-negative bacteria, although an increasing body of data is accumulating that indicates transferable drug resistance in the gram-positive bacteria.
    (a) *E. coli*, common bacteria found in the intestinal tract of both humans and animals and throughout the environment, are the largest reservoir of drug resistance. Drug resistance developed in E. *coli* can be transferred to other gram-negative bacteria that may be more pathogenic.
    (b) Salmonella, intestinal bacteria that can cause clinical disease, can develop resistance directly from the use of antibacterial or have resistance transferred to them from E. *coli.*
    (c) Other gram-negative bacteria, such as *H. influenzae* and *N.* gonorrhea, recently have been found to have drug-resistant properties that apparently have been transferred from drug-resistant E. *coli.*
  - —The use of tetracycline, widely used as antibacterial in animal feeds, leads to the dominance of bacteria with multiple drug resistance. Penicillin and, to a lesser extent, the sulfas are the other primary antibacterial whose uses are being examined.
- . DES, a synthetic estrogen used in beef cattle to promote growth and increase feed efficiency, and nitrofurans, antibacterial widely used in poultry, are proven or suspected carcinogens.
  - —DES has been shown to be carcinogenic in both animals and humans, The use of DES by women during pregnancy has been associated with the appearance of vaginal or cervical cancers in the daughters with whom they were pregnant at the time. Recent studies clearly show an increased rate of genital abnormalities in similarly exposed sons. So far there have been no definitive findings regarding testicular cancer or fertility in these men.
  - —Furazolidone, one of the nitrofurans, has been shown to cause cancer in laboratory animals.

3. The health risks from the development of bacterial resistance to antibacterial in feed are of greater concern than the risks of cancer from DES and furazolidone as used in livestock practices.

- The proposed FDA regulations would define "no residue" as an added cancer risk of one in one million per lifetime exposure. As determined under present standards of detection from present levels of use, the residue concentrations of DES and furazolidone expected in food animal byproducts border on this general range of acceptable risk. But FDA has indicated that, according to newer methods of measurement, the potential cancer risks from both DES and furazolidone will be higher than this proposed target risk.
- Loss of effectiveness of the most widely used antibacterial (i. e., tetracycline and penicillins) and of other antibacterial with plasmid-mediated resistances poses risks to both human and animal health, Therapeutic failure with these antibacterial would lead to large but presently unquantifiable morbidity and mortality in humans and animals. Once significant effects on human and animal health do become widely observable and quantifiable, it may be too late to address the problem. The development of alternative antibacterial may be one approach to alleviating increased morbidity and mortality, but this approach requires a great deal of time and would not be of immediate use, and it is likely that in time a resistance problem would develop in them as well.
  - —The percent of bacteria that are resistant to one or more antibacterial

has been increasing. The portion of this increase attributable to the subtherapeutic use of antibacterial in food animals and the portion attributable to human use, especially inappropriate or unnecessary use, cannot be measured directly. However, the fact that antibacterial are used for food animals in such large amounts and that animals and humanscanand do exchange bacteria with actual or potential drug-resistance properties leads to the conclusion that the addition of drugs to animal feed is a significant contributor to the increase in antibacterial-resistant bacteria.

4. **Most of these drugs could be replaced with alternative drugs** that **are already approved by FDA.**

   - In addition, the FDA proposals would not ban tetracycline in cases where replacement antibacterial were not available.

5. **The economic consequences of removing these drugs could be significant over the short term. Production may be decreased in the period immediately following a ban, but higher prices may offset the decrease in quantity and may lead to higher producer incomes. But consumer prices would also be higher.**

   - The long-term consequences are less certain, probably resulting in small decreases or no changes in production and small increases in both consumer prices and overall producer incomes.

6. **The tradeoff is therefore between immediate economic benefits and future health risks. These decisions involve value judgments that cannot be based simply on monetary considerations. And the lack of scientific certainty on the magnitude of both the probable health risks and the attributed increases in meat production makes the formulation of a balance-sheet approach difficult.**

CONGRESSIONAL OPTIONS

Option 1
Allow FDA to Decide the Issues, Subject to Congressional Oversight

FDA's proposed actions include:

1. ban the addition of low levels of penicillin in animal feeds,
2. restrict similar uses of tetracycline to situations where replacement antibacterials are not available,
3. monitor cross-contamination of feeds by antibacterial, and
4. ban all uses of nitrofurans and DES.

As an alternative to the actions on penicillin and tetracycline, FDA has proposed that their distribution in feed premixes be limited to feed mills holding approved medicated feed applications and to licensed veterinarians. The purpose of these proposals is to alleviate the drug-resistance problem by reducing the **continuous** use of these antibacterial.

The possibility exists that **total** penicillin and tetracycline use may be unchanged after the initial period of adjustment, as producers may increase drinking water and/or therapeutic uses. The impact of everyday use in drinking water would be comparable to the sustained antibacterial pressure from feed premixes. But therapeutic use may not reflect similar risks even though the total amount used might equal that for feed additive uses. Therapeutic use involves higher doses for much shorter periods of time.

Other, less controversial, steps can be taken to decrease continuous exposure to antibacterials. Close monitoring of cross-contamination of feeds and subsequent corrective actions should lead to decreased unintentional antibacterial exposure. Most of the evidence on the effectiveness of drug use in disease prevention, weight promotion, and feed efficiency reveals that the young bird or animal benefits the most. Some decrease in

use could probably be achieved if the period of use is limited to the early part of a bird's or animal's life and carefully monitored to assure that such use does not extend beyond that period.

The replacement antibacterial available for penicillin and tetracycline include some that also cause gram-negative bacterial resistance, but usually not as much as penicillin and tetracycline cause. Others may select for resistance among gram-positive bacteria, which at this time present less of a known problem than gram-negative bacteria. Other antibacterial are not known to select for resistance among either gram-negative or gram-positive bacteria.

For the nitrofurans and DES, the outcomes depend on FDA's current attempts: (1) to adopt new methods of measuring residue concentrations and (2) to define carcinogenic "no residue" as residue concentrations that result in added cancer risks of $1/10^6$ per lifetime exposure. Calculations of added risk based on the limits of current methods to measure residue concentrations indicate that the risks border on the $1/10^6$ target. However, FDA has indicated that, according to newer methods of detecting residues and their metabolic products, both DES and the nitrofurans would exceed the target risk of $1/10^6$.

Option 2
Enact Legislation Requiring Economic as Well as Scientific Assessments of Benefits and Risks

Objections filed against proposed regulations by FDA often raise economic issues. Apart from the laws under FDA's administration, most Federal agencies involved in regulating health problems can or are required to consider the economic impacts of their actions. A comparative examination of those Federal agencies using and not using such economic criteria may show whether or not these different criteria lead to different conclusions. Or the law could be changed to require the explicit evaluation of economic impacts along with scientific data on benefits and risks.

Much of the impetus for legislating such changes has come from those who want the monetary worth of benefits to be considered. However, if monetary values were established for benefits, they also have to be established for the risks, It is far more difficult to reach agreement on monetary values for risks than it is for benefits in this instance. Moreover, even if monetary values are established for benefits and risks, that does not resolve the fundamental problem of deciding when risks or benefits should prevail.

Option 3
Enact Legislation Removing the Special Approach to Carcinogens in Food Regulation

Present legislation already provides an exemption for drug residues in meat and other edible byproducts of food animals. The all-or-nothing approach of the Delaney clause will be avoided if FDA succeeds in implementing its target risk approach (defined as an added lifetime exposure risk of $1/10^6$ of developing cancer). In assessing risks from carcinogenic agents, the techniques for defining the target risk are still in a primitive state. There are major problems in setting an appropriate target risk, in deciding on methods of extrapolation, and in detecting residues of some substances even at the target-risk level. But these are all problems related to setting the level of use, not to determining whether a substance should be banned,

Option 4
Require FDA to Decrease Therapeutic Use of Antibacterial in Human and Veterinary Medicine as Well as in Food Animal Production

Both human and animal antibacterial uses contribute to the problem of drug-resistant organisms. Of the antibacterial produced in the United States, nearly half are used in animal feeds or for other nonhuman purposes. The review of the evidence on risks has shown that humans and animals serve as common hosts for bacteria and that resist-

ance transfer is not limited to those animals and humans in close proximity to animals given low-level doses of antibacterial in their food.

The majority of resistance in human bacterial populations is probably caused by widespread use of antibacterial in humans, in which overuse undoubtedly occurs as it does in both therapeutic and supplemental animal uses, However, regardless of why antibacterials are given, the key facts concerning the plasmid problem are that: (I) at any point in time, the number of animals exposed to antibacterial far exceeds the number of humans exposed, and (2) the length of therapy in humans averages less than 10 days, while antibacterial-supplemented animal feed use is often continuous.

As for methods of decreasing therapeutic and subtherapeutic uses of antibacterial, it would be easier to control and monitor the addition of antibacterial to feeds than it would be to regulate the practices of veterinarians and physicians.

Option 5
Approve Future Drugs Only if They Are More or Equally Effective as Those Already Approved

It is the most widely used antibacterial that are contributing to antibacterial resistance, and a limitation based on relative effectiveness would most likely aggravate the problem by discouraging the development of new antibacterial,