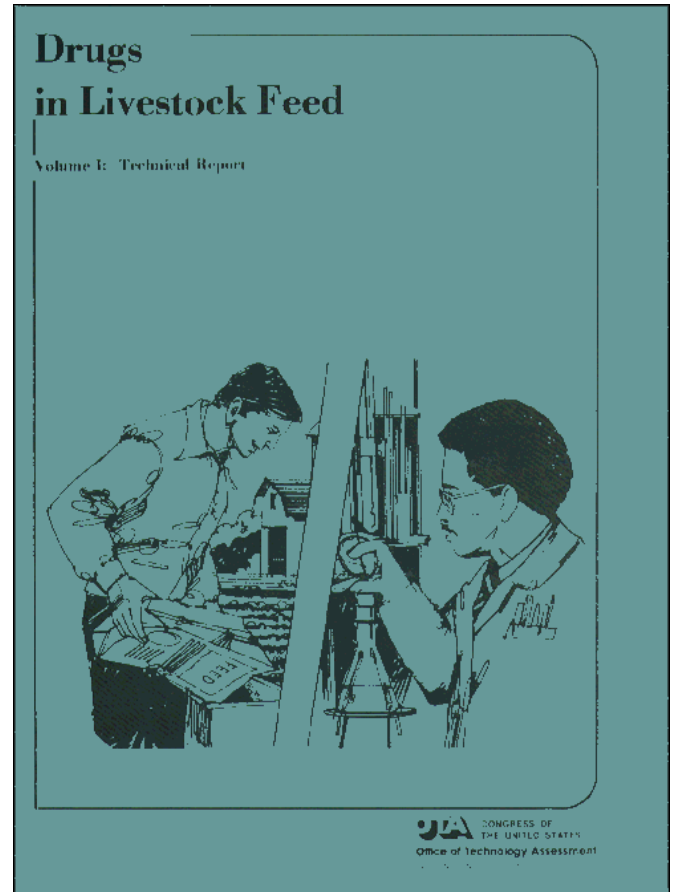


*Drugs in Livestock Feed*

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# Foreword

This report addresses the question of the continued use of certain drugs in livestock feed.

The assessment was undertaken at the request of Senator Herman E. Talmadge, Chairman of the Senate Committee on Agriculture, Nutrition, and Forestry.

The Office of Technology Assessment utilized a diverse range of personnel and methodologies for this assessment. An overall assessment advisory panel was appointed and individual papers dealing with the key issues were commissioned. This work was supplemented by a review of Food and Drug Administration documents, input from public participation meetings, and critical review of draft reports by a wide spectrum of individuals. These wide-ranging inputs from public interest and consumer representatives, agribusiness and producers, scientific experts, and Government officials helped shape the study and the congressional options. To all of these people OTA acknowledges a deep debt. Without their individual and institutional assistance and cooperation the report would not have been possible. This report is an OTA staff synthesis and does not necessarily reflect the position or views of any particular individual.

A handwritten signature in black ink, reading "John H. Gibbons". The signature is written in a cursive style with a large, prominent initial "J".

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

**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<sup>6</sup> 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<sup>6</sup>. 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 non-human 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 are defined in the glossary.

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 antibacterials. The resident bacteria in the intestines of animals and humans receiving antibacterials are soon replaced with resistant resident bacteria and thus serve as a reservoir for the spread of plasmid-mediated resistance to antibacterials.

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. gonorrhoea* 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. gonorrhoea* 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 neces-

sary for physicians to run sensitivity tests to determine alternative drugs to which a given strain of bacteria is still sensitive. Certain strains of gonorrhoea 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 antibacterials 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 sen-

sitive 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  $1/10^6$  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: (1) laboratory evidence provides scientific support for the identified benefits and risks; (2) 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 pre-

vention, 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. gonorrhoea*, 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 antibacterials 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 antibacterials with plasmid-mediated resistances poses risks to both human and animal health. Therapeutic failure with these antibacterials 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 antibacterials 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 antibacterials

has been increasing. The portion of this increase attributable to the sub-therapeutic 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 humans can and 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: (1) 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,

Chapter II

# FEDERAL REGULATIONS

# FEDERAL REGULATIONS

## REGULATORY BASIS

Except for minor involvement by several other Federal agencies, the safety, wholesomeness, and proper labeling of the food supply are the responsibility of the Food and Drug Administration (FDA) of the Department of Health, Education, and Welfare (HEW), and of the U.S. Department of Agriculture (USDA). USDA has concurrent jurisdiction with FDA over certain meat and poultry products through the Federal Meat Inspection Act<sup>1</sup> and the Poultry Products Inspection Act.<sup>2</sup> USDA is authorized to conduct its own inquiry into the safety of such products, but either through law or administrative deference, USDA's activities regarding safety involve enforcing decisions that have been made by FDA (USDA, 1978).

FDA's authority over substances added to animal feeds and over animal drugs comes primarily from two sections of the Federal Food, Drug, and Cosmetic Act (FFDCA):<sup>3</sup> (1) food additives, and (2) new animal drugs.

A substance is considered a food additive if:

... [Its] . . . intended use . . . results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized . . . to be safe under the conditions of intended use . . .<sup>4</sup>

To avoid regulation as a food additive, the petitioner must either provide evidence that the substance does not become a component or otherwise affect the characteristics of

food or, if it does, provide evidence that it is generally recognized as safe under the conditions of intended use.

The FFDCA expressly excludes "new animal drugs" from the definition of "food additive" and regulates them under a separate section of the law. New animal drugs are treated in the same way as new drugs for human use. An application must contain:

1. Full reports of investigations which have been made to show whether or not such drug is safe and effective for use;

2. A full list of the articles used as components of such drug;

3. A full statement of the composition of such drug;

4. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

5. Such samples of such drug and of the articles used as components thereof, of any animal feed for use in or on which such drug is intended, and of the *edible* portions or products (before or after slaughter) of animals to which such drug (directly or in or on animal feed) is intended *to be* administered, as the Secretary may require;

6. Specimens of the labeling proposed to be used for such drug, or in case such drug is intended for use in animal feed, proposed labeling appropriate for such use, and specimens of the labeling for the drug to be manufactured, packed, or distributed by the applicant;

7. A description of practicable methods for determining the quantity, if any, of such drug in or on food, and any substance formed in or on food, because of its use; and

8. The proposed tolerance or withdrawal period or other use restrictions for such drug if any tolerance or withdrawal period or other use restrictions are required in order to

<sup>1</sup>21 U.S.C. 601 et seq.

<sup>2</sup>21 U.S.C. 451 et seq.

<sup>3</sup>21 U.S.C. 301 et seq.

<sup>4</sup>21 U.S.C. 321(s).



assure that the proposed use of such drug will be safe (emphasis added),<sup>7</sup>

Some of the grounds for refusing the application include:

(A) [T]he investigations . . . do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

(B) [T]he results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; . . .

(D) [U]pon the basis of the information submitted, . . . or upon the basis of any other information . . . with respect to such drug . . . there is insufficient information to determine whether such drug is safe for use under such conditions;

(E) [E]valuated on the basis of the information submitted . . . and any other information with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; . . .

(H) [S]uch drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations . . .) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals . . . .<sup>6</sup>

The last reason for refusal enumerated above is one of the Delaney clauses in FFDCA that bans the use of carcinogenic substances that enter the food supply. The clause is similar to that applicable to food additives. In the latter, the exception to a total ban is for “the

use of a substance as an ingredient of feed for animals which are raised for food production.”

For animal feed ingredients and animal drugs, the law directs the Secretary to promulgate regulations defining when “no residue” will be found, (It should be noted that for noncarcinogens, residues are allowed, subject to safety considerations [see numbers 5, 7, and 8, supra, on information to be contained in new animal drug applications]). For food additives generally, the definition itself includes the finding that the substance becomes or may reasonably be expected to become a component of food. Thus once a substance is legally labeled a food additive and is found to be a carcinogen, it is automatically banned because, by definition, it is present in the food.

Finally, some of the grounds for withdrawing approval for animal drugs include: (1) experience or scientific data showing that such drug is unsafe for use under the conditions of use on which the application was approved; (z) new evidence, evaluated together with the evidence available when the application was approved, showing that the drug is not shown to be safe under the approved conditions of use; and (3) new evidence, evaluated together with the evidence available when the application was approved, showing that there is a lack of substantial evidence that the drug will have the effect claimed under the conditions of use.<sup>7</sup>

In order to avoid food additive status, a substance must be “generally recognized as safe” (GRAS) “under the conditions of intended use” if it enters the food. But a food additive is unsafe and prohibited from use unless a regulation is issued “prescribing the conditions under which such additive may be safely used.” Although the language is nearly identical, the practical difference is that food additive status gives FDA authority to prescribe the actual conditions of use.

For drugs, FFDCA requires that the applicant provide adequate data on both the safety and effectiveness of the drug under the in-

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<sup>6</sup>21 U.S.C. 360(b).

<sup>7</sup>21 U.S.C. 360(b)(d)(1).

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<sup>7</sup>21 U.S.C. 360( b)(e)(1).

tended conditions of use, but FDA may deny or withdraw the approval on either safety or effectiveness grounds. For example, FDA may deny the use of a drug for some purposes and approve it for others, even if it is safe to be used under all of the petitioned conditions. Here, effectiveness would be the ultimate determinant of approval. Or, conversely, FDA may deny use of a drug for some purposes and approve it for others even if it were effective for all the petitioned conditions. Here safety would be the ultimate determinant of approval.

Some have criticized FDA for failing to consider socioeconomic benefits and costs in determinations allowing or disapproving the use of food additives and drugs. These critics claim that present law allows the consideration of such costs and benefits. Whether or not the law should include these considerations is a separate question. But FFDCA is quite conspicuous in its absence of language supporting such claims.

The law is clear that safety and effectiveness will be determined by scientific assessments:

In determining whether such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, the Secretary shall consider,

among other relevant factors, (A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug, (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance, (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use.

... [The] term substantial evidence means evidence consisting of adequate and well-controlled investigations, including field investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Although the statute presents these as independent assessments and does not provide any guide for FDA to decide when effectiveness outweighs safety and vice versa, these decisions are in reality risk-benefit assessments limited to scientific considerations.

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<sup>21</sup> U. S. C. 360(b)(2-3).

## CURRENT ACTIVITIES

Antibacterial used in human treatment are often used in animals, and limitations on use have been proposed for animal antibacterials, particularly for their subtherapeutic uses in animal feed. Over 40 percent of all the antibacterial produced in this country are used as feed additives or for other nonhuman purposes. Research on antibacterial-resistant bacteria has shown that, in some cases, genes for antibacterial resistance can be transferred between bacterial types and that humans and animals are interchangeable hosts for such bacteria.

Another major concern has been the possibility of more direct, adverse human health effects from eating meat, eggs, etc., contain-

ing residues of drugs. The health effect primarily at issue here is carcinogenesis. Federal law prohibits the use of carcinogenic food additives and also requires that food products from animals given carcinogenic substances for any purpose (e. g., therapeutic, growth promotant, etc. ) cannot contain any residue of such carcinogens. Among the animal drugs in use, furazolidone and DES are known carcinogens,

The antibacterial problem began to be addressed in the 1960's in the United States and other countries. One consequence was Great Britain's decision in 1971 to restrict the use of antibacterial for food animals and, in particular, their feed-additive uses.

Similar reviews were initiated in the United States by the FDA (FDA, 1966, 1972, 1977). The general thrust of these reports was similar to the report leading to Great Britain's curtailment of antibacterial for food animal uses, although they differed in the emphasis placed on specific antibacterial. There were also differences on specific conclusions and recommendations between the Subcommittee on Antibiotics in Animal Feeds, its parent National Advisory Food and Drug Committee to the FDA, and the FDA itself. (See USDA, 1978, for a chronicle of these events.)

As a consequence of these reviews, in 1973 FDA began a series of actions to update the effectiveness and safety data of approved animal antibacterial and to extend the criteria to new antibacterial. These efforts subsequently were focused on the penicillins and tetracycline which, in the words of the FDA Commissioner, "were chosen as the initial subjects of regulation because of their importance in the treatment of human disease" (Kennedy, 1977).

In 1977, FDA proposed to withdraw approval of the use of penicillin and to restrict the use of tetracycline in feed premixes. The reasons for the proposed ban on the use of penicillin were that: (1) the new evidence on the hazards of bacterial resistance had shown that such use of penicillin was not safe, and (2) the applicants had failed to meet the record maintenance requirements of the law.<sup>10</sup> Similar reasons were given for the proposed restrictions on tetracycline, where they would be prohibited except where adequate substitutes for disease prevention were not available.<sup>11</sup>

As a corollary action, the FDA had proposed to limit the distribution of animal feed premixes containing penicillin and/or tetracycline to feed mills holding approved medicated feed applications for manufacturing these medicated feeds and to restrict further the distribution of those feeds to the order of a licensed veterinarian as part of the record maintenance requirements of the law.<sup>12</sup> Pub-

lic hearings on the proposal raised concerns over such matters as the inadequacy of the numbers, distribution, and kinds of veterinarians available to diagnose and write prescriptions under the proposed requirements; the economic disadvantage of the proposal to small producers; circumvention of the proposed restrictions, since soluble powder dosage forms would not be subject to the proposal; and allegations that it would interfere with the practice of veterinary medicine and State control over the feed industry. The FDA Commissioner therefore decided to delay a decision until such issues were resolved.<sup>13</sup>

Meanwhile, the U.S. Congress has taken several actions to delay the final outcome of these proposals. In May 1978 the House Appropriations Subcommittee on Agriculture and Related Agencies earmarked \$250,000 for fiscal year 1979 for a study on antibacterials used in animal feed, to be conducted by the National Academy of Sciences. In July 1978 the House Agriculture Committee approved a resolution to delay the proposed ban until new research studies could be completed and formal evidentiary hearings held. And in September 1978 House and Senate conferees agreed to require the FDA to hold up the proposals until such research and evidentiary hearings were completed.

The congressional actions have led the Director of the FDA's Bureau of Veterinary Medicine to conclude that the outcome of these proposals would not be reached before 1980 and that "(p)ublic and industry reaction to these proposals have made it abundantly clear that livestock producers are desirous of having penicillin, tetracycline, and similar antibiotics remain in animal feeds. Unless substitutions of antibiotics currently on the market are more readily accepted and unless viable alternatives to potentially restricted antibiotics can be developed, most likely the public outcry will continue regarding the proposed regulations. These are practicalities that are incident to the national acceptance of the proposed regulations" (Food Chemical News, Sept. 25, 1978).

Two other classes of antibacterial raise separate safety issues, in addition to the

<sup>10</sup>21 CFR 558.15

<sup>11</sup>42 F. R., 43772, Aug. 30, 1977.

<sup>12</sup>42 F. R. 56264, Oct. 21, 1977.

<sup>13</sup>43 F. R. 3032, Jan. 20, 1978.

<sup>14</sup>43 F. R. 35059, Aug. 8, 1978.

safety problems reflected in these proposals to restrict the use of penicillin and tetracycline. The sulfa drugs (i. e., sulfamethazine for swine feed and drinking water) have been found to have a high violation rate for residues in slaughtered hogs. And one of the nitrofurans, furazolidone, is carcinogenic in laboratory animals.

Specific tolerances for residues of sulfa drugs in edible tissues of food-producing animals are set at 0 to 0.1 parts per million (ppm).<sup>14</sup> For sulfamethazine the tolerance level in swine is 0.1 ppm. These tolerances are accomplished by specified withdrawal time periods between last treatment and slaughter. For the last 6 months of 1977, USDA had found that the percentage of sampled hogs in violation of the 0.1-ppm residual tolerance averaged 13.1 percent. An FDA study concluded that 54 percent of the violations were probably caused by contamination of the withdrawal feed (which should not contain the drug) through insufficient cleanout of equipment, 26 percent were probably caused by failure to observe the withdrawal period, 12 percent were caused by feeding or feed-mixing errors, and 9 percent from other causes (FDA, 1979). New research data led FDA to change the preslaughter withdrawal time for sulfamethazine in swine feed and drinking water from 5, 7, or 10 days to 15 days.<sup>15</sup> FDA also expected to issue a proposal to establish action levels for cross-contamination carryover of animal drugs (including but not limited to sulfamethazine in swine feed) by the end of 1978 (*Food Chemical News*, Oct. 16, 1978).

Three nitrofurans were approved previously for feed premixes; furazolidone (the most widely used), nihydrazone, and nitrofurazone. Furaltadone, a nitrofurantoin, is used in injectable form to treat mastitis in lactating cows. Assay methods to meet the "no residue" requirement have not been approved for the nitrofurans. Furazolidone has produced cancer in laboratory animals. The other three compounds are suspected of being carcinogens but have not been adequately tested. All uses of nihydrazone were revoked because no

hearings were requested. Of the two sponsors of furaltadone, one approval was revoked because a hearing was also not requested.<sup>16</sup> Actions were pending against furazolidone and nitrofurazone as of January 1979.

The "no residue" exception to the ban on carcinogenic substances added to food is sometimes referred to as the "DES exception." DES has been known to be carcinogenic almost from the time it was first produced in 1938 (DES Task Force Report, 1978), its carcinogenic effect generally attributed to its estrogenic properties. The Food Additive Amendments of 1958<sup>17</sup> contained the first Delaney clause barring carcinogenic food additives. In order to allow the continued use of DES in food animals, a "no residue" exception was inserted in the Animal Drug Amendments of 1968.<sup>18</sup>

DES is added to feed or used in implants to fatten beef cattle. To a lesser extent, implants are used in lambs. Other drugs used to fatten cattle include: (1) melengesterol acetate (MGA) in feed for heifers, with the additional purpose of suppressing estrus; (2) monensin in feed, authorized only for increasing feed efficiency, although it also is authorized for disease prevention and growth promotion in poultry; (3) estradiol benzoate plus testosterone propionate for heifers by implants; (4) estradiol benzoate plus progesterone for steers by implants; and (5) zeranol implants for calves, cattle, and lambs. Estradiol monopalmitate injections are authorized for use in roasting chickens. In addition to DES and the estradiols, zeranol has direct estrogenic activity, MGA (a synthetic progesterone) and progesterone result in increased estrogen production in treated heifers. Monensin is a compound produced by the bacterium *Streptomyces cinnamonensis* and is still used as an anticoccidial in poultry.

Starting in 1972, FDA first banned the use of DES in feeds and, later, in implants, on evidence of residues in beef livers detected

<sup>14</sup>21CFR 566.625-.700.

<sup>15</sup>43F.R. 19385, May 5, 1978.

<sup>16</sup>42 F.R. 17526, Apr. 1, 1977; 42 F.R. 18619, Apr. 8, 1977.

<sup>17</sup>Public Law 85-929.

<sup>18</sup>Public Law 90-399.

<sup>19</sup>21 CFR 522, 21 CFR 558.

by a new method. The withdrawal was vacated in 1974 by court order on the grounds that an insufficient notice of opportunity for hearing had been given to the affected parties because FDA had relied on a method of testing that it had not approved. Administrative hearings have been concluded and in September 1978 the administrative law judge recommended that DES be banned from feed and as an ear implant (*CNI Weekly Report*, Oct. 5, 1978). FDA's decision had not been made as of January 1979,

A closely related issue has been the method by which "no residue" would be determined. The increasing sensitivity of methods used to detect such residues has led FDA to seek methods "to keep the agency from always chasing zero in terms of an allowable tolerance of substances that will be administered to food-producing animals" (*Food Chemical News*, Oct. 16, 1978).

In early 1977, FDA issued new procedures and criteria for evaluating the assays for carcinogenic residues in edible products of animals.<sup>20</sup> Essentially, the intention of the new regulations was to cease trying to quantify the actual amount of carcinogenic residue because of the problem of chasing zero

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<sup>20</sup>42F.R. 10412, Feb. 11, 1977.

(newer methods were able to identify substances at less than one part per billion). Instead, the new regulations adopted a method whereby "no residue" would be defined through extrapolation from animal test data to man so that the lifetime risk to an individual would be less than 1 in 1 million (1/10<sup>6</sup> or 10<sup>-6</sup>). The published regulation stated that "such a risk level can properly be considered of insignificant public health concern." According to an FDA spokesman, the new method would "provide a mechanism whereby a reasonably safe level may be established and then, irrespective of further analytical developments, there will be that expectation that the originally set level will remain until toxicological evidence rather than analytical evidence demonstrates that to be an incorrect tolerance" (*Food Chemical News*, Oct. 16, 1978).

These regulations were revoked by FDA<sup>21</sup> after the U.S. District Court for the District of Columbia remanded the case to FDA "for further findings to rectify the omissions in the current record."<sup>22</sup> FDA expects to issue proposed new regulations in 1979.

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<sup>21</sup>43F.R. 22675, May 26, 1978,

<sup>22</sup>*Animal Health Institute v. Food and Drug Administration*, Civil No. 77-806, D. D. C., Feb. 8, 1978,

## APPROVED USES

Subtherapeutic uses of penicillin, tetracycline, sulfas, and nitrofurans vary according to the food animal. They may be used alone or in combination with each other or with other drugs. These other drugs may be antibacterial, anticoccidials, antihelminthics, or non-antibacterials, such as DES or other growth promotants. One drug may be approved for only some uses, but when combined with other drugs, the resulting feed mix may cover all uses.

**penicillin** is used extensively in poultry feeding programs and, to a lesser extent, in swine feeds, usually in combination with other drugs (sulfa, tetracycline, bacitracin, etc.). There are no approved uses for pen-

icillin in animal feed for cattle or sheep. Penicillin may be used alone for all possible indications—i.e., growth promotion, feed efficiency, disease prevention, and disease treatment. It also may be used in combination with other drugs.

Tables 1, 2, and 3 summarize the use of penicillin in animal feeds for chickens, turkeys, and swine. In chickens and turkeys, penicillin, when used alone, is approved for the separate uses of growth promotion, feed efficiency, disease prevention, or disease treatment. The amount of penicillin per ton of feed would vary for these uses. It may also be combined with other antibacterial so that the completed feed is approved for all uses,

**Table 1. –Approved Uses for Penicillin in Chicken Feeds**

<i>In combination with</i>	<i>Uses<sup>a, b</sup></i>
	Growth promotion, feed efficiency
	Disease prevention
	Disease treatment
Streptomycin <sup>c</sup>	Growth promotion, feed efficiency
Streptomycin <sup>c</sup>	Maintain or Increase egg production
Streptomycin <sup>c</sup>	Disease prevention
Streptomycin <sup>c</sup>	Disease treatment
Amprolium <sup>d</sup>	Growth promotion, feed efficiency
Amprolium <sup>d</sup> and streptomycin <sup>c</sup>	Treatment of disease
Amprolium <sup>d</sup> and ethopabate <sup>e</sup>	Growth promotion, feed efficiency
Amprolium, d ethopabate, and streptomycin <sup>c</sup>	Treatment of disease.
Bacitracin methylene disalicylate <sup>c</sup>	Maintaining or Increasing hatchability of eggs
Bacitracin methylene disalicylate <sup>c</sup>	Treatment of disease
Bacitracin zinc <sup>c</sup>	Treatment of disease
Buquinolate <sup>e</sup>	Growth promotion, feed efficiency
Hygromycin B <sup>f</sup>	Treatment of disease
Hygromycin B <sup>f</sup> and streptomycin <sup>c</sup>	Treatment of disease
Hygromycin B <sup>f</sup> and bacitracin <sup>c</sup>	Treatment of disease

<sup>a</sup>For a specific food animal different concentrations of same drug may be approved for different purposes –e.g. for chickens one concentration is approved for growth promotion and feed efficiency another concentration for prevention of disease

<sup>b</sup>Specific diseases omitted

<sup>c</sup>Same indications for use as penicillin

<sup>d</sup>For development of active immunity to or prevention of coccidiosis

<sup>e</sup>For prevention of coccidiosis

<sup>f</sup>For control of worms

SOURCE: 21 CFR 558 and related sections

even though the separate antibacterials are not. In swine, when penicillin is combined with tetracycline and sulfa, the completed feed is approved for all uses.

Tetracycline, as oxytetracycline or chlortetracycline, is used in all food animals. Like penicillin, it may be used alone or in combination with other drugs, and for all or only some of the approved uses. Tables 4, 5, 6, and 7 summarize the use of tetracycline in animal feed for chickens, turkeys, swine, cattle, and sheep. Tetracycline is the most widely used antibacterial in feed.

Sulfa drugs are used primarily in swine in combination with penicillin and tetracycline (tables 3 and 6) for disease treatment, disease prevention, growth promotion, and feed efficiency, or with tylosin for disease prevention. They also are used in combination with tetracycline for disease prevention in cattle (table 7). Sulfaethoxy-pyridazine premixes are used for disease treatment in swine and cattle for use by or on the order of a licensed veterinarian.<sup>23</sup> Sulfadimethoxine is used in chicken and

<sup>23</sup>21CFR 558.579.

**Table 2. –Approved Uses for Penicillin in Turkey Feeds**

<i>In combination with</i>	<i>Uses<sup>a, b</sup></i>
	Growth promotion, feed efficiency
	Disease prevention,
	Disease treatment
Streptomycin	Growth promotion, feed efficiency
Amprolium <sup>d</sup>	Growth promotion, feed efficiency.
Amprolium <sup>d</sup> and streptomycin <sup>c</sup>	Disease treatment
Amprolium <sup>d</sup> and bacitracin <sup>c</sup>	Disease treatment
Bacitracin methylene disalicylate <sup>c</sup>	Disease treatment
Bacitracin zinc <sup>c</sup>	Disease treatment

<sup>a</sup>For a specific food animal different concentrations of the same drug may be approved for different purposes

<sup>b</sup>Specific diseases omitted

<sup>c</sup>Same indications for use as penicillin

<sup>d</sup>For development of active immunity to or prevention of coccidiosis

SOURCE: 21 CFR 558 and related sections

**Table 3. –Approved Uses for Penicillin in Swine Feeds**

<i>In combination with</i>	<i>Uses<sup>a, b</sup></i>
	Growth promotion, feed efficiency
Streptomycin <sup>c</sup>	Growth promotion feed efficiency
Streptomycin <sup>c</sup>	Disease prevention
Streptomycin <sup>c</sup>	Disease treatment
Chlortetracycline <sup>c</sup> and sulfamethazine <sup>c</sup>	Growth promotion, feed efficiency, disease prevention, disease treatment
Chlortetracycline <sup>c</sup> and sulfathiazole <sup>c</sup>	Growth promotion, feed efficiency, disease prevention, disease treatment.
Bacitracin methylene disalicylate <sup>c</sup>	Disease treatment
Bacitracin zinc <sup>c</sup>	Disease treatment

<sup>a</sup>For a specific food animal different concentrations of the same drug may be approved for different purposes

<sup>b</sup>Specific diseases omitted

<sup>c</sup>Same indications for use as penicillin

SOURCE: 21 CFR 558 and related sections

turkey feeds for disease prevention. In chicken feed, it may be combined with a growth promotion and feed efficiency drug.<sup>24</sup> There are no approved uses for sheep feed. These uses of sulfa are summarized in table 8.

**Nitrofurans** are used extensively in chickens and turkeys and to a lesser extent in swine. Of the two nitrofurans still approved for use in feeds, furazolidone is the most widely used. It and, to a lesser extent, nitrofurazone are used in poultry for all four purposes—i.e., growth promotion, feed efficiency, disease prevention, and disease treatment. Furazolidone is used in sows for prevention of bacterial scours in baby pigs and is added to feed 1 week before farrowing and 2

<sup>24</sup>21CFR 558.575.

weeks after farrowing. It is also used for disease-prevention and treatment purposes. It is concurrently approved for growth promotion when the swine are on the medication for the purposes outlined. These uses are summarized in table 9.

**DES** is used to promote growth and increase feed efficiency in cattle and, to a lesser extent, in sheep. In feeds, it is given alone or in combination with antibiotics. It is administered separately by ear implantation. These uses are summarized in table 10.

**Table 4.—Approved Uses for Tetracycline in Chicken Feeds**

<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
----	Growth promotion, feed efficiency.
----	Disease prevention.
----	Disease treatment.
Monensin <sup>d</sup> (as coccidiostat).	Disease prevention, disease treatment.
Nequinat <sup>e</sup>	Disease prevention, disease treatment.
Robenidine hydrochloride	Disease prevention,
Amprolium <sup>e</sup>	Disease treatment.
Amprolium and ethopabate <sup>f</sup> .	Disease prevention, disease treatment,
Buquinolate <sup>g</sup>	Disease prevention, disease treatment,
Clopidol <sup>f</sup>	Disease prevention.
Decoquinat <sup>h</sup>	Disease prevention, disease treatment.
Hygromycin B <sup>i</sup>	Disease treatment.
Roxarsone <sup>j</sup>	Growth promotion, feed efficiency.
Zoalene <sup>k</sup>	Disease prevention, disease treatment.

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>For a specific food animal, different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>Same indications for use as penicillin  
<sup>e</sup>For development of active immunity to or prevention of coccidiosis  
<sup>f</sup>For prevention of coccidiosis  
<sup>g</sup>For prevention of coccidiosis, growth promotion, and feed efficiency  
<sup>h</sup>For prevention and treatment of disease  
<sup>i</sup>For control of worms  
<sup>j</sup>For growth promotion, feed efficiency  
<sup>k</sup>For development of active immunity to coccidiosis  
 SOURCE 21 CFR 558 and related sections

**Table 5.—Approved Uses for Tetracycline in Turkey Feeds**

<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
----	Growth promotion, feed efficiency.
----	Disease prevention,
----	Disease treatment.
Roxarsone <sup>d</sup> . . . . .	Growth promotion, feed efficiency, disease prevention,

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>Different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>For growth promotion, feed efficiency  
 SOURCE 21 CFR 558 and related sections

**Table 6.—Approved Uses for Tetracycline in Swine Feeds**

<i>in combination with</i>	<i>Uses<sup>b c</sup></i>
--	Growth promotion, feed efficiency,
----	Disease prevention.
----	Disease treatment.
Penicillin and sulfamethazine <sup>d</sup>	Growth promotion, feed efficiency, disease prevention, disease treatment.
Penicillin and sulfathiazole <sup>d</sup>	Growth promotion, feed efficiency, disease prevention, disease treatment.
Hygromycin B <sup>e</sup> . . . . .	Disease treatment.

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>Different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>Same uses as for tetracycline  
<sup>e</sup>For control of worms  
 SOURCE 21 CFR 558 and related sections

**Table 7.—Approved Uses for Tetracycline in Cattle and Sheep Feeds**

<i>Animal</i>	<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
Cattle	----	Growth promotion, feed efficiency, disease prevention.
	Sulfamethazine <sup>d</sup>	Disease prevention.
	Diethylstilbestrol <sup>e</sup> . . . . .	Disease prevention.
Sheep	----	Disease prevention, feed efficiency.

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>Different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>Same uses as for tetracycline  
<sup>e</sup>For growth promotion, feed efficiency  
 SOURCE 21 CFR 558 and related sections

**Table 8.—Approved Uses for Sulfa<sup>a</sup> in Animal Feeds**

<i>An/ma/</i>	<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
Chickens	Ormetoprim <sup>d</sup> Ormetoprim <sup>d</sup> and 3-nitro-4-hydroxy-phenylarsonic acid <sup>e</sup>	Disease prevention
Turkeys	Ormetoprim <sup>d</sup> Ormetoprim <sup>d</sup> and ipronidazole <sup>f</sup>	Disease prevention Disease prevention
Swine		Disease prevention Disease treatment (only for use by or on order of a licensed veterinarian)
	Penicillin <sup>d</sup> and tetracycline	Growth promotion, feed efficiency, disease prevention, disease treatment
Cattle	Tylosin <sup>d</sup>	Disease prevention Disease treatment (only for use by or on order of a licensed veterinarian)
	Tetracycline <sup>d</sup>	Disease prevention

<sup>a</sup>Identity of specific sulfonamide derivatives omitted

<sup>b</sup>Different concentrations of the same drug may be approved for different purposes

<sup>c</sup>Specific diseases omitted

<sup>d</sup>Same uses as for sulfa

<sup>e</sup>For growth promotion feed efficiency

<sup>f</sup>Prevention of blackhead (histomoniasis)

SOURCE 21CFR 558 and related sections

**Table 9.—Approved Uses for Nitrofurans<sup>a</sup> in Animal Feeds**

<i>Animal</i>	<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
Chickens and turkeys	----	Growth promotion, feed efficiency Disease prevention Growth promotion, feed efficiency, disease prevention Disease prevention, disease treatment
Swine	----	Disease prevention, growth promotion Disease treatment, growth promotion.

<sup>a</sup>Furazolidone or nitrofurazone

<sup>b</sup>Different concentrations of the same drug may be approved for different purposes

<sup>c</sup>Specific diseases omitted

SOURCE 21CFR 55815 and 558262

**Table 10.—Approved Uses for Diethylstilbestrol in Food Animals**

<i>An/real</i>	<i>Route of administration</i>	<i>In combination with</i>	<i>Uses</i>
Cattle.	Feed	----	Growth promotion, feed efficiency.
	F e e d	Bacitracin methylene disalicylate <sup>a</sup>	Growth promotion, feed efficiency
	F e e d	Bacitracin zinc <sup>b</sup>	Growth promotion, feed efficiency
	F e e d	Tetracycline <sup>c</sup>	Growth promotion, feed efficiency
	Ear Implant.	----	Growth promotion, feed efficiency
Sheep	Feed	----	Growth promotion, feed efficiency
	Ear implant (lambs)	----	Growth promotion, feed efficiency.

<sup>a</sup>For disease prevention

<sup>b</sup>F, r growth promotion feed efficiency

<sup>c</sup>Aschlortetracycline or oxytetracycline for disease prevention

SOURCE 21 CFR 522640 and 558225



Chapter III

# BENEFIT'S

# BENEFITS

## ANTI BACTERIALS

### Mode of Action

The subtherapeutic uses of antibacterial for food animals include not only disease prevention but also weight promotion and feed efficiency. All antibacterial have the ability to suppress or inhibit the growth of certain micro-organisms, but their chemical composition and effectiveness against specific organisms may vary widely. Yet there is no direct correlation between chemical composition and the weight-promotion and feed-efficiency effects, so even though specific, non-antimicrobial effects can be shown for certain antibacterial, there is disagreement over how low levels of antibacterial bring about increased growth and feed efficiency.

At least three modes of actions have been postulated, and each has varying degrees of research support.

1. **A metabolic effect**, where the antibacterial directly affects the rate or pattern of the metabolic processes in the host animal.
2. **A nutrient-sparing effect**, where antibacterial reduce the dietary requirement for certain nutrients by stimulating the growth of desirable organisms that synthesize vitamins or amino acids, by depressing the organisms that compete with the host animal for nutrients, by increasing the availability of nutrients via chelation mechanisms, or by improving the absorptive capacity of the intestinal tract.
3. **A disease-control effect**, through suppression of organisms causing disease that reduce weight gain but result in no obvious symptoms of disease in the host animal,

There is much evidence that metabolic reactions in the host animal are influenced by antibacterial. For example, tetracycline affects water and nitrogen excretion in rat liver homogenates (Brody et al., 1954). But the rate of metabolism may be influenced by systemic and digestive tract infections and absorption of microbially produced toxins from the gastrointestinal tract, so the metabolic effect could be attributed to a disease-control effect. Furthermore, the metabolic effects cannot account for the growth promotion in animals fed diets supplemented with moderate levels of antibacterial in view of the nature of the animal responses, the tissue levels of antibacterial when added to the diet at growth-promotant levels, and the levels necessary to mediate such biochemical processes. And, as to be discussed shortly, a direct metabolic effect should not vary greatly with environmental conditions.

The nutrient-sparing effect has considerable research support, but it could also be classified as a type of disease-control effect. Certain intestinal organisms synthesize vitamins and amino acids that are essential to animals, and other bacteria require and compete with the host animal for these essential nutrients. Diets containing penicillin may increase the number of intestinal coliforms other than *E. coli* (Anderson et al., 1952), and these organisms may synthesize nutrients that are dietary essentials for the host animal. If a diet is deficient in a specific nutrient, it could be partially corrected by microbial synthesis.

Antibacterial may also depress the growth of organisms competing with the host animal for nutrients. The bacteria most affected by chlortetracyclines are the lactobacilli (March and Biely, 1952). The lacto-

bacilli require amino acids in relatively similar proportional amounts as do pigs, and the levels and sources of protein that support maximum growth in pigs are also near optimum for the multiplication of lactobacilli in the intestinal tract (Kellogg et al., 1964). Those antibacterial most effective in reducing the number of these organisms in the intestinal tract are also the most effective as routine growth promotants (Kellogg et al., 1966).

Antibacterial may also improve absorption of nutrients by the host animal (Catron et al., 1953). Structurally, this seems to be related to thickness of the intestinal wall, which is thinner with rations containing antibacterials versus no antibacterial (Coates, 1953; Russoff et al., 1954, Braude et al., 1955). The thinner wall implies a potential for improved absorption and is assumed to result from the inhibition of the organisms that damage or produce toxins that damage the intestinal tissue.

The nutritive and antibacterial response relationships still appear secondary to the disease-control effect. Early in the history of antibacterial supplements to animal feeds, it was noted that the degree of response to antibacterial was inversely related to the general well-being of the experimental animals. Healthy, well-nourished animals do not respond to antibacterial supplements when housed in carefully cleaned and disinfected quarters that have not previously housed other animals (Speer et al., 1950; Catron et al., 1951; Coates et al., 1951; Hill et al., 1952).

Studies involving clean and contaminated environments illustrate that the response to antibacterial is greater in contaminated or previously used environments. For example, pigs housed in an old barn had an increased growth rate of 14.2 percent versus 7.5 percent in the new barn (table 11). The response of chicks to chlortetracycline in a new environment was a 12.6-percent improvement versus 18.2 percent for chicks from the same hatch that were reared in a previously used environment, and 1.6 percent versus 23.9 percent when penicillin was used (table 12). The relative improvements in growth rates from supplementing diets with antibacterial often are inversely related to the growth rate

**Table 11. —Effect of Chlortetracycline on Weight Gains of Pigs in Different Environments**

Environment and chlortetracycline fed	Daily gain		Feed efficiency <sup>b</sup>	
	Average (g)	Improvement (%)	Average	Improvement (%)
<b>New barn:</b>				
Control	604	—	4.15	—
Chlortetracycline (9 g/ton)	649	7.5	3.92	5.5
<b>Old barn:</b>				
Control	604	—	4.21	—
Chlortetracycline (9 g/ton)	690	14.2	3.78	10.2

<sup>a</sup>J. P. Bowland 1956 Influence of environment on response of swine to antibiotic and/or Vitogal supplements. *Univ. Alberta Press Bull* 41 (2) 12 Alberta Canada  
<sup>b</sup>Units of feed per unit of gain  
 SOURCE Hays 1978 table 7

**Table 12. —Response of Chicks to Chlortetracycline (CTC) and Penicillin in New and Previously Used Environment**

Environment	Treatment	4-week improvement	
		weight (g)	(%)
<b>Bird et al.<sup>a</sup></b>			
<b>New house</b>			
	Control	254	—
	CTC, 10 ppm	286	12.6
<b>Previously used house</b>			
	Control	176	—
	CTC, 10 ppm	208	18.2
<b>Coates et al.<sup>b</sup></b>			
<b>Greenford Lab<sup>c</sup></b>			
	Control	184	—
	Penicillin	187	1.6
<b>Reading Lab<sup>c</sup></b>			
	Control	155	—
	Penicillin	192	23.9

<sup>a</sup>H. R. Bird, R. J. Lillie and J. R. Sizemore 1952 Environment and stimulation of chick growth by antibiotics. *Poultry Sci* 31:907  
<sup>b</sup>M. E. Coates, C. D. Dickinson, G. F. Harrison, S. K. Kon, S. H. Cummins and W. F. J. Cuthbertson 1951 Mode of action of antibiotics in stimulating growth of chicks. *Nature* 168:332  
<sup>c</sup>Reading Lab had been previously used to house chicks but the Greenford Lab had not  
 SOURCE Hays 1978 table 8

of the controls—i. e., the difference in antibacterial response in clean versus contaminated environments is often the result of the controls in the contaminated environment doing poorly in comparison with controls in the clean environment. Tables 13 and 14 summarize this relationship across a number of experiments.

The growth-depressing effect can also build up over time with the continued use of specific animal facilities. This effect from nonspecific infections in a chick-starting facility is summarized in table 15. Emptying, cleaning, and fumigating the facility improved performance but did not approach the level of performance of the first hatch.

## Effectiveness

What is the quantitative gain in livestock production with the use of antibacterial in feed? Have they continued to be effective?

**Table 13. —Relationship Between Growth Rate of Control Animals and Animals Fed Antibiotics (Pigs)**

No. of tests	Daily gain /n weight (g)		Response to anti/b/et/c
	Ant/b/of/c-led		Improvement (%)
	Control animals	animals	
4	94	245	161
1	136	227	67
12	182	336	85
13	227	340	50
1	6 272	449	65
3	1 318	481	51
1	2 363	499	38
1	8 409	563	38
16	454	572	26
36	499	572	15
32	545	627	15
3	9 590	636	8
4	8 636	713	12
20	681	735	8
22	726	790	9
1	772	881	14

<sup>a</sup>Adapted from R Braude H D Wallace and T J Cunha 1953 The value of antibiotics in the nutrition of swine a review *Antibiotics and Chemotherapy* 3:271 SOURCE Hays 1978 table 13

**Table 14.—Relationship Between Growth Rate of Control Pigs and Pigs Fed a Combination of Penicillin and Streptomycin**

Daily gain /n weight of controls (g)	No of comparisons	Improvement over controls by pigs fed antibiotics	
		Gain in weight (0/0)	Feed efficiency (%)
91 to 182	2	220	8.2
181 to 272	3	270	4.5
272 to 363	4	204	5.6
363 to 454	7	161	11.1
454 to 545	9	123	6.4
545 to 636	9	94	1.9
636 to 726	20	56	4.7
726	7	38	1.8
<b>T o t a l</b>	<b>61</b>		
Average Improvement, %		<b>107</b>	<b>51</b>

<sup>a</sup>Data summarized from agricultural experiment station reports 1960 to 1967 V W Hays Biological basis for the use of antibiotics in livestock production *The Use of Drugs in Animal Feeds* Proc Symp Publ 1679 p 11 (Washington DC: National Academy of Sciences 1969) SOURCE Hays 1978 table 14

How effective are specific antibacterial compared to others? These questions are difficult to answer with any degree of precision, but the general conclusions can be made that antibacterial continue to be effective for increasing production and that some antibacterials are clearly more effective in specific food animals than in others.

There are a number of confounding factors that make an evaluation of the quantitative effect difficult. First, antibacterial now are so widely used that most of the experimental data comes from the early years of use—i.e.,

**Table 15.—Effect of a “Nonspecific Infection” on Chick Growth<sup>a</sup>**

Hatch no.	Average gain, 0 to 7 days (g)	Relative gain (%)
1	44.2	100.0
2	42.7	96.6
3	41.5	93.9
4	40.1	90.7
5	42.8	96.8
6	41.8	94.6
7	40.9	92.5
8	40.2	91.0
9	39.5	89.4
10	35.2	79.7
Depopulation and fumigation		
11	37.7	85.3
12	26.2	59.3
Depopulation and fumigation		
13	38.2	86.4
14	34.5	78.1
15	28.3	64.0

<sup>a</sup>H M Scott 1962 The effect of a non-specific infection on chick growth Proc III Nutr Conf p 23 University of Illinois Urbana SOURCE Hays 1978 table 1 f

from the 1950's and early 1960's. For experiments conducted later, especially those in which field trials were used, it is often difficult to tell whether the animals used were previously fed feeds containing antibacterial. And as discussed earlier, the housing conditions of the animals also contribute to the effect of antibacterial usage; previously used facilities usually result in greater response.

Second, controlled experimental conditions often produce results less than those found in field conditions. Aside from cleaner housing in controlled experiments, often less animals are housed per facility, and runt animals usually are not included.

Third, the degree of increased production also may depend on the animal's lifecycle and the conditions of feeding. Responses may vary depending on whether it is calves or heifers/steers being fed, whether they are on high-roughage (hay) or high-energy (grain) diets, whether it is the first few weeks of life versus the whole lifespan of the animal in which feeds are supplemented with antibacterial, etc. Animals are often fed antibacterial-supplemented feed throughout their lifespan, and the effects may be attributable mostly to certain periods of that time.

**Cattle.** Antibacterial approved for growth promotion and feed efficiency are the tetracyclines and bacitracins. Cattle show a greater response to tetracycline on high-roughage,

low-energy rations than on high-grain, high-energy diets. However, increased use of high-grain rations for the finishing of cattle increases the incidence of liver abscesses, and antibacterials are used continuously for prevention. The tetracyclines are the most widely used, but tylosin and bacitracin are also approved for such use. Although related to high-grain diets, the etiology of these abscesses is unknown.

The response to antibacterials varies with the type of feed, feedlot conditions, stress factors, and disease level of the cattle, so results are not consistent. A summary of a large number of experiments shows that tetracyclines at a level of 70 to 80 mgm daily per animal have on the average increased weight gain 6 percent and improved feed efficiency (feed per pound gained) 4 percent (Beeson, 1978). The incidence of liver abscesses from high-grain, high-energy diets is not known, but 30 percent or more of the livers could be expected to be abscessed without the use of antibacterials, and such abscesses also cause reductions in weight gain. Davis (1978) estimates that the use of antibacterials reduces the incidence of liver abscesses from over 50 percent to approximately 18 percent.

In its report on the economic impacts of a ban on antibacterials, USDA (1978) used the following criteria for weight gain: (1) 700-lb yearling cattle are fed for 156 days with antibacterial-supplemented feed, (2) with a marketing weight of 1,050 to 1,062 lbs with antibacterials, and (3) a marketing weight of 1,038 lbs without antibacterials. This would result in a reduced marketing weight of 12 to 24 lbs per animal, or a difference of 1.2 to 2.3 percent.

**Sheep.** Antibiotics are not generally used on a subtherapeutic basis but rather for treating specific diseases. Only the tetracyclines have been found to be beneficial for weight gain and feed efficiency, and they are primarily used in lambs. The major response occurs initially in the feeding period (Beeson, 1978).

**Pigs.** Table 16 provides rough comparisons of different antibacterials at different times in the feeding life of pigs. In the experiments summarized in the table: (1) "starter" pigs

initially weighed 11 to 27 lbs, with finished weights of 30 to 110 lbs; (2) "grower-developer" pigs initially weighed 34 to 45 lbs, with finished weights of 90 to 114 lbs; and (3) "growing-finishing" pigs initially weighed 32 to 59 lbs, with finished weights of 134 to 207 lbs. Responses were generally greater in young pigs. Excluding combinations that included penicillin or tetracycline, responses equal to tetracycline or penicillin were obtained with tylosin, virginiamycin, mecadox, tylan-sulfa, bacitracin, and lincomycin. Bacitracin had a smaller feed-efficiency effect, but the others were comparable to penicillin or tetracycline.

Table 17 summarizes the effect of tetracycline over three decades for swine at similar stages in the production cycle as covered in table 16. Effectiveness has been maintained for starter pigs and diminished but still positive for more mature swine.

Poultry. Table 18 summarizes the response to different antibacterials by chickens to 4 weeks and 8 weeks from hatch. The greatest response takes place early in the growth cycle. After 8 weeks from hatch, there is only a small difference between birds fed and not fed antibacterial-supplemented feeds. Several antibacterials produce similar results as tetracycline and penicillin—namely, virginiamycin, streptomycin, erythromycin, and lincomycin.

Table 19 averages the effectiveness of tetracycline, penicillin, bacitracin, and the arsenicals for chicks up to 4 weeks of age for specific years. Effectiveness in the early phase of the growth cycle has been maintained.

Table 20 summarizes the effectiveness of selected antibacterials on egg production and hatchability. Of the six antibacterials listed, tetracycline has the greatest effect, followed by bambarmycin and penicillin.

The results for turkeys are generally similar to those for chickens (table 21).

## Effect on Production

The effects of tetracycline, penicillin, sulfa, and nitrofurans on production of meat

**Table 16.—Response of Pigs to Antibiotics**

Antibiotic	Average daily gain (% Improvement)			Feed/gain (% Improvement)		
	Starter	Grower-developer	Growing-finishing	Starter	Grower-developer	Growing-finishing
Tetracycline	10.84	1093	6,58	625	388	255
Penicillin	945	—	—	868	—	—
Penicillin-streptomycin	1485	—	3.87	7.42	—	1,74
Tetracycline-penicillin-sulfamethazine	2250	1746	—	8.48	—	639
Bacitracin	9,72	510	2.50	326	250	267
Tylosin	1481	10,94	464	603	420	1,47
Virginiamycin	1100	10.69	573	502	660	325
Bambermycin	000	2.45	189	099	117	117
Tylan-sulfa	1765	512	—	676	215	—
Mecadox	18.56	1513	—	864	6.91	—
Lincomycin	1111	—	—	757	—	—
Nitrofurantoin	8,00	—	142	233	—	058

SOURCE V W Hays Effectiveness of Feed Additive Usage of Antibacterial Agents in Swine and Poultry prepared for the Office of Technology Assessment U S Congress 1978 (typescript) tables 5 26 and 27

**Table 17.—Continued Effectiveness of Tetracycline in Swine**

Time period	Average daily gain (% Improvement)			Feed/gain (% Improvement)		
	Starter	Grower-developer	Growing-finishing	Starter	Grower-developer	Growing-finishing
1950-56	870	17.36	940	545	6.27	455
1957-66	1169	6.02	588	793	195	114
1967-77	1063	597	455	299	242	092

SOURCE V W Hays Effectiveness of Feed Additive Usage of Antibacterial Agents in Swine and Poultry prepared for the Office of Technology Assessment U S Congress 1978 (typescript) tables 5 26 and 27

**Table 18.—Response of Chickens to Antibiotics**

Antibiotic	Weight gain (% Improvement)		Feed/gain (% improvement)	
	4 weeks	8 weeks	4 weeks	8 weeks
Tetracycline	733	369	509	231
Penicillin	811	293	446	276
Bacitracin	630	0.95	324	220
Arsenicals	494	3.44	701	315
Bambermycin	377	235	180	194
Lincomycin	9.25	448	828	3.30
Nitrofurantoin	328	198	261	1.47
Oleandomycin	501	448	225	1.78
Streptomycin	726	—	189	—
Virginiamycin	1598	—	9.06	—
Erythromycin	720	—	5.05	—
Tylosin	2.82	—	1.00	—

SOURCE V W Hays Effectiveness of Feed Additive Usage of Antibacterial Agents in Swine and Poultry prepared for the Office of Technology Assessment U S Congress 1978 (typescript) tables 35 and 36

**Table 19.—Improvement in Chick Performance: All Years Versus Since 1970 (To Approximately 4 Weeks of Age)**

Antibiotic	Weight gain (% Improvement)		Feed/gain (% Improvement)	
	All years	Since 1970	All years	Since 1970
Tetracycline	7.33	6.79	5.09	5.38
Penicillin	811	1220	446	714
Bacitracin	631	7.34	324	2.75
Arsenical	4.94	471	701	4.81

SOURCE V W Hays Effectiveness of Feed Additive Usage of Antibacterial Agents in Swine and Poultry prepared for the Office of Technology Assessment U S Congress 1978 (typescript) table 37

**Table 20.—Effect of Selected Antibiotics on Egg Production, Feed Per Dozen Eggs, and Hatchability (in % Improvement)**

Antibiotic	Egg production	Feed/dozen eggs	Hatchability
Tetracycline	11.91	891	147
Penicillin	5.52	504	397
Bacitracin	0.95	228	697
Arsenical	2.34	129	581
Bambermycin	879	11.73	249
Erythromycin	1.36	1.36	035

SOURCE V W Hays Effectiveness of Feed Additive Usage of Antibacterial Agents in Swine and Poultry prepared for the Office of Technology Assessment U S Congress 1978 (typescript) tables 39

Table 21 .-Response of Turkeys to Antibiotics

Antibiotic	Weight gain (% improvement)			Feed/gain (% improvement)		
	4 weeks	8 weeks	To market weight	4 weeks	8 weeks	To market weight
	Tetracycline	1489	13.21	—	8.37	5.88
Penicillin	1531	10.24	5.73	7.87	5.62	2.64
Bacitracin	9.82	4.97	7.23	4.71	2.73	1.59
Streptomycin	814	453	—	469	192	—

SOURCE V W Hays, Effectiveness of Feed Additive Usage of Anti bacterial Agents in Swine and Poultry, prepared for the Office of Technology Assessment U S Congress 1978 (typescript). tables 41, 42, and 43

have been estimated recently by USDA (1978) and Headley (1978). These estimates were designed primarily to estimate the effects on the income of livestock producers and on consumer prices. Both estimates were generated from the same model. However, the expected effects differ in magnitude and time trend because of the application of different assumptions (e.g., demand elasticities) to the basic model. The USDA analysis projected impacts for 5 years, and Headley's projected impacts for 10 years from the time of banning. In the USDA analysis, the initial decrease in production was expected to increase net producer revenues because of higher prices. Both production and prices of most affected species were projected to recover to approximately their baseline levels by the fifth year. Headley's analysis concluded that the banning of selected or all four antibacterial would increase aggregate farm income and increase consumer expenditures from \$5.70 to \$19 per capita.

In both analyses, the effects were assumed to be additive, and no consideration was given to the availability of alternative antibacterial. Both analyses mention that the estimated effects would be less if these were considered. Alternatively, the hypothesis that small producers may be forced out of business was not considered. Production decreases would be greater for the short term if this factor had been included. The long-term effects, however, might not have been affected.

The economic consequences for producers and consumers and the long-term effects postulated are obviously matters over which much disagreement exists. However, the estimates of immediate consequences of selected or complete banning of these four antibacterial can serve as first-order, rough approx-

imations of the kinds of production increases attributable to these antibacterial. As noted above, the availability of replacement antibacterial (see tables 16, 18, 19, 20, and 21) is not considered.

USDA's analysis estimated the effects of the four antibacterial separately for beef, pork, chickens, and turkeys. It also examined the effects on egg production, dairy calves, and lambs. Headley's analysis estimated the effects on beef, pork, chickens, and turkeys from a ban on (a) tetracycline and penicillin, (b) nitrofurantoin and sulfa, and (c) all four antibacterial. Since both analyses assumed these effects to be additive, they were comparable. Lambs, dairy calves, and egg production are not addressed here.

The percent changes in production are comparable and both use 1976 data, but the analyses differed slightly in the measure of production. Both used ready-to-cook weights for chickens (broilers) and turkeys, but Headley used carcass weights for beef and pork, while USDA used live weights at times of slaughter. USDA's estimates are therefore adjusted to reflect carcass weights. Headley's translation from percentage to pounds differs slightly from that obtained in USDA's analysis, so the former is adjusted to coincide with the latter.

Table 22 summarizes 1976 production figures for beef, pork, broiler chickens, and tur-

Table 22.-Production of Meat Animals, 1976

Animal products	Millions of pounds
Beef <sup>a</sup>	25,969
Pork <sup>a</sup>	12,425
Broiler chickens <sup>b</sup>	8,970
Turkeys	1,960

<sup>a</sup>Carcass weight  
<sup>b</sup>Ready-to-cook weight  
 SOURCE Extracted from USDA, 1978 and Headley, 1978

keys. Table 23 compares USDA's with Headley's estimates on the effect of banning selected antibacterial expressed in percentage decreases. The analyses are comparable for each meat product, although the effect of specific antibacterial may differ, such as for nitrofurans on chickens and turkeys,

Using USDA's separate analyses for each food animal and each antibacterial, table 24 summarizes the range of impacts for each antibacterial. Among the individual antibacterial, the greatest impact relative to total production would be through banning tetracycline; pork and chicken would be the most affected,

As mentioned earlier, USDA's and Headley's analyses differed in the estimated impact of banning these antibacterial. Though banning of the four antibacterial is estimated to decrease production by the percentages and pounds summarized in tables 23 and

24, the effect on the total market over a number of years would not be equivalent to these estimates. For both USDA's and Headley's analyses, table 25 summarizes the percent change in the quantity of meat produced or consumed, table 26 summarizes the percent change in farm prices, and table 27 summarizes changes in retail prices. Headley's analysis was for a 10-year period following a ban, while USDA's analysis extended only 5 years beyond the initial year of the hypothetical ban. The primary difference between the two analyses is that Headley consistently estimates a larger impact than USDA on decreased production, increased farm prices, and increased retail prices. Headley's estimates drop slightly after the first 2 years, but remain at a fairly constant level over the following years, while the USDA analysis has a high initial impact that diminishes over the 5-year period. Both analyses predict the minimal impact to be on beef and the maximum impact on poultry.

**Table 23. -Estimated Percentage Change in Livestock Production From Banning Selected Antibiotics (First Year)**

<i>Animal product</i>	<i>Projection</i>	<i>Penicillin</i>	<i>Tetracycline</i>	<i>Nitrofurans</i>	<i>Sulfa</i>	<i>Cumulative effect</i>
B e e f	USDA	NA <sup>b</sup>	- 0.4 to - 0.8	NA	NA	- 0.4 to - 0.8
	Headley	- 1.0	-	NA	-	- 1.0
Pork	U S D A	NA	- 3.4 to - 15.6	NA	- 1.5 to - 2.2	- 4.9 to - 17.8
	Headley	- 4.0	-	- 2.5	-	- 6.5
Broiler chicken	U S D A	- 2.1 to - 3.8	- 6.4 to - 11.5	+ 0.2 to - 5.7	NA	- 8.3 to - 21.0
	Headley	- 2.2	-	- 1.2	-	- 14.2
Turkey	USDA	- 1.4 to - 2.8	- 2.8 to - 4.6	- 1.9 to - 8.7	NA	- 6.1 to - 16.1
	Headley	- 3.2	-	- 1.2	-	- 15.2

<sup>a</sup>Penicillin, tetracycline and sulfa considered banned at subtherapeutic levels and nitrofurans considered banned at all levels

<sup>b</sup>Not applicable

SOURCE USDA 1978 Headley 1978

**Table 24.-Estimated Decrease in Livestock Production From Banning Selected Antibiotics (First Year) (millions of pounds)**

<i>Animal product</i>	<i>Total production (1976)</i>	<i>Penicillin</i>	<i>Tetracycline</i>	<i>Nitrofurans</i>	<i>Sulfa</i>
Beef <sup>b</sup>	25,969	NA	104 to 208	NA	NA
Pork <sup>b</sup>	12,425	NA	422 to 1,938	NA	186 to 273
Broiler chicken <sup>c</sup>	8,970	188 to 341	574 to 1,032	18 to 511	NA
Turkey <sup>c</sup>	1,960	27 to 55	55 to 90	37 to 171	NA

<sup>a</sup>Penicillin, tetracycline and sulfa considered banned at subtherapeutic levels and nitrofurans considered banned at all levels

<sup>b</sup>Carcass weight

<sup>c</sup>Ready to cook weight

SOURCE Table 22 and USDA percent estimate table 23



**Table 25. -Percent Change in Quantity of Meat<sup>a</sup> From a Ban on the Use of Selected Antibiotics**

Year <sup>c</sup>	Beef		Pork		Broiler-chicken		Turkey	
	USDA	Headley	USDA	Headley	USDA	Headley	USDA	Headley
1.	-0.19 to -0.28	-0.9	-4.86 to -17.90	-5.8	-8.24 to -22.70	-15.4	-5.98 to -14.70	-21.8
2.	0.04 to +0.04	-1.1	-3.86 to -14.17	-55	-3.61 to -9.10	-8.9	-4.23 to -10.45	-19.3
3.	+0.10 to +0.25	-0.7	-2.68 to -9.86	-5.8	-2.27 to -5.75	-9.7	-3.54 to -8.74	-17.7
4.	+0.14 to +0.24	-0.4	-1.40 to -5.15	-6.2	-2.15 to -5.46	-9.1	-2.71 to -6.66	-15.9
5.	+0.30 to +0.56	-0.4	-0.84 to -3.02	-6.0	-2.16 to -5.50	-7.7	-2.62 to -6.44	-16.7

<sup>a</sup>USDA's figures based on quantity of meat produced. Headley's figures based on annual civilian consumption. Only first 5 years of Headley's analysis included.  
<sup>b</sup>Penicillin, tetracycline, and sulfa considered banned at subtherapeutic levels and nitrofurans considered banned at all levels.  
<sup>c</sup>Year of banning equals year 0.  
 SOURCE: USDA, 1978, table 17; Headley, 1978, table 10.

**Table 26. -Percent Change in Farm Prices From a Ban on the Subtherapeutic Uses of Selected Antibiotics**

Year <sup>b</sup>	Fed beef (liveweight price)		Hogs (liveweight price)		Broiler-chickens (wholesale price)		Turkeys (liveweight price)	
	USDA	Headley	USDA	Headley	USDA	Headley	USDA	Headley
1.	+4.30 to +15.34	+4.7	+5.02 to +16.13	+18.5	+12.99 to +35.65	+51.8	+11.61 to +25.64	+37.6
2.	+3.30 to +11.27	+3.83	+12.97 to +12.2	+6.94	+20.00 to +28.4	+28.4	+6.70 to +16.42	+28.4
3.	+2.00 to +5.03	+4.0	+2.34 to +8.00	+12.4	+3.09 to +8.98	+38.4	+3.42 to +8.88	+38.4
4.	+1.00 to +2.00	+2.8	+1.59 to +5.24	+14.0	+2.67 to +7.46	+31.3	+3.51 to +8.79	+31.3
5.	0 to +0.96	+2.3	+1.14 to +3.53	+15.5	+2.25 to +6.04	+35.0	+3.54 to +8.88	+35.0

<sup>a</sup>Penicillin, tetracycline, and sulfa considered banned at subtherapeutic levels and nitrofurans considered banned at all levels.  
<sup>b</sup>Year of banning equals Year 0.  
 SOURCE: USDA, 1978, table 16; Headley, 1978, table 11.

**Table 27. -Percent Change in Retail Price<sup>a</sup> From a Ban on the Subtherapeutic Uses of Selected Antibiotics**

Year <sup>c</sup>	Beef		Pork		Poultry (chickens & turkey)	
	USDA	Headley	USDA	Headley	USDA	Headley
1.	+2.7 to +10.4	+3.6	+4.5 to +14.7	+16.8	+10.3 to +27.6	+13.3
2.	+2.2 to +7.7	+2.8	+3.5 to +11.8	+11.6	+5.7 to +15.9	+8.7
3.	+1.4 to +3.4	+3.2	+2.1 to +7.3	+11.8	+2.6 to +7.4	+10.3
4.	+0.7 to +1.4	+2.2	+1.4 to +4.8	+12.5	+2.4 to +6.5	+10.0
5.	0 to +0.7	+1.8	+1.0 to +3.2	+13.5	+2.2 to +5.6	+9.7

<sup>a</sup>USDA based on consumer price index. Headley based on retail price index.  
<sup>b</sup>Penicillin, tetracycline, and sulfa considered banned at subtherapeutic levels and nitrofurans considered banned at all levels.  
<sup>c</sup>Year of banning equals year 0.  
 SOURCE: USDA, 1978, table 21; Headley, 1978, table 12.

## DIETHYLSTILBESTROL (DES)

### Mode of Action

DES is a synthetic estrogen that differs in structure and metabolism from naturally occurring estrogen, but there is no evidence that natural or other synthetic estrogens differ substantially in their harmful or toxic effects (DES Report, 1978). DES has a potency 10 times that of the standard estradiol, and it is this relative potency that has made it the preferred drug for growth promotion and feed efficiency.

DES increases cellulose digestion by bovine rumen micro-organisms in vitro and in vivo.

Stilbestrol has been shown to increase the coefficients of digestibility of cellulose in sheep from 41.9 to 48.7 percent and the crude protein digestibility from 37.5 to 44.7 percent [Brooks et al., 1954]. However, the following evidence supports the hypothesis that the systematic growth-promotion and feed-efficiency effects of DES are the result of endogenous androgen (male hormone) production:

- DES accelerates protein anabolic processes in cattle and results in an increase in nitrogen retention (Clegg and Cole, 1954).

- Introduction of exogenous estrogen triggers **endogenous** androgen secretion as a compensatory mechanism (Gassner et al., 1951; Whitehair et al., 1953).
- **Melengestrol acetate (MGA)**, a synthetic **progesteronal** steroid also used for growth promotion and feed efficiency, produces biological effects closely related to the effect of naturally occurring progesterone. The effect of naturally occurring progesterone is cyclic and permits ovulation in the nonpregnant heifer. In the pregnant heifer **endogenous** progesterone maintains the **corpus luteum**, which prevents ovulation. **MGA** inhibits **estrus** and ovulation and allows the development of mature follicles in the ovary. These persistent, mature follicles produce increased amounts of estrogen, which in turn stimulate weight gain and improve feed efficiency. The interruption of **estrus** is temporary, normal **estrus** usually returning after **MGA** is discontinued. **MGA** will not stimulate weight gain in **nonovulating**, spayed, or pregnant heifers, in steers, or in bulls (Beeson, 1978).
- Testosterone also can be used to promote growth and increase feed efficiency. This can be accomplished by adding testosterone to the feed or by not castrating bull calves.

### Effectiveness

Dose responses from different levels of DES are not linear. Excessive levels will depress performance and lead to undesirable side effects. Steers (castrated males) and heifers (immature females) respond differently, and response varies with the type of feed (e.g., pasture vs. grain) and whether DES is given orally or under the skin. Approved oral doses of DES are 5 to 20 mg per head per day for cattle. <sup>1</sup> The approved implant levels for cattle are 30 or 36 mg.<sup>2</sup>

The effects of DES are limited to increased weight gain and feed efficiency. The effect on milk production has been inconsistent and it is not used for that purpose. **Feedlots** account

<sup>1</sup>21 CFR 558.225.

<sup>2</sup>21 CFR 522,690.

for most use. DES increases weight gain from 15 to 19 percent and feed efficiency from 7 to 12 percent in steers, and 10 percent for weight gain and 7 percent for feed efficiency in heifers (Beeson, 1978).

In addition to DES, several other drugs are used for fattening cattle. As previously discussed, these include **melengesterol acetate (MGA)**, **monensin**, **zeranol**, and **estradiol benzoate** plus testosterone or progesterone. **MGA** is a **progesteronal** steroid that is effective only in heifers. Studies covering a 10-year period (1968-77) show that it produces more weight gain and feed efficiency than either oral DES or estrogen implants. Table 28 summarizes these results. **Monensin** improves feed efficiency by 10 percent but has no effect on weight gain in cattle. Implants of **zeranol**, an estrogen-like compound, have from 30 to 50 percent of the growth-promotion and feed-efficiency effects of DES. Implants of estradiol-progesterone for steers and estradiol-testosterone for heifers have similar quantitative effects as DES. **Beeson** (1978) concludes that the data generally show that the quantitative effects are similar and recently reconfirmed previous research showing that estradiol-progesterone implants are equal to DES implants for improving weight gain and feed efficiency in steers (Beeson et al., 1977). Finally, the use of uncastrated young bulls will partially substitute for DES and other similar growth stimulants, improving both weight gain and feed efficiency about 10 percent (Beeson, 1978). But bulls are difficult to carry over as yearlings to be fed-out, and there is a consumer prejudice against bull meat.

Thus DES can be replaced by several already-approved drugs to promote weight gain and feed efficiency in cattle.

### Effect on Production

Headley's 1978 estimates on the effect on meat production of a ban on selected **antibacterials** also included estimates of a DES ban. A downward shift in supply of 3.75 percent was predicted for the first year. As for **antibacterial**, the long-term effect was predicted as a rise in total producer income, and a rise in consumer prices of \$7.75 per capita.

Table 28.—No Drug Versus MGA Versus DES Versus Estrogen Implant (1968 -77)<sup>a</sup>

Item	(47 experiments)		(36 experiments)		(12 experiments)			(experiments)		
	No drug	MGA	Oral DES	MGA	No drug	DES <sup>b</sup>	MGA	No drug	Estrogen implant	MGA
Daily gain lb	2.24	2.47	2.38	2.53	2.25	2.35	251	2.40	2.49	2.63
Improvement %	—	10.3	—	6.3	—	4.4	11.6	—	3.8	9.6
Feed/lb gain lb	9.95	9.30	8.85	8.44	8.78	8.59	823	755	7.34	7.14
Improvement %	—	6.5	—	4.9	—	2.2	6.3	—	2.8	5.4

<sup>a</sup>Summarizing experiments conducted by universities, feed manufacturers and Commercial feedlots

<sup>b</sup>Percent improvement not equal to that cited in text because these were comparison experiments and were not necessarily testing the maximum response from DES

SOURCE W. M. Beeson, Use of Drugs and Chemicals as Feed Additives to Increase the Productivity of Cattle and Sheep prepared for the Office of Technology Assessment U. S. Congress 1978 (typescript) table 5

However, Headley estimated that 90 percent of fed cattle received DES or MGA. A spokesman for the National Cattlemen's Association estimates that DES and similar growth stimulants such as zeranol are used in about 80 percent of fed cattle (CNI Weekly Report, Oct. 5, 1978). Therefore, if Headley's figures are adjusted by eight-ninths and applied to a total 1976 production of 25,969 million lbs carcass weight of beef (see table 22), DES is estimated to increase beef production by 3.33 percent, or 865 million lbs. This estimate is still high, because DES does not account for all growth-stimulant use.

As in the case of banning selected antibacterial, Headley estimated the effects of a ban on DES over a 10-year period from the time of banning. The combined response of antibacterial and DES approaches an additive effect in beef cattle meat production, but the effect on costs is not additive. When analyzed apart from a ban on the subtherapeutic use of antibacterial, the per capita consumer cost of a DES ban was estimated to be \$7.75. If penicillin, tetracycline, sulfa, nitrofurans, and DES were simultaneously banned, per capita consumer costs were estimated at \$21.90. If only the antibacterial were banned, per capita costs would be \$19. Thus when added to an antibacterial ban,

DES was estimated to add only \$2.90 to per capita consumer costs, in contrast to \$7.75 if only DES were banned.

Table 29 summarizes Headley's estimates of a DES ban on the percent changes in available beef supplies, farm prices, and retail prices. After 5 years, supply is slightly increased over supply before the ban, with decreases in farm prices and consumer prices. After 10 years, supplies are slightly decreased and farm prices and consumer prices increased, but none of these changes is as large as that expected in the 2 years immediately following the ban on DES.

Table 29.—Percent Change on the Supply, Farm Prices, and Retail Prices of Beef From a DES Ban

Year <sup>a</sup>	supply	(Farm prices, liveweight)		Retail prices
		Fed cattle	Nonfed cattle	
1	- 3.7	+ 11.9	+ 15.2	+ 9.1
2	- 3.2	+ 8.6	+ 12.5	+ 6.7
3	- 1.5	+ 5.7	+ 7.7	+ 4.7
4	- 0.5	+ 2.1	+ 2.6	+ 1.9
5	+ 0.5	- 2.5	- 3.6	- 1.7
6	+ 0.2	- 1.4	- 2.8	- 0.8
7	- 0.9	+ 4.0	+ 4.3	+ 3.3
8	- 1.7	+ 8.1	+ 10.2	+ 6.5
9	- 1.9	+ 10.4	+ 13.7	+ 8.4
10	- 1.2	+ 6.9	+ 9.5	+ 5.8

<sup>a</sup>Year of banning equals year 0

SOURCE Headley 1978: tables 1, 2, and 3

Chapter IV

# RISKS

# RISKS

## INFECTIOUS DISEASES

### Antibacterial-Related Risks

The increasing pool of drug-resistant bacterial pathogens is the greatest health risk posed by the widespread use of antibacterials in animal feeds. It is also the most difficult to evaluate in terms of:

1. quantifying the pool of drug-resistant bacterial pathogens,
2. assessing the relative contribution to the pool from the use of antibacterials in animal feeds, and
3. determining causality between the use of antibacterials in animal feeds and human disease.

Hazards to the food animals themselves from such use of antibacterials are closely related to these human health concerns because the development of resistant pathogens and subsequent failure or diminished effectiveness of antibacterial therapy are problems for both human and animal health. However, this sharing of potential, long-term, adverse consequences is obscured by the predicted short-term consequences for the livestock industries of limiting the subtherapeutic uses of certain antibacterials.

On the other hand, the long-term consequences for these industries might be significantly different. With limited use, although the supply of certain food animals could diminish, shifts in supply and demand for different foods (primarily beef, pork, and chicken) may produce little change in total income for producers and modest rises in consumer prices (USDA, 1978; Headley, 1978).

The threat to human health has been the primary reason why current efforts at limiting widespread use are underway. But such widespread use poses an identical threat to

the health of livestock and poultry and may even occur earlier and more visibly than the threat to human health. Present production is concentrated in high-volume, crowded, stressful environments, made possible in part by the routine use of antibacterials in feed. Thus the current dependency on low-level use of antibacterials to increase or maintain production, while of immediate benefit, also could be the Achilles' heel of present production methods.

Adverse effects on human health are possible from contact with treated livestock or the antibacterials themselves and through eating food products containing residues of animal drugs. Illness can result from poor management and sanitation practices in violation of standards, but this report is not concerned with such causes except when the circumstances show that prevention is not possible through standard-setting and compliance-monitoring. Nor is this report concerned with all disease acquired from ingesting contaminated foods but only when: (1) drug residues represent the threat or (2) antibacterials in the feed result in disease or threatened disease from antibacterial-resistant bacteria.

Human disease from contact with treated livestock or with the antibacterial(s) itself is more significant for building a case for the general risk of such uses than it is for concluding that direct disease transmission is presently a significant problem. That is, disease transmitted directly from food animals chronically fed antibacterial-supplemented feed is not of epidemic proportions, and isolated cases or limited epidemics have been so infrequently detected that they are newsworthy items even in the scientific community. But taken together with the growing num-

ber of research findings of asymptomatic spread of drug-resistant organisms from food animals to humans, they are significant in documenting the risk to human health from drug-resistant pathogenic bacteria.

### **Risks From Infectious Diseases**

A large body of literature shows that certain infectious diseases are transmitted directly from animals to humans. Such diseases are not limited to bacterial etiologies but cover the whole spectrum of infections—e.g., tapeworms, trichinosis, psittacosis, tuberculosis, etc. Some diseases are occupational hazards in the meat industry and carry common names such as “pork infection,” “swine erysipelas,” and “fish poisoning.”

While the causal chain between food animals or their edible products and disease in humans may not be completely demonstrated in any given case, each step in the chain has been documented repeatedly. With the added criterion that the infectious agent in the animal or its edible product be shown to be caused by antibacterial supplements in the feed, the causal chain is even more difficult to prove in any specific case. Thus there is disagreement over the interpretation of any specific case but no real disagreement over the overall conclusions that food animals are the source of some infections in humans and that the use of antibacterial in feeds is one cause of the growing pool of drug-resistant pathogenic bacteria. Instead, the disagreement is over the exact risk from this enlarging pool and the contribution of antibacterial in animal feeds to the problem.

The proliferation of antibacterial-resistant bacteria is encouraged by the presence of such drugs. Sensitive bacteria are killed or inhibited, allowing resistant strains or spontaneous mutations of sensitive-to-resistant bacteria to grow into the vacated environment. The situation is complicated because some resistant strains can transfer the resistant genes to other bacteria. Antibacterial resistance (and other properties of bacteria) are sometimes carried on bits of DNA that function independently of the organism's chromosomes. These extrachromosomal pieces of DNA are called plasmids.

Resistance plasmids (R-plasmids) may code both for antibacterial resistance and for the ability to transfer to other bacteria, or the two functions may be separate on different plasmids. Resistance to multiple antibacterial is frequently found on an R-plasmid. As in the case of single resistance, multiple resistance may or may not be transferable depending on whether the transfer code is associated with the resistance code—i. e., resistance to a specific antibacterial may be transferred alone or along with resistance to one or more other antibacterial.

Gram-negative and gram-positive bacteria also differ in plasmid-mediated transfer. R-plasmid transfer has not been found to occur between these two types of bacteria. The R-plasmid of gram-positives are not so freely transferred as those in gram-negative species, nor are linked, multiple resistances so frequently found in them.

For any antibacterial there may be: (1) no known plasmid-mediated transfer of resistance in either gram-positive or gram-negative bacteria, (2) transferred resistance only in one bacteria type but not in the other, or (3) varying degrees of linkages with other antibacterial resistances. For example: (a) bambarmycin has no known effect on gram-positive or gram-negative bacterial resistance patterns; (b) tylosin and virginiamycin select for erythromycin-resistant staphylococci and streptococci (gram positives), but their effect on the resistance patterns of gram-negatives is essentially nonexistent; and (c) tetracycline selects for resistance not only to itself but also for resistance to other antibacterial linked to it in both gram-positive and gram-negative bacteria (Falkow, 1978) .

Resistance can be transferred from non-pathogenic as well as from pathogenic bacteria. Although resistant nonpathogenic bacteria will not cause disease, they may be able to transfer antibacterial resistance to bacteria that can cause disease but which were previously responsive to antibacterial therapy. Thus a growing pool of plasmid-mediated resistance in nonpathogenic bacteria, even though of no direct clinical significance, poses a large threat because of the transfer of that resistance to pathogenic bacteria.

Plasmids have also been identified where drug resistance and pathogenicity are linked. Since the first reports on drug resistance and enteropathogenicity linkage in swine, similar occurrences have been found in human toxigenic *E. coli*. In *E. coli* that cause diarrheal disease by the production of an exotoxin, it has been shown that the intestinal toxin involved is often encoded by plasmids (Ent-plasmids) that can be transferred from strain to strain (Smith and Linggood, 1972; Gyles et al., 1974; So et al., 1975). A second plasmid-coded gene product, the K-antigen, which enables the organism to adhere to the wall of the intestine, is also required for pathogenicity of the organism by exotoxins. Although the K-antigen shows some species specificity, the Ent-plasmid does not.

The incidence of R-plasmids is very high among enterotoxigenic *E. coli* strains for both animals and humans (Gyles et al., 1974). The coexistence of Ent- and R-plasmids within the same cells raises the possibility of recombination between the plasmids, translocation, or independent cotransfer. Independent cotransfer has been shown *in vitro*. In an *E. coli* strain responsible for a hospital epidemic of infantile diarrhea, one plasmid was associated with the production of heat-stable enterotoxin, and another plasmid determined drug resistance against seven antibacterial. When the R-plasmid was transferred, the Ent-plasmid was also transferred to 36 percent of the drug-resistant recipients (Wachsmuth et al., 1976).

*E. coli* isolated from piglets with diarrhea have been found with Ent- and R-plasmids combined, presumably by recombination or translocation. These plasmids were conjugative (transfer by direct contact between bacterial cells) and determined the production of enterotoxin and resistance to multiple antibacterial (tetracycline, sulfonamide, and streptomycin) (Gyles et al., 1977). In addition, a conjugative plasmid encoding a K-antigen has also been found to carry resistance genes (So et al., 1976). These findings portend the possibility of a complete plasmid in the sense of combining conjugative, enterotoxigenic (Ent), adhesive (K), and resistance (R) properties in one package for transfer to completely nonpathogenic, gram-negative bacteria.

Humans and other animals are hosts to many of the same bacteria. It is now widely accepted that *E. coli*, some of the most ubiquitous gram-negative bacteria, are not composed of stably differentiated strains that are specific colonizers or pathogenic for separate animal species. Cross-colonization studies, serotyping, drug-resistance patterns, and plasmid types show extensive overlapping sets of human and animal organisms (Linton et al., 1977a, 1977b; Howe et al., 1976). Cross-colonization may be enhanced by plasmid-mediated factors. Colicin is a substance that kills *E. coli* except for the type producing it, thus giving competitive advantage to the producer. Oral administration of two colicin-positive bovine *E. coli* strains resulted in 100-percent replacement of the resident coliform flora in humans, whereas colicin-negative derivatives of these two strains were unable to colonize the same humans (Smith and Huggins, 1976).

Conjugative, colicin-positive plasmids carrying resistance genes are known to exist (Delhalle and Gratia, 1976). The potential therefore exists for animal feeding of antibacterial to cause a direct increase in the pathogenicity of *E. coli* in humans.

A single *Salmonella* serotype, *S. typhimurium*, is the most common cause of *Salmonella* infection in both animals and humans (CDC *Salmonella* Summary Report, 1973). Six of the most common human serotypes were among the ten most common animal serotypes in a recent CDC survey (CDC Report, 1974). In addition to shared serotypes between animals and humans, plasmids from *E. coli* can be transferred to *Salmonella* and other gram-negative bacteria.

In Connecticut in 1976, *S. Heidelberg* from calves infected humans, who in turn secondarily infected three infants. The organism was resistant to six antibacterial, *E. coli* with identical resistance patterns were isolated from two infected calves and from one human. This particular resistance pattern was not seen in over 10,000 pathogenic strains of *E. coli* isolated from the Northeastern United States in the same year, including 42 strains isolated from controls in the study (Cohen et al., 1977).

In a sampling of *E. coli* from a freshwater river system and within the saltwater bay into which it emptied: (a) nearly all the freshwater sites and about half of the saltwater sites sampled contained antibacterial-resistant coliforms, and (b) 20 percent of the 194 strains tested contained R-plasmids carrying multiple antibacterial resistance transferable to sensitive *E. coli*, *Salmonella typhimurium*, and *Shigella dysenteriae* (Feary, et al., 1972),

DNA base sequence homology studies of plasmids from different parts of the world have shown striking compatibility of plasmids. Plasmids with molecular weights of 57 million, one isolated from a bovine *S. typhimurium* in England in 1972, and the other from a human *S. typhi* in Vietnam in 1974, showed 100-percent homology. Table 30 summarizes these results (Anderson, et al., 1975).

Finally, a more serious occurrence than transferred resistance between *E. coli* and *Salmonella* has recently appeared. R-plasmids determining resistance in newly discovered ampicillin-resistant strains of *H. influenza* (Elwell et al., 1975) and in penicillin-resistant strains of *N. gonorrhoea* (Elwell et al., 1977) are identical to plasmids previously found in *E. coli*. It must be assumed that these identical plasmids have a common origin.

## Magnitude of the Risk

What proportion of antibacterial resistance is caused by subtherapeutic use in food animals as opposed to therapeutic use in both animals and humans is unknown. Thus this risk is not yet possible to fully quantify. For some aspects of the problem, such as the degree of compromise in treating *Salmonella* infection, it is possible to arrive at some quantitative notion of the magnitude of human risk. But for the overall risk to humans from increased antibacterial resistance, not only is it unclear what the final deleterious event should be whose frequency would be estimated, but there are also complicated interactions among human and animal populations with which we must contend.

As a rule the transmission of *Salmonella* infection is from animals to man, and the *Salmonella* reservoir in animals is considered the direct source of most of the *Salmonella* infections in humans (Sickenga, 1964). The antibacterial-mediated reservoir of resistant *E. coli* in animals provides a source of R-plasmids that can transfer to *Salmonella*.

A continuous increase in antibacterial resistance has been noted among *Salmonella* isolated from farm animals. There has been a dramatic increase in resistance to antibacte-

**Table 30<sup>a</sup>.—Homology Between Plasmids of Animal and Human Origin**

<sup>a</sup> The values indicate the degree of reassociation of <sup>32</sup>P-labeled plasmid DNA with unlabeled plasmid DNA relative to the reassociation both with DNA of the same plasmid (= 100) and with *E. coli* K 12 chromosomal DNA (= 0)

Unlabeled DNA from strains bearing plasmids			Labeled plasmid DNA											
Group	Human (H) or animal (A) origin	Plasmid no	f											
			FII			I <sub>1</sub>		N		H <sub>1</sub>			H <sub>2</sub>	
			240	R1.19K.	TP1 66	TP102	Δ	TP120	TP1 58	TP123	TP153	TP154	TP1 16	TP167
FII	H	240	100	57	64	14	13	0	0	3	—	4	0	3
	H	R1-19K.	—	100	93	—	—	—	—	17	—	—	—	—
	A	TP166	64	85	100	9	10	10	—	17	6	5	9	4
I <sub>1</sub>	H	TP102	13	—	11	100	75	7	4	2	—	3	—	—
	A	Δ	15	—	11	65	100	1	0	—	—	4	0	0
N	H	TP120	1	—	4	0	1	100	94	5	—	0	0	2
	A	TP158	1	—	3	1	0	101	100	10	—	—	—	—
H <sub>1</sub>	H	TP123	10	17	24	0	0	9	6	100	91	91	8	0
	H	TP153	—	6	12	—	—	—	3	94	100	95	5	0
	H	TP163	10	6	9	1	0	8	4	88	96	82	7	5
	A	TP1 71	—	—	—	—	—	—	—	—	100	—	—	—
H <sub>2</sub>	A	TP154	6	0	8	0	0	7	12	87	92	100	0	0
	H	TP1 16	2	—	—	—	0	8	—	4	0	—	100	65
	A	TP167	—	—	—	—	—	—	—	—	0	—	81	100

Note—The broken line encloses reactions of labeled plasmid DNA with unlabeled plasmids from the same compatibility group  
—, Not done

<sup>a</sup>Anderson et al., J. @n Microbiol 91 376.362, 1975. table 3



rials in human *Salmonella* infections, A review of several studies of human infections conducted over a period of years indicates that resistance of *Salmonella* to tetracycline has increased continuously from 1-percent resistant organisms prior to 1948 to more than 40-percent resistance in 1973.<sup>1</sup> A comparison of antibacterial resistance in *Salmonella* isolated from hospitals in 1967 and 1975 conducted by the Department of Health, Education, and Welfare's (HEW) Center for Disease Control showed overall resistance to at least one antibacterial increased from 41.1 to 69.4 percent, Multiple resistance to six or more antibacterial increased from 0.8 to 9.2 percent (table 31).

FDA estimated that there are 2.5 million cases of *Salmonella* infection in the United States each year; about 30 percent were severe enough to be seen by a physician, and approximately 1 percent of these develop life-threatening septicemia where appropriate antibacterial therapy is critical. In 27 percent of the cases treated, the first antibacterial chosen for treatment proves to be ineffective because the disease was caused by antibacterial-resistant bacteria.<sup>2</sup> Thus there are currently about  $2,500,000 \times 0.3 \times 0.01 \times 0.27 = 2,025$  Americans who annually contract a life-threatening *Salmonella* infection that requires antibacterial treatment and for whom treatment is compromised to some extent by antibacterial resistance of the infecting *Salmonella* strain. Additionally, there is an even larger number of people with nonsystemic infections who are treated with antibacterial and for whom treatment is also compromised.

All *Salmonella* infections cannot be ascribed to antibacterial use in food animals, but the risk is also not a static situation. If the risk were static, the lifetime risk of contracting systemic *Salmonella* infection and the subsequent treatment being compromised by antibacterial resistance could be approximated as  $(2,025 \text{ people/year} \times 70 \text{ years}) - 200,000,000 = 1/1,411$ . But in view of the rapid rise in multiple resistance, it must be assumed that both the degree and extent to which treatment is compromised are increasing at a rapid rate.

The risk from resistance 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 is unnecessary), but the enormous pool of R-plasmids as 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.

In assessing the risks to humans from the use of antibacterial in animals, the cumulative nature of these risks cannot be overlooked nor the importance of understanding the time rate of change of these risks. Although penicillin and tetracycline have both been used for over 25 years in animal feeds without seriously compromising the effectiveness of these drugs in the treatment of human disease, it cannot be assumed that there will be no problems in the future. Both the acquiring of resistance in animals and the passing of resistance from animals to humans are cumulative processes, and perhaps the point has not been reached, but will be at some future time, where significant deleterious effects will be observed in humans.

**Table 31. -Antibiotic Resistance in *Salmonella* Isolated From Hospitalized Patients**

	1967 400 strains	1975 754 strains
Resistance to one or more antibiotics		
<i>S. typhimurium</i>	41.1%	69.4%
Other serotypes	15870	43.9%
All strains	22.2%	49.7%
Resistance to two or more antibiotics	15.0%	26.5%
	(60 strains)	(200 strains)
Resistance to six or more antibiotics	0.80%	9.2%
	(3 strains)	(69 strains)

SO URCE 42 F R 56272 Oct 21 1977

<sup>1</sup>42 F.R. 56272, Oct. 21, 1977.

<sup>2</sup>Ibid.

# DRUG RESIDUES

## Types of Risk

Monitoring of drug residues focuses on the direct harm to humans from consumption of edible animal byproducts. There are two types of risks that are addressed: carcinogenic residues and residues with other health effects. As discussed earlier, there can be no residue of carcinogenic substances, with "no residue" determined by a method prescribed or approved of by the Secretary of HEW. Criteria by which the acceptability of a method will be judged have not been finalized, but the Food and Drug Administration (FDA) continues to proceed with regulations that would avoid the problem of always "chasing zero" that results from the increasing ability to measure extremely minute amounts of substances. There are approved drugs that are regulated on a "no residue" basis because they are known or suspect carcinogens. There are official methods for these drugs, although there is disagreement on whether or not these methods are adequate when reviewed by current scientific standards.

Residues of noncarcinogenic drugs do not have to meet the "no residue" requirement applicable to carcinogens but are governed by safety factors as described in the law. These factors include the probable consumption of the drug and of any substance formed in or on food, the cumulative effect, other safety factors deduced by scientific experts from animal experimentation data, and whether the conditions of use are reasonably certain to be followed in practice.<sup>3</sup> In practice, FDA sets specific tolerances for residues based on these safety factors and the availability of a practical analytical method to determine the quantity of residue. Chronic studies are required to support a finite tolerance. Acute toxicity studies of 90 days' duration are minimally required for a negligible tolerance. If it is determined that negligible residues will probably not occur, no tolerance is required. And if the drug may be metabolized and/or assimilated in such form that any possible residue would be indistinguishable

from normal tissue constituents, no tolerance is required.<sup>4</sup>

The treatment of carcinogens differs from that of noncarcinogens in that: (1) if finite residues are present, carcinogens are banned and noncarcinogens are not, the latter contingent on establishment of a tolerance, and (2) if it is not possible to determine whether residues will be present (a) for carcinogens, the manufacturer fails the burden-of-proof test for safety and the drug is not approved or withdrawn, whereas (b) for noncarcinogens, negligible tolerances or no tolerances are set, based on a showing that residues are expected to be below a level of potential toxicological significance. The judgments are not made without toxicological data. For carcinogens, even this distinction is somewhat artificial because in the case of either measurable or unmeasurable residues, the drug is not approved or withdrawn. FDA's current attempt to extrapolate from animal test data to man, so that "no residue" would be defined by risk, would be one method of regulating carcinogens on a more rational basis.

## Noncarcinogenic Risks

Tolerances for noncarcinogenic drug residues are determined by the general criteria for safety enumerated earlier and by the requirement that the residue level cannot be set higher than that reflected by the permitted use of the drug. When a specified level of residue is determined to be safe through toxicological data, a withdrawal period prior to slaughter of the animal may be required before the drug can be approved. Most approved drugs require a withdrawal period only because they are approved on a negligible-tolerance basis instead of on a finite-tolerance basis. Because the safety factor applied to establish a negligible as opposed to a finite tolerance is very large, withdrawal periods are necessary for residues to deplete below-tolerance levels. The withdrawal period for a specific drug may vary for different animal species or production classes and also may

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<sup>3</sup>21 U.S.C. 360 b[d]2].

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<sup>4</sup>21 CFR 556.1.

vary depending on its combination with other drugs.

Sulfamethazine residues in swine have caused the greatest problem in this area, with tissue residues in excess of the 0.1 ppm limitation averaging 13.1 percent of the samples tested in the latter half of 1977. As explained earlier, more than half of these violations were probably caused by contamination of the withdrawal feed. If so, then increasing the withdrawal time will have little effect on violation rates without parallel action in decreasing cross-contamination of feeds,

FDA subsequently did increase the withdrawal period for all uses of sulfamethazine to 15 days and was nearing completion of a proposal to set action levels for cross-contamination at the end of 1978. Prior to this action, the withdrawal period had been 5 days when in combination with tylosin and 7 days in combination with penicillin and tetracycline. These withdrawal periods had been established prior to new regulations issued in 1975 that established a 10-day withdrawal period for sulfonamides not already subject to regulation.<sup>7</sup> The 10-day period was set because the judgment was made at that time that 10 days would probably be adequate to assure that residues would be below 0.1 ppm and because of the degree of thyroid response to sulfonamide drugs,

Other sulfonamides have not been affected by the new withdrawal period. The withdrawal period for sulfathiazole, also used with tetracycline and penicillin in swine feed, remains at 7 days.<sup>6</sup> Sulfaethoxyypyridazine is used for therapeutic purposes in swine and cattle for use by or on the order of a licensed veterinarian. The withdrawal period remains 10 days.<sup>7</sup> Sulfamerazine is used in trout, with a withdrawal period of 3 weeks.<sup>8</sup>

Residue violations from other antibacterial have not been significant. Most of the residue problems result from therapeutic and not from feed-supplement use. The incidence of violations for some antibacterial is summarized in table 32.

<sup>6</sup>21 CFR 510.450.

<sup>7</sup>21 CFR 558.155,

<sup>7</sup>21 CFR 558.579.

<sup>8</sup>21 CFR 558.582.

Antibacterial residues were previously considered important in the development of antibacterial-resistant bacteria because of ingestion by humans, but this is now considered the least likely contributor. However, the evidence that violative residues of sulfamethazine were caused largely by contamination of the withdrawal feed may bring a new perspective to this issue. As previously discussed, the contribution of antibacterial-supplemented feed to the growth of drug-resistant bacteria comes primarily from selection and promotion of resistant strains of the micro-organisms in animals, not humans. So antibacterial residues in edible animal products are the wrong indicator of this potential problem if the level of such residues does not reflect dependably the antibacterial contamination.

Cross-contamination of feeds may also be occurring for other antibacterial, particularly penicillin and tetracycline, because they are widely used and mixing is not limited to certified feed mills or under the direction of a licensed veterinarian. The sulfamethazine problem was detected because contamination led to violative tissue residues. For other antibacterials, cross-contamination may be occurring but may not be reflected in increased concentrations of tissue residues. Thus, reliance on tissue residues as an indicator of cross-contamination of feed may not be appropriate, and direct monitoring of supposedly antibacterial-free feeds would have to be undertaken to eliminate cross-contamination as a possible significant contributor to the development of drug-resistant bacteria. A limited amount of this feed monitoring is presently conducted by FDA.

## **Carcinogenic Risks**

### **General Considerations**

Current reliance is on testing in small animals for both cause and effect and quantitative extrapolation to humans. All substances demonstrated to be carcinogenic in animals are regarded as potential human carcinogens. No clear distinctions exist between those that cause cancer in laboratory animals and those that cause it in humans. However, the accurateness of extrapolation from

**Table 32.—Incidence of Violations Among Different Antibiotics in Kidneys From Food Animals, Food Safety and Quality Service, Residue Monitoring Program, 1973-77**

Year and specie	samples analyzed		Total violations		Penicillin		Streptomycin		Neomycin		Tetracycline		Chlortetracycline		Oxytetracycline		Erythromycin		Unidentified microbial inhibitor				
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.			
1973:																							
Steers/heifers	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Cows	1,594	44	2.8	0	3	0.2	31	1.9	7	0.4	0	0	0	0	0	0	0	0	0	0	0		
Calves	1,889	152	8.0	0	5	0.3	45	2.4	24	1.3	7	0.4	0	0	5	0.3	2	0	64	3.4	1.9		
Swine	834	15	1.8	0	0	0	2	0.2	0	0	0	0	0	0	0	0	0	0	4	0.5	0.5		
Chickens	665	4	0.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0.6	0.6		
Turkeys	176	1	0.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.6	0.6		
1974:																							
Steers/heifers	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Cows	1,301	12	1.2	0	1	0.1	12	0.9	1	0.1	0	0	0	0	0	0	0	0	0	0	0	0	
Calves	2,849	94	3.3	0	1	0.1	3	0.2	7	0.6	7	0.6	0	0	0	0	0	0	21	0.7	0.7		
Swine	292	7	2.4	0	1	0.3	0	0	0	0	1	0.3	0	0	0	0	0	0	2	0.7	0.7		
Chickens	296	2	0.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Turkeys	218	2	0.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
1975:																							
Steers/heifers	222	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Cows	236	5	2.1	0	0	0	2	0.8	1	0.4	0	0	0	0	0	0	0	0	0	0	0	0	
Calves	2,13	155	7.3	0	5	0.2	20	1.3	58	2.7	29	1.4	0	0	0	0.04	0	0	33	1.5	0.4		
Swine	15 <sup>m</sup>	4	2.7	0	0	0	0	0	0	0	2	1.3	0	0	0	0	0	0	0	0	0	0	
Chickens	17 <sup>n</sup>	5	2.8	0	0	0	0	0	0	0	4	2.3	0	0	0	0	0	0	2	0.3	0.3		
Turkeys	49	17	3.5	0	1	0.2	1	0.2	5	1.0	6	1.2	0	0	0	0	0	0	4	0.8	0.8		
1976:																							
Steers/heifers	187	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Cows	353	9	2.5	0	0	0	6	1.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Calves	1,378	88	6.4	0	0	0	22	1.6	44	3.2	9	0.7	0	0	0	0.07	0	0	2	0.6	0.6		
Swine	247	3	1.2	0	0	0	1	0.4	0	0	0	0	0	0	0	0	0	0	1	0.4	0.4		
Chickens	155	1	0.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.6	0.6		
Turkeys	258	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
1977: <sup>a</sup>																							
Steers/heifers	198	1	0.5	0	0	0	0	0	0	0	1	0.5	0	0	0	0	0	0	0	0	0	0	
Cows	755	17	2.3	0	1	0.1	8	1.1	4	0.5	3	0.4	0	0	0	0	0	0	0	0	0	0	
Calves	566	28	4.9	0	2	0.4	1	0.2	9	1.6	5	0.9	0	0	0	0	0	0	0	0	0	0	
Swine	211	2	0.9	0	0	0	1	0.5	0	0	1	0.5	0	0	0	0	0	0	0	0	0	0	
Chickens	177	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Turkeys	204	2	1.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

<sup>a</sup>1977 data are from January to June SOURCE: USDA, 1978, table 3.

laboratory animal results to humans to quantify the effect is less certain (Cancer Testing Technology and Saccharin, 1977).

Short-term tests are developing as aids in evaluating the potential of substances to cause cancer. Short-term tests are based on the presumption that cancer is related to cellular DNA changes and that detection of such changes is predictive for a substance's potential carcinogenicity. These tests examine the capacity of a substance to cause mutations or other genetic alterations. Several hundred known animal carcinogens and non-carcinogens have been tested in the *Salmonella*/Ames test, which at this time is the most extensively studied short-term test. About 90 percent of the known carcinogens are positive in this test, in contrast to positive results in about 10 percent of substances that are not carcinogenic in animal tests (McCann et al., 1975; Purchase et al., 1976; Sugimura et al., 1976).

Typically, animal experiments use on the order of 100 animals at each experimental dose. If a particular experimental dose causes a lifetime increase in cancer risk of 1/10, this increase can be measured with a small degree of accuracy using 100 animals. If background or spontaneous carcinogenesis is present, even larger numbers of animals will be required. On the other hand, the extra human risk that we may want to estimate resulting from environmental exposure is usually much smaller than 1/100 for any given chemical, perhaps on the order of 1/10<sup>6</sup>. Clearly, it would not be practical to conduct an experiment with enough animals to measure directly an increase in risk this small.

For these reasons the procedure has been developed of conducting lifetime animal-feeding experiments using, in addition to a control dose of zero, several doses at which the projected extra cancer risk may be 1/10 or larger. The high-dose data are used to estimate a dose where the risk may be no larger than, say, 1/10<sup>6</sup>. That is, the high-dose data is used to estimate the risk at dose levels considerably below a level at which effects could be discerned from practical experimental feeding studies. An equally important variant to this problem is the calculation of the so-

called "safe" dose, for which there is some measure of statistical assurance that the extra risk at that dose is no more than, say, 1/10<sup>6</sup>. These problems are often referred to collectively in the literature as the "low dose extrapolation problem."

The most common animals used are rats and mice, and these species, as well as different inbred strains of them, often vary in their sensitivity to the substance being tested. Also, the number of animals used in these experiments is a compromise between large enough numbers of them to detect positive effects and the costs and time of conducting these experiments. Rats and mice live for 2 to 3 years, and when this time is added to the time needed to set up the experiment, examine tissues, write up the results, etc. a typical experiment takes about 4 years. And statistically speaking, the law of probabilities tells us that positive results cannot be expected all of the time even when the substance being tested is carcinogenic.

For these reasons, when both positive and negative results are obtained in different experiments and there is no known reason for the discrepancy, more weight is given to the positive results. Scientists would agree that statistically positive results obtained in at least two animal species by appropriate tests are reasonably conclusive evidence that the substance is likely to be a human carcinogen. Clearly positive results in one valid and appropriate animal species are also considered by a majority of scientists to be a sufficient basis for labeling a substance a carcinogen. In addition, short-term tests may be helpful in predicting that a substance is genotoxic and may, therefore, aid in the identification of a substance's carcinogenic potential.

Carcinogens may act in a variety of ways, ranging from a genotoxic interaction of the agent with the cell genome to the enhancement of the expression of tumorigenesis initiated by other known or unknown agents. Science is progressing rapidly in the elucidation of the mechanisms of carcinogenic action, but it is seldom possible at this stage to be certain by what mechanisms an individual agent acts.

The concept of a threshold below which a carcinogen may be ineffective has been the subject of debate. It is not possible to determine by experiment whether such a threshold exists because of the vast numbers of animals and the consequently large facilities and reservoir of trained personnel required. Nevertheless, there is substantial evidence that the lower the exposure to a carcinogen, the lower the risk of developing cancer. This established fact is the justification for attempts to extrapolate from the effects of carcinogens at high doses to their postulated effects at much lower doses. And even if threshold issues were resolved—i. e., for a given substance there is or is not a threshold—how to determine the threshold with a high degree of confidence would remain as a major issue.

In the absence of contrary data, it is prudent in extrapolating from the results of animal experiments to humans to give the most weight to the results of the most sensitive animal experiments. The general rationale is to err on the side of safety. Laboratory animals are deliberately inbred to have uniform characteristics so that confounding factors relating to individual animal variability are minimized within a specific experiment. Generally, these experiments attempt to introduce only one variable—the substance to be tested—so that causality can be deduced between it and the resulting carcinogenic effect.

When the risks from animal experiments are extrapolated to expected incidence in humans, the results are usually expressed in risks per lifetime exposure, the usual exposure period of present animal tests. Yet lifetime exposure is not a necessary precondition for carcinogenesis, since even single exposures to potent carcinogens can produce cancer. Lifetime exposure is intended to elicit the maximum response to a particular concentration of the tested substance.

Lifetime exposure to large doses by experimental animals and the use of these findings to extrapolate to low doses in humans are often misunderstood. The usual misunderstanding is to equate the concentrations used in the experiments with that consumed by humans. For example, in announcing the re-

sults of positive carcinogenic tests on saccharin and its intention to ban it as a food additive, the initial press release from FDA made the statement that “The dosages of saccharin fed the rats in the Canadian study were in excess of the amount that a consumer would receive from drinking eight hundred (800) 12 oz. diet sodas daily over a lifetime” (FDA Press Release, Mar. 9, 1977).

These misunderstandings leave the impression that animal experiments predict unrealistically high carcinogenic effects in humans. Yet these experiments are conducted in carefully controlled conditions where other carcinogens are not present, in contrast to the conditions of human exposure. There is a rough similarity between (1) the correlation of experimental conditions with environmental exposure to which humans are subject and (2) the correlation of experimental with field results on the effectiveness of antibacterial for growth promotion and feed efficiency in food animals. In the latter, the quantitative effect in the field is greater than under controlled, experimental conditions, though the precise mechanisms are not known. Perhaps a similar result might be hypothesized for carcinogenic effects, but at the minimum, the conditions are not so radically different that in carcinogenic testing the opposite result should be expected. That is, there is no strong argument that animal data overstate the risk to humans.

#### Quantification of Risk

It is not scientifically possible to determine the slope of the carcinogenesis dose-response curve for any carcinogen at low exposure levels. Therefore, performing a low-dose extrapolation involves the choice of a mathematical function to model the dose-carcinogenic response relationship and the choice of statistical procedures to apply to the mathematical function. The choice for this mathematical function turns out to be extremely crucial to the outcome of low-dose risk estimation. If the assumed relationship between tumor occurrence and dose does not apply in the regions to which the extrapolation is being made, a serious overestimate of the “safe” dose may result (Mantel and Bryan, 1961). For example, a comparison of five standard dose-re-

sponse models showed that they could differ by many orders of magnitude at low dose levels for which extra risks are on the order of  $1/10^6$  (Chand and Heel, 1974).

It is theoretically possible to discriminate among the various potential dose-response functions on the basis of experimental data; however, two different dose-response functions can often fit experimental data equally well but still differ by several orders of magnitude at very low doses. Moreover, even if a particular dose-response function were to give a significantly better fit to data than several others, this would still not furnish assurances that this function would necessarily correlate in any way with the true dose response at very low doses where it is not feasible to measure the true extra risk directly. As a consequence of the great disparity of dose-response functions at low doses, the dose-response function should reflect known or at least plausible information regarding the biological mechanisms through which a chemical induces or promotes cancer and not solely on the basis of how well it can be made to fit "experimental data."

For genotoxic carcinogens probably the substance itself or a metabolite acts directly at the cellular level and produces a heritable change that eventually leads to tumor formation (Crump et al., 1977). Carcinogens that are carcinogenic by reason of their mutagenicity should fall into this category. Therefore, carcinogens that test positively in the *Salmonella*/Ames mutagenicity screening test are very likely to be genotoxic. As 90 percent of the known carcinogens tested have been found to be mutagenic, most known carcinogens are probably genotoxic.

A partial solution to the low-dose extrapolation problem for the case of genotoxic chemical carcinogens has been given (Crump et al., 1976; Guess and Crump, 1976; Pete, 1977). The key result is that, at least as long as background carcinogenesis is present, the dose-response curve should not be expected to be absolutely flat at zero dose. What this means is simply that when risk is plotted against dose response on ordinary linear scales, the tangent line to the dose-response curve at zero dose should have a positive

slope. When a dose-response function has this property, it is *linear* at low dose. This simple property can have far-reaching consequences on low-dose extrapolation. For example, consider the two potential dose-response functions (1)  $0.1 [(99/999) \times d + (900/999) \times d^2]$  and (2)  $0.1 \times d^2$  for the dose interval  $0 \leq d \leq 3$ . Both of these curves give a risk of  $1/10$  at a dose of  $d = 1$  and are practicably indistinguishable at higher doses. However, at a dose of  $d = 1/10^3$  (1) predicts a risk of  $1/10^5$  and (2) predicts a risk of  $1/10^7$ , a difference of two orders of magnitude.

One explanation of why the dose-response function should be linear at low dose when background is present is that the cellular mechanism through which the test agent produces cancer should already be operative in producing background tumors. When this is true, the effect of the test agent is to add to an already ongoing process (Crump et al., 1976; Pete, 1977). If background carcinogenesis is allowed for by positing an effective background dose, the wide range of risks obtained using different models effectively disappears. This does not imply that the dose-response curve is not expected to be linear at low dose in the absence of background carcinogenesis (Crump et al., 1976; Watson, 1977).

The evidence for low-dose linearity given above applies mainly to genotoxic carcinogens. A nongenotoxic carcinogen might cause some gross physiological change such as suppression of ovulation, which could predispose the subject to cancer. For such carcinogens the shape of the dose-response curve at low dose is highly speculative. There could possibly be a threshold dose below which the agent has no carcinogenic effect at all on an individual. However, even if a threshold mechanism is operative, there is likely to be considerable variation in individual thresholds in a large population. Consequently, the dose-response curve for the entire population could still exhibit a linear trend at risks as low as  $1/10^6$  or lower,

The effects of metabolic activation and detoxification on carcinogenic dose response have been recently considered through a kinetic model that encompasses free toxic substance, metabolite, deactivator, and the inter-

actions of these substances (Cornfield, 1977). Only a steady state situation is studied in that variation over time of the concentrations of these agents is not considered. The model predicts a threshold dose below which there is no carcinogenic risk under the assumption that the deactivator is 100 percent efficient in deactivating the carcinogen. However, in a naturally occurring process it is likely that deactivation would not be perfect and would be less than 100 percent effective in always combining with 100 percent of the carcinogen before an amount of the active metabolize reaches a cancer target site. Any of a number of modifications to the model to allow for nonperfect deactivation would rule out a threshold and would lead directly to a model for which carcinogenic response varies linearly with dose at low doses. Cornfield's own modification of perfect deactivation, that of allowing the deactivating reaction to be reversible, leads, as Cornfield points out, to a model that is linear at low dose. This occurs regardless of how slowly the reverse reaction takes place, as long as the possibility is not eliminated entirely. Furthermore, even in the extremely unlikely case of perfect deactivation, an otherwise realistic model should still imply low-dose linearity, since the theoretical time required for perfect deactivation would not be zero and would likely be infinite.

For most, perhaps all, carcinogens, the mechanisms through which cancer is produced are not sufficiently understood so that the shape of the carcinogenic response curve can be predicted with certainty. As pointed out earlier, experiments of sufficient size cannot be conducted that would permit direct experimental investigation of the dose-response curve at low doses. There are plausible arguments that the dose-response curve is linear at low dose for many carcinogens. In view of these uncertainties, it would seem reasonable to base estimates of added risk of cancer on a mathematical model that encompasses low-dose linearity unless the mechanism through which the carcinogen operates is sufficiently understood so that low-dose linearity can be conclusively ruled out. Once the principle of low-dose linearity is accepted, the problem of estimation of risks at low doses is nearly solved. This is because the

disagreement between the upper statistical confidence bounds on risk at low doses based on a model that incorporates low-dose linearity, and one that does not is typically several orders of magnitude; whereas the corresponding disagreement between two reasonable models, both of which incorporate low-dose linearity, is usually much less than this.

The new procedures and criteria for evaluating the assays for carcinogenic residues in edible products of animals that FDA is attempting to implement (see chapter II) originally adopted the Mantel-Bryan mathematical model (Mantel and Bryan, 1961; Mantel et al., 1975) to quantify the residue level corresponding to a risk of  $1/10^6$  in test animals. This residue level, or  $S_0$ , is expressed as a fraction of the total diet—i.e., in parts per billion (ppb). This level is adjusted to account for the respective portion of the human diet that is represented by the various food products containing residues of the carcinogen being tested, the transfer from animals to man being made on a fraction-of-total-diet basis. The resulting dose level,  $S_m$ , is “the level of total residue of carcinogenic concern that can be operationally defined as satisfying the no-residue requirement of the Act for specific tissues.”<sup>9</sup> The dose level  $S_m$  represents the upper bound to the lowest limit of reliable measurement that an approved assay method must satisfy. The specific mathematical model chosen is thus an integral part of defining “no residue.”

Crump (1978) discusses the Mantel-Bryan model, simple linear extrapolation models to low doses (Heel et al., 1975; Brown, 1976), and multistage dose-response models (Guess and Crump, 1976, 1978; Crump et al., 1977; Hartley and Sielkin, 1977). In the Mantel-Bryan procedure, the mathematical model used for the dose-response model is what is termed the “probit” function. The Mantel-Bryan procedure, as was to be applied in the FDA regulations, rules out linearity at low dose in favor of a “flatness property” at low doses. This results in “safe” dose estimates that are considerably higher than those obtained using the multistage model because it

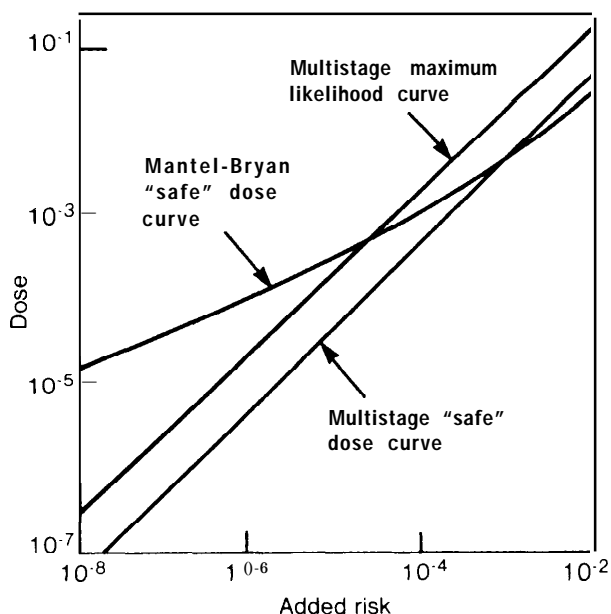
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<sup>9</sup>42 F.R. 10422, Feb. 22, 1977.



assumes away linearity at low dose, an assumption that is probably unwarranted for the majority of carcinogens, which appear to be genotoxic. Figure 1 illustrates this difference. Note that for the data reflected in

Figure 1.—Comparisons of “Safe” Doses Computed From the Mantel-Bryan Procedure and From a Procedure Based On the Multistage Model<sup>a</sup>



Source: Crump K S 1977 Response to OpenQuery Theoretical Problems in the Modified Mantel-Bryan Procedure *Biometrics* 33: 752-755

this graph, the Mantel-Bryan “safe” dose lies above the multistage “safe” dose at values of added risk below  $5 \times 10^{-4}$ . When the Mantel-Bryan method predicts that a cancer risk is no greater than  $1/10^6$  the true risk could easily be one or two orders of magnitude higher, or between  $1/10^4$  and  $1/10^5$  (Crump, 1978).

FDA has now proposed that linear extrapolation be used, rather than the Mantel-Bryan procedure, because, among other reasons, linear extrapolation is least likely to underestimate the risk.

Since extrapolation based on the multistage model will often be linear at low doses, the question arises as to how different the result will be from simple linear extrapolation. For some data the difference will be minimal, but for other data sets the difference could be considerable. For example,

from DES data in C3H female mice (Gass et al., 1964), the “safe” dose based on linear extrapolation is lower than the “safe” dose based on the multistage model by a factor of about five and there are doubtless cases where the difference could be greater than an order of magnitude ( $10 \times$ ).

#### Diethylstilbestrol (DES)

DES has been shown to be carcinogenic in both animals and humans. The association between the use of DES by women during pregnancy and the appearance of clear-cell adenocarcinoma of the vagina or cervix in their exposed daughters was recently reviewed by a task force at the National Institutes of Health (DES Task Force Report, 1978). The main conclusions were as follows:

1. **DES daughters.** A clear association between in utero exposure to DES and clear-cell adenocarcinoma of the vagina or cervix is established. Estimates are that the incidence will be between 0.14 to 1.4 per 1,000 through age 24 among the exposed daughters. Cancers of this type and histological sites were almost unknown in women of that age group prior to this discovery. (The eventual incidence as these women grow older obviously is unknown.)
2. **DES mothers.** A relationship between DES during pregnancy and risk of cancer in the mothers is unproved. However, existing studies indicate that this population, like others exposed to high levels of estrogens, may in the future develop excessive incidence of specific tumors.
3. **DES sons.** Until recently, DES effects on exposed sons had not been reported. Recent studies clearly show an excess of genital abnormalities in these individuals. As yet, there is no definitive information on the fertility implications of these findings nor firm evidence of an association between DES exposure in sons and an increased risk of testicular cancer.

The animal data currently available on carcinogenic dose response to DES consists primarily of mice data (Gass et al., 1964; Gass et al., 1974), although new experiments at the

<sup>a</sup>4 F.R. 17070, Mar. 20, 1979.

National Center for Toxicological Research in Jefferson, Ark., are nearing completion. DES was given in the diet beginning from 4 to 6 weeks after birth and continued throughout their lives. (Note that this is less than maximum lifetime exposure, so the cancer response might have been greater.) The 1964 micedata are summarized in table 33.

Crump (1978) analyzed these data sets according to specified methods for analyzing animal carcinogenicity data (Crump et al., 1977) to estimate the risks to mice at dose levels comparable to those encountered by humans through DES residues in beef. Because suppression of appetite at the two highest doses was reported, the data at 500 ppb and 1,000 ppb were omitted from analysis.

The average food intake of Americans is about 24 lbs a week (Riedman, 1971), about 2.3 lbs of which is beef (CAST report, 1977). The lowest limits of reliable measurement of the FDA-approved mouse uterine method for measuring DES residues is 2 ppb. The concentration of DES residues in liver is about 10 times that in beef muscle (U.S. Congress, 1971). Tested livers cannot exceed 2 ppb; otherwise DES would be detected and the present "no residue" test would be violated. Thus the average DES residue in beef muscle might be 0.2 ppb. This gives an average dose of DES to Americans from DES residues in beef muscle to be:

$$\frac{(2.3 \text{ lbs a week})}{(24 \text{ lbs a week})} \times (0.2 \text{ ppb}) = 0.02 \text{ ppb}$$

Table 34 summarizes the estimates of extra cancer risks at the dose of 0.02 ppb based on applying the multistage model and related statistical theory to these mice data. The most sensitive mice data predict a risk of 1/13,000, and the least sensitive a risk of 1/82,000. As explained earlier, when the Mantel-Bryan model predicts a risk of 1/10<sup>6</sup>, the true risk could easily be between 1/10<sup>4</sup> and 1/10<sup>5</sup>, or within the same range as summarized in table 34.

Assuming that the population at risk is 200 million people, lifetime exposure to DES in meats at 0.02 ppb would result in 15,385 extra cancers as derived from the most-sensitive mice strain (200 million x 1/13,000), and 3,390 or 2,439 extra cancers as derived from the less-sensitive mice results from table 34. These estimates should be compared with 200 extra cancers, which would be the "no residue" level of the 1/10<sup>6</sup> target risk from the proposed FDA regulation.

Table 35 summarizes the doses derived from these same experimental data that result in an added carcinogen response of 1/10<sup>6</sup>, the target "no-residue" level of the proposed FDA regulation. In contrast to the 0.02 ppb estimate exposure to DES from present consumption of food, these doses are in the range of 0.001 to 0.0003 ppb, or 1/20 to 3/200 the estimated exposure.

The evidence for DES's carcinogenicity points to a nongenotoxic mechanism, so an effect at low doses can be disputed (Weisburger, 1977). In addition, the response might be

Table 33. -Occurrence and Latent Period of Mammary Carcinoma in Mice Fed Varying Concentrations of DES in the Diet (Gass et al., 1964)

DES /n diet ppb <sup>a</sup>	C3H females			C3H males			Strain A castrate males		
	No. of mice	Percent with tumors	Latent period in weeks	No. of mice	Percent with tumors	Latent period in weeks	No. of mice	Percent with tumors	Latent period in weeks
0	121	3.30	49.12	115	0	—	136	0	—
6.25	56	4.82	49.96	59	0	—	78	0	—
125	60	4.33	46.57	58	17	—	78	1.3	6200
25	60	4.33	51.07	62	0	—	70	2.9	48,50
50	68	5.29	45.19	62	4.8	66.00	77	3.9	69,66
100	64	6.56	42.19	60	5.0	44.67	74	8.1	61.33
500	59	8.47	30.66	60	38.3	39.95	52	13.5	5400
1,000	58	8.62	31.40	71	42.3	36.03	76	19.7	4780

<sup>a</sup>Mice consumed approximately 2.5 to 3.6 g of food per day animals receiving the two highest concentrations consumed slightly less due to estrogenic suppression of appetite ppb = parts per billion  
SOURCE: Crump 1978

**Table 34.—Extra Risk of Mammary Tumors at a Dose of 0.02 ppb (Mice Data, Gass et al., 1964)**

Mice strain	Most likely estimate	Upper 95% confidence bound
C3H females	1/13,000	1/18,000
C3H males	1/82,000	1/47,000
Strain A castrate males	1/59,000	1/37,000

Source: Gass et al., 1964

**Table 35.—Estimates of Dosage (ppb) of DES Required To Effect an Added Carcinogen Response of 1/108 (Mice Data, Gass et al., 1964)**

Mice strain	Most likely estimate	Lower 95% confidence bound
C3H females	0.000258	0.000162
C3H males	0.00164	0.000944
Strain A castrate males	0.017117	0.000748

Source: Gass et al., 1964

largely limited to females. However, in both animal experiments and from what is known about DES effects in humans: (1) cancer is known to occur even in the absence of continuous DES stimulation, and (2) effects in males have been observed. The rough estimates for the number of extra cases expected in humans are for lifetime exposure risks. If DES has a carcinogenic effect at low doses, these estimates would not be overstating the effect.

### Nitrofurans

In 1964, in the course of conducting toxicity studies, scientists at the University of Wisconsin discovered that a substantial number of mammary tumors had developed in rats fed nitrofurazone. Subsequent studies in 1966 and 1967 showed that animals fed nitrofurans had significantly higher incidence of tumors. Since that time, Norwich Pharmacal Company has conducted four chronic toxicity studies to assess the tumorigenic and carcinogenic effects of one of these nitrofurans, furazolidone. In all of these studies, the experiments were started when the animals were about 2 months of age, and three of these studies fed furazolidone for a limited period, followed by a furazolidone-free diet until the experiment was terminated. A more pronounced carcinogenic effect might have been observed if the doses had been continued throughout the experiment.

Brief descriptions of these experiments follow:

- The High-Dose Sprague-Dawley Rat Study .<sup>11</sup>**—Four hundred Sprague-Dawley rats approximately 2 months of age were divided into four groups of 50 male and 50 female rats each. The diet of the four groups contained furazolidone in the feed in the amounts of 0 ppm, 250 ppm, 500 ppm, and 1,000 ppm for approximately 18 months. All groups were then maintained on a furazolidone-free diet until mortality in each group reached 90 percent, at which time the remaining animals were sacrificed.
- The Fischer Rat Study .<sup>12</sup>**—This study was performed identically to the High-Dose Sprague-Dawley Rat Study except that Fischer 344 rats were used instead of Sprague-Dawley rats.
- The Low-Dose Sprague-Dawley Rat Study .<sup>13</sup>**—Three hundred and twenty Sprague-Dawley rats approximately 2 months old were divided into four groups of 40 male and 40 female rats each. The diet of the four groups contained furazolidone in the feed in the amounts of 0 ppm, 17.6 ppm, 87.9 ppm, and 264.4 ppm. These are average amounts since the concentrations of furazolidone in the diet were increased as the animals continued to grow. The animals were treated continuously until the experiment was terminated after 2 years.
- The Mouse Study .<sup>14</sup>**—Four hundred Swiss MBR1ICR mice approximately 2 months of age were divided into four groups of 50 male and 50 female mice each. The diets of the four groups contained furazolidone in the feed in the amounts of 0 ppm, 75 ppm, 150 ppm, and 300 ppm for approximately 13 months.

<sup>11</sup>“Tumorigenesis Evaluation of NF-180 in Sprague-Dawley and Fischer Rats, Part I, Sprague-Dawley Evaluation.” Nov. 9, 1973, Project No. 475.091).

<sup>12</sup>“Tumorigenesis Evaluation of NF-180 in Sprague-Dawley and Fischer Rats, Part II, Fischer 344 Evaluation.” Jan. 31, 1974, Project No. 475.09D.

<sup>13</sup>“Chronic Toxicopathologic Safety Study [two years] of NF-180 in Rats.” Nov. 9, 1973, Project No. 475.09C.

<sup>14</sup>“Tumorigenesis Evaluation [twenty-three months] of Furazolidone [NF-180] in Mice.” Jan. 31, 1974, Project No. 475.09E.

The four groups were then maintained on a furazolidone-free diet for 10 additional months, at which time the experiment was terminated and the surviving animals were sacrificed.

Table 36 summarizes the tumorigenic and carcinogenic findings. There is a high rate of spontaneous tumors in all four groups. The mice results are the most sensitive. Although exposed to the lowest concentrations of furazolidone, they developed the greatest percentages of tumors, particularly when malignant tumors were separated from nonmalignant ones.

The results of various statistical tests performed on the data are given in table 37. A chi-square goodness-of-fit test of no carcinogenic-dose-related effect is significant at the 0.01 level of significance for four of the data sets. More importantly, a test of no dose-related effect versus the alternative of a one-stage effect (a multistage model) is significant at the 0.01 level for six of the data sets including all four of the data sets for mice. Thus furazolidone had a statistically significant effect in mice. A chi-square goodness-of-fit test for compatibility with the one-stage model of carcinogenesis was significant at the 0.05 level in only 2 of the 16 data sets. The two data sets for which significance was found

**Table 36.—Summary of Tumorigenic and Carcinogenic Results From Four Experiments With Furazolidone (N F-180)**  
(Data is presented in the form "no. responders/no animals tested")

	Dose (ppm)	All neoplasms		Malignant neoplasms	
		Males	females	Males	Females
High-dose Sprague-Dawley Rat Study	0	29/50	44/99	10/50	11/49
	250	33/49	46/50	12/49	6/50
	500	35/50	48/50	15/50	12/50
	1,000	40/49	45/50	13/49	13/50
Fischer 344 Rat Study	0	48/49	39/49	15/49	14/49
	250	49/50	46/50	2/50	10/50
	500	45/50	50/50	15/50	11/50
	1,000	44/49	45/50	13/49	16/50
Low-dose Sprague-Dawley Rat Study	0	21/34	26/34	3/34	7/34
	176	13/34	24/35	5/34	11/35
	879	17/35	29/33	9/35	9/33
	2644	23/32	33/35	6/32	12/35
Mice Study	0	25/49	35/50	21/49	32/50
	75	30/48	35/50	26/48	28/50
	150	36/50	40/47	32/50	37/47
	300	46/51	42/48	43/51	40/48

SOURCE Crump 1978

**Table 37.—Levels of Significance of Various Goodness-of-Fit Tests Performed on Data in Table 36**

		Test 1	Test 2	Test 3
Test 1 Chi-square goodness-of-fit test (3 d. f.) of no dose-related effect.				
Test 2 Test of the hypothesis no dose-related effect versus the alternative hypothesis of a one-stage model (Crump, Guess, and Deal, 1977)				
Test 3 Chi-square goodness-of-fit test (2 d. f.) of a one-stage model				
		High-dose Sprague-Dawley rats		
All neoplasms	Males	31	< .01	92
	Females	64	.49	47
Malignant neoplasms	Males	73	.21	64
	Females	38	.18	25
		Fischer rats		
All neoplasms	Males	13	.50	06
	Females	< .01	.05	01
Malignant neoplasms	Males	< 0.1	.28	< .01
	Females	48	.26	37
		Low-dose Sprague-Dawley rats		
All neoplasms	Males	.03	.03	07
	Females	03	< 0.1	47
Malignant neoplasms	Males	29	16	23
	Females	61	17	61
		Swiss MBR11BR mice		
All neoplasms	Males	< .01	< .01	72
	Females	.05	< .01	47
Malignant neoplasms	Males	< .01	< .01	76
	Females	.01	< 0.1	14

SOURCE Crump 1978

were quite anomalous and would likely not be compatible with any dose-response function for which the risk increases with increasing dose.

Before using these data to estimate extra risks for furazolidone residues, it is first necessary to assess the level of furazolidone residue likely to occur in food products from animals exposed to furazolidone. In 1971 it was announced by FDA that a method for measuring residues of furazolidone would be required that would reliably measure residues as low as 2 ppb. The FDA concluded in 1976 that there was at that time no method available for reliably measuring residues of 2 ppb.<sup>15</sup> Thus there currently is no way to know if food products from animals treated with furazolidone do not have at least 2 ppb in them.

Table 38 presents estimates of extra risk at a dose of 2 ppb based on the rodent data in table 36. Since these estimates are all very

<sup>15</sup>41 F.R. 19919, May 13, 1976.

**Table 38. —Estimates of Extra Risk From a Dose of Two Parts Per Billion of Furazolidone Using the Data in Table 36**

		<i>Most likely estimate of extra risk</i>	<i>Upper 97 5% confidence limits for extrarisk</i>
<i>High-dose Sprague-Dawley rats</i>			
All neoplasms	Males	1/1 <b>500,000</b>	1/760 000
	Females	1/375 000,000	1/4 800,000
Malignant neoplasms	Males	1/6 900,000	1/1 <b>900,000</b>
	Females	1/6 900,000	1/2 100,000
<i>Fischer rats</i>			
All neoplasms	Males	0	1/5 500,000
Malignant neoplasms	Females	1/9,400 000	<b>1/2,200,000</b>
<i>Low-dose Sprague-Dawley rats</i>			
All neoplasms	Males	<b>1/490,000</b>	1/21 <b>0000</b>
	Females	1/260,000	1/130,000
Malignant neoplasms	Males	<b>1/1 300,000</b>	<b>1/430,000</b>
	Females	1/1 300 000	1/390 000
<i>Swiss MBR 11BR mice</i>			
All neoplasms	Males	1/ <b>200,000</b>	1/120,000
	Females	1/470 000	1/1230,000
Malignant neoplasms	Males	1/220,000	1/130,000
	Females	1/420,000	1/21 0000

SOURCE: Crump, 1978

nearly linear with dose at risks below 1 percent, risk estimates for other doses can be determined from the table by simply multiplying by the appropriate factor. For example, to compute risks at 20 ppb, multiply the results in table 38 by 10.

The risk estimates in table 38 are based on the statistical procedures of Crump et al. (1977) associated with a multistage model. To obtain the "most likely estimates," the particular multistage model was selected (Guess and Crump, 1976) that maximized the likelihood of the data. Risk estimates are not given for the Fischer rats for "females, all neoplasm," nor for "males, malignant neoplasm," because these data are not consistent with the multistage model. For the most sensitive result—namely, in the mice—the extra risk at a dose of 2 ppb furazolidone exceeds the proposed regulatory "no residue" risk level of  $1/10^6$  by two to five times.

It should be noted that the estimates of risk are higher for the mice and low-dose rats than for the high-dose rats because the high-dose rats had lower or approximately equivalent tumor rates as rats and mice in the other experiments. High-dose rats were fed 250 ppm, 500 ppm, or 1,000 ppm furazolidone. Low-dose rats were fed approximately

17.6 ppm, 87.9 ppm, or 264.4 ppm furazolidone; and the mice were fed 75 ppm, 150 ppm, or 300 ppm furazolidone. When extrapolated to extra risks from a dose of 2 ppb furazolidone (table 38), the low-dose experiments result in higher incidence of tumors than the high-dose experiments.

Two ppb may be the residue level in meat, but it is not the dose to which humans are exposed. These risks can be translated at low doses for mice into comparable risks for humans in the following way: Furazolidone is used extensively in chickens and turkeys and for limited periods in swine. In the estimates of effects from banning selected antibacterial, banning nitrofurans (of which furazolidone is one) was estimated to have an effect on chickens and turkeys but not on pork. (See table 23.) Thus, human exposure from meat consumption comes from chickens and turkeys.

For DES, Americans were assumed to consume an average of 2.3 lbs of beef a week and 24 lbs of food a week. Thus beef was assumed to average about 0.2 ppb DES, for an average dose of 0.02 ppb. Taking a population of approximately 200 million and a total beef supply in 1976 of 25,969 million lbs (see table 22), the average amount of beef consumed by Americans was approximately 2.3 lbs a week (25,969 million lbs of beef - 200 million people - 52 weeks). This correlates with the 2.3 lbs used in calculating the DES risk, where average dose from DES residues was 0.02 ppb.

A comparable calculation for furazolidone is as follows: Total chicken and turkey production in 1976 was 10,930 million lbs (table 22). The average weekly consumption per person was therefore:

$$\frac{10,930 \text{ million lbs}}{200 \text{ million people}} - 52 \text{ weeks} = \frac{1.05 \text{ lbs}}{\text{a week}}$$

Using the same calculation as used for DES, the average dose of furazolidone per person from residues in chicken and turkey meat would be:

$$\frac{1.05 \text{ lbs a week}}{24 \text{ lbs a week}} \times (2 \text{ ppb}) = 0.09 \text{ ppb}$$

The estimates of extra risk in table 38 for a dose of 2 ppb can be used to estimate the risks for other doses by multiplying by the appropriate factor, 0.09/2, or approximately 1/20. Taking the most sensitive animal data, that for Swiss MBR1IBR mice, and multiplying by 1/20, these risks are approximately  $1 - (4 \times 10^{-6})$ ;  $1 - (9.4 \times 10^{-6})$ ;  $1 - (4.4 \times 10^{-6})$ ; and  $1 - (8.4 \times 10^{-6})$ . Thus the risk to humans from furazolidone in poultry is 4 to 10 times less than the target "no residue" risk of  $1/10^6$ . In contrast to expected extra cancers of 200 for the "no residue" risk of  $1/10^6$ , these exposures to furazolidone are estimated to produce 20 to 50 extra cases of cancer.

These estimates also can be illustrated by contrasting the calculated exposure of humans to furazolidone with estimates of the dose of furazolidone required to produce an extra risk of  $1/10^6$  (table 39). The most sensitive mice data result in doses of 0.41 to 0.95 ppb, as contrasted to the 0.09 ppb dose calculated for human exposure.

The mice and rat strains used in these experiments all had rather high spontaneous rates of both tumors and malignancies, Mantel (1977) has not recommended using the

**Table 39.—Estimates of Dose in Parts Per Billion of Furazolidone Required To Produce an Extra Risk of  $1/10^6$  Using the Data in Table 36**

		<i>Most likely estimate of extra risk</i>	<i>Upper 97.5% confidence limits for extra risk</i>
<i>High dose Sprague-Dawley rats</i>			
All neoplasms	Males	3.0	15
	Females	750	95
Malignant neoplasms	Males	13.7	3.9
	Females	139	4.1
<i>Fischer rats</i>			
All neoplasms	Males	—	402 ppm
Malignant neoplasms	Females	189	43
<i>Low-dose Sprague Dawley rats</i>			
All neoplasms	Males	0.988	0.429
	Females	0.527	0.253
Malignant neoplasms	Males	7.58	0.862
	Females	2.56	0.783
<i>Swiss MBR1IBR mice</i>			
All neoplasms	Males	0.410	0.247
	Females	0.946	0.454
Malignant neoplasms	Males	0.431	0.265
	Females	0.836	0.424

1 R E P D 1 1

Mantel-Bryan procedure for data with high spontaneous rates, In his analysis of the experiments described here,<sup>16</sup> Mantel selected a "cut off" time and only considered tumors detected prior to this time. This modification of the data used by Mantel was applied to the mice data and was found to have relatively little effect, the maximum change in the upper confidence bounds on risk being less than a factor or two (Crump, 1978). Therefore, the risk estimates in table 38 would not have been significantly different if the test animals had had a lower spontaneous rate of tumor production or if the data had been modified so as to discount tumors that occur late in life.

There should be neither statistical nor theoretical grounds for rejecting the risk estimates in table 38 as unreasonable estimates of rodent risk at 2 ppb. Each of the 14 nitrofurans tested with the Salmonella/Ames test were mutagenic (McCann et al., 1975). Consequently, furazolidone should be considered to be a genotoxic carcinogen with the property of being linear at low dose. The upper confidence bounds on risk computed from the multistage model also have this property. (See figure 1.) Moreover, as is shown in table 37, the multistage model cannot be ruled out on the basis of a chi-square goodness-of-fit test for those data sets for which risk estimates are listed in table 38,

Since the carcinogenic effect of furazolidone in man has not been measured directly, data such as in table 36 constitute the currently available dose-response information for estimating the carcinogenic risk to man.

The assumptions underlying the kinds of risk estimates as calculated for DES and furazolidone are not unanimously accepted, and calculations based on different assumptions could lead to different estimates. The point of the foregoing quantitative exercise was to test the usefulness of a target risk approach to the definition of "no residue" and whether that approach would avoid the problem caused by using actual physical presence of residues for the definition. As discussed earlier, technical improvements in measuring

<sup>16</sup>Ibid.

very minute quantities of residue have led to problems in continuing to use the physical presence approach.

Present FDA regulatory authority is risk-oriented. A regulated substance must be shown to have its intended effect, but more importantly for this discussion, risks must be estimated because safety as well as effectiveness is a regulatory criterion. Thus, even if there were agreement that the 1/10' added lifetime exposure risk of cancer was an appropriate definition of "no residue," determining the amount of drug that corresponds to that risk level remains a problem.

Similar differences exist among researchers in quantifying the benefits of using animal drugs. The estimates summarized in the previous chapter on benefits of the use of certain antibacterial and DES produced different quantitative results, even though the USDA and Headley analyses began with the same model,

In contrast to risk assessment, FDA's regulatory decisionmaking basis does not include a quantification of benefits. Furthermore, FDA will not make an official estimate of relative effectiveness of the different drugs they approve for similar uses, FDA's position is that the Agency does not deal in relative effectiveness and that any product with the same claims may be used interchangeably as a substitute for the others (FDA, 1979). The USDA and Headley analyses on benefits lead to different results, although starting from the same model. If FDA had to quantify benefits, it most likely would have reached different quantitative results.

FDA does have to estimate risks. In contrast to the estimate of cancer risks from DES and furazolidone included in this report, FDA has indicated that, according to the estimates they have made, present DES and furazolidone uses would lead to cancer risks in excess of the proposed target risk of 1/10' (FDA, 1979). The difference in results comes primarily from two different assumptions. FDA uses the ninth decile for consumption distribution rather than average per capita con-

sumption "to provide protection for the vast majority of the population. But use of average per capita consumption does not necessarily underestimate the risk to humans. The estimates used here assumed all beef contained at least 2 ppb of DES, when in fact DES or other weight-promoting chemicals are given to about 80 percent of fed cattle, and FDA itself reports that DES has dropped considerably in the dollar-volume sales list.

Second, FDA is also concerned that risks occur from both the parent drugs and their metabolites and that for both DES and furazolidone, the parent drug represents only a small percentage of the total residue, which has not been well-characterized or shown to be safe. FDA states that: "Without identification and testing of the compounds which comprise the residue, no estimates of risk are of much value in judging the safety of the drug use. At best it may be said that the information available gives rise to the possibility that residue exposure may greatly exceed an acceptable level of risk from cancer" (FDA, 1979). The estimates used here were based on residue levels that were at the limits of detection by methods presently approved by FDA, whereas FDA's estimates are based on newer methods not yet approved. In addition, if FDA's use of the target-risk approach leads to no practical difference on how regulatory decisions are made, the FDA statement that no estimates of risk are of much value without identification and testing of the metabolites raises the question of whether a target-risk approach is any improvement over physical presence criteria. Furthermore, this would be a contradiction to the previously quoted statement by FDA's Director of the Bureau of Veterinary Medicine that the new method would "provide a mechanism whereby a reasonably safe level may be established and then, irrespective of further analytical developments, there will be that expectation that the originally set level will remain until toxicological evidence rather than analytical evidence [demonstrates that to be an incorrect tolerance]" (*Food Chemical News*, Oct. 16, 1978).

# APPENDIX

Commissioned Papers  
References



## COMMISSIONED PAPERS

Chapters III and IV, which summarize the evidence on the benefits and risks of the use of drugs in livestock feeding, were based on reviews commissioned by the office of Technology Assessment and on a paper originally prepared for the Council for Agricultural Science and Technology's Task Force on Antibiotics in Animal Feeds. The authors and their reviews are as follows:

W. M. Beeson  
Professor Emeritus, Animal Nutrition  
Department of Animal Science  
Purdue University

“Use of Drugs and Chemicals as Feed Additives to Increase the Productivity of Cattle and Sheep”

Kenny S. Crump  
Professor of Mathematics and Statistics  
Louisiana Technical University

“Estimating Human Risks From Drug Feed Additives”

George K. Davis, Professor of Animal Science  
Institute of Food and Agricultural Sciences  
University of Florida

“Drugs and Chemicals as Feed Additives for the Protection of the Health of Cattle, Sheep, and Goats”

L.C. Grumbles, Head  
Department of Veterinary Microbiology and Parasitology  
College of Veterinary Medicine  
Texas A&M University

“Protection of the Health and Performance of Poultry and Swine by the Use of Drugs and Chemicals as Feed Additives”

Virgil W. Hays  
Professor and Chairman  
Department of Animal Sciences  
University of Kentucky

“Effectiveness of Feed Additive Usage of Antibacterial Agents in Swine and Poultry Production”

J.C. Headley  
Professor of Production Economics  
University of Missouri

“Economic Aspects of Drug and Chemical Feed Additives”

Richard P. Novick, Chief  
Department of Plasmid Biology  
Public Health Research Institute  
City of New York

“Transmission of Bacterial Pathogens From Animals to Man With Special Reference to Antibiotic Resistance” (originally prepared for the Council for Agricultural Science and Technology's Task Force on Antibiotics in Animal Feeds, Ames, Iowa)

J.H. Weisburger, Vice-President  
Research  
American Health Foundation  
Valhalla, New York

“Comments on the Physiological and Pathological Effects of Diethylstilbestrol (DES)”

These papers are available from OTA on request.

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