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Drug Residues in Food Animals

by Kent J. Trembly*

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During the past several years, drug residues in food animal products have become a serious problem for livestock producers and veterinarians. The reasons for concern are threefold: first, increased sensitivity of testing methods; second, percentage of product containing residues; and third, restrictions on potential carcinogens dictated by the Delaney Amendment. The Federal government monitors foods for residues in order to provide the American people with food that is safe and unadulterated by exogenous chemicals. The use of drugs in the livestock industry today has become widespread, both as feed additives and therapeutic agents.

Residue monitoring is a function of the Meat and Poultry Inspection Program (MPIP) of the Food Safety and Quality Service (FSQS), a division of the United States Department of Agriculture (USDA). Residue tolerance levels are set by the Bureau of Foods of the Food and Drug Administration (FDA) from data submitted by commercial firms during drug approval procedures and by research conducted by the FDA. For any substance that has been shown to have carcinogenic activity, the tolerance level is zero, as dictated by the Delaney Amendment to the Pure Food and Drug Act. When illegal residue levels are found, they are investigated cooperatively by the FDA’s Bureau of Veterinary Medicine and MPIP to determine both the cause of the residues and the possibility for prosecution of the parties at fault. Continued violations or purposeful disregard for regulations can lead to prosecution. Practicing veterinarians play an important role in helping clients find and eliminate residue problems as well as avoid future problems with drug residues.

The two products currently causing the greatest residue problems are diethylstilbestrol (DES) in cattle and sulfonamides (primarily sulfamethazine) in swine. In 1976, 94.5 percent of the residue violations in swine were caused by sulfonamides and 52 percent of the residue violations in other species were due to sulfonamides. Of the 94.5 percent of the swine residues caused by sulfas, 97.2 percent were sulfamethazine. Due to the high incidence of sulfa residues the rest of this paper will deal primarily with sulfa residues in swine.

Drugs have different tolerance levels in animal products as set by the FDA based on safety and human health considerations. The burden of proof for the safety of human consumption lies with the applicant for the New Animal Drug Application (NADA), usually a drug company. Carcinogens for use in food animals must also be shown to not adversely affect such animals and have no residues in edible portions of the carcasses under use as specified by the labeling. The tolerance levels for other substances (non-carcinogens) are set by the FDA following experiments with the target specie(s) to determine what levels of the drug are found following “reasonable” withdrawal periods. DES, a growth-stimulating implant or feed additive for cattle, has a zero tolerance level because it has been shown to have carcinogenic activity. Commonly used sulfonamides have not shown carcinogenic activity and have a residue tolerance level of 0.1 parts per million (ppm) in tissue.

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In controlling residue levels, the government has three primary concerns. First is the fear that low level residues will produce microflora in humans that are resistant to common human drugs. Theoretically therapy in humans who consumed residue-containing animal products could be jeopardized, thereby limiting selection of human effective drugs for treatment purposes. This transferable drug resistance is induced by phage transfer from resistant to sensitive [to specified antibiotic(s)] microorganisms; therefore, producing a microflora which would theoretically be totally resistant to the specific antibiotic or sulfonamide. Although such phage transfer has been demonstrated in laboratory situations, there exists no proof that it contributes to the production of resistant microflora in the field. Experiments by the American Cyanamid Company with Salmonella spp. using chlortetracycline alone or in combination with sulfamethazine or sulfamethazine combined with penicillin did not increase the quantity, prevalence or duration of shedding Salmonella spp., nor did these drugs select for resistance in their phage transfer.\textsuperscript{18,19}

Second, substances which have been shown to be carcinogenic are not found in the human food chain. Every substance that stimulates tumor formation is labeled a carcinogen irregardless of the relative amount required to produce neoplasia in test animals.

Third, residues are controlled to prevent sensitization of humans consuming adulterated foods to these drugs such that at later date contact with the same drug could produce anaphylaxis and possibly death.

Drug residues and the issues surrounding it arise as a result of the federal government’s protection of the American consumer. The FSQS of the USDA is given the responsibility of assuring the public that the meat and poultry they consume is wholesome and unadulterated. This protection is dictated by law—the Wholesome Meat Act and the Wholesome Poultry Products Act.\textsuperscript{5} Routine residue testing was initiated by FSQS in 1967 to monitor the overall situation. Residue monitoring has been stepped up significantly the past few years to help monitor more closely the increased incidence of illegal residues found at slaughter.

When a producer is found to have a sulfanilamide residue violation he receives an official notification from MPIP that all future shipments from his farm will be retained when presented for slaughter, unless acceptable evidence that animals produced under his management meet residue requirements at the time of slaughter. To produce this evidence requires slaughter of at least five animals to allow collection of tissue samples for laboratory analysis. The actual laboratory analyses may be conducted at the owner’s expense by a recognized commercial laboratory (a laboratory that has proven to MPIP that they are capable of doing the analyses) or at an MPIP laboratory where the owner does not have to pay for the analyses, but the process may be more time consuming.\textsuperscript{23}

It takes little imagination to realize the consequences a producer faces when his pork is found with illegal drug residues. The producer must bear the expense of either testing future shipments at private laboratories or holding his hogs off the market while MPIP tests a sample of his herd. Neither alternative is inexpensive.

Residue violations have far-reaching effects that most producers don’t realize—the entire swine industry as well as veterinarians and feed companies may suffer losses. The American people must have confidence in the products they purchase and if they are overly concerned with drug residues, consumption of meat and meat products will decrease.

Because of the concern of the Federal government over risks involved by using certain drugs in animals as well as man, a ban on subtherapeutic use of penicillin and tetracyclines has recently been proposed. Presently this field is moving extremely rapidly and the latest proposal was published in the Federal Register.\textsuperscript{9} That proposal is to allow the use of penicillin and tetracyclines in the feed only on the order of a licensed veterinarian. Such feed must be manufactured by a feed mill with an approved medicated feed application for each restricted medicated animal feed produced. The order by the veterinarian may be written or oral, but an oral order must be promptly confirmed in writing. Records of all restricted medicated feeds sold must be kept at the point of sale for a minimum of two years. These requirements also apply to individual producers who have approved medicated feed

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applications and manufacture their own feeds. The uses for these feeds would only be for approved levels and indications. The only exception to these regulations would be to allow the sale of 50 pound bags of feed containing a level of 2 grams/pound of penicillin, chlortetracycline or oxytetracycline to deal with immediate problems, but this must only be sold by a licensed veterinarian or by a feed mill on veterinary order. This will restrict usage of tetracyclines and penicillins significantly for both veterinarians and producers, as the only source of these drugs in feed would be feed manufactured, licensed and controlled by the FDA.

It has been estimated (by the FDA) that removing (1) DES from use in beef cattle, (2) furazolidone from use in poultry and swine and (3) penicillin and tetracycline use as feed additives in swine and beef cattle would cost approximately $5 billion annually due to decreased feed efficiency. This amounts to $20 for each and every American. Removal of penicillin and tetracycline from therapeutic usage would have far-reaching effects on both the livestock industry and the veterinary profession. Satisfactory replacement drugs simply are not available at a price that is competitive and it seems unlikely that they will become available in the near future. Increasing government regulation has caused a dramatic decrease in the number of new drugs reaching the market. Drug companies simply cannot afford to research and develop new drugs unless the drug is sure to reach the market and then to have a large demand awaiting it. 21

In 1958 when the Delaney Clause (for testing for carcinogens and banning them from food and food product) was introduced, testing for DES was done by biological assays using mice. This method was sensitive to a level of 20 parts per billion (ppb). At that same time, testing methodology for all other compounds was sensitive only to the parts per million (ppm) level. In the last 20 years, new testing methods have been developed and utilized including gas chromatography, immunofluorescence and radioisotope tracing. These new testing methods are able to detect residues to the parts per trillion (ppt) level. This means that sensitivity is 1,000 times that of 20 years ago for DES and up to 1,000,000 times on other drugs. So, while only making slight changes in the law we are imposing much tighter regulations on livestock producers.

There has been much criticism aimed at the federal government as well as its policies, agents and testing methods during the last couple of years. Several months ago the MPIP officials stated vehemently that all problems could be resolved by producers observing withdrawal times. Since that time several cases have been documented where either withdrawal times were observed or no sulfonamides were used at all. There is little doubt that producers may have been within the limits of the law on several occasions and still found to have excessive residue levels, but in the majority of cases, the residue could have been prevented. Unfortunately, it seems that producers and veterinarians alike don’t realize the seriousness of this situation. On January 16, 1978, at a meeting in Washington, D.C., the FDA threatened to restrict or remove sulfas from use as a swine feed additive. Since that time there has been a similar proposal concerning penicillins and tetracyclines. DES has been on and off the market for the past several years. It seems unlikely that it will be on the market much longer. It will probably just be a matter of time before penicillin and tetracyclines are either banned or available on a limited basis.

Some scientists have tried to convince FDA that we should use a biological zero rather than an absolute zero for regulating carcinogens. The Sensitivity of Method document currently being discussed is an attempt to establish the biological zero concept within the Delaney Clause. Many problems exist with this proposal, but the alternative to biological zero regregulations is continued elevation of detection sensitivity and pressure on drugs from infinitissimal animal residue levels. In a meal of ground round steak from DES-implanted cattle, whole wheat bread, mashed potatoes, green peas and salad; the food containing the least estrogen is the meat. 25

I cannot over emphasize the importance of this crisis, not only to you, your employer and your clients; but to our profession, the livestock industry and the American consumer. We must bring this situation under control or the federal bureaucracy will do it for us—it may already be too late. It appears that the Federal government has become
insensitive to the needs of agriculture, which may be true, yet none of us want to eat adulterated food products. Practitioners must keep accurate records of drugs used, amount given and route of administration. The owner must be notified of the withdrawal time in writing. Feed mills are to clean bins, grain legs, mixers, augers and other equipment thoroughly after handling medicated feed in order to prevent contamination of subsequent batches of feed. Drug companies must be certain that their premixes don't contain more than the prescribed amount of active ingredient(s). Identification of animals injected or treated in any way is important, both as individuals and in groups of animals. A good example of such identification methods is the tail tags used on dairy cattle. If a veterinarian uses an unapproved drug, he must be able to determine an effective withdrawal period. Practitioners must realize the capabilities of their clients and the limitations each one's facilities places on drug selection.

The day is past when we just reach for the "best" drug—we must take a rational approach to medication—selecting drugs to fit each client's individual circumstances. If a producer uses the same auger in one building for both growing and finishing pigs, the residual feed left in such an auger can be enough to cause residue problems if it is not cleaned.

I'm sure many of us have been around practices where records were poor if kept at all. We are too young and hopefully too smart to think that we can leave here this year and telling our clients to withhold their animals for both growing and finishing pigs, the residue feed left in such an auger can be enough to cause residue problems if it is not cleaned.

I'm sure many of us have been around practices where records were poor if kept at all. We are too young and hopefully too smart to think that we can leave here this year and survive without keeping good records and telling our clients to withhold their animals from slaughter until the specified withdrawal time is past. We are facing a complex issue to which there are no quick, easy answers.

**BIBLIOGRAPHY**


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