UNIVERSITY OF MINNESOTA

Dairy Extension
Department of Animal Science
101 Haecker Hall
1364 Eckles Ave.
St. Paul, Minnesota 55108
(612) 624-4995

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ANTIBIOTIC RESIDUES IN MILK: CURRENT STATUS OF DRUG RESIDUE TESTING IN MILK AND DAIRY PRODUCTS

Jeffrey K. Reneau, D.V.M., M.S.
Extension Animal Scientist, Dairy Management

What's the Problem?

The dairy industry is committed to the production of wholesome milk and dairy products. Low somatic cell and bacteria counts are encouraged through quality premium payments. Detectable levels of antibiotics, antibacterials, and other drug contaminants are illegal and are carefully monitored by state and federal agencies responsible for human health.

Recently, there has been concern about the level of sulfamethazine in milk and dairy products. This concern was prompted by the National Center for Toxicological Research studies linking increases in thyroid tumors in mice fed sulfamethazine.

Sulfamethazine residues were found in a variety of milk sources in the New York City and New Jersey metropolitan areas. Of the 64 milk samples collected, 63% were positive for one or more residues. Tetracycline and sulfamethazine were the most prevalent.

In March 1988, the FDA tested 49 samples of milk collected from grocery stores in 10 U.S. cities. Again high percentages of the samples were contaminated with sulfamethazine. Canadian researchers reported in August 1988 that 86% of the 175 samples taken from 16 cities across the U.S. and Canada tested positive for drug residues. Again, sulfamethazine or tetracycline were the main offenders.

An obvious question is: Why have sulfamethazine residues suddenly become such a problem? Why weren't they ever discovered before? The answer is quite simple; the introduction of new detection methodologies have now made it possible to detect virtually all the drugs available for use on dairy cattle and at very low levels. The Charm II test procedure, for example, will detect some 97 drugs and at sensitivities ranging from 10 to 1,000 times more

sensitive than previous tests. With today's new testing methods there is no escaping detection. We cannot think of dilution as the solution to antibiotic contamination. For example, accidental use of the milk from a cow treated in one quarter with 100,000 IU of penicillin will easily be detected in milk from 1,000 cows. Just 1/2 cc of the commonly used antibiotic Combiotic could be easily detected if accidently put in a large semi-tanker truckload of milk. Without a doubt, we face a great challenge in preventing the contamination of our nation's milk supply. However, let's not lose perspective. In spite of the seriousness represented by individual cases of contaminated milk, the overall incidence is quite low.

Historically, the U.S. dairy industry has responded well to the challenge of minimizing antibiotic contamination of milk supplies. With each new generation of more sensitive testing methods has come quick compliance and the production of safer, more wholesome milk. Prior to 1960, surveys suggested that 5% of the U.S. milk supply was contaminated with antibiotics. This declined to 0.5% after 1960. In 1975, a more sensitive antibiotic testing procedure revealed that up to 15% of the U.S. milk supply was contaminated. Again, the industry responded to this new challenge. By 1987, testing laboratory results showed that only 0.1% of farm milk samples contained detectable levels of antibiotics or growth inhibitors. Emphasizing the positive, 99.9% of farm samples were negative for antibiotics. Yet by the standards of today's new antibiotic test procedures, we must not become complacent and must be even more careful in preventing contaminated milk from entering the food supply.

Why all the Concern?

There are basically four reasons:

1. It is estimated that approximately 5 to 10% of the population are allergic to penicillin. Approximately 4% are allergic to the sulfonamides.

2. There is concern that low levels of antibiotics in human diets will result in the development of resistant strains of pathogens rendering ineffective therapeutic drugs in the treatment of human disease.

3. There is need to protect the reputation of dairy products. Health conscious consumers today are unwilling to accept any adulterants in foods. What good would all the "health kick" American Dairy Association advertising campaigns be if reports of drug contamination of milk began to appear in the news media? Survey studies show that consumers concerns of drug residues and hormones in food was second to concerns over herbicides and pesticides and greater than the concern over cholesterol.

4. Antibiotics and other growth inhibitor substances interfere with manufacturing of several dairy products.

What's the Source?

The most common source of antibiotic contamination of the milk supply is improper use of antibiotics in the treatment of mastitis and metritis. Oxytetracycline, gentamicin, and sulfamethazine are the most common drugs found in residue violations.

Sources of antibiotic residues in milk:

Extended usage or excessive dosage of approved drugs.
Poor records of treatment.
Failure to observe recommended label withdrawal time.
Prolonged drug clearance.
Treated animal identification problems.
Contaminated milking equipment.
Multiple dosing.
Milker or producer mistakes -- accidental transfer into bulk tank.
Products not used according to label directions.
Lack of advice on withdrawal period.
Withholding milk from treated quarters only.
Early calving or short dry periods.
Purchase of treated cows.
Use of dry cow therapy to lactating cows.

The beef industry has claimed that the greatest percentage of antibiotic residues in meat is caused by culled dairy cows treated for mastitis. Michigan studies show that farmers that used medicated feeds were more likely to have residues in their milk and meat products. Antibiotic residues do not appear to be a problem in dry cow therapy when the dry period is 6 weeks or greater.

Current Approved Drugs

Currently, there are only 11 antibiotic or antibacterial drugs approved for use in lactating dairy cattle. Each of these products has a very definite prescribed use and withdrawal time for milk and meat. When their label instructions are carefully followed, there is rarely a drug residue problem. Those drugs are listed in Table 1.

Table 1. Approved antibacterial and antibiotic drugs for lactating cows.

Drug	Trade name	Labeled use	Route of administration	Withdrawal times: Milk (hrs)	Withdrawal times: Meat (days)
*Dihydrostreptomycin Sulfate Penicillin G (Procaine)	Distrycillin	Subclinical mastitis	Injectable	48	30
	Combiotic	"	"	72	30
*Penicillin G (Procaine)	Special Formula 17900-FORTE	Subclinical mastitis	Intramammary	72	15
	Albacillin	"	"	72	15
	Penicillin G Procaine Aqueous	Mastitis and Shipping Fever	Injectable	48	10
	Veticil; Districillin	"	"	48	30
*Erythromycin	Gallimycin 36	Mastitis and Shipping Fever	Intramammary	36	14
	Erythro-36	"	"	36	15
	Erythro-100/Erthro-200	"	Injectable	72	14
*Cephapirin	CEFA-LAK/TODAY	Mastitis	Intramammary	96	4
*Oxytetracycline	Terramycin Soluble Powder	Bacterial diarrhea	Oral	60	5
	Terramycin-100 Premix	"	"	120	5
	TM-10; TM-50 Premix	"	"	120	5
	Terramycin TM-500	Antibacterial	"	120	5
*Sulfadimethoxine	ALBON/AGRIBON	Foot rot	Oral	60	7
	AGRIBON Injection 40%	"	Injectable	60	5
Sulfaethoxyprydazine	S.E.Z. IV Solution	Foot rot	Injectable	72	16
Cloxicillin	DARICLOX		Intramammary	48	10
Amoxicillin	Amoxi-Mast		Intramammary	60	12
Hetacin-K	Hetacin-K		Intramammary	72	10
Ampicillin	Polyflex		Injectable	48	6

*Those available for over the counter sale to farmers.

Concern Over Extra-labeled Use

An approved drug use means that it has been cleared by the FDA for use in dairy cattle according to the specific label directions established by the manufacturer. Extra-labeled use is: any unapproved use of an approved drug or use of a drug not approved for use in dairy cattle.

When a drug is used by a producer, whether approved or unapproved, it is the producer's responsibility to withhold the treated animal from slaughter and prevent the sale of milk or meat products until the drug is eliminated from the animal's system or has been reduced to a non-violative level. If the drug is not approved by the manufacturer for use in dairy cattle, specific withholding information is not available, and the drug should then be used only as prescribed by a veterinarian.

There are extra-label drugs used in dairy cattle. Veterinarians are responsible only for drugs they prescribe "off-label" (prescription drugs), and they legally are bound to advise the animal's owner about the pharmacology of those drugs. Their advice includes dosage, routes of administration, dosage interval and drug clearance times (withdrawal time) for both meat and milk producing animals.

Since extra-label drugs do not have manufacturer's withdrawal times established, veterinarians use their knowledge of excretion time considering the dosage used, condition of the animal, and the route of administration to estimate the clearance times. As veterinarians are responsible, they will add several extra days of withholding to positively assure clearance of the drug from the animal. On-farm tests to detect residues are available and recommended.

Why do veterinarians recommend unapproved drugs at all? Because sometimes the response to an approved drug at the recommended dosage is poor or does not occur.

In attempting to improve the outcome of the treatment and prevent loss of the animal, some drugs are needed at higher dosage for extended days of treatment. Veterinarians are within the law if the drug is legal, a valid client/patient relationship exists, animal identification is established, and the animal's owner is informed of all ramifications involving the drug.

The Food and Drug Administration (FDA) policy, which relates to extra-label use of drugs in food producing animals, states that: "Although it has been and remains the policy of the FDA not to interpose itself into the practice of veterinary medicine, this policy does not extend to situations where the public health may be adversely affected. Both producers and veterinarians may be subject to prosecution under the Food, Drug and Cosmetic Act for such extra-label use, particularly when it results in violative residues in edible products of treated animals."

The Food Safety Inspection Service (FSIS) (USDA), and the Food and Drug Administration (FDA) increasingly are concerned about what appears to be a rather widespread use of extra-label drugs. Producers and veterinarians must work together to address their concerns, but the ultimate responsibility lies with the producers.

Once antibiotics are in milk, they cannot be removed from milk in the processing plant. The only solution is prevention. This must be done, of course, at the farm. Responsible and careful use of antibiotics and other drugs or chemicals are mandatory by farmers, veterinarians and others. It is clear the public is not going to tolerate adulterated foods. Without question, farmers want to provide the consumer with a safe, wholesome product.

Dairy producers need to carefully observe milk and meat withdrawal times for all antibiotics including sulfa drugs. Now would be a good time to review your program for avoiding antibiotic residues.

Recommendations for Avoiding Antibiotic Residues

1. Seek advice, in writing, from your veterinarian on proper antibiotic usage. Together you can develop a plan for your herd as to when and how antibiotics will be used.

2. One person on the farm should be responsible for the antibiotics and other treatment supplies. Drug label instructions change frequently -- always look closely for the correct dosage and withdrawal times each time you buy and use antibiotics. Allow only responsible persons to treat cows.

3. Keep an accurate written record on all treated animals including date of treatment, product used, dosage and withdrawal times for milk and meat. This applies to antibiotics prescribed or administered by your veterinarian as well as antibiotics purchased over the counter. Use these records to monitor antibiotic usage in your herd.

4. Treated cows must be identified! This must be done so that treated cows can be identified quickly and accurately in the milk parlor -- markings on legs, tails or flanks. Be sure an unexpected absence of a milker will not result in the milk from a treated cow going into the tank. The most foolproof procedure, and the only suitable procedure in large herds, is to be able to separate out treated cows from the rest of the herd. Dry cows that have been dry treated must be removed from the milking herd. Since separated, treated cows have the unique ability to find their way back to the milking herd, it is also important to mark these cows.

5. Purchased milking cows should be regarded as treated cows unless the producer has information to the contrary. Most dairy plant laboratories will run an antibiotic test on questionable milk (bulk tank or cows) prior to milk shipment.

6. Follow label directions exactly to avoid residues in milk and meat. This applies to any method of antibiotic treatment (udder, bloodstream, muscle, uterus or oral). Dairymen generally believe that label times for intramammary preparations are longer than necessary -- this is not the case. New milk testing procedures may actually cause withdrawal times to be too short. Remember, the withdrawal time begins the last time the drug is administered. If more treatments are used than prescribed on the label, the withdrawal time will be longer.

7. With intramammary treatment, discard milk from all four quarters regardless of the number of quarters treated. Follow your veterinarian's instructions on milk and meat withdrawal after every uterine infusion when antibiotics are used.

8. Be extremely careful with dry cow treatment preparations. These products must be used as long as six weeks before the cow freshens (see label for specific days). Thus, accurate breeding records are essential if these products are to be used. Accidental use of a dry cow product in a lactating cow will result in milk residues for at least three weeks.

9. Treated animals must not be sold for slaughter until the withdrawal time for meat (shown on the label) has elapsed. Thus, particular emphasis should be placed on the use and selection of injectable products -- since many have long pre-slaughter withdrawal times. For example, dihydrostreptomycin has a 30-day withdrawal time and oxytetracycline, a 15 to 22-day withdrawal time.

10. If in doubt, have milk tested. Most dairy plant laboratories will gladly run an antibiotic test on questionable milk prior to shipment. Be sure that the test used is sensitive enough for the antibiotic in question. Currently no effective, fast, affordable test is available for a dairyman to test his own milk for the sulfonamides.

On-Farm Testing?

Any time there is any doubt about whether an individual cow's milk or a bulk tank of milk is contaminated with antibiotics it should be tested. Milk plants offer such services and would prefer that patrons have milk checked before contamination occurs. There are also available on-farm test kits for cowside testing of antibiotics in milk. However, one should realize that these tests vary both in their sensitivity and the spectrum of drugs that can be detected (Table 2). Some of the tests will only pick up the penicillin family of drugs; others have a broader spectrum. The new Charm II test now in use by many milk plants can pick up virtually all antibiotics likely to be used on dairy cattle. Table 3 shows all the antibiotics that can be detected by the Charm tests. Farmers should be sure they understand the capability of any antibiotic test they are using so that they do not erroneously ship contaminated milk thinking it is clear of antibiotic contaminations.

Table 2. Comparison of several antibiotic test methods.

Test marketed by	Test name	Test time	Techonology	Sensitivity	Cost/ test	Antibiotic
Penicillin Assays 617-332-1523	Charm I	12 min.	Receptor	Pen/3 ppb Chlor/95 ppb Sulfon/10 ppb	$1.90	Penicillin Chloramphen. Sulfon.
Penicillin Assays	Charm II	10 min.	Receptor		$1.80	7 Families
Penicillin Assays	Cowside	9 min.	Receptor		$3.00	Pen., Sulfon.
Penicillin Assays	CIA	3.5 hr.	Micro	Pen/3 ppb Sulfon/5-20 ppb Tetra/250 ppb Eryth/200 ppb	$0.80	Penicillin Sulfon. Tetra. Erythro.
Smith Kline 215-251-7500	EZ Screen	<10 min.	ELISA	Sulfam/10 ppb	$7.50	Sulfameth.
Smith Kline	Signal	30 min.	ELISA	Sulfam/10 ppb	$2.50	Sulfameth.
Smith Kline	Penzyme	20 min.	Enzyme	Pen/5 ppb	$1.65	Pencillin
Angenics 617-876-6468	Spot	6 min.	Latex agg.	Pen/5 ppb	$1.35	Pencillin G Cephap. Cloxac.
Agri-Tech 800-548-6733	Cite	<6 min.	ELISA	10 ppb	$2.80	Sulfameth.
Gist-Brocades 704-527-9000	Delvo P	3 hr.	Micro	Pen/ 3ppb Sulfon/ 500-1000 ppb	$1.00/ amp.	Penicillin Sulfon.
Gist-Brocades	Delvo P	3 hr.	Micro	Pen/3 ppb	$1.00/ amp.	Pencillin
Idtech 800-433-8351	N/A	13 min.	ELISA	≤10 ppb	$2.50 (less for multiple test kit)	Sulfameth.
	B. Strotherm.	3 hr.	Micro			Penicillin
	B. Subtilis	5 hr.	Micro			Penicillin
	Cylin. Plate	18 hr.	Micro			Penicillin
	HPLC	8 hr.	Instr.			Sulfon.
	GC Mass Spec.	Unknown	Instr.			Several

Table 3. Antibiotic detection capability of the new Charm tests.

Partial list of antibiotics detectable with:
◆ CHARM TEST
■ CHARM TEST II
● CHARM FIELD TEST

BETA-LACTAMS (P)
- ● ◆ ■ Penicillin BT
- ● ◆ ■ Penicillin G.
  (benzylpenicillin)
  (benzathine)
  (potassium)
  (procaine)
  (sodium)
  (benethamine)
  (calcium)
- ● ◆ ■ Penicillin O
- ● ◆ ■ Penicillin S
- ● ◆ ■ Penicillin N
- ● ◆ ■ Methicillin
- ● ◆ ■ Nafcillin
- ● ◆ ■ Ticarcillin
- ● ◆ ■ Penicillin V.
  (benzathine)
  (hydrabamine)
  (potassium)
- ● ◆ ■ Oxacillin
- ● ◆ ■ Cloxacillin
  (benzathine)
- ● ◆ ■ Dicloxacillin
- ● ◆ ■ Flucloxacillin
- ● ◆ ■ Ampicillin
  (trihydrate)
- ● ◆ ■ Amoxicillin
  (trihydrate)
- ● ◆ ■ Piperacillin
- ● ◆ ■ Hetacillin
- ● ◆ ■ Carbenicillin
- ● ◆ ■ Cephalothin
  (Cephaloglycin)
- ● ◆ ■ Cephapirin
- ● ◆ ■ Cephapirin Benzathine
- ● ◆ ■ Cephradine
- ● ◆ ■ Cephacetrile
- ● ◆ ■ Cephalexin
- ● ◆ ■ Cephaloridine
- ● ◆ ■ Cefazolin
- ● ◆ ■ Cefoxitin
- ● ◆ ■ Cefaclor
- ● ◆ ■ Cefadroxil
- ● ◆ ■ Cefamandole
- ● ◆ ■ Cefatrizine
- ● ◆ ■ Cefazedone
- ● ◆ ■ Cafmenoxime
- ● ◆ ■ Cefmetazole
- ● ◆ ■ Cefonicid
- ● ◆ ■ Cefoperazone
- ● ◆ ■ Ceforanide
- ● ◆ ■ Cefotaxime
- ● ◆ ■ Cefotetan
- ● ◆ ■ Cefotiam
- ● ◆ ■ Cefroxadine
- ● ◆ ■ Cefsulodin
- ● ◆ ■ Ceftazidime
- ● ◆ ■ Ceftezole
- ● ◆ ■ Ceftizoxime
- ● ◆ ■ Ceftriaxone
- ● ◆ ■ Cephalosporin C
- ● ◆ ■ Cephamycin A
- ● ◆ ■ Cephamycin B
- ● ◆ ■ Cephamycin C
- ● ◆ ■ Cephapirin Sodium
- ● ◆ ■ Cephradine

TETRACYCLINES (T)
- ■ Tetracycline
- ■ Choritetracycline
- ■ Oxytetracycline
- ■ Demeclocycline
- ■ Methacycline
- ■ Doxycycline
- ■ Minocycline

AMINOGLYCOSIDES (ST)
- ■ Dihydrostreptomycin
- ■ Streptomycin sulfate
- ■ Neomycin
- ■ Kanamycin
- ■ Amikacin
- ■ Gentamicin
- ■ Tobramycin

MACROLIDES (E)
- ● ◆ ■ Troleandomycin
- ● ◆ ■ Erythromycin
  Erythromycin Stearate
  Erythromycin Estolate
  Erythromycin Gluceptate
  Erythromycin
  Lactobionate
  Erythromycin Phosphate
- ● ◆ ■ Spiramycin
  Erythromycin Thiocynate
- ● ◆ ■ Oleandomycin
- ● ◆ ■ Tylosin
- ● ◆ ■ Lincomycin
- ● ◆ ■ Clindamycin

SULFONAMIDES(SM)
- ● ◆ ■ Sulfamethazine
- ● ◆ ■ Sulfadimethoxine
- ● ◆ ■ Sulfabromomethazine
- ● ◆ ■ Sulfadimthoxine
- ● ◆ ■ Sulfamethoxypyridazine
- ◆ ■ Hydrochlorothiazide
- ◆ ■ Chlorothiazide
- ◆ ■ Furosemide
- ◆ ■ Trichloromethiazide
- ◆ ■ Dexamethasone
- ◆ ■ Sulfasuxidine
- ◆ ■ Dapsone
- ◆ ■ P-Aminosalicyclic acid
- ◆ ■ Trisulfapyrimidine
- ◆ ■ Sulfamethoxazole
- ◆ ■ Phthalylsulfathiazole
- ◆ ■ Sulfachloropyridizine
- ◆ ■ Sulfanitran
- ◆ ■ Sulfaquinoxaline
- ◆ ■ Sulfathiazole
- ◆ ■ Sulfomyxin
- ◆ ■ Thiabendaxole

■ NOVOBIOCIN (N)

● ◆ ■ CHLORAMPHENICOL (C)

Source: Pennicillin Assays Inc.

Conclusion

Antibiotics alone are not a cure-all or even the best approach to control animal disease. They are, however, one of the tools that aid in reducing the duration of infection to allow time for the immune system to protect the animal.

A total herd health program and the advice of a veterinarian is important in determining animal drug selection. The veterinarian is aware of drug activity and the prevention of residues.

Treating disease properly is much more than a simple injection; the producer must realize this to produce quality meat and milk. Ultimately, it is the producer's responsibility at the farm level.

Quality, residue-free food animal products are necessary to ensure consumer confidence; the producer can provide this quality. Producers should use their knowledge in the production of residue-free animal products.

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