FRI BRIEFINGS

Veterinary Drug Residues in Processed Meats — Potential Health Risk

A Review of the Scientific Literature

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Introduction

Veterinary drugs are used to treat disease and improve health in animals as pharmaceuticals are in humans. Since the discovery and development of the first antibiotics prior to the Second World War, these drugs have played an important role in veterinary and human medicine. Experiments conducted 50 years ago showed that low, subtherapeutic levels of antibiotics could increase feed efficiency and growth in farm animals and this has led to the widespread incorporation of antibiotics into animal feeds. Subtherapeutic levels of antibiotics have been shown to reduce the incidence or severity of a number of animal diseases. It has been suggested that they also prevent irritation of the intestinal lining and improve digestive processes and metabolic processes throughout the animal. In addition to positive effects on growth and efficiency, there are associated reductions in excretion of nitrogen, phosphorus, and manure by some farm animals.

However, the potential for widespread use of agricultural antibiotics to provoke development of antibiotic-resistant bacteria has stimulated intense debate. Antibiotic-resistant strains of bacteria known to be foodborne pathogens, including *Salmonella* spp., *E. coli*, and *Campylobacter* spp, have been isolated from farm animals (*1–3, 6, 7, 11, 12, 17–19, 27*). These resistant bacteria could cause human diseases that are difficult to treat. In fact, a recent report found that a multi-state outbreak of a multi-drug resistant strain of *Salmonella enterica* serotype Typhimurium DT104 was associated with ground beef (*16*). Even if the antibiotic-resistant bacteria in meat animals are not human pathogens, they may pass their resistance genes to other, pathogenic bacteria (*2, 35, 40*).

Moreover, there has been some concern about carryover of veterinary drugs into meat, eggs, and milk and the possible adverse effects of residues on people consuming these foods. Surveillance programs do detect drug residues in a small percentage of samples. Withdrawal periods, ranging from a few days to a few weeks, are recommended for approved animal drugs. These times vary according to the drug used, dosage, route of administration, and animal species and are defined as the time required for 99% of the animals in a population (treated according to label instructions) to be free of drug residues above the tolerance level. Failure to adhere to these recommended periods is reported to be the primary cause of violative levels of veterinary drugs in food (*37*).

Suggested Adverse Effects of Veterinary Drug Residues

A number of possible adverse health effects of veterinary drug residues have been suggested. These include the following:

- Allergic/toxic reactions to residues.
- Chronic toxic effects occurring with prolonged exposure to low levels of antibiotics.
- Development of antibiotic-resistant bacteria in treated animals. These bacteria might then cause difficult-to-treat human infections.
- Disruption of normal human flora in the intestine. The bacteria that usually live in the intestine act as a barrier to prevent incoming pathogenic bacteria from getting established and causing disease. Antibiotics might reduce total numbers of these bacteria or selectively kill some important species.

Veterinary drug residues in meat have been reported to cause toxic or allergic reactions in humans although such reports are uncommon. The most notable recent occurrence involved consumption of Mexican beef containing residues of the illegal growth promoter, clenbuterol. During December 2005, at least 225 people in Jalisco reported symptoms of trembling, headache, and malaise after consuming beef or beef liver containing residues of this drug (*41*). Another outbreak associated with clenbuterol in beef affected at least 125 people in Spain in 1990. In the past, there have been other reports of human illness attributed to consumption of meat from animals that had been treated with hormone implants. In some cases these were attributed to consumption of tissue near or at the location of a hormone implant; in other cases, there was not enough data to prove that hormone residues caused illness (*55*).

A few reports indicate that sensitive individuals may experience allergic reactions to antibiotic residues, particularly penicillin residues, in meat. Anaphylactic reactions have been reported to result from consumption of beef or pork containing penicillin (*26, 47*). It is possible that some minor reactions, such as skin rashes, may also have occurred but these have not been reported. Estimates of the prevalence of drug sensitivity vary but are estimated to be about 7% in the general population. However, not all of these people experience severe symptoms, and residue levels detected in meat are likely to be below the threshold that would induce a hypersensitive response (*26, 46, 54*).

Identification of Drugs as Potentially Important Residues

There are no clear-cut data available from the government or other sources on how much of each drug is administered to each class of animals (chickens, turkeys, swine and cattle) in the U.S. on an annual basis. Therefore, to get an idea of which drugs are more frequently used, or at least which are detected most often in carcasses or meat, information was gathered from several sources: FSIS recalls and residue monitoring plans, FDA warning letters concerning residues detected in animals brought for slaughter, and published studies on the prevalence of drug-resistant bacteria in different animals. These drugs would probably be the most likely to be detected in meat.

Only one recall of a packaged meat product that might contain violative drug residues was found on the FSIS web site. This involved sausage and bologna from a Pennsylvania firm in 2001. Penicillin and sulfadimethoxine were detected in meats used to produce these products. No reports of illnesses or adverse reactions were associated with these products.

Results from the 2003 FSIS National Residue Monitoring Plan (Tables 1 and 2) indicate that penicillin and sulfonamide drugs were most commonly detected at violative levels in swine and cattle. Neomycin and gentamicin were also detected in a number of cattle, particularly calves. Other drugs detected in cattle and swine included tilmicosin, flunixin, and tetracyclines. Arsenicals were detected in poultry. Data from 1996 indicated the percentage of violative residues accounted for by each drug: CAST (calf antibiotic sulfa test), 32%; penicillin, 20%; oxytetracycline, 10%; sulfamethazine plus sulfadimethoxine, 10%; tetracycline, 8%; gentamicin, 6%; neomycin, 3%; other, 7% (*44*).

Warning letters sent by FDA to cattle producers with animals containing violative residues were tallied for 2003–2005. Numbers of animals in violation and ranges of concentrations of drugs detected in muscle, liver and kidney were tabulated (Table 3). Penicillin, sulfonamides, gentamicin, flunixin, and neomycin were most often detected in violation. Other drugs detected were tetracyclines, tilmicosin and ivermectin.

Table 1. 2003 FSIS National Residue Monitoring Plan (# violations detected) (*20, 21*)

	Monitoring Program			Enforcement Program				
				FSIS Lab	SOS	STOP		FAST
Residues	Cattle	Swine	Turkey	Cattle	Swine	Cattle	Swine	Cattle
penicillin	1	1		7		39	4	628
neomycin	30					2		405
gentamicin sulfate	3			6		6		230
erythromycin	1							
chlortetracycline		1					1	
tylosin								5
tilmicosin				3		4		37
tetracycline						1		22
oxytetracycline				4		4		60
arsenicals			1					
sulfamethazine	3	3		5	10			90
sulfadimethoxine	6			4		6		225
ivermectin	1							
sulfadiazine	1							
sulfamethoxazole	1							3
flunixin	2							113

SOS = sulfa on site; STOP = swab test on premises; FAST = fast antimicrobial screen test

Table 2. Total Positive results from 2003 National Residue Monitoring Program

Residues	Cattle	Swine	Turkey
penicillin	675	5	0
neomycin	437		
gentamicin sulfate	245		
erythromycin	1		
chlortetracycline		2	
tylosin	5		
tilmicosin	44		
tetracycline	23		
oxytetracycline	68		
arsenicals	0	0	1
sulfamethazine	98	13	
sulfadimethoxine	241		
ivermectin	1		
sulfamethoxazole	4		
sulfadoxine	11		
flunixin	115		

Table 3. Warning letters sent by FDA 2003–2005 for cattle found to contain violative drug residues at slaughter

	# animals cited			Range of concentrations [ppm]		
Drugs	'05	'04	'03	Kidney	Liver	Muscle
Dihydrostreptomycin	3			4.19–6.37		
Flunixin	4	17	14		0.125–14.12	
Gentamicin	4	14	13	0.19–106.54	0.297–5.0	0.32
Ivermectin		0	1			252.7 ppb
Neomycin	11	22	4	0.02–443.39	15.27	detectable
Oxytetracycline/tetracycline	1	7	8	14.83–154.7	6.1–48.17	2.86–42.88
Penicillin	24	37	55	0.06–18.68	0.06–0.80	0.12–0.83
Sulfadimethoxine / sulfamethazine	17	22	49	4.93–6.1	0.10–52.33	0.1–54.91
Tilmicosin	4	2	11	2.2–28.17	1.44–38.96	0.94–13.19

Data from studies of antibiotic-resistant bacteria isolated from meat (reported in papers published 2000–2005) were examined (*8, 10, 13, 22, 28, 38, 39, 42, 43, 49–51, 56, 57*). The hypothesis was that the greater the amount of a drug used, the more likely bacteria would develop resistance to it. Not all reports tested for resistance to all the drugs that were likely to have been used, but an attempt has been made to list the drugs most frequently associated with resistance in bacteria from different meats:

Beef: tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > cephalothin

Pork: tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > gentamicin

Chicken: tetracycline > sulfa > streptomycin = cephalothin > ampicillin > chloramphenicol > gentamicin

Turkey: sulfamethoxazole > tetracycline > streptomycin > ampicillin > cephalothin > gentamicin

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From a consideration of all these sources, the following drugs were considered as the most likely to be detected in meat:

Penicillin (including ampicillin)
Tetracycline (including chlortetracycline and oxytetracycline)
Sulfonamides (including sulfadimethoxine and sulfamethazine and sulfamethoxazole)
Neomycin
Gentamicin
Flunixin
Streptomycin
Arsenicals

Residues of all veterinary drugs are higher in liver and/or kidney tissue as compared to muscle tissue. Analyses have shown that residue levels of some antibiotics can be different in different poultry muscle tissues (*48*). Pharmacokinetic models have been developed to describe metabolism and distribution of drugs in different animals. These models can also be used to estimate withdrawal times required to deplete drug levels in different tissues (*4, 5, 9, 14, 20, 21, 23–25, 36, 37, 52, 53*).

Potential Adverse Effects

Penicillin

Penicillin derivatives (β-lactam antibiotics) are widely used in cattle, swine and poultry to treat infections and as feed or drinking water additives to prevent some diseases. Penicillin is usually cleared rapidly from the blood via the kidneys and into the urine. Results cited by JECFA in 1990 indicated that penicillin residues in kidney and liver (as determined by HPLC) were about 100 times higher than those in muscle (*29*).

Allergic reactions were considered by JECFA to be the determining factor for safety evaluation of residues (*29*). Overall prevalence of allergy to penicillin in different populations has been estimated at 3–10%. There has been no evidence that exposure to penicillin residues in food caused sensitization to penicillin, but there have been a few adequately documented cases of persons with known sensitivity to penicillin suffering an allergic reaction when exposed to food containing penicillin residues. It has been estimated that 10 IU (0.6 μg) could cause an allergic reaction in a sensitive individual. As little as 0.01 IU/ml of milk could cause an allergic reaction in a very sensitive individual (*54*). However this may vary with the individual and the type of food (which may affect absorption of the drug). Some reactions were reportedly caused by ingestion of <40 μg of the drug. In two cases, anaphylactic reactions were observed in people with known hypersensitivity to penicillin, after consuming steak (in 1984) and after consuming pork (in 1972) (*58*).

JECFA estimated that if residues in meat (including liver and kidney) were at the MRL (maximum residue limit) of 0.05 ppm and for milk were 0.004 ppm, the maximum daily intake of benzylpenicillin from residues would total 29 μg (15 μg from muscle, 5 μg from liver, 3 μg from kidney, 6 μg from milk) (*29*).

Tetracyclines

Oxytetracycline is a broad-spectrum antibiotic used to treat a variety of infections and is also used as a growth promoter in animals. In studies with humans, about 60% of an ingested dose of oxytetracycline was absorbed from the gastrointestinal tract and was then widely distributed in the body, particularly to liver, kidney, bones and teeth. There appeared to be little, if any, metabolism of this drug in humans or animals and it was primarily excreted in the urine (*29*).

Toxicological studies indicated that this drug was not mutagenic, carcinogenic, or teratogenic. Some toxic effects were observed at high doses with a no-effect level of 18 mg/kg

body weight/day. At therapeutic doses, tetracyclines are occasionally associated with discolored teeth, allergic reactions, or peripheral blood changes (*54*). Oxytetracycline did induce antibiotic resistance in coliforms in the human intestine, and JECFA used this as its marker to determine acceptable levels of intake. A no-observed-effect level of 2 mg/person/day was observed (*29*).

There have been reports of allergic reactions to tetracyclines but no cases that have involved exposure to residues in foods (*54*).

JECFA estimated that if oxytetracycline residues in meat, milk and eggs were at the recommended MRL, the maximum daily intake of oxytetracycline from residues would total 260 µg (30 µg from muscle, 30 µg from liver, 30 µg from kidney, 150 µg from milk, 0.5 µg for fat, 20 µg for eggs) (*29*).

Sulfonamides (sulfadimethoxine, sulfamethazine, sulfamethoxazole)

Sulfonamides are generally used to treat a wide variety of bacterial and coccidial infections in food producing animals and are used as growth promoters in swine. Sulfonamides are metabolized by numerous pathways with the major metabolite in humans, swine and cattle being an acetyl derivative.

Data cited by JECFA indicate that the primary mechanism of toxicity of sulfonamides is associated with the thyroid–hypothalamus–pituitary axis and therefore toxicity should be measured by parameters of thyroid and pituitary function. The level causing no toxicological effects in rats was 40 ppm (2.2 mg/kg bw/day) (*30*).

Hypersensitivity reactions (primarily skin rashes) to therapeutic levels of sulfonamides have been reported but there have been no cases that involved exposure to residues in foods (*45, 54*).

Neomycin

Neomycin is an aminoglycoside antibiotic that is used to treat intestinal, respiratory, and wound infections and mastitis. Neomycin is not readily metabolized in animals or in humans (*32*).

Neomycin is not genotoxic. Like streptomycin and gentamicin, it has been reported to cause damage to the kidney and to hearing (*54, 58*). Recent data indicate that people with a rare mutation in their mitochondrial DNA may be more susceptible to deafness caused by aminoglycosides and other environmental factors than the general population. JECFA based its recommendation for a maximum daily intake of 3.6 mg/kg bw on results on effects of hearing loss in guinea pigs (*34*).

JECFA calculated that the estimated dose of neomycin from veterinary drug residues was 3 mg/day, primarily from milk (2.25 mg), kidney (0.5 mg), and muscle (0.15 mg). This was 3000 times less than the recommended oral therapeutic dose of neomycin (*34*).

Gentamicin

Gentamicin is an aminoglycoside antibiotic and, like streptomycin and neomycin, has been reported to cause damage to the kidney and to hearing (*58*) (*see sections on neomycin and streptomycin*). Gentamicin is depleted rapidly from muscle and fat but tends to persist in kidney and liver. Gentamicin is not readily metabolized in animals or in humans.

JECFA estimated that if gentamicin residues in meat were at the recommended MRL, the maximum daily intake of gentamicin from residues would total 785 µg (30 µg from muscle, 200 µg from liver, 250 µg from kidney, 5 µg from fat, 300 µg from milk) (*31*).

Flunixin

Flunixin is a non-steroidal anti-inflammatory drug (NSAID) and analgesic and is the only such drug allowed for use by veterinarians. Flunixin inhibits prostaglandin synthesis apparently by a mechanism similar to aspirin. Since NSAIDs are commonly used in human medicine, it is believed that flunixin is a relatively safe drug and residues should not be very harmful. However

it appears that this drug has not been tested adequately on humans, particularly for hypersensitivity reactions (USDA web site: www.usda.gov).

Streptomycin

Streptomycin is an aminoglycoside antibiotic used for treating bacterial infections in food-producing animals. Studies in animals and humans indicate that the drug is not readily absorbed from the gastrointestinal tract because of its high molecular mass and it is not metabolized significantly when injected. Oral doses of the drug are eliminated unchanged in the feces (*32*, *33*).

Toxicological studies in animals indicated that the most sensitive end point was a decrease in weight, and this was used to set a maximum acceptable daily intake of 30 µg/kg bw for humans (*32*, *33*).

There have been reports of allergic reactions to streptomycin but no cases that have involved exposure to residues in foods (*45*). There has been one significant adverse effect in humans that occurred during treatment of pregnant women with tuberculosis. Infants of women treated with injections of 1 g streptomycin twice weekly during the first trimester suffered damage to a cranial nerve and this resulted in congenital deafness. Streptomycin may also have adverse effects on kidney function. Other than this, there was no evidence of adverse effects on fertility or reproductive performance in animals or humans (*32*, *33*).

In light of the low levels of residues that might be present in foods and the low rate of absorption of oral doses of this drug, it is not expected that residues would affect fetal development (*32*, *33*).

Arsenicals

Arsenical compounds are used in swine and poultry as growth promoters and to prevent bacterial enteritis. The most commonly used arsenic compound for poultry is roxarsone. Most of the roxarsone is excreted unchanged, but some metabolites have been detected in hen urine. Little roxarsone is retained in poultry meat (FDA limit is 0.5 ppm in chicken muscle). (There is some concern about arsenic levels in poultry litter.)

Inorganic arsenic is a known carcinogen and may adversely affect the circulatory and nervous systems. Organic arsenic is generally less toxic and some arsenic compounds are considered harmless. A National Toxicology Program study of the effects of roxarsone on rats and mice found that diets containing 800 ppm roxarsone caused decreased body weight in mice; rats were more sensitive, showing lower body weights on diets containing 200–400 ppm roxarsone. There was equivocal evidence for carcinogenicity in male rats fed 100 ppm roxarsone for 2 years but no evidence of carcinogenicity in female rats and both sexes of mice (http://ntp.niehs.nih.gov/).

Summary

Veterinary drug residues tend to be higher in liver and kidney than in muscle. Most meat samples tested do not have violative residues but there are occasional samples that do contain excessive amounts of these drugs. Usually these are a result of not observing the withdrawal period or from off-label use of an antibiotic (Table 4).

All antibiotics have the potential to cause allergic reactions; penicillins are most commonly implicated, affecting up to 10% of people receiving these drugs therapeutically. Sulfonamides may cause allergic reactions in up to 3% of those using these drugs. Other antibiotics are implicated less often. Allergic reactions may involve skin rashes or asthma and in the worst cases, anaphylactic shock. Concentrations of residual veterinary drugs in foods are not high enough to cause an initial hypersensitive reaction but may cause such an effect in a person who has already become sensitized to the drug. One study of 15 people known to be very sensitive to penicillin found that three reacted after drinking milk containing a total of 2.5 µg penicillin, and two sensitive volunteers developed rashes after eating pork containing 0.02–0.04 ppm penicillin (*15*).

Some drugs have been shown to have adverse effects at high doses — much higher than residue levels detected in meats. These include hearing loss and kidney toxicity for neomycin, gentamicin, and streptomycin; possible carcinogenicity for arsenicals; and effects on thyroid and pituitary function by sulfonamides.

Table 4. U.S. Residue Limits for Veterinary Drugs (ppm) (*21*)

	Fat	Meat	Meat by-product	Liver	Kidney	Edible tissue
Arsenic		0.5[bc]	0.5[c], 2.0[b]	2.0[c]	2.0[c]	
Flunixin		0.025[a]		0.125[a]		
Gentamicin	0.4[c]	0.1[c]		0.3[c]	0.4[c]	0.1[b]
Neomycin[g]	7.2[acf]	1.2[acf]		3.6[acf]	7.2[ac]	
Penicillin						0.05[a], 0.01[f], 0[cd]
Ampicillin						0.01[ac]
Streptomycin	0.5[acd]	0.5[acd]	0.5[acd]	0.5[acd]	2.0[acd]	0.5[acd]
Sulfadimethoxine						0.1[ab]
Sulfamethazine						0.1[abc]
Tetracycline	12.0[bce]	2.0[bce]		6.0[bce]	12.0[bce]	
Chlortetracycline / Oxytetracycline	12.0[abc]	2.0[abc]		6.0[abc]	12.0[abc]	

[a]Cattle; [b]Poultry; [c]Swine; [d]Chicken only; [e]Calves; [f]Turkey only; [g]Zero tolerance for neomycin in veal calves

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