Animal Drug Residues in Food

Food Toxicology
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Learning Objectives

- Define animal drug residues.
- Explore the relationships between food animals and drugs.
- Understand the major classes of drugs used in food animals.
- Understand the hazards associated with food animal drug use and how risk assessment is used to determine tolerances.

Learning Objectives

- Review the role of pharmacokinetics in the development of withdrawal times.
- Review food animal drug testing results.
- Understand the potential adverse effects of drugs that appears as residues in food animals.
- Discuss the issue of development of antibiotic resistant bacteria.

Animal Drug Residues

- *"Residues of veterinary drugs include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned."*

Codex Alimentarius Commission Procedural Manual, Fourteenth Edition (2004).

Food Animals - Food Animal Health - Drugs

- Food animals convert one source of nutritional energy (grass, grain, hay) into another (meat, milk, eggs).
- Food animal production practice requires management of animal health and this can require the use of drugs.
  - Animal health management
  - Animal industry economics
- Human health effects of food animal drugs can arise from drug residues.
- Human health effects can also arise when food animal drugs are not used (pathogens).

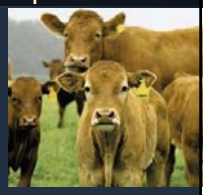
NAS

Meat, Fish, and Dairy Consumption

- The average American consumes 200 pounds of meat and fish, 67 pounds of poultry, 30 pounds of eggs, and 600 pounds of dairy products each year.
- Drug residues are analyzed, regulated, and monitored by FDA-CFSAN/CVM, USDA-FSIS, state milk ordinances, JEFCA (Joint FAO/WHO Expert Committee on Food Additives), international food agencies.
- Veterinary drugs are used by veterinarians and by food animal producers.
  - Pre-market drug tests
  - Residue avoidance testing
  - Drugs labels

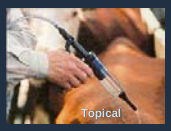
Food-Producing Animal Species

- Major species
  - Cattle, cows
  - Swine
  - Chickens
  - Turkeys
- Minor species
  - Sheep
  - Goats
  - Llamas/Alpacas/Camels
  - Deer and other wildlife
  - Others



Major Classes of Drugs Used in Food Animals

1. Topical antiseptics, bactericides, and fungicides
2. Ionophores
3. Steroid anabolic growth promoters and peptide production enhancers
4. Antiparasite drugs
5. Antibiotics



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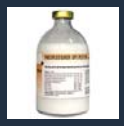
Other Food Animal Drugs

- Drugs that modify the gastrointestinal environment to reduce the likelihood of rumen foaming and bloat in cattle.
- Organic and inorganic water treatments that reduce the chances for water or fish infection in aquaculture.
- Miscellaneous drugs and compounds used with the advice of veterinarians to treat specific conditions.



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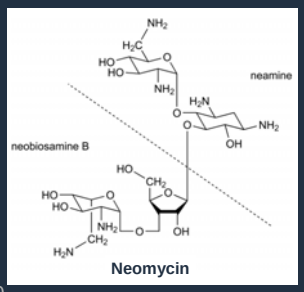
Topical Antiseptics-Bactericides-Fungicides

- Used to treat surface skin, or hoof infections, cuts, and abrasions.



Neomycin

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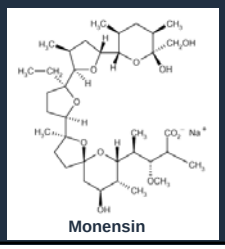
Ionophores

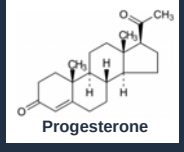
- Alter rumen microorganisms to provide more favorable and efficient energy substrates from bacterial conversion of feed.
- Impart some protection against some parasites.



Monensin

Steroid Anabolic Growth Promoters and Peptide Production Enhancers

- Mechanism of action resides in the interaction of estrogen-, progesterone-, or testosterone-like compounds with specific classes of hormone receptors in animal cells.
  - Recombinant bovine somatotropin (BST) for increased milk production in dairy cows.



Progesterone

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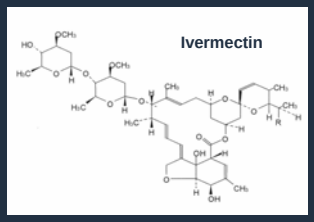
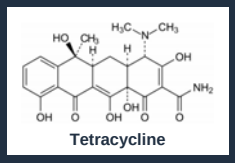
Antiparasite Drugs

- Used to control fleas, ticks, mange (mites), worms, giardia, coccidia and other intestinal parasites.



Antibiotics

- Used to control overt and occult (sub-clinical) diseases.
- Used to promote growth in sub-therapeutic doses.



Drugs in Food-Producing Animals

- Potentially dangerous residues in food of animal origin.
- Risk and benefits analysis required.
- Risk modifiers include “withdrawal time” and “residue avoidance practice.”

Human Health Risk Issues

- Drug residue allergy
- Cancer, reproductive, and developmental effects
- Hormones
- Development of antibiotic resistant microbes
- Drug misuse

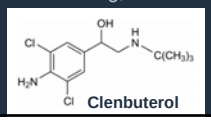
Animal Drug Residue Tolerance Levels

Tolerance: Hazard Identification

- Short term
  - Allergenicity
  - Toxicity
- Long term
  - Microbiological effects
  - Carcinogenicity
  - Reproductive effects
  - Teratogenicity

Toxicity: Clenbuterol

- Non-steroidal anabolic and metabolism accelerator.
- Spain, 1990 outbreak: 135 people ill from eating contaminated liver.
  - Several hospitalizations: tachycardia, muscle tremors, headaches, nausea, fever, chills
- Jalisco Mexico, December 2005: at least 225 people ill after consuming beef/liver.
  - Trembling, headache and malaise



Clenbuterol

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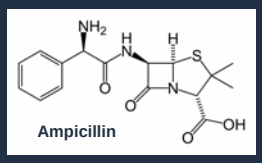
Allergenicity: β-Lactam Antibiotics

- Anaphylactic reactions have been reported to result from consumption of beef or pork containing penicillin.



Ampicillin

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Microbiological Effects

- Disruption of normal human flora in the intestine.
  - Bacteria that usually live in the intestine act as a barrier to prevent incoming pathogenic bacteria from getting established and causing disease.
- Antibiotic residue might reduce total numbers of these bacteria or selectively kill some important species.

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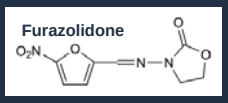
Carcinogenicity: Nitrofurans, Nitroimadazoles

- Furazolidone and its metabolites have been shown to induce cancer in animals.
- Had been labeled and approved for anti-protozoal and other uses for a wide variety of conditions in poultry and swine.
- FDA approval withdrawn 1991.
- FDCA Delaney Clause.



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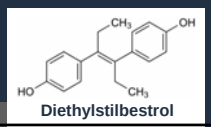
Reproductive and Teratogenic Effects: DES

- Diethylstilbestrol: a synthetic estrogen formerly used commercially as a growth promoting agent in livestock.
- Drug used in pregnant women in 1940's.
  - Vaginal clear-cell adenocarcinoma in female off-spring exposed *in utero* (1 in 1000)
  - Structural abnormalities of uterus (69%)



Diethylstilbestrol

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Dose-Response and Exposure Assessment

- Toxicological tests in laboratory animals.
  - Part of pre-clinical drug development.
- Development of NOAEL.
- Safety factors.
- Acceptable daily intake (ADI).
- Sub-population sensitivity.
- Exposure assessment.
  - Food consumption.
  - Aggregate exposure.
- Use to develop *Tolerance Level.*

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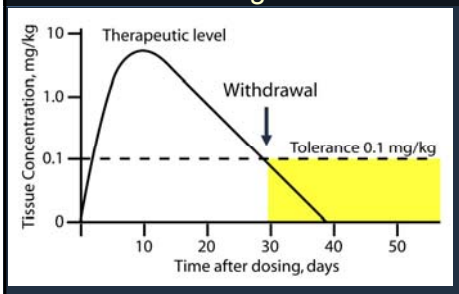
Tolerance Level

- The maximum permissible residue level which may be present in tissues or food animal products.
- Tolerances are specific for species and tissue (liver, kidney, fat, muscle) or product (milk, eggs).

Withdrawal Time

- Time required for a drug or chemical concentration to fall below the *Tolerance Level* established in a specific target animal tissue.
- Dependent upon drug, dose, formulation, route of administration, species, target tissue and disease / management factors.
- Pharmacokinetics-toxicokinetics of the drug is the main factor.
  - Therapeutic level vs. elimination
- PK of elimination can be different for different tissues.

Animal Drug Withdrawal Time



Residues of all veterinary drugs are higher in liver and/or kidney tissue as compared to muscle tissue.

Animal Drug Withdrawal Time

- Experimentally determined.
- Time required that concentrations in all food animal tissues or products are below tolerance.
- Margin of safety (MOS) increased to 95% confidence interval for 99% of population.
  - MOS = LD_1/ED_{99}
- Expensive
  - Limited products
  - Healthy animals

Animal Drug Withdrawal Time

- Other considerations
  - Aesthetic considerations
  - Risks perceived by public
  - Sensitive populations and issues
  - International relations and trade barriers

Extralabel (Off-Label) vs. Label Drug Use

- Higher dose than label
- Different route than label
- Different species than label
- Different disease indication than label

AMDUCA 1996

- Animal Medicinal and Drug Use Clarification Act 1996
- Permits extralabel drug use in animals
  - Does not apply to feed and water additives
  - Several drug classes have been excluded
- Some drugs are prohibited from use in food animals
  - Clenbuterol, chloramphenicol, nitroimidazoles, nitrofurans
- Withdrawal time extrapolations from other known applications
  - WDT = 10 x $T_{1/2}$

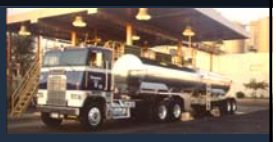
Over-The-Counter (OTC) Veterinary Drugs

- Majority of animal drugs sold in US
- Can still cause residues if not used according to label.

Drug Residue Testing

- Target tissues tested
  - Milk
  - Kidneys often tested at slaughter
- STOP
  - Swab test on premises
- FAST
  - Fast antimicrobial screen test
- SOS
  - Sulfa-on-site
- CHARM II; SNAP
  - Milk residues
- Lab tests
  - HPLC/GC/Mass Spectrometry

FDA Milk Drug Residue Database 2003



- 4,382,974 samples were analyzed for animal drug residues.
- 2,945 were positive for a residue.
- Samples:
  - Bulk Milk Pick-Up Tanker
    - Bulk raw milk from a dairy farm
  - Pasteurized Fluid Milk and Milk Products
    - Finished product in package form or bulk
  - Producer

FDA Milk Drug Residue Database 2003

Source of Sample	Total Samples	Number Positive	Percent Positive	Regulatory Disposition (Pounds)
Bulk Milk Pick-Up Tanker	3,571,834	1,899	0.053%	70,106,000
Pastur. Fluid Milk and Milk Prod.	54,932	8	0.015%	64,000
Producer	665,627	1,009	0.152%	4,881,000
Other	90,581	29	0.032%	1,319,000
Totals	4,382,974	2,945	*	76,370,000

Regulatory Disposition = not for human consumption

Milk Residue Screening by Drug Family

Family/Drug 2003	Total Tests	Total Positive
AMINOGLYCOSIDES	1,290	1
Neomycin	1,858	2
AMPHENICOLS	201	0
BETA lactams	4,354,087	3,207
Cloxacillin	317	3
MACROLIDES	64	0
SULFONAMIDES	66,124	23
Sulfadimethoxine	4,478	3
Sulfamethazine	17,466	3
TETRACYCLINES	10,138	4
Tetracycline	118	0
TOTALS	4,456,141	3,246

FDA CFSAN

2003 FSIS Meat Residue Monitoring

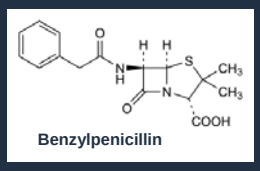
- Penicillin and sulfonamide drugs were most commonly detected at violative levels in swine and cattle.
- Neomycin and gentamicin were also detected in a number of cattle, particularly calves.
- Other drugs detected in cattle and swine included tilmicosin, flunixin, and tetracyclines.
- Arsenicals were detected in poultry.

Drugs 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

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.



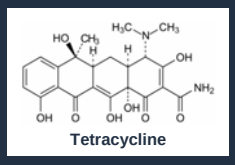
Benzylpenicillin

Potential Adverse Effects: Penicillin

- Usually cleared rapidly from the blood via the kidneys and into the urine (kidney, liver about 100x higher than muscle).
- Allergic reactions determining factor for safety evaluation of residues.
  - Allergy to penicillin in different populations 3–10%.
  - No evidence that penicillin residues in food caused sensitization.
  - Some cases of persons with known sensitivity suffering allergic reaction
- Estimated that 10 IU (0.6 µg) could cause an allergic reaction in a sensitive individual.
  - 0.01 IU/ml of milk in a very sensitive individual.
- 2 cases of anaphylactic reactions with known hypersensitivity to penicillin, steak (in 1984) and pork (in 1972).
- JECFA estimated that if residues in meat (including liver and kidney) were at the MRL of 0.05 mg/kg and for milk were 0.004 mg/kg, the maximum daily intake of benzylpenicillin from residues would total 29 µg.

Tetracyclines

- Oxytetracycline is a broad-spectrum antibiotic used to treat a variety of infections and is also used as a growth promoter in animals.



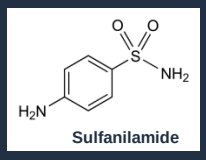
Tetracycline

Potential Adverse Effects: Tetracyclines

- Humans, ~ 60% of an ingested dose absorbed from GIT and widely distributed in the body.
  - Particularly to liver, kidney, bones and teeth.
  - Little metabolism of this drug in humans or animals and it was primarily excreted in the urine
- Not mutagenic, carcinogenic, or teratogenic in animal studies; some toxic effects were observed at high doses.
  - NOAEL 18 mg/kg body weight/day.
- Therapeutic doses occasionally associated with discolored teeth, allergic reactions, or peripheral blood changes
- Oxytetracycline did induce antibiotic resistance in coliforms in the human intestine; JECFA used this for MRL.
  - NOEL 2 mg/person/day
- There have been reports of allergic reactions but no cases that have involved exposure to residues in foods.
- JECFA estimated that if OTC residues in meat, milk and eggs were at the MRL. residues would total 260 µg.

Sulfonamides

- 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.



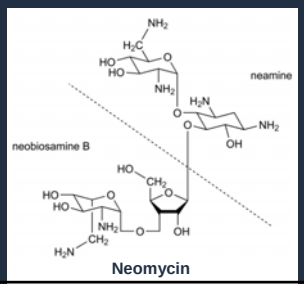
Sulfanilamide

Potential Adverse Effects: Sulfonamides

- 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
  - Toxicity should be measured by parameters of thyroid and pituitary function.
- NOAEL 2.2 mg/kg bw/day.
- 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.

Neomycin

- Neomycin is an aminoglycoside antibiotic that is used to treat intestinal, respiratory, and wound infections and mastitis.



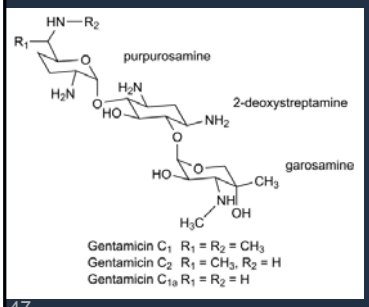
Neomycin

Potential Adverse Effects: Neomycin

- Neomycin is not readily metabolized in animals or in humans.
- Not genotoxic. Like streptomycin and gentamicin, it has been reported to cause damage to the kidney and to hearing.
  - 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 hearing loss in guinea pigs.
- 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.

Gentamicin

- Gentamicin is an aminoglycoside antibiotic

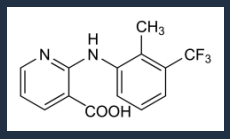


Potential Adverse Effects: Gentamicin

- Like streptomycin and neomycin, gentamicin has been reported to cause damage to the kidney and to hearing.
- Depleted rapidly from muscle and fat but tends to persist in kidney and liver.
- Not readily metabolized in animals or in humans.
- JECFA estimated that if 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.

Flunixin

- Flunixin is a non-steroidal anti-inflammatory drug (NSAID) and analgesic and is the only such drug allowed for use by veterinarians.

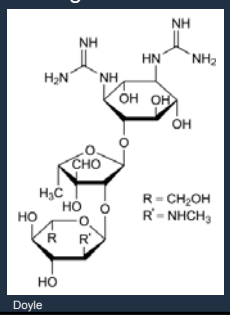


Potential Adverse Effects: Flunixin

- 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.

Streptomycin

- Streptomycin is an aminoglycoside antibiotic used for treating bacterial infections in food producing animals.

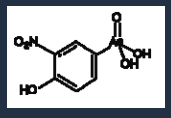


Potential Adverse Effects: Streptomycin

- Not readily absorbed from the GIT because of its high molecular mass and not metabolized significantly w/ inj.
- Oral doses of the drug are eliminated unchanged in the feces.
- Animal studies indicate most sensitive end point was a decrease in weight; used to set ADI of 30 µg/kg bw.
- Reports of allergic reactions to streptomycin
  - No cases that have involved exposure to residues in foods.
- One significant adverse effect in humans that occurred during treatment of pregnant women with TB.
  - Infants of women treated IM 1 g BIW 1st trimester: damage to a cranial nerve and congenital deafness.
- Streptomycin may also have adverse effects on kidney fn.
- No other evidence of effects on fertility or reproduction.
- It is not expected that low food residues/low abs. would affect fetal development.

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.

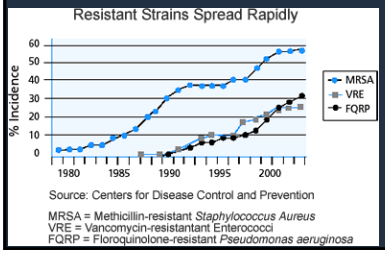


Potential Adverse Effects: Arsenicals

- Most of the roxarsone is excreted unchanged, but some metabolites have been detected in hen urine.
- Roxarsone is poorly retained in poultry meat (FDA limit is 0.5 mg/kg in chicken muscle).
- 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.
- Diets containing 800 mg/kg roxarsone caused decreased body weight in mice; rats were more sensitive, showing lower body weights on diets containing 200–400 mg/kg roxarsone.
- There was equivocal evidence for carcinogenicity in male rats fed 100 mg/kg roxarsone for 2 years, but no evidence of carcinogenicity in female rats and both sexes of mice.

Development of Antibiotic-Resistant Bacteria

- Bad bugs → no drugs
- A major issue of drug use in food animals as well as over-use of antibiotics in humans



Antibiotic-Resistant Bacteria Isolated From Meat

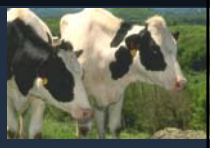
- Hypothesis was that the greater the amount of a drug used, the more likely bacteria would develop resistance to it.
- Beef:
  - Tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > cephalothin
- Pork:
  - Tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > gentamicin
- Chicken:
  - Tetracycline > sulfa > streptomycin = cephalothin > ampicillin > chloramphenicol > gentamicin
- Turkey:
  - Sulfamethoxazole > tetracycline > streptomycin > ampicillin > cephalothin > gentamicin

Less Antibiotic Use In Food Animals Leads To Less Drug Resistance In People

Clinical Infectious Diseases (2006)42:1368-1374

- *Campylobacter jejuni* is a leading bacterial cause of foodborne illness in industrialized countries.
- Drug resistance can make Campylobacter infections difficult for to treat, and can result in longer bouts of and a higher risk of serious or even fatal illness.
- Australia prohibited the use of fluoroquinolones, in food animals such as poultry.
- Researchers examined *C. jejuni* isolates collected from 585 patients in five Australian states.
- Only 2% of the locally acquired Campylobacter isolates were resistant to ciprofloxacin, a type of fluoroquinolone (29% in countries w/o ban).
  - Sweden prohibited the use of fluoroquinolones for food animals in 1986
  - Norway has never licensed their use in food animals
- FDA proposed banning fluoroquinolones in poultry in 2000; finally enacted in September 2005.

Animal Drug Residue Concerns



- Consumer health risk
  - Environmental concerns
- Consumer preference
- Production loss for the producer
  - Lost milk product ($6,000 to $80,000)
  - Lost animal ($500 to $2000)
- Legal action against the producer
  - Violative (illegal) residues