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Veterinary Medicine Residue and Its Effect on Food Safety : A Review

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Abstract

Veterinary medicine is an essential part of livestock and poultry farming and will continue to be aim important part of providing safe and abundant animal products for human consumption. In this regard various rules under SPS agreement quotes that every country has the right to set its own appropriate level of sanitary or phytosanitary food safety protection. The European Union and other developed nations are required to establish and maintain inspection system that is equivalent to those in the importing nations. According to food, drug and cosmetic Act (1958) stated that no additive shall be deemed safe. It is found to induce cancer either injected by man or animals; and for this FDA requires that sponsor should conduct chronic feeding studies on rat and mice and should fix the upper limit of life time risk of cancer to be one in one million. From 1983 to 1988 investigation made by Food and Drug Administration (FDA), in cooperation with the center for veterinary medicine of the FDA reported that antibiotic residue was by far with the sulfamethzine and long acting medicine release slowly than that of penicillin and tetracycline. The codex for residue limit (MRLS) for veterinary drugs (MRLVD) are not legally binding but are not recommended by Codex Alimentarius Commission and the maximum residues medicine of pesticide and antimicrobial drugs should be in accordance with the codex MRLs. Certain drugs / chemicals like sulfonamides, alcohol are being excreted into the urine, similarly hormone like thyroxin is also secreted into the milk and excreted in the urine, while oxytocin injected into milch animal is secreted into the milk which can easily be destroyed at 60 C within few minutes.

Key words : Veterinary medicines, Food safety, Monitoring agencies, MRLs.

Humans are at the top of the food chain. As a result, we are vulnerable to pathogens, drugs, and contaminants consumed by the animals. We eat on an average of less than 5 kg meat per year as compared to world's average of 14 kg of meat per year.Food animals used to eat what grew naturally–grass and grain for cows and chickens; small fish or other sea life for big fish. Apart from this it is impossible to check every steak or chioken to ensure it is safe. Good hygienic practices must be followed throughout the production process, just as a chef works in a hygienic way from the beginning to the end and does not only rely on cooking to make the food safe. Therefore on a national or an international scale, a holistic approach to food safety, which pays attention to the whole process of food production, from animal nutrition, veterinary drugs, and slaughter to further product processing, is necessary to ensure food safety.

Under the SPS Agreement (Sanitary and Phyto-Sanitary), every country has the right to set its own appropriate level of sanitary or phyto-sanitary food safety protection. Different nations food safety standards vary greatly. The United States has the oldest legislation on food safety and hygiene. The European Union's sanitary standards, today, are patterned after those in the United States. They were applied in Europe at the request of US inspectors some 20 years ago. Apart from retaining the right to set national food safety standards, countries also retain the right to regulate food safety standards of imports.

An importing country has the right to decide whether a food regulatory system employed by an exporting country is equivalent to its own or is adequate to achieve the importing country's appropriate level of sanitary or phyto-sanitary protection. Foreign countries that export meat, poultry, and egg products to the United States, the European Union, and other developed nations are required to establish and maintain inspection systems that are equivalent to those in the importing nation.

Table 1. Maximum residue limits (MRLs) of pesticides (ppm) in meat. '–' Data not available, Source : MOHFW (7).

Pesticide standard	PFA rules Meat and poultry	Codex standards Cattle meat	US Cattle meat
Aldrin/dieldrin	0.2	0.2	0.3 (fat)
Chlordane	–	0.05	0.3 (fat)
Aldicarb	–	0.10	0.01
Carbaryl	–	0.10	0.10
Chlropyrifos	0.1	2.0	0.2
Cypermethrin	0.2	0.02	0.05
DDT and its metabolites	7.0 (fat)	5.0 (fat)	5.0 (fat)
Decamethrin/deltamethrin	–	0.03	–
Endosulfan	–	0.10	0.2
Fenvalerate	1.0	1.5	1.5
Heptachlor	0.15	0.2	0.2
Hexachlorabenzene	0.2	0.2	0.5
Lindane	2.0	1.0	7.0
Monocrotofos	0.02	0.02	–
Propoxur	–	0.05	–

Determinimg whether an importing nation is equivalent in inspection system not simply a process of comparing end-product specifications; rather it is the holistic assessment of the overall production hygiene and an evaluation of the exporter's ability to deliver an effective inspection system. This requires an assessment on how the legislative, executive, and judicial systems of the exporter's nation work to regulate and ensure food safety standards.

Residues in Animal Derived Foods

About 80% of all food animals are administered drugs during their lifetime. Some 750 drug products, containing about 100 basic drugs, are used in food animal production. Most are needed to ensure a continuing safe, wholesome, affordable food supply for the population. About 30% of chickens, 80% of veal calves and pigs, and 60% of beef cattle are routinely fed medicated rations. Livestock are also routinely treated with dewormers and insecticides.

The drug sponsor (usually the manufacturer) must establish scientifically that the substance is safe and effective. The sponsor must also demonstrate that any drug residues remaining in a food-producing animal at slaughter pose no threat to human health. As science progresses and scientists are able to detect extremely tiny amounts of a substance, regulatory agencies are beginning to have problems enforcing rules about residues. In fact, tests can now detect one in one quadrillion (1/1,000,000,000,000,000). Yet Section 409 of the Federal Food, Drug and Cosmetic Act contains the Delaney Clause (1958) which states that, "no additive shall be deemed safe if it is found to induce cancer when ingested by man or animal..." Development of sensitive tests since 1958 has made the Delancy Clause unworkable. If toxicological studies raise the suspicion that a drug may cause cancer, the FDA now requires the sponsor to conduct chronic feeding studies in rats and mice. If the results show that the chemical causes cancer, the FDA uses a conservative risk assessment procedure to determine how much residue presents the consumer with no significant risk of cancer. Under this procedure the FDA allows the upper limit of lifetime risk of cancer to be one in one million (that is, if one million consumers ingested the residue for their entire lifetime of 70 years, one of them might get cancer from the drug residue). This risk is approximately 10 times less than the risk of being struck by lightning.

Meat products and animal products, such as milk and eggs, intended for human consumption may have some residual amounts of veterinary drugs which remain in edible tissues after harvest. In those animals where the manufacturers and national legislative directions are followed by the farmer/producer, drug residue levels will be within safe limits. In the relatively few cases where levels of residue levels exceed permitted maximum limits, the causes is nearly always improper use and as such are not legally allowed into the food system. Biswas et al. (1) reported that the residues in meat and their products are generally classified as naturally present, caused by man and arise secondarily. In the past most contamination of the meat resulted from natural toxicants. However, usage of synthetic chemicals for regular house-hold and agricultural practices while benefiting society has also provided new sources of potential contamination.

However, toxic substances originating from animal feed like f. ex. pesticides or dioxin or else contamibating are still found in food. Mycotoxins enter in human food via animal feed and are toxic. Substances like poly-chlorinated biphenyls (PCB). DDT and different heavy metals concentrate in meat. Disinfectants can enter in food during the production process.

Table 2. Codex Maximum Residue Limits (MRLs) and Acceptable Daily Intake (ADI) levels of some important antimicrobial drugs in food of animal origin. '–' Data not available.

Antimicrobial	Acceptable daily intake (ppb)	Target tissue (ppm) Muscle	Liver	Kidney	Fat
Ampicillin	–	0.05	0.05	0.05	0.05
Benzyl/Procaine benzyl penicillin	0.30	0.05	0.05	0.05	0.05
Cloxacillin	–	0.30	0.30	0.30	0.30
Erythromycin	–	0.40	0.40	0.40	0.40
Gentamicin	0.20	0.10	0.20	0.50	0.10
Sulfadimidine	0.50	0.10	0.10	0.10	0.10
Sulfonamides (combinations)	0.50	0.10	0.10	0.10	0.10
Streptomycin	0.50	0.60	0.60	0.10	0.60
Oxytetracycline	0.30	0.10	0.10	0.10	0.10
Tetracyclines (OTC–CTC+TC)	0.30	0.10	0.10	0.10	0.10
Trimethoprim	–	0.05	0.05	0.05	0.05

A total of 292 field investigative reports of drug residues in food animals for 1983 to 1988 were analyzed. The investigations had been conducted by the Food and Drug Administration (FDA) and the Virginia State Veterinarian's Office, in cooperation with the Center for Veterinary Medicine of the FDA, to trace residues reported by the USDA (2—6). The analysis disclosed the following. (1) Antibiotic residues were most often associated with streptomycin, penicillin, oxytetracycline, and neomycine. Sulfamethazine was, by far, the most frequently cited sulfonamide. (2) Residues are being found predominantly in cows, veal calves, and market hogs (barrows and gilts). (3) The cause of drug residue most frequently cited by the field investigators was failure to observe the withholding time for the drug. Almost half of these investigations revealed that the individual responsible for the sale of the animal did not know the proper withholding time for the drug. Failure to maintain adequate records was also a contributing factor. (4) The producer was considered to be the responsible party in over 80% of the cases for which responsibility was determined. (5) Residues associated with injectable drugs were investigated most frequently. Long-acting and sustained-release products were most often associated with penicillin and oxytetracycline residues. (6) The two most common sources of purchase for the drugs involved in the investigations were the feed/farm supply store and the veterinarian and (7) Unapproved drug use was not a major cause of residues.

Tolerances

As part of the drug approval process, the FDA establishes what levels of each drug's residues are acceptable in edible animal tissues. These levels are called tolerance levels and are based on regulatory risks; that is, the tolerance includes a built-in safety factor or margin to assure that the drug has no harmful effects on consumers. To come up with that extra safety factor, the sponsor must first determine the highest dose at which the drug does not produce any measurable physiological effect in laboratory animals. Tolerances are then set at 1,000 or 100 times below the "no-effect" level. If no safe threshold has been established, the tolerance is zero. The tolerance is legally zero for any substance known to be carcinogenic.

Need of Veterinary Medicines

Like physicians who treat human infections use drugs to treat, control and prevent disease in humans, veterinarians use medicines to treat and prevent illness in food animals. Healthy animals are essential for a safe food supply. Commercially produced veterinary drugs have been used safely for food animal production for over 50 years. The main benefits are to ensure a safer food supply through improved animal health and to reduce production costs by limiting illness which may slow growth and increase costs of livestock and poultry production.

Usage of veterinary medicines is tightly controlled and monitored for example these are restrictions defining which medicines may be used in a particular food animal species and the interval required between administration and harvesting of milk, eggs or meat. There are requirements for veterinary involvement to prescribe or use antibiotics. The quality, safety and efficacy of each drug product are reviewed by government regulatory authorities.

The antimicrobial agents : a general term that refers to a group of drugs that includes antibiotics, antifungals, antiprotozoals, and antivirals, are powerful

weapons against disease-causing microorganisms in veterinary and human medicine. The long-term use of animal feed supplemented with low doses of antimicrobials has come under the greatest scrutiny. The main concern has focused on potential emergence of antimicrobial resistance. Scientists have determined that the potential for antibiotic resistance to occur in food borne bacteria exists, but using science-based risk analysis, assess the human medical consequence as low. It is thought that the growing problem of human infections that are difficult to treat due to antimicrobial resistance is rooted in antimicrobial overuse and inappropriate use of antibiotics in human medicine with antimicrobial resistance in food borne bacteria being only a smaller contributor.

Veterinary medicines generally have to satisfy three major criteria before they can be authorized, licensed or approved for use. These are safety, quality and efficacy. Most countries have in place a regulatory system for the approval and safe, use of veterinary medicines.

Before the safety of residues can be assessed, appropriate studies in the food-producing animal are required to identify and quantity the residues. The studies would simulate the recommended conditions of commercial use of the veterinary drug in animal production. In addition, acute toxicity studies, with rigorous observations of the experimental animals, are conducted to provide indications of effects on physiological systems. Longer term studies are also designed to investigate the effects of repeat dosing. These studies usually last 28 days (short term repeat dose studies) or 90 days (sub-chronic studies) and occasionally they may be of life-time durations. In these studies, effects (if any) of the medicine on internal organs such as the heart, kidney and lungs is determined either directly by examination of tissues or indirectly through clinical assessment such as blood and urine samples.

Monitoring Agencies

Several government agencies and their subsidiaries, along with state agencies, share the responsibility to keep our food supply safe. Still a lot of work has to be implementing regarding veterinary drug residues and food safety in India. As the present procedure of testing the drug residues is very costly along with it the proper monitoring of the usage of veterinary drug. The Joint FAO/WHO Expert Committee on Food Additives (JEFCA) conducts food safety assessments for residues of veterinary drugs in food. The WHO group of experts within JECFA is responsible for the toxicological evaluation and establishment of an Acceptable Daily Intake (ADI), while the FAO group of experts reviews the residue and metabolism studies relevant for establishing MRLs for veterinary drugs.

Trace amounts of some drug residues may pass into our food through the food chain and can be detected by analysis of food products in the laboratory. It is of paramount importance that there exist safety standards by which food producers can adhere to. For this the Codex Committee on Residues of Veterinary Drugs is the lead agency on veterinary drugs residues in foods and recommends MRLs for veterinary drugs. Codex MRLs for Residues of Veterinary Drugs (MRLVD) are not legally binding but are recommended by the Codex Alimentarius Commission to be legally permitted maximum concentrations in or on a food. The maximum residue limits of pesticides and antimicrobial drugs in the food of animal origin are given in Tables 1 and Table 2 respectively.

Different Types of Measures

Withdrawal Time. A withdrawal period is a time allowed for residues to deplete to safe levels (tolerances) between the last treatment and slaughter or milking.

Labeling. The label accompanying a drug for animal use must contain all necessary information, including : species in which it may be used, conditions for which it may be used, dosage for each application, and withdrawal periods. Any use or dosage not specified on the label is termed “extra-label” and must be administered only with a veterinarian’s order and supervision. The veterinarian is responsible for determining and ordering a withdrawal period (usually extended) to assure no residues inedible product, when a drug is prescribed for extra-label use. A drug can still be approved with liberal tolerances when a sponsor proves to the FDA that it does not threaten human health. Some drugs are not granted approval for use in food animals because of proven or potential toxicity. Some are banned after having been ap-

proved or used in an "extra-label" manner.

Accidental Exposure. Food-producing animals may accidentally consume feedstuffs contaminated with pesticides, industrial chemicals or natural toxicants. They can absorb, metabolize and retain those substances in muscle tissue, organ meats, fat, milk, and eggs. Livestock may be fed waste by-products from many and varied sources. There is hardly any form of agricultural or industrial processing from which someone doesn't try to salvage livestock feed. Some waste products have nutritional value, some provide bulk and some just need disposing of. Examples include : paper, grain dust, ethanol distillers by products, poultry litter, waste fat and oil, grain and oilseed hulls, citrus pulp, packing plant offal and meat and bone meal. Products fed illegally that have resulted in contaminated animal-derived foods include pesticide-treated seed and PCB-contaminated industrial oils. Some recent incidents of human food becoming contaminated with chemicals occurred because people eat contaminated animal products. Discontinued and restricted-use pesticides are a potential source of poisoning and contamination. Persistent and dangerous chlorinated hydrocarbons include DDT, heptachlor, endrin, aldrin, and chlordane. Chlorinated hydrocarbons have mostly been replaced by organophosphates and carbamates. If not less toxic, they are least less persistent in the environment and in animal tissues. Livestock exposed to substances like PCBs and chlorinated hydrocarbons continue to have residues in body fat for several months. Incidents of accidental exposure of livestock to hazardous chemicals are usually publicized in the press. This results in increased public concern about the wholesomeness of meat and other livestock products. Some positive results of the publicity are increased awareness by other livestock producers of the problem, and continued vigilance by the agencies and persons responsible for assuring the safety of our food supply.

Ceftiofur is an antibiotic marketed since 1988 and structurally similar to penicillin, is presently labeled only to treat respiratory infections in cattle. It was developed by Upjohn specifically for use only in animals, not in humans. Upjohn proved to FDA that people allergic to penicillin should not have adverse reactions if exposed to ceftiofur. They also proved that it had an extremely low toxicity. Consequently, ceftiofur has no withdrawal period. An animal can be slaughtered immediately after the last injection of a 5-day treatment. The tissue tolerance level is 3 ppm in muscle, 12 ppm in fat, and 30 ppm at the injection site, very high compared to most drugs.

Chloramphenicol is a very toxic antibiotic. It is used to treat people with life-threatening infections that are unresponsive to other antibiotics. However, a few people's lives are jeopardized by contact with a minute quantity of chloramphenicol. Chloramphenicol was never approved for use in food animals. However, veterinarians found that it worked well to treat stubborn cases of diarrhea and pneumonia in calves and pigs, so they prescribed it extra-label. Because of the extraordinary risks associated with exposure of hypersensitive people to chloramphenicol FDA has made it illegal to use in food animals, even by veterinarians.

Ampicillin is an antibiotic in the class of drugs called penicillin. Ampicillin fights bacteria in the body. It is used to treat many different types of infections, such as tonsillitis, pneumonia, bronchitis, urinary tract infections, gonorrhea and infections of the intestines such as salmonella (food poisoning). As an antibiotic it kills bacteria including flora in the gut, which may affect digestion and/or elimination.

Erythromycin directly kills acne causing bacteria without the side effects of oral antibiotics which include upset stomach, diarrhea and dizziness. Topical antibiotics are safer to use animal oral or systematic antibiotics. But antibiotic treatment is prone to bacterial resistance. Bacterial resistance is a condition where the acne causing bacteria is already immune to the germ killing power of the specific antibiotic used. The only solution to bacterial resistance is the use of another antibiotic or the use of products which does not induce bacterial resistance like benzoyl peroxide or azelaic acid. Thus, animal topically treated with Erythromycin can safely be used for consumption.

Gentamicin is used to treat minor skin infections (such as impetigo, folliculitis) or minor infections related to some skin conditions (such as eczema, psoriasis, minor burns/cuts/wounds). It works by stopping the growth of certain bacteria. It belongs to a class of drugs known as aminoglysocide antibiotics. Gentamicin cream is usually used for wet, oozing, greasy types of skin infections. Gentamicin ointment helps to keep moisture in the skin, so it is usually used for the dry types of skin infections. This antibi-

otic only treats bacterial infections. It will not work for virus or fungus infections. Unnecessary use or overuse of any antibiotic can lead to its decreased effectiveness. It is safety drug and products produced from such animals treated with Gentamicin can be used without any harm.

Streptomycin is used in various types of infections like Tuberculosis, Tularemia, Plague and in Bacterial Endocarditic which of two types i.e. Streptococcal endocarditic and Enterococcal endocarditic. This antibiotic having certain common side effects which are as follows vestibular ototoxicity (nausea, vomiting, and vertigo); paresthesia of face; rash; fever; urticaria; angioneurotic edema; and eosinophilia. Apart from this there are following are less frequent side effects cochlear ototoxicity (deafness); exfoliative dermatitis; anaphylaxis; azotemia; leucopenia; thrombocytopenia; pancytopenia; hemolytic anemia; muscular weakness; and amblyopia. When 1.8 to 2 g/day are given, symptoms are likely to develop in the large percentage of patients-especially in the elderly or patients with impaired renal function-within four weeks. Presently the treatment of tuberculosis is being performed with the drug like AKT-4 and AKT-2 instead of streptomycin.

Sulfonamide drugs are generally being used in the animals as an antiseptic and bacteriostat. The sulfonamides are being used to treat such individuals who are suffering from any systemic infection occurring in the respiratory tract, urinogenital infection. In addition to that it is also being used (sulfanilamide and sulfamethoxin) to cure the absces and boils found on the body surface. Further, it is also being used to cure the bacterial diarrhoea (sulfaguanadine).

Therefore, when this drug is given to any infected individual one must be cautious to take sufficient quantity of water otherwise there may be chance of formation of renal calculi. And the product produce from such animals can not be used for human consumption before 72 hours of last dose of sulfonamide.

Tetracycline antibiotic family provides broad antibacterial protection by inhibiting bacterial protein synthesis. Tetracycline binds to bacterial protein-synthesis structured but not to mammalian ones. It is effective in treating prostate infections and can permeate cells to address intracellular parasites.

Nausea and vomiting are the most commonly reported side effects of tetracycline in dogs and cats, particularly cats. Tetracycline should not be given with food as food binds the drug and prevents its absorption into the body. Drugs of the Tetracycline class have potential to permanently stain teeth if given to immature animals. Tetracycline has potential to be toxic to the kidney. Long term use may induce actual urinary stones made of tetracycline. It also causes a false positive urine test for glucose. Therefore, the use of tetracycline in animal feed has been completely banned because it may have adverse effect on the kidney and the stone formation may be noted.

D-Tubocurarine is a neuromuscular-blocking drug or skeletal muscle relaxant in the category of non-depolarizing neuromuscular-blocking drugs, used adjunctively in anesthesia to provide skeletal muscle relaxation during surgery or mechanical ventilation. The main disadvantage in the use of tubocurarine is its significant ganglion blocking effect (8) that manifests as hypotension (9) in many patients; this severely precludes its use in patients with myocardial ischaemia. This is specially being used to poison the tips of arrow by the different tribes for hunting the wild animals. As such the hunted animals fall on the earth. Thus the hunted animal can be used for table purposes after disposing of the injured body parts. Presently, D-tubocurarine is rarely used as an adjunct for clinical anesthesia because safer alternatives such as cisatracurium and rocuronium are available.

Oxytocin is a mammalian hormone that acts primarily as a neurotransmitter in the brain. Oxytocin is best known for its roles in female reproduction as it is released in large amounts after distension of the cervix and vagina during labor and after stimulation of the nipples, facilitating birth and breastfeeding. It establishes the maternal behavior of females and stimulates the milk ejection (milk letdown). The oxytocin (from posterior pituitary) injected into the milch animal neither being secreted into the milk nor being excreted into the urine.

Conclusion

Veterinary medicine is an essential part of livestock and poultry farming, and will continue to be an important part of providing safe and abundant animal products for human consumption. It is only through

strict regulation and vigilance that a safe and clean environment can be provided for livestock, and the farming community, while at the same time ensuring that the final product (or derivatives) destined for human consumption remains safe, of high quality, affordable and nutritions. Apart from above one can say that the drugs chemicals like sulphonamides, alcohol are being excreted into the urine similarly hormone like thyroxin is also being secreted into the milk and excreted into the urine while the oxytocin (from posterior pituitary) injected into the milch animal being secreted into the milk which in turn get destroyed at 60 C within few minutes; not excreted into the urine. In addition to the above D-lubocurarine which is being used at the tip of arrows for hunting the animals is made from the wild herbs which restrict the animal movement due to which animal can be easily captured. Thus the said animal is fit for human consumption after discarding the affected body part with D-lubocurarine. At last we can say that the foods from animal origin are safer than the plant origin because in plant there might be good quantity of pesticides and insecticides as well.

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