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Review on effect of antimicrobial residual on human health

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Abstract
Human beings can get protein-rich foods from animal as by product (milk, meat, and eggs), to fulfill their nutritional requirements, and the quality and nature of this animal origin food may be directly or indirectly associated with the health human that consumed this animal origin food. "Veterinary drug" means any substance or mixture of substances that are essential for treatment of diseased animal (as therapeutic purpose), prevention of diseases (prophylaxis), modification of physiological functions (such as tranquilizers, anesthetic drugs), improvement of growth and productivity (growth promoters) as well as for ensuring food safety or restoring, correcting or modifying any physical, mental or organic function in an animal. However, the benefits of drug utilization to farm animals used for food production are also accompanied by the risks associated with drug residues in the edible parts of treated animals. The drug itself and their metabolites left over in the body after their administration for longer time are termed as residues. Residues are defined as chemical substances or metabolites of medicinal products that may accumulate within the tissues or edible parts of treated animals. These residues may result from failure to observe the proper withholding period following treatment, failure to maintain treatment records, overdose, or using prohibited drugs for economic animal treatment. Age of animal, disease statues, Extra-label drug use and Improper Withdrawal Time are the major risk factor for drug residues. The major potential effect of veterinary drug residues on public health are development of drug resistance, hypersensitive reaction, mutagenicity, carcinogenic disruption of intestinal micro flora and microbial drug resistance. Drug residue control and prevention responsible organs not only lie on within a governmental agency; rather the responsibility must be shared by all responsible bodies which includes, the government, producers, animal health practitioner and academicians, marketing associations, livestock producers, farmers and other interested parties, who must strive for both healthy and efficiently grown animals as well as a safe food supply. Proper maintenance of treatment records and identification of treated animals; institute a workable health record for each animal to record all health related events, including administration of medication, this for all about mentioned above points are the way of prevention and control strategies of drug residues.

Keywords: Antimicrobial, risk on public health, residue

Introduction
Human beings can get protein-rich foods from animal as by product (milk, meat, and eggs), to fulfill their nutritional requirements, and the quality and nature of this animal origin food may be directly or indirectly associated with the health human that consumed this animal origin food [7]. Because the animal byproducts easily affected by residue of drug due to administration of drug to animals for different purpose, quality of animal-based products is of great concern with regard to consumer health globally. "Veterinary drug" means any substance or mixture of substances that are essential for treatment of diseased animal (as therapeutic purpose), prevention of diseases (prophylaxis), modification of physiological functions (such as tranquilizers, anesthetic drugs), improvement of growth and productivity (growth promoters) as well as for ensuring food safety [49] or restoring, correcting or modifying any physical, mental or organic function in an animal [16]. However, the benefits of drug utilization to farm animals used for food production are also accompanied by the risks associated with drug residues in the edible parts of treated animals. The drug itself and their metabolites left over in the body after their administration for longer time are termed as residues. After the treatment of infected animals with drugs, the residues of drugs are may present at some level in edible animal byproducts like milk, eggs and meat of treated animals [8].

These residues may result from inappropriate use of drugs, failure to maintain proper drug withdrawal periods, or poor livestock production practices are the major cause of drug residue [40]. The treated animals may rapidly and efficiently metabolize some drugs while others may be slowly and poorly metabolizing; thus, the residues accumulate in the edible portion of the animals. Subsequently, consumers are exposed to these residues, resulting humans exposed to many diseased related to drug residue. Even if they use they use the same drugs as veterinarians, they have little understanding of the conditions and the amount of dose to administer or the poor knowledge of proper withdrawal periods, livestock producers treat their animals by themselves are the main cause of health hazards arise from drug residue. The extensive use of anti-infectious agents improperly can lead to residues in animal products, especially when users fail to respect waiting proper withdrawn periods. These Antibiotic residues in foods of animal origin may cause of numerous health problems in humans. The main effect on animal health includes, toxic effects, transfer of antibiotic resistant bacteria to humans, immunopathological effects, carcinogenicity (e.g. sulphamethazine, oxytetracycline, and furazolidone), mutagenicity, nephropathy (e.g., gentamicin), hepatotoxicity, reproductive disorders, bone marrow toxicity (e.g., chloramphenicol), and allergy (e.g., penicillin) [36]. Proper drug administration and proper identification of treated animals before administering or dispensing drugs one has to: know the drugs approved for all classes of cattle on the farm and be familiar with approved dosage, route of administration, and withholding time; Proper maintenance of treatment records and identification of treated animals are the possible ways of the reduction of the effect of antimicrobial drug residue and the subsequent effect on human health [42].

The use of drug in animal husbandry and its occurrence in related food may lead to selection of resistance in microorganism populations that do not respond to treatment commonly used for human diseases. Residues are also concern due to their possible adverse effects on inhibition of starter cultures used to produce cultured milk products such as yogurt and cheeses [30].

Though the use of drugs in food animals and their residue in human consuming foods of animals' origin need great concentration, so much works was not conducted to create awareness and emphasis them. Therefore, objectives of this paper were to review the potential cause of veterinary drug residues and their effects on the health of the public and highlight prevention, control, and reduction strategies of drug residues in food producing animals.

Sources of veterinary drug residues

Veterinary drug residues are one of the major problems for food contamination and the one of the cause harmful effects to humans. Residues and chemical food contaminants arise from a variety of sources, including ingredients from natural toxins; industrial food contaminants [35]. The major causes of drug residue accumulation in food-producing animals include improper observation of withdrawal periods, failure to maintain treatment records, overdose, or using prohibited drugs for economic animal treatment [7]. Depending on physicochemical properties and pharmacokinetic parameters of the drugs, residue may also accumulate in edible part of animal tissues and in some cases; the residues may result from contaminated animal feedstuffs [12].

Risk factors for drug residue occurrence

Veterinary drug residues are one of the major problems for food contamination of animal origin food products (like meat, milk, egg) [13]. VMPs and agricultural chemicals used according to label directions should not cause drug residues at slaughter. However, possible reasons for such residues include one is drug related factors which includes: Use drug without following recommended label directions or dosage (extra-label usage); not respect recommended withdrawal period; administering too large volume of drug at a single injection site; use of drug-contaminated equipment, or failure to properly clean equipment used to mix or administer drugs; high dose utilization, inappropriate measuring, or mixing of different drugs; allowing animals access to spilled chemicals or medicated feeds and animal related factors are:- age, pregnancy, congenital, disease status, allergies are included. Other factors, chemical interactions between drugs; variations in water temperature for fish species; environmental contamination; and improper use of agricultural chemicals such as pesticides are the main risk factors drug residue occurrence [8].

Veterinary drugs or VMPs residues usually accumulate in the liver or kidney rather than other tissues. It has been noted that different residue levels can be found in different tissue positions such as site and route of administration [13]. The most likely reason for drug residues may result from human management, such as improper usage, including extra-label or illegal drug applications. However, the most obvious reason for unacceptable residues might be due to failure to keep to the proper withdrawal period, using overdose and long acting drugs [7]. Inadequate good sanitary care during animal or product transportation, including the cross contamination of animal feeding stuffs with inadvertently applied drugs, environmental and animal to animal transfer of drugs may also cause residues. Risk factors responsible for the development of residue are Age of animal.

Weaning status and, to a lesser extent, the age of the animal affect drug disposition [7]. For instance, the study conducted on comparisons of the pharmacodynamics of norfloxacin nicotinate between weaning and unweaned calves revealed that the distribution of the drug did not differ between the two groups of calves, but the total body clearance time was increased in weaned calves, possibly due to increased weight from the presence of rumen fluid [22]. Calves fed grain had shorter clearance times (approximately four days) for sulfamethazine than unweaned calves. Elimination half-life of tindazole is shorter in unweaned calves than in adult cows, while the elimination half-life of apramycin is longer in calves than in adult cattle, possibly due to the immaturity of the drug clearance system [28].

Disease status

The disease status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues. This can occur either when the disease affects the metabolic system (and consequently drug metabolism), or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues. For example, cattle with acutely inflamed mastitis quarters, apramycin penetrates these areas of the

body, and concentrations of the drug have been observed at ten times over the level recorded from cows without mastitis [5].

Extra-label drug use

Extra-label drug use (ELDU) refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. It occurs when a drug only approved for human use is used in animals, when a drug approved for one species of animal is used in another, when a drug is used to treat a condition for which it was not approved, or the use of drugs at levels in excess of recommended dosages. For instances, the use of enrofloxacin solution as a topical ear medication (Only approved for use as an injection) are the common ELDU in veterinary medicine [23].

Improper Withdrawal Time

Improper withdrawal time is another risk factor; the withdrawal time (also known as the depletion or clearance period) is the time required for the residue of toxicological concern to reach a safe concentration as defined by the tolerance. Depending on the drug product, dosage form, and route of administration, the withdrawal time may vary from a few hours to several days or weeks. It is the interval necessary between the last administration to the animals of the drug under normal condition of used and the time when treated animal can be slaughtered for the production of safe food stuffs [28].

Safety evaluation and detection methods of drug residues

Safety Evaluation

Acceptable daily intake

Acceptable daily intake (ADI) is the amount of substance that can be ingested daily over a lifetime without appreciable health risk. The evaluation of the safety of residues is based on the determination of the ADI on which in turn maximum residues limits (MRL) is based. The ADI is determined by consecutive estimate of a safe ingestion level by the human population on the lowest no effect level of toxicological safety studies [15]. If the drug is not a carcinogen, the no observed effect level (NOEL) of the most sensitive effect in the most sensitive species divided by a safety factor is used to determine an ADI for drug residues. The FDA will calculate the safe concentration for each edible tissue using the ADI, the weight in kg of an average adult (60 kg), and the amount of the product eaten per day in grams as follows; Safe concentration = [ADI (µg/kg/day) x 60 kg] /[Grams consumed/ day].

Maximum residue level: A tolerance level (or maximum residue levels, MRLs) is the maximum allowable level or concentration of a chemical in feed or food at a specified time of slaughter or harvesting, processing, storage and marketing up to the time of consumption by animal or human. The MRL in various foodstuffs (muscle, liver, kidney, fat, milk and eggs) is determined to minimize the risk of consumer exposure, considering dietary intake. Such considerations as food technology, good farming practices and the use of veterinary medicinal products may also be considered when setting the MRL [32].

Calculating Withdrawal Period

The withdrawal period is determined when the tolerance limit on the residue concentration is at or below the permissible concentration. Withdrawal times are determined in edible, target tissues. Most commonly, they are liver or kidneys as they are primary organs of elimination and typically display a residue for the longest time. During withdrawal studies, the target organ is determined and animals are sampled at various times after drug administration is stopped. For those drugs for which only a kidney or liver tolerances has been established, if a violative residue is found in the target organ, the whole carcass would need to be discarded. On the other hand, for the drugs for which a muscle tolerance has been established, even if a violative residue is found in the kidney or liver a violative residue is not found in the muscle, the carcass would not need to be discarded [18].

Detection Methods

Screening Test :- Screening of food products from animal origin for the presence of antimicrobial residues started soon after the introduction of antibacterial therapy in veterinary medicine. Initially it mainly concerned process monitoring in the dairy industry to prevent problems in fermentative dairy production, but from the early 1970s regulatory residue screening in slaughter animals also became more commonly introduced. An efficient screening method needs to be low-cost and high-throughput, able to effectively identify potential noncompliant samples from a large set of negative samples [36]. Advantage of these methods is that they have a wide detection spectrum; they are simple to carry out and cheap; and can be used for the screening of a large number of samples; [32] Possibility of automatization; Reduced time to obtain the result; Good sensitivity and specificity and Detection capability with an error probability (b) < 5% [39]. This method includes a large variety of detection methods, ranging from physico-chemical analysis or immunological detection to microbiological method [4].

Immunological Detection

The immunological methods are based on the interaction of antigen-antibody which is very specific for a particular residue. The most usual technique consists in the enzyme linked immune sorbent assay (ELISA) and the detection system is usually based on enzyme-labeled reagents. There are different formats for antigen quantification like the double antibody or sandwich ELISA tests and direct competitive ELISA tests [40]. ELISA kits are allowing the analysis of a large number of samples per kit, do not require sophisticated instrumentation, the results are available in a few hours and are quite specific and sensitive. It has good performance for the analysis of antibiotic residues in meat like tylosin and tetracycline, chloramphenicol [22], nitroimidazoles [25] and sulphonamides [45] and also for sedatives [22].

Microbiological Detection

Microbial inhibitions assays are very cost-effective and they have the potential to cover the entire antibiotic spectrum within one test. There are two main test formats: the tube test and the (multi-) plate test. A tube (or vial, or ampoule) test consists of a growth medium inoculated with (spores of) a sensitive test bacterium, supplemented with a pH or redox indicator.

At the appropriate temperature, the bacteria start to grow and produce acid, which will cause a color change. The presence of antimicrobial residues will prevent or delay bacterial growth, and thus is indicated by the absence or delay of the color change. This format is commonly applied in routine screening of milk, but it is also increasingly used for analysis of other matrices [43]. A plate test consists of a layer of inoculated nutrient agar, with samples applied on top of the layer, or in wells in the agar. Bacterial growth will turn the agar into an opaque layer, which yields a clear growth-inhibited area around the sample if it contains antimicrobial substances.

Biosensors

Different types of biosensors have been developed in recent years as an alternative approach to screen veterinary drugs in meat. In general, these sensors usually contain an antibody as a recognition element that interacts with the analytic. The resulting biochemical signal is measured optically or converted into an electronic signal that is further processed in appropriate equipment's [46]. Biosensors can be able to detect simultaneously multiple veterinary drugs residues in a sample at a time [48]. In general, these sensors are valid for control laboratories because they can detect multiple residues in one sample and can thus allow the analysis of a large number of residues and samples [21].

Identification and Confirmation

The next step after initial screening consists in the unambiguous identification and confirmation of the veterinary drug residues in foods of animal origin. The full procedure and the methodologies for confirmatory analysis are costly in time, equipment's and chemicals. In addition, they require trained personnel with high expertise [42]. Different analytical techniques are available for such purpose. When the target analytic is clearly identified and quantified above the decision limit for a forbidden substance or exceeding the maximum residue limit (MRL) in the case of substances having a MRL, the sample is considered as noncompliant (unfit for human consumption). Identification is easier for a limited number of target analyses and matrices of constant composition [33]. Some examples of the available confirmatory methodologies are as follows: The use of HPLC-electrospray ionization (ESI) tandem mass spectrometry [41] or liquid chromatography-mass spectrometry with atmospheric pressure chemical ionization (APCI) [43].

ESI technique facilitates the analysis of small to relatively large and hydrophobic to hydrophilic molecules and is thus very adequate for the analysis of veterinary drug residues. Even though it is more sensible to matrix effects than APCI ionization. ESI and APCI interfaces are the sources of choice to promote the ionization of antibiotics and both complement each other well with regards to polarity and molecular mass of analyses [43].

Potential Effect of Veterinary Drug Residues on Public Health

The non-restrictive usage of antimicrobials in animals rearing may lead to problems due to the presence of residues in food and raw materials of animal origin. Human health can either be affected through residues of drugs in foods of animal origin, which may cause direct side effects or indirectly through selection of antimicrobial resistance determinant that may spread human pathogen. Human health problems that may result from intake of sub chronic exposure levels include allergic reactions in sensitive people, toxicity and carcinogenic effect. Penicillin especially, as well as other beta-lactam antibiotics such as cephalosporin could cause allergies if high level of residues persists in milk consumed by penicillin allergic persons. Tetracycline residue also has the potential to stain teeth of young children [37]. The effect drug residues on human health are described below.

Development of drug resistance

Human health can either affect through residues of drugs in food of animal origin, which may cause direct side effect [6] or indirectly, through selection of antibiotic resistance determinants that may spread human pathogen. Resistant microorganism can get access to human, either through direct contact [9] or indirectly via milk, meat, and or egg. As the bacteria of animal origin, they may either colonize human endogenous flora or superimpose and additional load to the reservoir of resistance genes already present in man. The potential resistance to antibiotics microorganism can be transferred from animal to human may existed. Clearly, the use of antibiotic in livestock production has been associated with the development of human antibiotic resistance [31]. The animal feed with the low prophylactic level of antibiotic may develop bacteria evolving resistance to this antibiotic during the preparation or consumption of food of animal origin [34]. It has been documented that human develop drug resistant bacteria such as Salmonella, Campylobacter, and Staphylococcus from food of animal origin [9]. Fluoroquinolones and avaoparin are the two examples of drugs that have been shown to cause the growth of resistant bacteria in food of animal. WHO was suggests subtherapeutic uses of penicillin, tetracyclines, and sulfa drugs; in agriculture are high priority issue causes of arising of the resistance of microorganisms (National Research Council [34].

Drug hypersensitivity reaction

Drug hypersensitivity is defined as an immune mediated response to a drug agent in a sensitized patient, and drug allergy is restricted to a reaction mediated by IgE. An allergic or hypersensitive effect occurred following administration of a drug (i.e., drug allergy is quite similar to that typified by allergic response to protein, carbohydrate, and lipid macromolecules. Allergic reactions to drugs may include anaphylaxis, serum sickness, cutaneous reaction, a delayed hypersensitivity response to drugs appear to be more commonly associated with the antibiotics, especially of penicillin [38]. About 10% of the human population is considered hypersensitive to an amount of a substance, including penicillin, but in animals, the extent of hypersensitive to, the drug is not well known. Certain macrolides may also in exceptional be responsible for liver injuries, caused by a specific allergic response to macrolide modified hepatic cells [12].

Carcinogenic effect

The term carcinogen refers to an effect produced by a substance having carcinogenic activity [2], considerable confusion has existed because a carcinogen applies to substances that are so varied in their qualitative and quantitative characteristics. The potential hazard of

carcinogenic residues is related to their interaction or covalently binding to various intracellular components such as proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), glycogen, phospholipids, and glutathione [1]. Drug residues have the ability induce cancer in humans or consumers are: like Nitrofurans, Nitroimdazoles. Inorganic arsenic is also a known carcinogen and may adversely affect the circulatory and nervous systems. Although, furazolidone had been labeled and approved for anti-protozoal and other uses for a wide variety of conditions in poultry and swine, its metabolites also have been shown to induce cancer in animals and human beings [26].

Mutagenic effect

Several drugs that have a characteristics containing chemicals, including alkalizing agents and analogous of DNA bases, have been shown to elicit mutagenic activity [8]. Currently, there has been increasing concern that drugs as well as environmental chemicals may pose a potential hazard to the human population by production of gene mutagen or chromosome breakage [7] that may have adversely affects human fertility [19].

Disruption of Normal Intestinal Flora

Drugs can cause disruption of normal human flora in the intestine and 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 [50]. Bacteria that are sensitive to antimicrobials are killed or put at a competitive disadvantage, while bacteria that have the ability to resist antimicrobials have an advantage and are able to grow more rapidly than more susceptible bacteria. In addition, bacteria can become resistant when resistance genes are passed from a resistant bacterium to a sensitive one. Thus, antimicrobial agents may increase the prevalence of resistant bacteria among both target pathogens and normal bacterial flora [26].

Toxic effect

Toxic effects of the drug residue mostly resulted from the consumption of animal origin food. Products medicated with drugs [27]. The toxic effects drug residue to human beings includes hearing problems caused by streptomycin and allergy problems and anaphylactic shock caused by penicillin. In addition, it is widely recognized that the indiscriminate use of such substances promotes the development of resistant microorganisms hindering the antibiotic therapy. They are also heat resistant, so the temperatures used in the UHT process are ineffective in eliminating them [10]. In cause of tetracycline, some toxic effects were observed when the drug given at high doses. High therapeutic doses of drugs are occasionally associated with discolored teeth, allergic reactions, or peripheral blood changes [27]. Some antibiotics like streptomycin, neomycin and, gentamicin has been reported to cause damage to the kidney and hearing ability. They depleted rapidly from muscle and fat but tend to persist in kidney and liver, not readily metabolized in animals or in humans [17]. One significant adverse effect of gentamycin in humans that occurred during treatment of pregnant women with tuberculosis and also infants of women treated first trimester: damage to a cranial nerve and congenital deafness. It is not expected that low food residues/low absorption would affect fetal development (Seguin *et al*., 1974). Data cited by JECFA indicate that the primary toxicity effect of sulfonamides was associated with the thyroid–hypothalamus function. The toxicity of some drug residue should be measured by parameters of the thyroid and pituitary function which can be directly associated to their activities. Hypersensitivity reactions or primarily skin rashes to therapeutic levels of sulfonamides have been reported: but, there have been no cases that involved exposure to residues in foods [20]. The main classes of antimicrobials and potential risks to human are described below the table.

Table 1: The main class of antimicrobial and their toxic effect [47]

Class	Health risks
Sulfamides	Allergies (with skin rashes), Sweet's syndrome, DRESS syndrome, leukopenia
Quinolones	Immediate hypersensitivity reactions (urticaria, angioedema, anaphylaxis), exanthema, Sweet's syndrome
Beta-lactamines	Immediate reactions: urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis, haemolyticanaemia, neutropenia, eosinophilia. Skin rashes, Stevens-Johnson syndrome, Lyell's syndrome
Tetracyclines	Drug hypersensitivity syndrome, drug-induced lupus erythematosus such as a rash, anaphylaxis, DRESS syndrome, Sweet's syndrome
Aminoglycosides	Allergic contact dermatitis
Phenicols	Rare bone marrow suppression: aplastic anemia
Macrolides	Rare
Lincosamides	Neuromuscular blockade with post-anesthetic paralysis, cardiac depression after too rapid IV injection, allergies and moderate hepatic degeneration

Prevention and control of residue

Self-monitoring and the control of residues are based on standardized laboratory analytical methods; the residue control strategy is based on a two-step approach; namely, the detection of residues using sensitive tests followed by confirmation [14]. Drug residue control and prevention responsible organs not only lie on within a governmental agency; rather the responsibility must be shared by all responsible bodies which includes, the government, producers, animal health practitioner and academicians, marketing associations, livestock producers, farmers and other interested parties, who must strive for both healthy and efficiently grown animals as well as a safe food supply. Several prevention and control approaches can be taken to achieve this goal: The first step in residue prevention is to make individuals and organizations aware the effect of drug residue on public health through education. When the animal is slaughtered or its edible products are collected

there should be a legal requirement that drug concentrations in these products are not at levels greater than those established as safe by the relevant regulatory authority in the country of origin [39]. Hence, the residue Prevention and control strategy is based on preventing entry of residues in meat or milk intended for human consumption by proper drug use guide developed for use by both veterinarians and food animal (dairy and beef) producers include the following [3]. All food animals should be maintained in a clean and healthy environment whenever possible one of the first method to avoid occurrence of drug residue by maintaining animal healthy and this leads minimizing drug utilization. Implementing good management practice (good nutritional to meet growth, maintenance and lactation needs) and herd health program that keep animals healthy and producing efficiently, dairy and beef producers should not use or store unapproved drugs, special mixes or products within adequate labels as unapproved drugs have no data regarding efficacy, safety or withholding time are the best methods of drug residues prevention and control strategies [24]. The use of prescription drug and a veterinary-client patient relationship, which is established hence a veterinarian is closely with the owner in health management of the herd; Proper drug utilization and identification of treated animals before administering or dispensing drugs one has to make drug residue prevention and control strategies: To know the drugs approved for all classes of cattle on the farm and be familiar with approved dosage, route of administration, and withholding time are also another methods; Proper maintenance of treatment records and identification of treated animals; institute a workable health record for each animal to record all health related events, including administration of medication, this for all about mentioned above points are the way of prevention and control strategies of drug residues [42].

Reference

1. Aiello SE, Lines PR, Kehn CM. Anthelmintics In: He Merck Veterinary Manual. (9th Edn) Co. IOC. NJ, USA; c2005. p. 2111-2124.
2. American Cancer Society (ACS). Known and probable human carcinogens; c2014.
3. AVMA, NMPF. American Veterinary Medicine Association and National Milk Production Federation: Milk and beef residue prevention. A quality assurance protocol. J. Ame. Vet. Assoc. 1991;2:1-24.
4. Babapour A, Azami L, Fartashmehr J. Overview of antibiotic residues in beef and mutton in Ardebil, North West of Iran. World Appl Sci J. 2012;19:1417-1422.
5. Babington R, Matas S, Marco M, Galve R. Current bio-analytical methods for the detection of penicillins. Analytical and Bio analytical Chemistry. 2012;403(6):1549-1566.
6. Beyene T. Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. Journal of Veterinary Science and Technology. 2014;7(1):285.
7. Beyene T, Tesega B. Rational veterinary drug use: Its significance in public health. J Vet Med Anim Health. 2016;6:302-308.
8. Booth NH, Mc Donald LE. Toxicology of drug and chemical residues. In: veterinary pharmacology and therapeutics. (6thedn) Iowa state university press, USA; c1988. p. 1149-1195.
9. Booth NH. Development of a regulatory and research program in veterinary medical toxicology. Vet. Toxical. 1973;15:100.
10. Brancher C, Fagundes CM. Adaptation of Reductase Method to detect antibiotic residues in milk. Brazilian Journal of Agro Science. 1998;2(1):80-84.
11. Canadian Food Inspection Agency (CFIA). Chemical residues. In: Meat Hygiene Manual of procedures: Chapter 5-Sampling and Testing Procedures. Meat Hygiene Directives; c2014.
12. Cooper J, Delahaut P, Fodey TL, Elliott CT. Development of a rapid screening test for veterinary sedatives and the beta-blocker carazolol in porcine kidney by ELISA. Analyst. 2004;129(2):169-174.
13. Kilnic B, Meyer C, Volker H. International Journal Food Science and Technology. 2007;42:635-628.
14. Cotter PD, Stanton C, Ross RP, Hill C. He impact of antibiotics on the gut micro biota as revealed by high throughput DNA sequencing. Discov Med. 2012;13:193-199.
15. Cristofani E, Antonini C, Tovo G, Fioroni L, Piersanti A, Galarini R. A confirmatory method for the determination of tetracyclines in muscle using high performance liquid chromatography with diode array detection. Analyt.chim. Acta. 2009 Apr 1;637(1-2):1-2.
16. Darwish WS, Eldaly EA, El-Abbasy MT, Ikenaka Y, Nakayama S, *et al*. Antibiotic residues in food: the African scenario. Jpn J Vet Res. 2013;61Suppl: S13-22.
17. Doyle ME. Veterinary drug residues in processed meats-potential health risk. FRI briefings, Food Research Institute, University of Wisconsin-Madison, Madison; c2006.
18. Eberhart RJ, Watros GH, Hokanson JF, Burch GE. Persistence of Antimicrobial agents in milk after intramammary treatment of clinical mastitis. Journal of American Veterinary Medicine Association. 1998 Aug 15;143:390.
19. EC-European Commission. Commission staff working document on the implementation of national residue monitoring plans in the member states in 2009 (Council Directive 96/23/EC); c2012.
20. European community (EC). Notice to applicant and note for guidance. Establishment of maximum residue limits for residue of veterinary medicinal Products in Food Stuffs of Animal Origin, Fingleton J (2004) Legislation for Veterinary Drugs Control, FAO legal papers online #38; c2001. p. 4-10.
21. Fechner T, Topfer H, Pannwitz E. Beitragzur Ruckstands-analtika und dynamic Von; c1974.
22. Food and Drug administration Center for Veterinary Medicine (FDACVM). Guidance for approval of a withdrawal period In: Contains-Binding Recommendations: Guidance for Industry- General Principles for evaluating the safety of compounds used in food producing animals. U.S. Department of Health and Human Services; c2006.
23. Foster W, Beecroi ML. Chemical Exposures and Human Fertility. Infertility Awareness Association of Canada; c2014.
24. Franek M, Hruska K. Antibody based methods for environmental and food analysis: A review. Veterinary Medicine Czech. 2005;50:1-10.

25. Gerald BG, Joseph CP. Report from symposium on prevention of unwanted Drug Residues. J. Amer. Vet. Med. Assoc. 1991;26:89-111.
26. Gips M, Soback S. Norfloxacin nicotinate pharmacokinetics in unweaned and weaned calves. J Vet Pharmacol Her. 1996;19:130-134.
27. Gregory M. Food Toxicology. University of Idaho; c1988. p. 1-12.
28. Gustavsson E, Degelaen J, Bjurling P, Sternesjo A. Determination of beta lactams in milk using a surface plasmon resonance-based biosensor; c2004.
29. Huet AC, Mortier L, Daeseleire E, Fodey T, Elliott C, *et al*. Development of an ELISA screening test for nitroimidazoles in egg and chicken muscle. Analytica Chimica Acta. 2005;534:157-162.
30. Jackson BA. US Food and Drug Administration, Center for Veterinary Medicine. Hosted at University of Nebraska Lincoln. Jam Vet Med Assoc. c1980;176:1141.
31. Jones GM, Seymour EH. Cow side antibiotic residue testing. Journal of Dairy Science. 1988;71(6):1691.
32. Kaneene JB, Miller R. Problems associated with drug residues in beef from feeds and therapy. Rev Sci Tech. 1997;16:694-708.
33. Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. Public Health Rep. 2012;127:4-22.
34. McEvoy JDG. Contamination of animal feedstuffs as a cause of residues in food: A review of regulatory aspects, incidence and control. Analytical Chimica Acta. 2002;473:3-26.
35. Mitchell J, Griffiths M, Mc Ewen S, Mcnab W, Yee A. Antimicrobial drug residues in milk and meat: Causes, concerns, prevalence, regulations, tests and test performance. Journal Food Protection. 2002 Jun;61(6):742-756.
36. National Research Council (NRC). The use of drugs in food animal benefits and risks. He National academies Press. 1991;253:284.
37. Nisha AR. Antibiotics residues A global health hazard. Vet. World. 2008;1(12):375-377.
38. Phillips E, Lovie M, Knowles R, Simor K: A cost effectiveness analysis of six strategies for cardio vascular surgery prophylaxis in patient labeled penicillin allergic residues review. Asian-Australian. J. Ani. Sci. 2000;14:402-413.
39. Pikkemaat MG. Microbial screening methods for detection of antibiotic residues in slaughter animals. Analytical and Bio analytical Chemistry. 2009;395(4):893-905.
40. Riviere JE. Pharmacologic principles of residue avoidance for veterinary practioners. J AVMA. 1999;198(5):809-815.
41. Rokka M, Eerola S, Perttila U, Rossow L, Venalainen E, Valkonen E, *et al*. The residue levels of narasin in eggs of laying hens fed with unmedicated and medicated feed. Mol Nutr Food Res. 2005;49:38-42. DOI: 10.1002/mnfr.200400042.
42. Schwark WS. Factors that a ٶect drug disposition in food producing animals during maturation. Department of Pharmacology. New York State College of Veterinary Medicine, Cornel University. 2014;70:3635-3645.
43. Scippo ML, Degand G, Duyckaerts A, Maghuin-Rogister G, Delahaut P. Control of the illegal administration of natural steroid hormones in the plasma of bulls and heifers. J. Analyst. 1994;119:2639-2644.
44. Shankar BP, Manjunatha PBH, Chandan S, Ranjith D, Shivakumar V. Rapid Methods for detection of Veterinary Drug residues in Meat. Veterinary World. 2010;3(5):241-246.
45. Tajick MA, Shohreh B. Detection of antibiotics residue in chicken meat using TLC. Int J Poult Sci. 2006;5:611-612. DOI: 10.3923/ijps.2006.611.612.
46. Thevis M, Opfermann G, Schanzer W. Liquid chromatography/ electrospray ionization tandem mass spectrometric screening and confirmation methods for b2-agonists in human or equine urine. Journal of Mass Spectrometry. 2003;38(11):1197-1206.
47. Toldra F, Reig M. Methods for rapid detection of chemical and veterinary drug residues in animal foods. Trends in Food Science and Technology. 2006 Sep 1;17(9):482-489.
48. Ture M, Fentie T, Regassa B. Veterinary Drug Residue: The Risk, Public Health Significance and its Management; Dairy and Vet Sci J. 2019;13(2): JDVS.MS. ID.555856
49. Turnipseed SB, Roybal JE, Andersen WC, Kuck LR. Analysis of avermectin and moxidectin residues in milk by liquid chromatography tandem mass spectrometry using an atmospheric pressure chemical ionization/ atmospheric pressure photionization source. Analytica Chimica Acta. 2005 Jan 24;529(1-2):159-165.
50. Wageh SD, Elsaid AE, Mohamed TE, Yoshinori ISN, Mayumi I. Antibiotic residues in food. The African scenario Japanese Journal of Veterinary Research. 2013 Feb;61(Supplement):S13-22.
51. Woodward KN. Hypersensitivity in humans and exposure to veterinary drugs. Veterinary and Human Toxicology. 1991 Apr 1;33(2):168-172.