Int.J.Curr.Res.Aca.Rev.2025; 13(9): 133-144

EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 (Online) Volume 13 Number 9 (September-2025)

Journal homepage: http://www.ijcrar.com

doi: https://doi.org/10.20546/ijcrar.2025.1309.007

Review on Drug Residue: its Drug Resistance and Public Health Significance

Hassen Jilo[1], Tariku Geinoro[2*] and Haso Hamid[3]

[1]Hawassa University, College of Veterinary Medicine, Hawassa, Ethiopia
[2]Ethiopian Agricultural Authority, South West Center, Hawassa, Ethiopia
[3]Oromia Region West Arsi Zone, Shashemene City Agricultural Office, Ethiopia

**Corresponding author*

Abstract

Veterinary drugs are used to treat livestock and aquatic diseases and thus are introduced into animal-derived foods, endangering consumer health and safety. Antibiotic resistance is rapidly becoming a major worldwide problem, and there has been a steady increase in the number of pathogens that show multi-drug resistance. Illegal and excessive use of veterinary drugs in animals and aquaculture has serious adverse effects on humans and on all other environmental organisms. They are used throughout the world and more than half of all medicines are prescribed, dispensed or sold improperly. It is necessary to develop simple extraction methods and fast analytical methods to effectively detect veterinary drug residues in animal-derived foods. In Ethiopia, also different studies revealed the improper utilization of drugs is common. The use of veterinary drugs in food-producing animals has the potential to generate residues in animal derived products and poses a health hazard to the consumer. The most likely reason for drug residues might be due to improper drug usage and failure to keep the withdrawal period. The residual amount ingested is in small amounts and not necessarily toxic. The use of veterinary drugs in food-producing animals has the potential to generate residues in animal derived products (meat, milk, eggs and honey) and poses a health hazard to the consumer. There are many factors influencing the occurrence of residues in animal products such as drug's properties and their pharmacokinetic characteristics, physicochemical or biological processes of animals and their products. Generally the major public health significances of drug residue are development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity, and disruption of intestinal normal flora.

Article Info

Received: xx July 2025
Accepted: xx August 2025
Available Online: 20 September 2025

Keywords

Drug residue, Public health, Residues, Veterinary drugs

Introduction

Veterinary drug means any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use Fingleton (2004)[24]. The diagnosis, treatment, mitigation or prevention of disease or abnormal physical or mental state or the symptoms thereof in an animal; or restoring, correcting or modifying any physical, mental or organic function in an animal. The use of veterinary drugs in livestock production is inevitable as they are essential for treatment of diseases (therapeutic), 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 WHO (2017)[25]. The veterinary drugs are used throughout the world and they comprise a broad variety of classes of chemical compounds including vaccines, antimicrobials, antiparasitics and β-agonists (Fischer *et al*., 2003)[26].

Antimicrobials are the most important and most frequently used group of veterinary drugs. Antimicrobials are medicine (natural, synthetic or semi-synthetic origin) that inhibits the growth of or destroys microorganisms when applied at low concentrations without causing host damage. Among the antimicrobials that are commonly used in livestock production are tetracyclines, amprolium, penicillin, streptomycin, sulphonamides, tylosin, aminoglycosides, β-lactams, macrolides and lincosamides, quinolones and sulfonamides (Alhaji *et al*., 2018)[4]. While that of antiparasitic agents include anthelmintics or coccidiostats, stilbenes, amphenicols, nitrofurans, nitroimidazoles, carbamates, pyrethroids and sedatives (Prajwal *et al*., 2017)[39].

To date, veterinary drugs are still used to treat diseases in farmed animals and in aquaculture. Veterinary drugs are introduced to the animal's body through three routes via animal feed, oral administration, or injection and most are added to the feed. Veterinary drugs are metabolized by animals, and some of the drugs remain in the animal body, while others enter the environment through excreta. In aquaculture, veterinary drugs usually enter fish, shrimp, and crabs as well as other aquatic products and rivers. The veterinary drugs in these excretions and in rivers are absorbed by vegetables and by fruit trees. Humans drink water and eat vegetables and fruit containing veterinary drugs. These drugs re-enter the body and seriously endanger human health. We summarized the information on veterinary drug residues in the environment and animal-derived foods (Ture *et al*., 2019)[42] (Figure 1). To protect the health and safety of consumers, the European Union (EU), United States, China, and other countries have established maximum residue limits (MRLs) for veterinary drugs in animal-derived foods (Prajwal *et al*., 2017)[39]. Veterinary drugs are generally used in farm animals for therapeutic and prophylactic purposes and they include a large number of different types of compounds which can be administered in the feed or in the drinking water. In some cases, the residues may proceed from contaminated animal (McEvoy, 2002)[36]. But many of these substances may feed stuffs exert other effects when administered to animals for other purposes like growth promotion.A primary effect is the increase in the protein deposition, usually linked to fat utilisation that decreases the fat content in the carcass and increases meat leanness. Even though, veterinary drugs have a great importance in treating, preventing and diagnosing diseases, it has major public health hazards. To avoid this it is important to use these drugs rationally, the safety levels of food must be strictly observed, drug products should be used in accordance with the labeled directions and public awareness should be created on the public health significance of drug residue. There for the objective of this paper is to review risk of veterinary drug residue, public health significant and management.

Veterinary Drug and their Use in Food Animals

Drug in animals can be used as therapeutic, prophylactic and growth promotion. Therapeutic use refers to the treatment of established infections whereas prophylaxis is the use of drugs either in individual or groups to prevent the development of infections. Growth promoters (GPs) are any antimicrobial agents administered at low or sub therapeutic dose to destroy or inhibits growth of microbe which reduce the yield of food animals. The use of antimicrobials as feed supplements can promote the growth of food animals and also enhance feed efficiency. The uses of GPs are resulting in meat of better quality with less fat and increased protein contests (Beyene and Tesega, 2014)[10]. The use of drugs in food animals is fundamental to animal health and well-being and to the economics of industry.

There are five major classes of drugs used in food animals: Fingleton (2004)[24]. topical antiseptics,. bactericides, and fungicides used to treat surface skin or hoof infections, cuts, and abrasions; ionophores, which alter rumen microorganisms to provide more favorable and efficient energy substrates from bacterial conversion of feed and to impart some degree of protection against some parasites; L and Lanusse (2017)[34]. Steroid anabolic growth promoters (for meat production) and peptide production enhancers (bovine somatotropin for increased milk production in dairy cows); (Fischer *et al*., 2003)[26]. Antiparasite drugs; (Prajwal *et al*., 2017)[39]. Antibiotics as used to control overt and occult diseases, and to promote growth (National Academies Press, 1999)[37] (Figure 2).

Historical Background

A whole series of known or new food borne biological and chemical hazards are threatening health (FAO, 2007)[6]. In the European Union (EU), following a string of health crises, the food safety mechanism has evolved towards a risk analysis approach. This shift to the concept of 'farm to fork' risk management led to the establishment of food safety agencies at the European level. The risks of residues from veterinary medicinal products used in livestock production were taken on

board in the 1980s, most notably through European harmonization of the regulations on medicinal products for veterinary use. Human health is related directly to the environment (Fingleton, 2004)[24], and in particular the nature and quality of the food. Quality of food from animal products is widely concerning public health agencies around the world since veterinary drugs have played an important role in the field of animal husbandry and agro-industry, and increasing occurrence of residues, and resistance have become interesting issues (L and Lanusse, 2017)[34]. Veterinary drugs or veterinary medicinal products (VMPs) are critically needed to meet the challenges of providing adequate amounts of food for the growing world population as drugs improve the rate of weight gain, improve feed efficiency, or prevent and treat diseases in food producing animals (Prajwal *et al*., 2017)[39].

Prohibited Veterinary Antimicrobials

Prohibited antimicrobials are substances for which it is not possible to determine the Maximum Residue Level (MRL). Chloramphenicol, dimetridazole, ipronidazole, nitroimidazoles, furazolidone, nitrofurazone, and fluoroquinolones are prohibited for extra-label use in food-producing animals (Bayou and Haile, 2017)[11]. Chloramphenicol is a broad-spectrum antimicrobial against Gram-positive and Gram-negative bacteria. It was not possible to determine an MRL based on the available data. The inability to set a threshold value and shortcomings in the marketing authorization application led to chloramphenicol being classified in 1994 as a prohibited substance for use in food-producing animals. Dapsone, which is used to treat leprosy in humans, is not authorized for use in food-producing animals in Europe because of insufficient toxicology data, making it impossible to determine the acceptable daily intake (ADI) (EC, 2010)[23]. In the year 1995 European Union (EU) prohibited the use of nitrofurans for the treatment of bacterial diseases in livestock production, due to concerns about the carcinogenicity of their residues in edible tissue. In subsequent years Australia, USA, Philippines, Thailand and Brazil also prohibited the use of nitrofurans in food animals (Vass *et al*., 2008)[43] (Table 1).

Origin of Residue

Veterinary drugs are generally used in farm animals for therapeutic and prophylactic purposes and they include a large number of different types of compounds which can be administered in the feed or in the drinking water. The great majority of residues found in edible tissues of animals (Table 2) have their source at the farm of origin. In some cases, the residues may proceed from contaminated animal feed stuffs. By far the most common cause of residues is the failure to observe the proper withholding period following treatment (McEvoy, 2002)[36].

Anthelmintics, such as benzimidazoles and probenzimidazoles, are veterinary drugs used against endoparasites for the prevention of animal infestations caused by nematodes, cestodes and trematodes in food producing animals.

Risk of Drug Residue for the Public Health

Human health risk can result from the presence of residues of veterinary drugs and/or their metabolites in edible organs and tissues of treated animals, in particular residues in concentrations exceeding the MRL established by Council Regulation 2377/90 (Gehring *et al*., 2006)[28]. Occurrences of veterinary drug residues pose the broad range of health consequences in the consumers. The residues of antibacterial may present pharmacological, toxicological, microbiological and immunopathological health risks for humans (Drackova *et al*., 2009)[18].

Risk Factors for the Development of Residue in Food producing

Veterinary drug residues are one of the major problems for food contamination (WHO, 2017)[25]. VMPs and agricultural chemicals used according to label directions should not result in residues at slaughter. However, possible reasons for such residues include: Not following recommended label directions or dosage (extra-label usage); not adhering to recommended withdrawal times; administering too large a volume at a single injection site; use of drug-contaminated equipment, or failure to properly clean equipment used to mix or administer drugs; dosing, measuring, or mixing errors; allowing animals access to spilled chemicals or medicated feeds; animal effects- age, pregnancy, congenital, illness, allergies; chemical interactions between drugs; variations in water temperature for fish species; environmental contamination; and improper use of agricultural chemicals such as pesticides (Hassan *et al*., 2014)[30]. 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 (WHO, 2017)[25]. 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 mostobvious reason for unacceptable residues might be due to failure to keep to the withdrawal period including using overdose and long acting drugs (FAO, 2007)[6]. Inadequate good sanitary care during animal or product transportation, including the cross contamination of animal feeding stuffs with inadvertently applied drugs, environmental and Risk factors animal to animal transfer of drugs may also cause residues. Risk factors responsible for the development of residue are:

Disease status

The disease status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues (Beyene, 2016). 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. Ketoprofen levels in milk increase during clinical mastitis where there is an influx of serum components into the udder.

Age of animal

Weaning status and, to a lesser extent, the age of the animal affect drug disposition (Schwark, 2014)[2]. 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. Calves fed grain had shorter clearance times (approximately four days) for sulfamethazine than unweaned calves. The 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 (Kaneene and Miller, 1997)[32].

Feeding

Diet can affect the bioavailability of drugs. For instances, study conducted to determine the effects of diet content on the bioavailability of orally administered fenbendazole to cattle and Indian buffalo and fed dry hay either with or without fresh green herbage showed that animals receiving feed containing fresh herbage had lowered bioavailability of the drug. Fenbendazole stays in the rumen and is progressively released with digesta, and the presence of fresh herbage increases gut activity and the flow rate of digesta, which depletes the available stores of fenbendazole in the rumen. In regard to feeds, actual gut contents can also affect drug uptake and pharmacodynamics (Bushra *et al*., 2011)[13].

Absorption

It is described as the process, which a compound passes from its site of administration into the bloodstream. Absorption is influenced by many factors such as the properties of cell membrane, drug properties and route of administration and physiopathological state of the animal. An indication of the rate of drug absorption is obtained from the peak plasma concentration (Cmax) and time reaching the maximum concentration (Tmax) (Beyene, 2016).

Distribution

It is the process where by a drug is transported to all the tissues and organs. After entering the systemic circulation, in whatever route of administration, drugs are conveyed throughout the body and reach their site of action. There are four major factors responsible for the extent and rate of distribution. These are the physico-chemical properties of the drug, the concentration gradient established between the blood and tissue, the ratio of blood flow to tissue mass, and the affinity of the drug for tissue constituents and serum protein binding. Only the fraction free form (unbound) of the drug is capable of exiting the circulation to distribute through the body and exert activity at the site of action. The parameter, which defines the process of distribution, is the volume of distribution (Botsoglou and Fletouris, 2001)[14].

Metabolism

It is the principal mechanism of elimination for the transformation of drugs or xenobiotics into metabolites of the chemical reaction. Hepatocytes play an extremely

important role in the metabolism of drugs and xenobiotic-compounds that are foreign to the body, some of which are toxic. The kidneys are responsible ultimately to dispose of these substances, but for effective elimination, the drug or its metabolites must be made hydrophilic (polar, water-soluble). This is because reabsorption of a substance by the renal tubules is dependent on its hydrophobicity. The more hydrophobic (non-polar, lipid-soluble) substance is, the more likely it will be reabsorbed. Many drugs and metabolites are hydrophobic, and the liver converts them into hydrophilic compounds by using the two classes of enzymatic pathways of biotransformation; phase I (non-synthesis) and phase II (conjugation). Phase I corresponds to functionalization processes including oxidation, reduction, hydrolysis, hydration and isomerization reactions. Phase II reactions involve conjugation of the drug or phase I metabolite with the endogenous substrate such as glucuronic acid, sulfate, acetate and methyl group. Although some drugs are eliminated from the body by uncharged, most drugs undergo metabolism where the liver is the main organ of reaction. In addition, the liver's function may change the drug's form to be inactive and easy to excrete but some drugs may be converted to an activating form (Riviere *et al*., 1991)[40].

Excretion

It is the process by which the parent drug or its metabolites are removed from the body fluids. The kidney is the most important site of drug excretion. There are three renal mechanisms; glomerular filtration, carrier mediated proximal tubular secretion and pH dependent, passive tubular resorption in the distal nephron. Renal insufficiency usually significantly affects drug excretion. The systemic clearance and elimination half-life are important parameters referring to the overall rate of elimination (metabolism and excretion). Although most compounds are excreted primarily by the renal, some drugs are partially or completely excreted through the bile. It has been reported that there is an extensive species variation among animals in their general ability to excrete drugs in the bile; example, chicken are characterized as good biliary excretes, whereas sheep and rabbit are characterized as moderate and poor excretes(Riviere *et al*., 1991)[40].

Improper withdrawal time

The withdrawal time (also known as the depletion or clearance period) is the time 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 foodstuffs (Kaneene and Miller, 1997)[32].

Extra-label drug use (ELU)

Extra-label Drug Use (ELU) refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. ELU 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 (Beyene, 2016). For instances, the use of phenobarbital (a drug only approved for use in humans) to treat epilepsy in dogs and cats; the use of ivermectin in dogs and cats (an antiparasitic only approved for use in cattle); and the use of enrofloxacin solution as a topical ear medication (only approved for use as an injection) are the common ELU in veterinary medicine (Bayou and Haile, 2017)[11].

There are conditions for ELU in food animals. For example, when considering ELU of an approved human drug in food animals: the veterinarian must have medical rational for the use; the veterinarian may not use an approved human drug if an animal drug approved for use in food-producing animals can be used instead for the particular ELU; and if scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply (Gillian, 2003)[29].

Incidence of veterinary drug residues

In many countries, VMPs may be used indiscriminately for the treatment of animal diseases or they may be used as feed additives for domestic animals. Different studies have been conducted by Zuo *et al*. (2012)[44], in Pennsylvania and others to show the incidence rate of VMPs residue in different parts of the world. The studies revealed that low level of heavy metals and gentian violet residue from catfish was detected (Ozbay *et al.,* 2013)[38].

Figure.1 Formation of residues in food (Ture et al., 2019)[42]

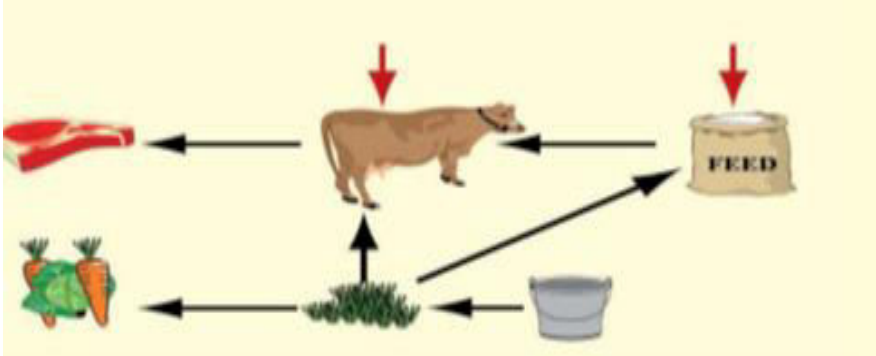

Figure.2 Distribution of antibiotic residue in African countries (Ture *et al*., 2019)[42]

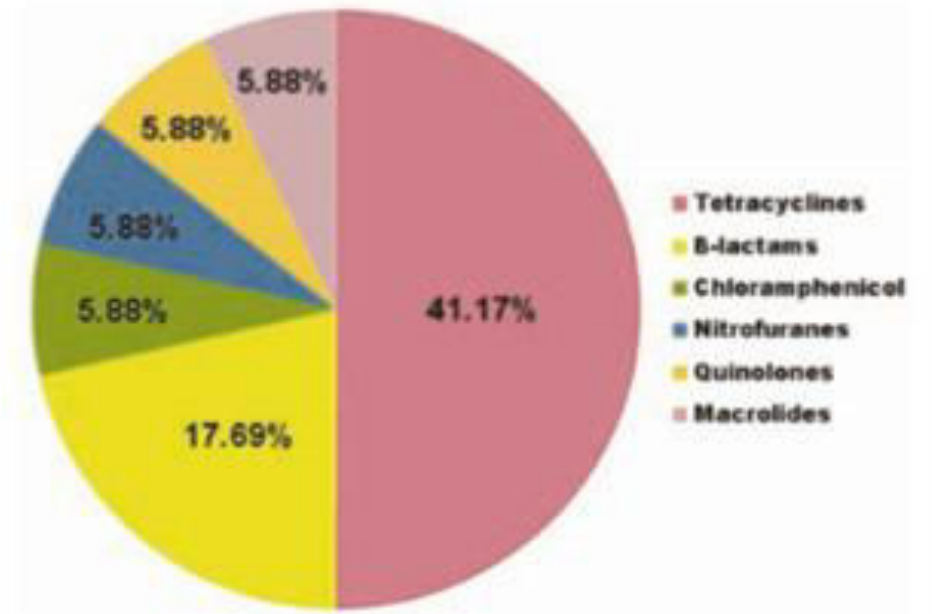

Table.1 Main classes of antimicrobials and potential risks

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
Lincosamides	Neuromuscular blockade with post-anesthetic paralysis, cardiac depression after too rapid IV injection, allergies and moderate hepatic degeneration

Table.2 Maximal residual level of chemical in tissue (synthetic antimicrobials) (mg/kg).

Chemicals	Target Animals	Organs	MRLs
Penicillin G	Cattle, Pig	Kidney	0.05
		Liver	0.05
Oxytetracycline	Cattle, Pig, Chicken, Sheep, Turkey	Fat	0.01
		Kidney	0.6
		Liver	0.3
Albendazole	Cattle, Sheep	Fat	0.1
		Kidney	5.0
		Liver	5.0
Flubendazole	Pig, Chicken, Duck, Turkey,	Liver	0.01
		Liver	0.5
Sulfamethazine	Pig, Chicken, Duck, Turkey, Sheep, Goat, Deer, Rabbit, Horse	Fat	0.1
		Kidney	0.1
		Liver	0.1
Thiabendazole	Cattle, Pig, Goat, Sheep	Kidney	0.1
		Liver	0.1

Source: (McEvoy, 2002)[36]

Other studies conducted in Nigeria also revealed the detection of antimicrobial drug residues in commercial eggs, in meat from slaughtered cattle. Furthermore, oxytetracycline and penicillin G from milk, and tetracycline from cattle beef (Addisalem *et al.,* 2012)[3], were also detected in Ethiopia.

The ongoing threat of antibiotic contamination is one of the biggest challenges to public health that is faced by the human population worldwide. Such residues are spreading rapidly, irrespective of geographical, economical, or legal differences between countries (Darwish *et al*., 2013)[19].

Additionally, the study reported in 2004 by EU also revealed that the majority of residues confirmed in animals were antibacterial agents (EC, 2010)[23].

Currently, the joint FAO/WHO Expert Committee on Food Additives (JECFA) has also reported various veterinary drugs and other environmental substances residues in a series of working documents. Additionally, the JECFA has been participating in further evaluating the safety of residues of veterinary drugs in food and in establishing acceptable daily intakes (ADIs), and recommend maximum residue limits (MRLs) for substances when they are administered to food-producing animals in accordance with good veterinary practice in the use of veterinary drug (Who, 2024)[12].

Potential effect of veterinary drug residues on public Health

Drug low-level contamination generally may not generate a violation problem on public health. However, extensive use of drugs may increase the risk of an adverse effect of residues on the customer including the occurrence of antibiotic resistanc and hypersensitivity reaction Samanidou and Nisyriou, 2008)[41]. Therefore, prudent use of drugs in the manner of preventing feed contamination is necessary.

Development of drug resistance

Human health can either affect through residues of drugs in food of animal origin, which may cause direct side effects or indirectly, through selection of antibiotic resistance determinants that may spread human pathogen. Resistant microorganism can get access to human, either through direct contact (Chang *et al*., 2014)[17] 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 for animal to human transfer of resistance is existed. Clearly, the use of antibiotic in livestock production has been associated with the development of human antibiotic resistance (Landers *et al*., 2012)[35].

The animal fed 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, It has been documented that human develop drug resistant bacteria such as Salmonella, Campylobacter, and Staphylococcus from food of animal origin. Examples of drugs that have been shown to cause the growth of resistant bacteria in food of animal are fluoroquinolones and avaoparin. The resistance of microorganisms, arising from subtherapeutic uses of penicillin, tetracyclines, and sulfa drugs; in agriculture is suggested by the WHO to be a high priority issue (NRC,1991)[37].

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 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 (Beyene, 2016). 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 (Darwish *et al*., 2013)[19].

Carcinogenic effect

The term carcinogen refers to an effect produced by a substance having carcinogenic activity 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 (Kumar *et al*., 2004)[33]. And also the term carcinogenic refers to any substance or an agent capable of altering the genetic makeup of an organism so that they multiply and become rancorous while carcinogen refers to any substance that promotes carcinogenesis, the formation of cancer or having carcinogenic activity. Carcinogenic residues functions by covalently binding intracellular components including DNA, RNA, proteins, glycogen, phospholipids and glutathione (Aiello *et al*., 2005)[7].

Teratogenic effect

The term teratogen applies to drug or chemical agent that produces a toxic effect on the embryo or fetus during a critical phase of gestation. Consequently, a congenital malformation that affects the structural and functional integrity of the organism is produced. The well-known thalidomide incident involving a number of children in Europe was a direct testimony to the hazard that may occur when such agent is administered during pregnancy (Kumar *et al.,* 2004)[33]. Of the anthelmintics, benzimidazole is embryo toxic and teratogenic when given during early stage of pregnancy because of the anthelminthic activity of the drug. In addition to embryo toxicity including teratogenicity, the benzimidazole drug of oxfendazole, has also exhibited a mutagenic effect (El-Makawy *et al*., 2006)[20].

Disruption of Normal Intestinal Flora

The bacteria that usually live in the intestine acts as a barrier to prevent incoming pathogen from being established and causing diseases. Antibiotics may reduce the total number of the bacteria or selectively kill some important species. The broad-spectrum antimicrobials may adversely affect a wide range of intestinal flora and consequently cause gastrointestinal disturbance. For example, use of drugs like, flunixin, streptomycin and tylosin in animals, and also use of vancomycin, nitroimidazole, and metronidazole in humans are known for this effect (Cotter *et al*., 2012)[15].

Safety Evaluation for VMPs Residue

Acceptable daily intake (ADI)

It is the amount of a substance that can be ingested daily over a lifetime without appreciable health risk. Calculation of ADI is based on an array of toxicological safety evaluation that takes into acute and long-term exposure to the drug and its potential impact (EC, 2001)[21]. 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 (FDACVM, 2006)[27]. Safe concentration [ADI (µg/kg/day) x 60 kg] / [Grams consumed / day].

Maximum residue limit

It is defined as the maximum concentration of a residue, resulting from the registered use of an agricultural or veterinary chemical, which is recommended to be legally permitted or recognized as acceptable in or on a food, agricultural commodity, or animal feed. The concentration is expressed in milligrams per kilogram of the commodity (or milligrams per liter the case of a liquid commodity) (Boisseau, 1993)[8].

Calculating withdrawal time

The withdrawal period or the milk discards time is the interval between the time of the last administration of a veterinary drug and the time when the animal can be safely slaughtered for food or the milk can be safely consumed. The withdrawal period is determined when the tolerance limit on the residue concentration is at or below the permissible concentration. A tolerance limit provides an interval within which a given percentile of the population lies, with a given confidence that the interval does contain that percentile of the population (FDA/CVM, 2006)[27]. Withdrawal times are determined in edible, target tissues by FDA/CVM during the drug approval process. These target tissues are most commonly the liver or kidney. As the primary organs of elimination, they will 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. Statistical procedures are used to determine when almost every animal given the drug would be below the drug tolerance concentration in the target organ. A muscle tolerance has also been established for some drugs. 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. The disposition of such carcasses cannot be determined by testing of liver, kidney, and muscle is completed (Apley, 2003)[1].

Control and preventive measures

In the EU, self-monitoring and the control of residues are based on standardised analytical methods. The regulatory framework in force in the EU is based on Directive 96/23/EC, which structures the network of laboratories approved for official residue control, laying down requirements in terms of quality and performance of analytical methods (Decision 2002/657). In general, the residue control strategy is based on a two-step approach: the detection of residues using sensitive tests with a low rate of false negatives; followed by confirmation, requiring quantification against the MRL and identification with a low rate of false positives. Hence, the residue prevention strategy is based on preventing entry of violative 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: Herd health management; all food animals should be maintained in a clean and healthy environment whenever possible (EC, 2002)[22]. Drug residues are best avoided by implementing management practice (good nutritional to meet growth, maintenance and lactation needs) and herd health program that keep animals healthy and producing efficiently; Use of approved drugs; dairy and beef producers should not use or store un- approved drugs, special mixes, or products within adequate labels as unapproved drugs have no data regarding efficacy, safety, or withholding time. The herd veterinarian should be certain that ELU involves only approving products; Establishment of valid veterinarian-client-patient relationship; the use of prescription drug and the ELU necessitate a veterinary-clientpatient relationship, which is established hence a veterinarian is closely with the owner in health management of the herd; Proper drug administration and 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; institute a workable health record for each animal to record all health related events, including administration of medication. Record the identification of all animals in the permanent health record book; Having proper drug residue testing capabilities really available on and off the farm; this control point address the conditions under which residue testing should be considered; the proper selection and interpretation of tests; the inherent limitation and potential misuse of residue testing; and Creating awareness of proper drug

use, and methods to avoid marketing adulterated products principally educational, total residue avoidance program is based upon the objective of improving the livestock producer's management and quality control of marketing animals with emphasis on avoidance of drug residues (NMPF, 1991)[5].

Recommendations

Globally, more than half of all medicines are prescribed, dispensed or sold improperly. However the veterinary drugs have played a great role in control and prevention of disease in animals and promote the growth of food animals, its use is associated with problems such as development of resistance and residue effects in food animals. Many livestock producers treat their animals by themselves. The uncontrolled use of anti-infectious agents can lead to residues in animal products. The use of veterinary drugs in food-producing animals has the potential to generate residues in animal derived products and poses a health hazard to the consumer. However, the most obvious reason for unacceptable residues might be due to improper usage, illegal drug applications. failure to keep to the withdrawal period, including using overdose and long-acting drugs. The development of resistant microorganisms in animals and the presence of drug residue in food of animal origin have significant effect on public health.

Based on above conclusion, the following recommendations are forwarded

- The government should regulate irrational and unauthorized use of drugs.
- Improperly prescribed, dispensed and sold drug should be regulated.
- Proper maintenance of treatment records and identification of treated animals should be implemented,
- Creating awareness of farmers, consumers and health professionals about drug residues and its public health significance.

References

Addisalem HB, Bayleyegn MZ, Bayleyegn MZ (2012) Tetracycline Residue Levels in Slaughtered Beef Cattle from Three Slaughterhouses in Central Ethiopia. Global Veterinaria 8: 546-554

Aiello SE, Lines PR, Kehn CM (2005) Anthelmintics. In the Merck Veterinary Manual. (9th edn), Kenilworth, NJ, USA, pp. 2111-2124.

Alhaj NB, Haruna AE, Muhammad B, Lawan MK, Isol TO (2018) Antimicrobials usage assessments in commercial poultry and local birds in North-Central Nigeria: Associated pathways and factors for resistance emergence and spread. Preventive veterinary medicine 154:139-147.

American Veterinary Medicine Association (AVMA) and National Milk Production Federation (NMPF) (1991) Milk and beef residue prevention: a quality assurance protocol. J Ame Vet Assoc 2: 1-24.

Apley M (2003) How do violative residues happen in swine? Pork Safety Sheet. National Pork Board, Iowa State University. USA.

Bayou K, Haile N (2017) Review on Antibiotic Residues in Food of Animal Origin: Economic and Public Health Impacts. Applied Journal of Hygiene 6(1): 1-8.

Beyene T (2016) Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. Journal of Veterinary Science and Technology 1(7): 285.

Beyene T, Tesega B (2014) Veterinary drug use: its significance in public health. Journal Veterinary Medicine Animal Health 6(12): 302-318.

Boisseau J (1993) Basis for the evaluation of the microbiological risks due to veterinary drug residues in food. Vet Microbiol 35: 187-192.

Botsoglou NA, Fletouris DJ (2001) Drug residues in foods pharmacology: food safety, and analysis. Marcel Dekker (Ed) New York, USA pp. 98-150.

Bushra R, Aslam N, Khan AY (2011) Food-drug interactions. Oman Med J 26: 77-83.

Chang Q, Wang W, Regev-Yochay G, Lipsitch M, Hanage WP (2014) Antibiotics in agriculture and the risk to human health: how worried should we be? Evolutionary Applications, 8: 240-247.

Code of Federal Regulations (CFR) (2006) Food and Drug Administration

Cotter PD, Stanton C, Ross RP, Hill C (2012) The impact of antibiotics on the gut microbiota as revealed by high throughput DNA sequencing. Discov Med 13: 193-199.

Darwish WS, Eldaly EA, El-Abbasy MT, Ikenaka Y, Nakayama S, et al. (2013) Antibiotic residues in food: the African scenario. Jpn J Vet Res 61 Suppl: S13-22.

Drackova M, Navratilova P, Hadra L, Vorlova L, Hudcova L (2009) Determination residues of penicillin G and cloxacillin in raw cow milk

using fourier transform near infrared spectroscopy. Acta veterinaria brno 78: 685-690.

El-Makawy A, Radwan HA, Ghaly IS, El-Raouf AA (2006) Genotoxical,teratological and biochemical effects of anthelmintic drug oxfendazole Maximum Residue Limit (MRL) in male and female mice. Reprod Nutr Dev 46: 139-156.

European Commission (EC) (2002) Commission Decision of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results. Off J Eur Communities 221: 8-36.

European Commission (EC) (2010) Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. Official Journal European Union, 15: 1-72.

European community (EC) (2001) Notice to applicant and note for guidance. Establishment of maximum residue limits for residue of veterinary medicinal Products in Food Stuffs of Animal Origin, p. 4-10.

Fingleton J (2004) Legislation for Veterinary Drugs Control, FAO legal papers online #38.

Fischer WJ, Tritscher AM, Schilter B, Stadler RH (2003*) Contaminants resulting from agricultural and dairy practices*. In Roginski H.: *Encyclopedia of Dairy Sciences*. Elsevier Science, London, UK, 1: 516- 525.

Food and Agriculture Organization of the United Nations (FAO) (2007) Food safety risk analysis. A guide for national food safety authorities. FAO Food and Nutrition Paper 87. FAO, Rome, pp. 145.

Food and Drug administration Center for Veterinary Medicine (FDACVM) (2006) 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.

Gehring R, Baynes RE, Riviere JE (2006) Application of risk assessment and management principles to the extra label use of drugs in food-producing animals. Journal of Veterinary Pharmacology and Therapeutics 29: 5-14.

Gillian C (2003) Avoiding drug carry over during feed processing and delivery. Food and Drug Administration Veterinarian Newsletter 6: 30-45.

Hassan MM, Amin KB, Ahaduzzaman M, Alam M, Faruk MS, et al. (2014) Antimicrobial resistance pattern against E. coli and Salmonella in layer poultry. Research journal veterinary practice 2(2): 30-35.

Joint FAO/WHO Expert Committee on Food Additives (JECFA) (2013) Residue evaluation of certain veterinary drugs. 8th Meeting, FAO/ JECFA Monographs, pp. 15.

Kaneene JB, Miller R (1997) Problems associated with drug residues in beef from feeds and therapy. Rev Sci Tech 16: 694-708.

Kumar K, Thompson A, Singh AK, Chander Y, Gupta SC (2004) Enzyme-linked immunosorbent assay for ultratrace determination of antibiotics in aqueous samples. Journal of Environmental Quality 33(1): 250-256.

L, and Lanusse C. (2017) *Veterinary drug residues in meat-related edible tissues. In: New Aspects of Meat Quality. Woodhead Publishing Limited, United Kingdom,* pp. 581-603.

Landers TF, Cohen B, Wittum TE, Larson EL (2012) A review of antibiotic use in food animals: perspective, policy, and potential. Public Health Rep 127: 4-22.

McEvoy J DG (2002) Contamination of animal feedstuffs as a cause of residues in food: A review of regulatory aspects, incidence and control. Analytica Chimica Acta 473: 3-26.

National Research Council (NRC) (1991) The use of drugs in food animal benefits and risks. The National academies Press 253: 284

Ozbay G, Babu BK, Chen G (2013) Prevalence of veterinary drug residues and heavy metals in catfish nuggets. Journal of Food Processing & Technology S11: 1-7.

Prajwal S, Vasudevan VN, Sathu T, Irshad A, Nayankumar SR (2017) Kuleswan Pame antibiotic residues in food animals: Causes and health effects. The Pharma Innovation Journal 6(12): 1-4.

Riviere JE, Craigmill AL, Sundlof SF (1991) Handbook of comparative pharmacokinetics and residues of veterinary antimicrobials. Boca Raton, FL (Ed) CRC press, Inc, Florida, USA.

Samanidou V, Nisyriou S (2008) Multi-residue methods for confirmatory determination of antibiotics in milk. J Sep Sci 31: 2068-2090.

Schwark W S (2014) Factors that affect drug disposition in food producing animals during maturation. Department of Pharmacology. New York State

College of Veterinary Medicine, Cornel University, 70:3635-3645.

Ture, M., Fentie, T., & Regassa, B. (2019). Veterinary drug residue: the risk, public health significance and its management. Vet Sci J, 13, 555-856.

Vass M, Hruska K, Franek M (2008) Nitrofuran antibiotics: a review on the application, prohibition and residual analysis. Veterinarni Medicina 53: 469-500.

WHO (2017) World Health Organization Guidelines on Use of Medically Important Antimicrobials in Food-producing Animals?

World Health Organization. (2024) *Residue evaluation of certain veterinary drugs–Joint FAO/WHO Expert Committee on Food Additives, Ninety-eighth Meeting 20–29 February 2024*. World Health Organization.

Zuo XN, Xu T, Jiang L, Yang Z, Cao XY, et al. (2012) toward reliable characterization of functional homogeneity in the human brain: preprocessing, scan duration, imaging resolution and computational space. Epub 65: 374-386.

How to cite this article:

Hassen Jilo, Tariku Geinoro and Haso Hamid. 2025. Review on Drug Residue: its Drug Resistance and Public Health Significance. *Int.J.Curr.Res.Aca.Rev.* 13(09), 133-144. doi: https://doi.org/10.20546/ijcrar.2025.1309.007