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Public Health Significance of Veterinary Drug Residue in Food Animal Products - A Review

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Abstract: The objective of this review paper was to investigate the public health significance of veterinary drug residues in food of animal origin. Data were collected by means of the search engine and all relevant journals published between 2019 and 2022 and stocked under Google Scholar were retrieved for analysis. The use of veterinary medications in animals that produce food has the potential to leave residues in animal-derived products (meat, milk, eggs and honey), which puts the consumer's health at risk. The inability to follow the withdrawal period and incorrect drug use are the most likely causes of drug residues. The development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity and alteration of intestine natural flora are the main public health implications of drug residue. The frequent application of tandem or high-resolution mass spectrometry along with liquid chromatography has greatly enhanced analytical methods for residue analysis. This advancement made it possible to quickly conduct targeted searches for hundreds of target compounds in complicated matrices like milk, eggs, honey, or meat and organs after slaughter. Reduction of antimicrobial drug resistance problem has been indicated as one of the most challenging issues related to food safety in the forthcoming years. There is little data available on the extent of veterinary drug residue globally. Therefore, a significant amount of work must be done to assess the scope of the issue, prevent the occurrence of veterinary drug residues and to familiarize animal health professionals with the pharmacokinetics, pharmacodynamics and toxicological effects of veterinary drugs in order to reduce the potential public health risk posed by drug residues in food derived from animals.

Key words: Food of Animal Origin · Veterinary Medicinal Product · Antibiotic Resistance · Public Health

INTRODUCTION

The issues of producing enough food for the expanding global population need the use of veterinary pharmaceuticals or veterinary medicinal products (VMPs), as these drugs increase the rate of weight gain, increase feed efficiency, or prevent and treat diseases in animals used for food [1-4]. Currently, it is anticipated that more than 100 mg of antimicrobials are consumed annually per kilogram of animal production worldwide. Additionally, it has been demonstrated that more than 80% of all antibiotics used in the veterinary industry are growth promoters, exceeding the overall usage of antibiotics in human medical treatment in most instances [4].

The consumption of meat, milk, eggs and honey from animals that produce food could contain residues from veterinary medications, which could be harmful to the consumer's health [5]. The primary VMPs that may contaminate foods of animal origin are antibiotics and hormonal growth boosters. Therefore, veterinary medication residue, often known as VMPs, is one of many global hazards relating to food contamination [6]. However, it should be noted that the medication is administered to the animal at a therapeutic dose, making it theoretically somewhat deadly because it contains the same active chemicals used, with a few exceptions, in human medicine [2]. Since People's health is directly impacted by the type and quality of their diet in particular; controlling veterinary medicine residues in food is crucial for maintaining the quality and safety of food items in the worldwide market, especially in light of the growing threat that antimicrobial resistance poses to public health [7].

Following drug administration to an animal, most medicines are metabolized under normal physiological circumstances to aid in excretion and, to a significant part, detoxification. Typically, the majority of the parent

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product and its metabolites are eliminated through the urine and to a lesser extent through the feces. They can also be found in milk, eggs and meat [2]. Antimicrobial drugs, such as antibiotics, antivirals, antifungals and anti-parasites, are used to prevent and cure infections in people, animals and plants [5]. The hardest clinical and public health issue is antibiotic resistance. Infectious diseases are among the leading causes of death worldwide, despite the fact that we live in an era of cutting-edge biomedical research technologies. The two main factors contributing to the growth of antibiotic-resistant bacteria in hospitals, human communities and animal farms are increased human and animal antibiotic use [4] and also in industry and national regulatory laboratories Controlling veterinary drug residues in food is difficult because of (i) the large number of pharmaceuticals (antibiotics, anti-parasitics, anti-inflammatory agents, etc.); (ii) the variety of foods with animal origins; and (iii) the regulatory framework's complexity [5, 7]. Our ability to cure common diseases is still under danger due to the creation and spread of bacteria that are resistant to drugs and has developed new resistance mechanisms. The increasing global development of multi- and pan-resistant bacteria commonly referred to as "superbugs, " which cause diseases that cannot be treated with currently available antimicrobial medications like antibiotics, is particularly concerning [4].

Rationally, no product derived from a treated animal should be consumed unless all of the drug administered has been eliminated, but improper and excessive use of antimicrobial medications as well as lax infection control procedures have made AMR a serious threat to public health globally [1, 8]. Therefore, monitoring medication residues in food derived from animals is beneficial on a number of levels. This assures, at the very least with regard to withdrawal durations between treatment and slaughter, that neither permitted substances nor compounds that are prohibited due to their toxicity are present or used [5]. The objective of this review was to assess the current status of veterinary drug residue in food of animal origin and its public health implications, latest detection methods of veterinary drug residue in food of animal origin and investigate the most recent prevention and control measures of drug residue in food of animal origin.

Veterinary Drug Residue in Food Animal Products

Definition of Veterinary Drug Residue: In the United States, the Food and Drug Administration (FDA/CVM) and the European Union (EU) both define residues as "pharmacologically active substances (whether active principles, recipients, or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the VMPs in question has been administered." [2]. Veterinarian drugs, such as antibiotics, anti-parasiticides and growth promoters, are widely used in animal husbandry and residues of veterinary medications are significant issues in food safety since they raise public concern and pose a significant danger to consumer health [3]. The EU Health and Food Safety Commission states that AMR has a direct impact on both human and animal health and imposes a significant financial burden due to higher treatment costs and lost production as a result of illness. Moreover, antibiotic residues cause serious economic losses to the food processing industry because they interfere with the fermentation of cheese and yogurt. Accordingly, it is very important to control the residues of antimicrobial drugs in milk [9, 10].

Use of Veterinary Drugs in the Raising of Livestock: Many different species of food-producing animals, including cows, pigs, chickens, sheep, rabbits, horses, fish and even bees, who occasionally need treatment, are given medications around the world [8, 11-13] to manage pests and diseases and enhance the quality of edible animal products. However, the overuse and abuse of veterinary medications in animal production are now prevalent due to a lack of scientific understanding and the pressure of economic interests. Due to the over usage of these medications, there are safety issues with drug residues in edible animal products [3].

Animals and people have greatly benefited by the introduction and use of antimicrobials in animals [14]. Since the 1928 discovery of penicillin, antibiotics have evolved into the cornerstone of contemporary medicine. They belong to a group of secondary metabolites made by microorganisms. They are chemically created or partially created similar chemicals that can stop other microbes from growing and surviving [6]. In general application of veterinary drugs in livestock production is inevitable as they are essential for treatment of diseases, prevention of diseases, modification of physiological functions; improvement of growth and productivity as well as for ensuring food safety [4]. Meat of higher quality with less fat and more protein is the consequence of growth promoters (GP) usage [14].

Veterinary Drug Residue Detection Method: The need of sensitive and rapid analytical techniques to detect and quantify pharmacologically active compounds, in animal

food and foodstuff of animal origin has become mandatory for food security [15]. In the late 1960s and early 1970s, most European nations, including Belgium, the Netherlands and Luxembourg, began studying the antimicrobial and drug residues in various animal-derived foods [16].

Since antimicrobial resistance is viewed as a growing hazard to public health, controlling veterinary antibiotic residues in food is crucial for guaranteeing the quality and safety of food items in the worldwide market [7]. Controlling antibiotic residues in animal-derived foods involves two fundamental steps: The animal product is first either qualitatively or quantitatively screened. Here, antimicrobial residue is found through qualitative analysis and it is often classified as either positive or negative. The quantitative screening method is used to identify and quantify a specific residue and the residue's concentration is also given. If results are favorable, a confirmatory procedure using a more delicate physico-chemical technique is typically carried out for a particular antibiotic [4].

Microbiological Assays: The microbial inhibition assay adopts either the tube test or the plate test. The tube test utilizes a tube, vial, or ampule containing a growth medium injected with (spores of) a sensitive test bacteria, supplemented with a pH or redox indicator. There is a color from the acid produced by the developing bacteria when the temperature and pH are adequate [17]. It is typically a normal practice in the milk industry that absence or delay of the color change indicates the presence of an antibacterial residue [18]. However, it has been used to the study of other matrices. In the plate test, the test sample is applied to the layer of the plate that has nutrient agar that has been inoculated. A visible growth-inhibited region surrounds the sample when the developing bacteria create an opaque layer, indicating the presence of an antibiotic residue. This method is commonly used in Europe for screening of antibiotics residues in slaughter animals [4, 7, 17]. The pH indicator shifts from purple to yellow as a result of the microorganism's normal growth after incubation [4].

Immunological Techniques: Immunological methods are very specific for a given residue because they are based on the interaction between the antigen and antibody. The most popular method is an enzyme-linked immunosorbent assay and the detection method typically uses reagents that have been enzyme-labeled. Figure 1 illustrate enzyme-linked immunosorbent assay. Tylosin and tetracycline in particular have showed good performance in ELISA kits' investigation of antibiotic residues in meat. Antigen quantification can be done in a variety of ways, including with double antibody or sandwich ELISA testing and direct competitive ELISA assays as shown in Figure 1. The radioactivity of the immunological complex is measured in radioimmunoassay [4, 19].

Antibody-based screening procedures are more focused on a given medication family. Such tests give a rough idea of the amounts and compounds present, or at the very least they show which drug family is present. Antibody-based tests are dependent on each substance and provide significantly variable sensitivity levels for each substance. Because maximum residue limits (MRLs) and detection limits for members of the same drug family can vary greatly, it is extremely dangerous to interpret quantitative results. Additionally, due to cross reactivity with the matrix, complex matrices like foodstuffs frequently produce false-positive results [20]. As a result, confirmatory methods for contaminants are required to offer information on the chemical structure of the analyte and results acquired by such techniques must thus be systematically verified by a different analytical technique [20].

Biosensors: Biosensor is a device that closely integrates a recognition element with an antibody/antigen pair, a receptor and its particular ligand, or even living cells and an analyte that binds exclusively to them. Biosensors essentially comprise three components: a biological recognition element, a transducer and data recording device. A transducer transforms a biosensor's biological signal into an electrical signal. A microprocessor processes these signals later to provide the output[4]

Liquid Chromatography: The use of liquid chromatography has drastically dropped over the past ten years, but it is still beneficial for qualitative and quantitative screening of several residues in food animals. In order to move a pressurized liquid solvent carrying the sample combination through a column that is packed with a solid adsorbent material, high-performance liquid chromatography (HPLC) uses pumps. The adsorbent material and each component in the sample interact slightly differently, resulting in various flow rates for the various components and their separation as they exit the column. It has been used to find antimicrobials in fish, meat and internal organs [4].

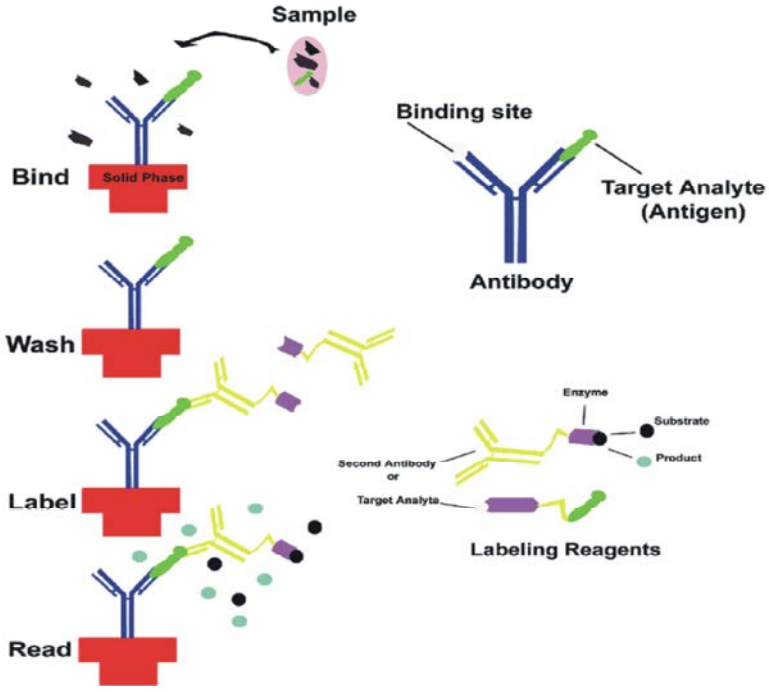


Fig. 1: Illustration of enzyme-linked immunosorbent assay [Source: Figure prepared by Manthena Nava Bharath]

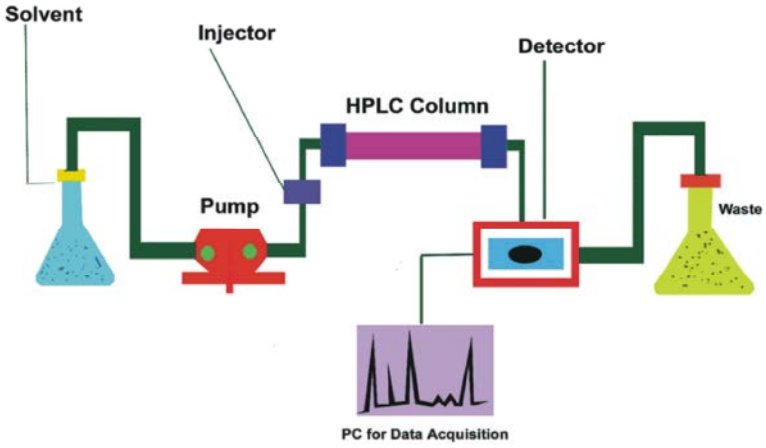


Fig. 2: Flow diagram of high-pressure liquid chromatography [Source: Figure prepared by Manthena Nava Bharath]

HPLC has been used by laboratories more and more frequently and it can quickly assess a number of residues in a sample. Additionally, the apparatus is fully automated (column washing, injection, elution and detection) and computer-controlled. Consequently, it can be applied as a screening method [4]. Figure 2 illustrate flow diagram of high- pressure liquid chromatography.

Risk Factors for Residue Build up in Animals Raised for Food: Residues from veterinary medications typically build up in the liver or kidney as opposed to other tissues. It has been discovered that various tissue positions, such as the site and method of administration, might have various residue levels. The most likely cause of drug residues is bad human management, such as extra-label or illicit drug applications, or improper consumption. However, failing to adhere to the withdrawal time, including using overdose and long-acting medicines, may be the most obvious cause of inappropriate residues [20-22]. In general the following risk factors can lead to the formation of residue:

Disease Status: The animal's illness status may have an impact on the pharmacokinetics of the medications given,

which may have an impact on the possibility of residues. This may happen when a disease inhibits drug metabolism (and, as a result, metabolic function in general), or when an infection or inflammatory response causes the medication to build up in the tissues that are affected. Apramycin, for instance, has been reported in amounts 10 times higher in cows with intensely inflamed mastitis quarters than those found in cows without the condition [23].

Age of Animal: Drug disposition is influenced by the animal's age and, to a lesser extent, its weaning condition. For instance, a study comparing the pharmacodynamics of norloxacinnicotinate in weaning and unweaned calves found that although the drug was distributed similarly in both groups of calves, weaned calves had a longer total body clearance time, possibly as a result of their increased weight from the presence of rumen fluid [23]. Tindazole has a shorter half-life in unweaned calves than in adult cows, whereas apramycin has a longer half-life in calves than in adult cattle, presumably because the drug clearance mechanism is still developing in calves [24].

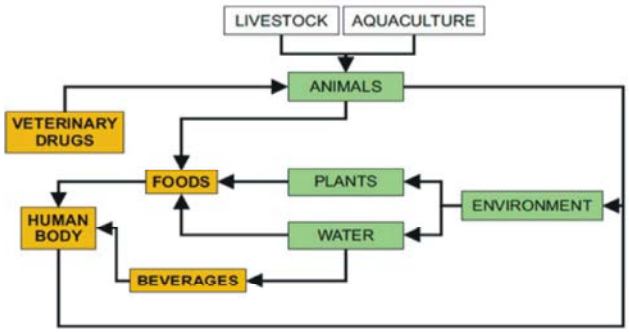
Feeding: Diet can impact a drug's bioavailability. For instance, a study done to see how diet content affected the bioavailability of fenbendazole given orally to cattle and Indian buffalo and fed dry hay with or without fresh green herbage revealed that animals receiving feed with fresh herbage had decreased bioavailability of the medication. Fresh herbage stimulates stomach activity and the slow release of digesta, which depletes the rumen's reserves of fenbendazole. Fenbendazole remains in the rumen and is gradually released with digesta. Actual gastrointestinal contents in feeds can impact drug absorption and pharmacodynamics [24, 25]

Extra-Label Drug Use (ELU): Extra-label Drug Use (ELU) is the term for using a drug that has been approved but not in the way that is recommended on the label. ELU happens when a medication intended only for human use is administered to animals, when a medication intended for one species of animal is administered to another, when a medication is administered to treat a condition for which it was not intended, or when a medication is administered at a dosage that is higher than what is advised [26]. In veterinary medicine, common ELU include, for example, the use of phenobarbital, a medication only approved for use in humans, to treat epilepsy in dogs and cats, the use of Ivermectin, an antiprastic only approved for use in cattle, in dogs and cats and the topical application of enroloxacin solution, a medication only approved for use as an injection, to treat ear infections in animals [4, 26, 27].

Incorrect Withdrawal Time: The withdrawal time, sometimes referred to as the depletion or clearance period, is the amount of time required for the residual of toxicological concern to reach the tolerance-defined safe concentration. The withdrawal period may last anywhere between a few hours and many days or weeks, depending on the drug product, dose form and mode of administration. It is the amount of time required between the last time a medicine was administered to animals under normal use conditions and the period at which the treated animals could be slaughtered to produce safe foods [28].

Potential Economic and Health Effects of Veterinary Drug Residues: Antibiotic residues may be present in products if antibiotics are not administered rationally, as in the case with overdosing, using low doses for an extended period of time and illogical combination. Drug residues have a number of negative effects on residents' health, including the development of "mutagenic, teratogenic, carcinogenic" toxic actions, the development of drug-resistant strains, the development of gastrointestinal disorders, toxic reactions and allergic reactions etc. [10]. Table 1: indicates main classes of antimicrobials and potential risks [23]. Most anthelminthic agents are overused due to their being over-the-counter products and widely used for chemoprophylaxis. Therefore, these drugs may remain in the edible tissues of chicken, pork, beef, milk and eggs produced from anthelmintic-treated livestock and may pose a threat to public health. Consumption of these contaminated foods may lead to toxic effects, development of resistant strains of parasite and/or allergic reactions in hypersensitive individuals [30].

Resistance to Drugs Developing: Antimicrobial resistance (AMR) is a condition in which bacteria, viruses, fungi and parasites evolve over time and cease to respond to antibiotics, making infections more difficult to cure and raising the risk of disease transmission, life-threatening sickness and death [26]. Swan noted the emergence of vancomycin resistance to Enterococci in animals administered avoparcin in 1969, signaling the possibility of transmission of resistant bacteria through the food chain in treated animals. Animal feeds containing antibiotics, have been reported to result in antimicrobial resistance, leading to failure of medical treatment both in



Pictur 3: Mechanisms that lead to veterinary drug residues in human tissue [29]

Table 1. Main classes of antimicrobials and potential risks

Class	Health Risks
Sulfamides	Allergies (with skin rashes), Sweet's syndrome, DRESS syndrome, leukopenia Quinolones
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

animals and humans. Situations whereby drugs are completely ineffective have also been reported to be a possibility [4]. The hardest clinical and societal health issue to solve is antibiotic resistance. Although we now live in an era of cutting-edge biomedical research, numerous infectious diseases that are incurable remain the leading causes of mortality for people around the world [27]. Because lengthier hospital stays and the requirement for more expensive and intense care result in decreased productivity for patients or the caregivers, AMR has a severe financial impact on national economies and health systems [26].

AMR develops throughout time, typically as a result of genetic alterations. The environment, humans, animals, food, plants and the environment all include antimicrobial resistant microbes (in water, soil and air). They can transmit from person to person, through humans and animals, or even via animal products in food. Antimicrobial misuse and overuse, lack of access to clean water, sanitation and hygiene (WASH) for humans and animals, inadequate infection and disease prevention and control in healthcare settings and farms, poor access to high-quality, reasonably priced medications, vaccines and diagnostics, ignorance of the issue and lack of legal enforcement are the primary causes of antimicrobial resistance [10, 26, 27].

Hypersensitivity to Drugs: Drug hypersensitivity is defined as an immune-mediated response to a drug agent in a sensitized patient, as opposed to drug allergy, which is restricted to a reaction mediated by IgE. Effects of drug delivery that are allergic or hypersensitive (i.e., drug allergy is fairly similar to allergic reaction to protein, carbohydrate and lipid macromolecules). Anaphylaxis, serum sickness, cutaneous reactions and delayed hypersensitivity reactions to medications are only a few examples of allergic reactions to medications. Antibiotics, particularly penicillin, seem to be more frequently linked to allergic reactions to medications. Penicillin is one of the substances that about 10% of people are said to be hypersensitive to, however it is unknown how sensitive animals are to the antibiotic in general. In rare cases, particular allergic reactions to hepatic cells that have been changed by certain macrolides may result in liver damage [3, 4].

A Cancer-Causing Factor: The term "carcinogenic" refers to any substance or agent that has the ability to change an organism's genetic makeup, causing them to proliferate and become violent. In contrast, the term "carcinogen" refers to any substance that encourages carcinogenesis, the development of cancer, or has carcinogenic activity. Covalently binding intracellular elements like DNA, RNA,

proteins, glycogen, phospholipids and glutathione is how carcinogenic residues work. Diethylstilbestrol (DES), a hormone-like substance used in animals raised for food, was outlawed due to its potent carcinogenic properties. The International Agency for Research on Cancer (IARC) states that there is ample evidence that metronidazole causes cancer in animals, but not enough to prove it in people [3, 4, 10].

Mutagenic Effect: Chemical or physical substances that have the potential to alter DNA molecules or harm an organism's genetic material are referred to as mutagens. Numerous substances, such as alkalizing agents and substances that resemble DNA bases have been found to exhibit mutagenic activity. Drugs and environmental pollutants may represent a risk to the human population by producing gene mutagens or chromosome breaks that may have a negative impact on human fertility, according to growing concerns [4, 13].

Teratogenic Effect: Any medication or chemical that has a harmful effect on the embryo or fetus during a crucial stage of gestation is referred to as a teratogen. As a result, the organism develops a congenital deformity that compromises its structural and functional integrity. The well-known thalidomide event, which involved several children in Europe, was a stark illustration of the dangers associated with using such a substance while pregnant. Because of its anthelminthic activity, benzimidazole is among the anthelmintics that is embryotoxic and teratogenic when administered in the early stages of pregnancy. The benzimidazole medication oxfendazole has demonstrated teratogenicity and embryotoxicity in addition to mutagenicity [3, 4, 27].

Alteration of the Normally Occurring Intestinal Flora: Regularly existing intestinal bacteria serve as a barrier to stop foreign pathogens from becoming established and spreading disease. Antibiotics may lower overall bacterial populations or kill specific species that are significant. The vast range of intestinal flora that the broad-spectrum antibiotics may adversely affect may result in gastrointestinal distress. Vancomycin, nitroimidazole and metronidazole use in humans as well as the use of medications like lunixin, streptomycin and tylosin in animals are examples of those known to have this impact [4, 8].

Economic Impact: The use of antibiotics in livestock, whether at therapeutic or subtherapeutic doses and the resulting residues in food animals, has become a global problem and cause for worry. Consuming such "compromised" food of animal origin has decreased consumer confidence and had a detrimental effect on the global economy due to the growing awareness of the risk of diseases like cancer and the distortion of the body's functional and system integrity (i.e., the endocrine, nervous, reproductive and immune systems). Additionally, the maximum residual limits (MRLs) set by Codex Alimentarius Commission (Codex) for veterinary drug residues as an international food safety standards are however not generally accepted by the committee of nations. The limitation of Codex and World Trade Organization (WTO) to enforce adoption of MRLs has resulted in differences in food safety standards across countries and nations. Such differences usually end as trade disputes leading to a gradual decline in animal and animal products exported [4].

Safety Assessment of VMPs Residue

Acceptable Daily Intake (ADI): During the evaluation of new animal drugs for food-producing animals, traditional toxicology assessments are performed to determine an acceptable daily intake (ADI) and to establish a safe concentration for veterinary drug residues in food. The ADI is an estimate of the amount of a substance, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable risk to human health [8].

Maximum Residue Limit (MRL): To ensure food quality and safety, many countries have established the MRLs of veterinary drugs in food. However, because of the differences in science, technology, economy and society, differences exist in national laws and regulation standards for veterinary drug residues in the food of animal origin. Table 4 indicates an example of Maximal residual level of chemical in tissue (synthetic antimicrobials) (mg/kg). The term MRL may be defined as the maximum concentration of marker residue (e.g., parent compound, metabolites, etc.) resulting from the use of a veterinary drug, expressed in parts per million (ppm) or parts per billion (ppb) on a fresh weight basis, that is legally permitted or recognized as acceptable in or on food. The MRL is based on the acceptable daily intake (ADI) for that compound. The ADI is a rough estimate of the daily dose of a veterinary medicine that a human can consume over their lifetime without posing a significant risk to their health, expressed on a body weight basis. It can be regarded as the safety standard for that substance [8, 13].

Calculating Withdrawal Time: The withdrawal period is the minimal interval between the last suggested treatment and the time of slaughter or collection for use as food, is at this time (e.g., milk and eggs). During this period, the veterinary drug's levels and any leftovers can fall to levels below the set MRL [8].

Reducing Drug Residues in Animal Products: Healthy and fresh edible animal products may result from proper medication use and sound veterinary procedures. However, the negative consequences of drug use, such as drug residues, continue to affect food; the levels of these residues sometimes exceed the limits of safe consumer levels. However, several drug-related factors such as drug formulation type, site and route of administration, dose and animal-related factors such as breed, age, sex and body condition, have potential effects on the pharmacokinetics and drug residue levels in milk, meat, eggs and other edible tissues [31].

Veterinarians should be updated with the latest information, to create awareness among producers and employees, as well as the general public. Moreover, avoiding unapproved or illegal drugs and practicing proper drug use and best farm and livestock management can lead to the control of drug residues. Moreover, different cooking conditions (temperature and time), fermentation and pH, play a major role in decreasing veterinary drug residues. Generally, cooking and other processes do not ensure full drug residue degradation, but can contribute to a marked decrease in concentration. Although some veterinary drug residues are reduced and degraded by processing, it is essential to perform toxicology experiments to monitor the potential adverse effects of drug residues on consumer health [7, 25, 31].

CONCLUSION AND RECOMMENDATION

A review of recent literature on the public health impact of veterinary drug residue arising from food of animal origin shows that antimicrobial drugs are frequently used in the intensive livestock production system to safeguard the health and welfare of animals and to enhance productivity. The use of these medications in food animals has the potential to leave residues which puts the consumer's health at risk. The most common causes of drug residue includes extra-label or illicit drug applications, failure to adhere to the withdrawal time, overdose and using long-acting medications. A range of measures, including improving access to veterinary services, strengthening supervision on veterinary drug production and distribution, increasing research and development efforts and enhancing animal health management, have been used to facilitate rational use of veterinary drugs, particularly antimicrobials and to reduce the public health risk arising from AMR development. Finally, it would be worthwhile to mention that the worldwide information on the extent of veterinary drug residue is generally scarce and requires great attention

Based on the findings of this review paper the following recommendation points are forwarded

- Researches on the surveillance of veterinary drug residue in food of animal origin should be conducted extensively in order to understand the national and global occurrence, distribution and extent of veterinary drug residue
- Wide range public trainings should be given to prevent the occurrence of veterinary drug residue
- Food animal production farms should be trained on veterinary drug use management including keeping the withdrawal period of medication and development of veterinary drug residue

REFERENCES

1. Etefa, M., A. F. Beyi, D. Ayana, T.J. Beyene and T.B. Tufa, 2021. "Veterinary Drug Prescribing Practices at Selected District Veterinary Clinics of Rift Valley Areas of Ethiopia," 2021, pp: 2-8.
2. Tufa, T.B., D. Ayana, F.T. Woldemariyam, E. Hailemarium, F.D. Gutema and J.A. Stageman, 2018. Veterinary medicinal product usage among food animal producers and its health implications in Central Ethiopia," pp: 1-7.
3. Yang, Y., H. Zhang, G. Zhou, S. Zhang, J. Chem, X. Deng, X. Qu, Q. Chem and B. Niu, 2022. "Risk Assessment of Veterinary Drug Residues in Pork on the Market in the People's Republic of China," J. Food Prot., 85(5): 815-827, doi: 10.4315/JFP-21-411
4. Falowo, A.B. and O.F. Akimoladun, 2019. "Veterinary Drug Residues in Meat and Meat Products: Occurrence, Detection and Implications, " Vet. Med. Pharm., vol. 3, 194, [Online]. Available: http://www.intechopen.com/books/trends-in-telecommunications-technologies/gps-total-electron-content-tec- prediction-at-ionosphere-layer-over-the-equatorial-region%0AInTec

5. Liang, C.P., C. Sack, S. McGrath, Y. Cao, C.J. Thompson and L.P. Robin, 2021. "US Food and Drug Administration regulatory pesticide residue monitoring of human foods: 2009-2017, " Food Addit. Contam. - Part A Chem. Anal. Control. Expo. Risk Assess (38) 9: 1520-1538, doi: 10.1080/19440049.2021.1934574
6. Zhang, Y., J. Lu, Y. Yan, J. Liu and M. Wang, 2021. "Antibiotic residues in cattle and sheep meat and human exposure assessment in southern Xinjiang, China, " Food Sci. Nutr., 9(11): 6152-6161, doi: 10.1002/fsn3.2568.
7. Desmarchelier, A., T. Bessaire, M. Savoy, A. Tarres, C. Mujahid, A. Beck, P. Mottier and T. Delatour, 2021. "Screening of 154 Veterinary Drug Residues in Foods of Animal Origin Using LC-MS/MS: First Action 2020.04," J. AOAC Int(104)3, 650-681, doi: 10.1093/jaoacint/qsaa168
8. Piñeiro, S.A.and C.E. Cerniglia, "Antimicrobial drug residues in animal-derived foods: Potential impact on the human intestinal microbiome, " J. Vet. Pharmacol. Ther., 44(2): 215-222, 2021, doi: 10.1111/jvp.12892.
9. Wu, Q., Q. Zhu, Y. Liu, M.A. Shabbir, A. Sattar, D. Peng, Y. Tao, D. Chem, Y. Wang and Z. Yuan, 2019. "A microbiological inhibition method for the rapid, broad-spectrum and high-throughput screening of 34 antibiotic residues in milk," J. Dairy Sci., doi: 10.3168/jds.2019-16480
10. Ma, X., L. Chen, L. Yin, Y. Li, X. Yang, Z. Yang, G. Li and H. Shan, 2022. "Risk Analysis of 24 Residual Antibiotics in Poultry Eggs in Shandong, China (2018–2020)," Vet. Sci., 9(3), doi: 10.3390/vetsci9030126
11. Jung, H.N., D.H. Park, K.H. Yoo, H.J. Cho, J.H. Shin and A.M. Abd El-Aty, 2021. "Simultaneous quantification of 12 veterinary drug residues in fishery products using liquid chromatography-tandem mass spectrometry," Food Chem., (348) September 2020, pp: 129105, 2021, doi: 10.1016/j.foodchem. 129105
12. Penagos-Tabares, F., M. Sulyok, J. Faas, R. Kriska, R. Khiaosa-ard and Q. Zebeli, 2022. "Residues of Pesticides and Veterinary Drugs in Diets of Dairy Cattle from Conventional and Organic Farms in Austria, " SSRN Electron. J., (316) January, 1-34, doi: 10.2139/ssrn.4194726
13. Monir, H.H., Y.M. Fayez, C.K. Nessim and A.M. Michael, 2021. "When is it safe to eat different broiler chicken tissues after administration of doxycycline and tylosin mixture?," J. Food Sci., 86(3): 1162-1171, doi: 10.1111/1750-3841.15640
14. Ame, N.Y. and M.M. Ame, 2022. "importance and methods of detection in Ethiopia Review on drug residue in foods of animal origin and its public healthy importance and methods of detection in Ethiopia," November, doi: 10.33545/27080013.2022.v3.i2b.78
15. Colombo, A.P.R., 2019. "Advances in the Analysis of Veterinary Drug Residues in Food Matrices by Capillary,".
16. Parmar, J.K. and K.K. Chaubey, 2021. "Assessment of various veterinary drug residues in animal originated Food Products," 14: 1650-1664.
17. Ezenduka, E.V., 2019. "Screening of antimicrobial residues in poultry meat in Enugu metropolis, Enugu State, South East Nigeria," Vet. Ital, 55(2): 143-148, doi: 10.12834/VetIt.395.1870.4
18. Shi, R., Z. Yu, W. Wu, H. Ho, J. Wang, Y. Wang and R. Han, 2020. "A survey of 61 veterinary drug residues in commercial liquid milk products in China," J. Food Prot., 83(7): 1227-1233, doi: 10.4315/JFP-20-048.
19. Ni, T., D. Peng, Y. Wang, Y. Pan, S. Xie, D. Chen, Y. Wang, Y. Tao and Z. Yuan, 2019. Development of a broad-spectrum monoclonal antibody-based indirect competitive enzyme-linked immunosorbent assay for the multi-residue detection of avermectins in edible animal tissues and milk," Food Chem., 286 December 2018, 234-240, 2019, doi: 10.1016/j.foodchem. 02.011
20. Canton, L., C. Lanusse and L. Moreno, 2021. "Rational pharmacotherapy in infectious diseases: Issues related to drug residues in edible animal tissues," Animals, 11(10): 1-32, doi: 10.3390/ani11102878
21. Singh, A.K. and A.K. Bhunia, 2019. "Animal-Use Antibiotics Induce Cross-Resistance in Bacterial Pathogens to Human Therapeutic Antibiotics," Curr. Microbiol., 76(10): 1112-1117, doi: 10.1007/s00284-019-01744-2.
22. Cramer, G., L. Solano and R. Johnson, 2019. "Evaluation of tetracycline in milk following extra-label administration of topical tetracycline for digital dermatitis in dairy cattle," J. Dairy Sci., 102(1): 883-895, doi: 10.3168/jds.2018-14961
23. Ture, M., T. Fentie and B. Regassa, 2019. "Veterinary Drug Residue?: The Risk , Public Health Significance and its Management," J. Dairy Vet. Sci., 13(2): 555856, doi: 10.19080/JDVS.2019.13.555856

24. Yoo, K.H., D.H. Park, A.A. El-Aty, S.K. Kim, H.N. Jung, D.H. Jeong, H.J. Cho, A. Hacuftuoglu, J.H. Shim, J.H. Jeong and H.C. Shin, 2021. "Development of an analytical method for multi-residue quantification of 18 anthelmintics in various animal-based food products using liquid chromatography-tandem mass spectrometry," J. Pharm. Anal., 11(1): 68-76, doi: 10.1016/j.jpha.2020.03.008
25. Gil-Gil, T., P. Laborda, F. Sanz-García, S. Hernando-Amado, P. Blanco and J.L. Martínez, 2019. "Antimicrobial resistance: A multifaceted problem with multipronged solutions," Microbiologyopen, 8(11): 1-4, doi: 10.1002/mbo3.945.
26. Iredell, J., 2019. "Antimicrobial resistance," Microbiol. Aust., 40(2): 55-56, doi: 10.1071/MA19016
27. Talebi Bezmin Abadi, A., A.A. Rizvanov, T. Haertlé and N.L. Blatt, 2019. "World Health Organization Report: Current Crisis of Antibiotic Resistance," Bionanoscience, 9(4): 778-788, doi: 10.1007/s12668-019-00658-4
28. Tabor, D. and B. Dar, 2018. "Antimicrobial residue occurrence and its public health risk of beef meat," 11: 902-908, doi: 10.14202/vetworld.2018.902-908
29. Wang, B., K. Xie and K. Lee, 2021. "Veterinary drug residues in animal-derived foods: Sample preparation and analytical methods," Foods, 10(3): 1-32, doi: 10.3390/foods10030555
30. Yoo, K.H., D.H. Park, A.A. El-Aty, S.K. Kim, H.N. Jung, D.H. Jeong, H.J. Cho, A. Hacimuftuoglu, J.H. Shim, J.H. Jeong and H.C. Shin, 2021. "Development of an analytical method for multi-residue quanti fi cation of 18 anthelmintics in various animal-based food products using liquid chromatography-tandem mass spectrometry," pp: 11, doi: 10.1016/j.jpha.2020.03.008
31. Abral, H., J. Ariksa, M. Mahardika, D. Handayani, I. Aminah, N. Sandrawati, E. Sugiarti, A.N. Muslimin and S.D. Rosanti, 2020. "Effect of heat treatment on thermal resistance, transparency and antimicrobial activity of sonicated ginger cellulose film," Carbohydr. Polym., (240) January, 116287, doi: 10.1016/j.carbpol.2020.116287