Review on Chemical and Drug Residue in Meat

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Abstract: Recently, consumers have expressed concern regarding the presence of chemical adulterants or residues, mainly antimicrobials, hormones and pesticides in animal’s meat and the health impact of drug residues in food of animal origin. The animal drug approval process worldwide is based upon the premise that the presence of drug residues in meat above tolerance is a public health hazard. Animal drug residues in animal tissues above the legal tolerance clearly have an impact on human health. Tolerances represent the maximum level of concentration of a drug permitted in animal tissues at the time of slaughter. The tolerances are intended to ensure that residual drugs will have no harmful effects if ingested. This paper describes the existing evidence for specific health hazards of certain pharmacological classes of drugs, the impact of food-borne drug residues on public health and residue detection methods. The primary focus is on possible public health consequences that may occur as a result of acute and/or chronic exposure to food of animal origin contaminated with drug residues above tolerance. Although, at present most residues of veterinary drugs occur in food at such low levels that they rarely pose a chronic or long-term health hazard to consumers, the importance of vigilance about food safety through the reduction of residues in food supply cannot be overemphasized. Food safety remains a major concern for society.

Key words: Drug residue • Hazard • Meat • Public health • Veterinary drugs

INTRODUCTION

Human beings consume protein-rich foods to supply their nutritional requirements, mainly of animal origin, such origin lying in meat from different species (cattle, sheep, caprines, birds, pigs, fish and seafood/shellfish), milk and eggs. With the exception of some products derived from fishing, these foods are obtained from financial exploitations in which the animals’ health must be guaranteed, thereby ensuring that food is harmless. In several countries the safety of such food has mainly been focused on avoiding the transmission of zoonotic diseases, less attention thus being paid to potentially present chemical residues, perhaps due to the course of the resulting disease. Infectious processes are frequently of the acute type, toxicosis caused by contaminants in foods (more than acute) may be chronic, silent and often lacking a known etiological agent [1].

The contaminants of food-stuff in the world include microorganisms and their metabolites, mycotoxins, heavy metals, nitrates, nitrites, hormones, pesticide residues, antibiotics, dioxins, polychlorinated biphenyls, genetically modified organisms, toxic pigments and melamine. Meat and meat products are integral parts of the daily diet for many people due to tradition, variety, reasonable prices, versatility and taste. It is the nutritional value of meat which distinguishes it as a beneficial component in a balanced diet. Meat provides a ready source of protein, minerals and some vitamins (B6 and B12). Meat is a rich source of many nutrients per unit energy; therefore, emphasis should be placed on the importance of meat safety for human consumption [2].

Drug residues could result from chemotherapeutic or chemoprophylactic use of drugs in food animals. The presence of this residue in meat and offal may result from incorrect usage of drugs [3]. This occurrence of residue in animal food products has received enormous worldwide attention from some local, international and public health agencies [4]. Some drugs are quickly excreted from the animal, others are not readily metabolized or excreted and so, their residues will persist in the animal tissues and hence enter the human food chain constituting health...
The presence of antibiotics in beef meat is associated with several adverse public health effects including hypersensitivity, tissue damage, gastrointestinal disturbance and bacterial resistant strain [6]. The use of veterinary drugs in developing countries is likely to rise as a result of increased production and availability of drugs through imports from developed countries [7]. In addition, the use of drugs in the markets is likely to increase as their application can significantly raise animal-borne food production levels [8].

The European Food Safety Authority has recently issued an opinion on the effect of residues in meat and reflected that epidemiological data provided evidence for an association between some forms of residues dependent cancers and meat consumption [9]. The presence of these residues and its associated harmful health effects on humans makes the control of veterinary drug residue an important measure in ensuring consumer protection. Therefore the objectives of this paper are:

- To highlight the source of chemical residues and its public health importance
- To describe methods used for detection of residues in meat.
- To review prevention and control of residues in a meat of animal origin.

Source of Chemical Residues in Meat: The chemical substances to which animals may become exposed during their production cycle which have been identified to date could come from drugs and growth promoters aimed at treating diseases and improving production parameters, biologically-derived toxins (mycotoxins, phycotoxins, phytotoxins) and/or environmental contaminants linked to atmospheric pollution, from the soil and/or water [1].

Therapeutic Veterinary Drugs: Veterinary drugs are used to treat disease and improve health in animals as pharmaceuticals are in humans. They include a large number of different types of compounds. The most likely cause of violative drug residues is the failure to observe withdrawal periods [10-13]. The other causes for the presence of drugs residues in food of animal origin are improper maintenance of treatment records or failure to identify treated animals adequately that may lead to their omission [14], overdosing and use of banned drugs for treatment of economic animals [15]. The residues of these drugs may also originate from contaminated animal feedstuffs [16].

Antimicrobials: The discovery and development of the first antibiotics prior to the Second World War have played an important role in veterinary and human medicine [17]. Antimicrobials are classified according to their chemical structure. Each class is characterized by a typical core structure and the various members of the class are differentiated by the addition or removal of secondary chemical structures from the core structure [18]. The most commonly used antimicrobials in food-producing animals are \( \beta \)-lactams, tetracycline, amino glycosides, lincosamides, macrolides, pleuromutilins and sulfonamides. They are administered to animals by injections (intravenously, intramuscularly, or subcutaneously), orally in feed or water, topically on the skin and by intramammary and intrauterine infusions [19]. Subcutaneous and intramuscular administrations increase the potential for residues at the injection sites [20, 21].

Fecal recycling, where the drug excreted in feces of treated animals contaminates the feed of untreated animals, can be the cause of residues of certain antimicrobial groups. Housing of unmedicated animals in boxes where animals had previously been treated orally with sulfamethazine resulted in residues in urine, kidney and diaphragm. Volatile drug residues can also occur as a result of improper use of a licensed product or through the illegal use of an unlicensed substance. Extra label dosages and use of drugs which have not been approved for the species in question may lead to volatile residues [22-23].

Fig. 1: Classification of antibiotic residue present in food of animal origin

Source: [24]

Parasitic Drugs: Parasitic helminth infection affects food producing animals worldwide. Example; Ivermectin is a broad-spectrum macrocyclic lactone endectocide and is widely used for the treatment and prevention of both nematode and arthropod parasites in food-producing animals. Ivermectin has been shown to be effective in the treatment of Ascardia columbae and Capillaria spp. in pigeons [25]. Ivermectin is lipophilic and residues will be
found in the tissues of the treated animal, particularly in those with a high fat content. The meat withdrawal time of ivermectin in mammalian livestock is long [26].

**Growth Promoters:** In recent years, hormones and hormone like substances have been recently used in livestock production to obtain a high yield performance in a shorter period of time. Many endogenous steroids, including their semi-synthetic and synthetic analogues, have been produced and administered to animals to improve growth of animals for food production, storing protein, to decrease fatness, as well as to regulate and enhance fertility [27]. However, depending on the use of anabolic agent in animal feed, anabolic residues may occur in meat and meat products that present risks to the consumer [28].

**Mycotoxin:** These substances are characterized by acute and chronic toxic properties, while some of them are potent carcinogens. Although animals are an effective toxin eliminator, residues of mycotoxin can still be present in animal tissue [29]. Mycotoxins are secondary metabolites from fungi, mainly from the species *Aspergillus*, *Fusarium* and *Penicillium*, aflatoxins, ochratoxins, zearalenone, trichotheccenes and fumonisins having been the most studied to date [1].

**Heavy Metals:** Cattle and other ruminants graze freely on environment and drink water from ponds, streams, rivers and other possible contaminated water sources. Animals in this process may be exposed to high levels of these metals in the environment [30]. Contamination by heavy metals has recently become a major international concern due to the industrial revolution. Heavy metal pollution in rural areas is due to disposal of industrial effluents and sewage sludge on pastures grasses or forages which causes problem for grazing animals [31]. With respect to human health impacts, cadmium, copper and mercury are of primary concern because of their known toxicity to human being [32].

**Pesticides:** Most pesticides are administered topically, allowing some amount of percutaneous absorption and sequestration in edible tissues. They can be absorbed by all routes, including inhalation, ingestion and dermal absorption. Example Lindane has been detected in the fat deposits of sheep dipped in a 0.0125% lindane emulsion 12 weeks after topical exposure. A large number of pesticides may potentially be used in the production of agricultural crop commodities, leading to indirect exposure of animals through feed and the potential for residues in animal products. It has been estimated that about three million cases of pesticide poisoning occur worldwide each year, with 220,000 deaths [33].

Pesticides can be taken up by livestock in their feed or water and may be incompletely eliminated at the time of slaughter [34, 33]. These compounds tend to accumulate in body tissues in varied concentrations and they are resistant to chemical or biological degradation and persist in the environment for a considerable period of time. Fat solubility of these compounds is responsible for their varied concentrations in tissues and their accumulation in the lipoproteins of the cell membranes, thus changing their structure and permeability [35]. The accumulation of pesticides in the liver may be as much as 100 times higher than other body tissues [36].

**Methods of Residues Detection in Meat:** Detection of drug residues from tissues and other animal products could be quite an expensive, time consuming and laborious venture. Typically, muscle, liver, kidney and fat are analyzed because they are the tissues that are storage points for fat-soluble residues, or tissues that metabolize the major portion of the drug in the process of body elimination (microbiological methods are quite suitable for the detection of antimicrobial residues especially as they are less expensive than immunochemical and chromatographic methods) and are able to screen a large number of samples at minimal cost [37].

**Microbiological Assays:** The microbiological methods used for detecting antimicrobial residues in foodstuffs are based on inhibiting microbial growth, microbial receptor activity and enzymatic reactions. Microbial inhibition assays involve culturing a microorganism from a standard strain, usually Bacillus stearothermophilus, Bacillus subtilis, Bacillus cereus, Micrococcus luteus, Escherichia coli, Bacillus megatherium, Sarcina lutea and/or Streptococcus thermophilus [38].

**Immunological Techniques:** 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-immunosorbent assay and the detection system is usually based on enzyme-labeled reagents. ELISA kits have shown good performance for the analysis of antibiotic residues in meat especially for tylosin and tetracycline [39, 40].
There are different formats for antigen quantification like the double antibody or sandwich ELISA tests and direct competitive ELISA tests. Radioimmunoassay is based on the measurement of the radioactivity of the immunological complex [41].

**Biosensors:** Biosensors are used for a large number of applications within biotechnology, including the pharmaceutical industry and life sciences. Biosensors have been developed in recent years as an alternative approach to screen veterinary drugs in meat. In general biosensor is an instrument combining, in close contact, a recognition element with an antibody/antigen pair, a receptor and its specific ligand, or even living cells and an analyte that binds specifically to them [42]. The biochemical signal of biosensors are converted by a transducer into an electronic signal. Then, these signals are processed by a microprocessor that gives the final result [43].

Biosensors are designed to operate in real time and be able for the simultaneous detection of single or multiple veterinary drugs residues in a sample at a time [44]. The primary limitation of biosensors is the uncertainty of the biological sensing element. For instance, the sensing mechanism may be affected by duration of use, type of molecules and/or environmental factors (pH, temperature and ionic strength). Another restriction of biosensors is the transducer size within the biosensors [45]. In general these new technologies are getting good reception in control laboratories due to the reduction in total time and possibility to analyze simultaneously multiple residues in short time for a large number of samples [46].

**Liquid Chromatography:** Liquid chromatography has been applied successfully for the qualitative and quantitative detection of multi-residues in food samples even though its use has rapidly decreased during the last decade [48]. This technique can be done a separation method in which the substances are injected in the LC system when the mobile phase (liquid solvent) carries the sample, which is separated in a stationary phase (chromatographic column). Chromatographic process occurs as a result of interaction and affinity during the movement of the analytes along the stationary phase [49]. The information obtained from this technique can be useful for identification purposes and for determining the amount of an analyte [50]. Therefore, it is desirable to be able to generate structural information of chemical residue from such techniques [49, 50].

**Public Health Importance:** Worldwide national and international public health agencies have a deep concern about the presence of drugs residues in meat and edible viscera of food producing animal. Drug residues that persist in edible tissues may become introduced into the human diet as a consequence of the farmer’s negligence to observe the withdrawal period for the drug(s) and/or applying drugs incorrectly to animal [51, 3].

Drugs used in food animals can affect the public health because of their secretion in edible animal tissues that are intended for human consumption [52, 53]. There are several channels through which drug residues can cause adverse effects on human which include development of resistant pathogens that may be directly transmitted from animals to humans [54], hypersensitivity reaction [55], effects on intestinal microbiota and the immune system are important [56, 57].

![Fig. 2: Schematic representation of the configuration of a biosensor](source: [47])
Development of Resistant Strains: Some study have shown that exposure to antimicrobial residues in food of animal products could result to the transfer of resistant strains of microorganisms to humans [58, 59]. Resistant microorganism can get access to human, either through direct contact or indirectly via meat or other animal product and it has been documented that human develop drug resistant bacteria such as salmonella, campylobacter and staphylococcus from food of animal origin [60]. The emergence of fluoroquinolone resistant Campylobacter is one of several bacterial species that cause food poisoning in humans [61] and Antibiotic resistance in E. coli is widespread globally, with agents such as penicillin that found decreasing efficacy against it (Heritage et al., 2001). Generally, the resistance of microorganisms arising from sub-therapeutic of penicillin, tetracycline and sulfa drugs in agriculture is suggested by the WHO to be high priority issues [62].

Hypersensitivity Reaction: Hypersensitivity reaction following administration of drugs may include anaphylaxis, serum sickness and cutaneous reaction that occur more commonly in response to administration of antibiotics especially penicillin [63]. About ten percent of human population is considered hypersensitive to an amount of substance, including penicillin, but in animals, the extent of hypersensitivity to drug is not well known [64].

Carcinogenic Effect: Some scientific reports stated that the highest rates of hormone related cancer, including cancer of breast, ovary, prostate, testes and colon were found where hormone treated meat is consumed. In light of the carcinogenic potential of drugs’ residues and obvious human health risks, the European Community forbade the use of steroids as growth-promoting agents in livestock breeding [65].

Teratogenic Effect: The well-known thalidomide incident involving a number of children in Europe is a direct testimony to the hazard that may occur when such agent is administered during pregnancy [65]. From the anthelmintic, benzimidazole is embryo toxic and teratogenic when given during early stage of pregnancy because of the anthelmintic activity of the drug [66].

Other Harmful Effects: Hazards of chloramphenicol observed in association with clinical use in humans include dose-related, reversible suppression of the bone marrow, gray baby syndrome, which is a circulatory collapse in children less than 30 days on high doses and irreversible, idiosyncratic, non-dose related aplastic anemia [1, 56]. Aplastic anemia can occur in susceptible individuals exposed to concentrations of chloramphenicol that might remain as residues in edible tissues of chloramphenicol-treated animals [67]. Aminoglycosides can produce damage in urinary, vestibular and auditory functions (Shaikh and Allen, 1985). Toxic and allergic reactions in humans and animals caused by tetracyclines have only been observed at therapeutic doses [21].

Control and Prevention: Although public awareness of the drug residue problem in food is high and several governmental agencies spend large amounts of time attempting to control this problem, residues in animal tissues are still an important concern today [68]. Quality traits of meat comprise hygienic aspects in relation to safety and toxicology (presence of undesirable microorganisms or residues such as antibiotics, hormones or chemical contaminants), nutritional value and technological and sensory attributes [69].

When the animal is slaughtered or its edible products are collected, there is 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. In order to safeguard human health, WHO and FAO have set standards for acceptable daily intake and maximum residue limits in foods [70]. In many countries of the world, this upper level is referred to as the maximum residue level (MRL), while in United States it is termed as tolerance [71]. According to the European Union’s definition, the MRL is the maximum legally acceptable amount of pharmacologically active substances or degradation products and their metabolites in foodstuffs originating from animals. The purpose of the MRL is to limit the exposure of consumers to residues of medicines used in food animals, to concentrations that do not pose human health risk [72]. The MRL or tolerance is the target concentration in a residue-depletion study. It should be established purely on the basis of safety to the person consuming the product and has no pharmacodynamic reality in the animal to which the drug has been administered [73].

Withdrawal Period: is a time allowed for residues to deplete to safe levels (tolerances). Withdrawal period is the time between the last dose of the administered drug and the time when the animal can be safely slaughtered for food and it promote consumer safety by certifying that the MRL is not exceeded. They also ensure reinforced safety in case when the MRL is not met [74].
The Food Safety and Inspection Service (FSIS) is a branch of the US Department of Agriculture (USDA) that monitors and investigates conditions in slaughter plants by taking tissue samples from slaughter plants and analyzes them for chemical residues and then it may recommend that carcasses or products found in violation are condemned and destroyed. Generally control and prevention of residues can be resolved by taking into consideration three steps i.e. risk assessment, risk management and risk communication. HACCP systems are increasingly used to replace or supplement traditional meat inspection and end-point sampling. Livestock producers and veterinarians must be aware of these changing requirements for farm-animal food safety. The applications of GMPs and/or HACCP at the farm or the slaughterhouse require a level of management sophistication that usually is not available in developing countries [75]. For the effective prevention and control of residues establishments that slaughter certain categories of food animals must address chemical residues within their HACCP system [76].

To prevent international trade barriers associated with drug residues in beef, the conditions must be implemented include standardization of testing methods used to detect drug residues, standardization of methods for determining minimum residue levels and establishment of active surveillance programs to monitor residues [20].

**CONCLUSION**

Consuming food contaminated by chemical substances could lead to chronic exposure leading to the presentation of diseases lacking an apparent cause and being difficult to diagnose. Foods of animal origin presuppose the risk of contamination, whether from drugs and growth promoters used for optimizing livestock production systems, or with biological toxins present in food ingested by animals. It is thus necessary to control these substances in foods, thereby supposing technological and institutional efforts sanitary authorities must thus promulgate and ensure compliance with standards and guidelines concerning the production of harmless foodstuffs. Achieving such objective represents a great challenge for underdeveloped and developing countries due to institutional difficulties and the limited availability of equipment and qualified personnel. All nations must make it a priority to try to ensure the safe consumption of foodstuffs by their populations, exercising strict sanitary control aimed to avoid problems of health in the population and preventing the appearance of new problems affecting the development of the agro-food industry and global trade in foodstuffs.

Based on the above conclusion the following recommendations are forwarded;

- Drugs should be used properly in relation to their dose, site of administration, withdrawal period and implanted by appropriate professionals.
- Testing for drug residues must be done at meat distribution centers and farmers must be aware of drug residues on human health.

**REFERENCE**

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