

# New Class of Antibiotic residues in food producing animals: pharmacological and toxicological risks

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**Abstract**— Spread of these concerns are related to the use of antibiotics in food-producing animals for therapeutic, prophylactic, and growth promotion purposes, leading to significant concerns about the presence of antibiotic residues in foods of animal origin. The presence of trace amounts of antibiotics in meat, milk, eggs, and other animal products is a significant issue in pharmacology and toxicology for human health. The toxicological effects of the antibiotic residues have been linked with prolonged consumption and include hepatotoxicity, nephrotoxicity, reproductive toxicity, immunotoxic effects, carcinogenicity, and developmental toxicity. Antibiotic residues are also a key driver in the emergence, and spread of antimicrobial resistance (AMR), a current global health crisis impacting human, animal and environmental health. Non-compliant drug use by veterinarians, lack of proper withdrawal periods and monitoring systems all affect the persistence of drug residue. Liquid chromatography and mass spectrometry are becoming more often used advanced analytical techniques to detect and quantify veterinary drug residues in foods with a high level of accuracy. To limit residue contamination and maintain food safety, effective regulation, surveillance programs, antimicrobial stewardship and using alternative disease control strategies in livestock production are important. The knowledge about the pharmacological and toxicological effects of antibiotic residues is still basic for the prevention of public health risks and optimizing animal production systems.

**Keywords** — Antibiotic residues; Food-producing animals; Antimicrobial resistance; Toxicological risk; Food safety; Veterinary drugs; Public health.

## INTRODUCTION

The extensive use of antimicrobials for therapeutic and growth-promoting purposes has resulted in the persistent presence of antibiotic residues above permissible levels in meat, milk, and other animal-origin products, including processed foods, many developing countries. These residues pose a risk to human health, contributing to the development

of antimicrobial resistance, provoking hypersensitivity reactions, and potentially causing carcinogenic effects. Regions with inadequate detection facilities and residual monitoring systems, such as South Asia and Africa, face heightened risks from antibiotic contamination in food (1). The irrational use of antimicrobials, including failure to observe withdrawal periods following treatment exacerbates the problem. Widely detected antibiotics include amoxicillin, tetracycline, and ciprofloxacin in poultry meat and eggs (2,3). Antibiotic residues represent but one facet of the broader challenge of antimicrobial resistance across the food chain. The indiscriminate use of antibiotics in food animals and aquaculture, coupled with their misuse in human therapies, exerts selective pressure fostering resistant strains capable of commandeering pathogenicity islands and moving directly from the farm to humans (4). Resistant organisms originating from feed, soil, water, manure, contaminated equipment, and other sources have been detected in vertebrate intestinal microflora, influencing human exposures and potentially compromising the efficacy of vital therapeutic agents. Unlike other chemical residues, food-borne residues of antimicrobial substance together with antibiotic-bearing products undelivered to slaughter houses can promote co-selection for resistance to unrelated antimicrobials (5).

## Pharmacology of Antibiotics Used in Food-Producing Animals

Antibiotics approved for food-producing animals mainly comprise  $\beta$ -lactams, tetracyclines, macrolides, sulfonamides, and fluoroquinolones. These pharmaceuticals serve to enhance feed efficiency and promote growth and productivity and also to prevent and treat bacterial infections. Collections of approved classes span animal species and application contexts; the National Food Safety Standard lists 29 antibiotics with Maximum Residue Limits (MRLs) in food. MRLs and withdrawal periods for drugs and classes in specific species prevent or contain residues in edible tissues while providing empirically supported technical advancement (6,7).

Antibiotics combat bacterial infections by disrupting synthesis of the cell wall ( $\beta$ -lactams), protein (tetracyclines,

macrolides, and sulfonamides), or nucleic acid (fluoroquinolones) or by interfering with metabolic functions (sulfonamides). Drugs in each class share low acute oral toxicity (informal estimate  $LD_{50} > 300$  mg/kg). Administration routes vary according to species, environments, and enterprises; injection (subcutaneous or intramuscular) is the most common method animal health uses and one that generates consistent collections of pharmacokinetic data. Routes of administration affect delivery, retention, and ultimate residues in edible tissues, but limited data exist for several classes, species, and preparations. All antibiotics are regulated and guided by various national standards, including MRLS, withdrawal times, veterinary prescription, and approval and safety requirements (8).

### **Mechanisms of Residue Formation and Dispersion**

Amino acids, carbohydrates, vitamins, hormones, minerals, and pharmaceuticals such as antibiotics are incorporated into feedstuffs for livestock (9). The uncontrolled use of these compounds can lead to unacceptable levels of residues in food products of animal origin. Food residues arise mainly from the administration of veterinary drugs and agrochemical products, which are either intentionally or inadvertently applied during production, storage, distribution, processing, and preparation. Antimicrobials contribute to these food residues, and since humans are continuously exposed to various residues through the consumption of treated animal products, the possibility of a risk to human health cannot be overlooked (10).

Pharmaceuticals such as  $\beta$ -lactams, tetracyclines, macrolides, sulfonamides, and fluoroquinolones are often administered in animal husbandry to improve health, control disease, or for growth promotion. The use of these compounds unambiguously raises the risk of contamination, in an era of widespread concern over antimicrobial resistance among human pathogens (11).

Antibiotic residues can occur in edible tissues and fluids from food-producing animals because of absorption, metabolism, and excretion. Residues present in animal by-products may enter the human food chain via the consumption of milk, eggs, or meat, resulting in exposure to veterinary medicines that could potentially affect human health. Examples of such cases include the excretion of tetracycline in milk,  $\beta$ -lactam antibiotics in chicken egg white, and the deposition of the long-acting sulfonamide sulfadimidine in liver, kidney, and muscle after intramuscular injection in pigs (12).

### **Toxicological Risks in Humans**

Acute Toxicity: wide-ranging adverse effects of antibiotics can occur at different levels of exposure and vary depending on the route of administration. They include disturbances in the central nervous system (CNS), increased excitability, seizures, arrhythmias, respiratory depression, increased heart and respiratory rates, overheating, nausea, vomiting, and various hypersensitivity reactions. The quantity ingested and the individual's predisposition are the two key factors determining the type and severity of these responses.

Moreover, it has been reported that children are especially vulnerable to acute poisonous concentrations of antibiotics. For most antibiotics, the quantity that constitutes the threshold for acute toxicity remains an unknown factor. Hence, it is advisable to assume that any detectable residue constitutes a risk, particularly in the young and elderly population groups (13,14).

Chronic Health Effects range of chronic effects known to occur after prolonged or repeated exposure to low levels of antibiotics could derive from extra-origin exposure to such compounds via the food chain. Although the presence of a particular antibiotic in food at a given concentration may be tolerated for long periods without evident deleterious effect, it must be emphasized that certain chronic effects start to appear after the animal has been weaned and feeding is continued on a solely animal-origin diet, highlighting the close attention required for the issue of residual antibiotics in animal-derived food. Furthermore, such chronic effects may involve only one organ or activity, while subclinical effects such as those affecting the immune system or reproductive organ could go unperceived by the consumer. Any of these chronically conditioned effects could then be subject to accelerated development through the consumption of a food concurrently contaminated with any one of the other currently widespread industrial pollutants entering the food chain (15,16).

development of antimicrobial resistance The evolving global health threat posed by antimicrobial resistance has been widely recognized. In the context of antibiotic residues in food animals, the major question concerns the potential that their consumption initiates, maintains, or augments resistance to the corresponding therapeutic agents. Although the risk of developing resistance in humans through food remains uncertain, selection pressure can occur through both treatment and subtherapeutic concentrations. The consumer can become infected by resistant bacteria through 1-direct contact with foodstuffs containing resistant bacteria; 2- contact with contaminated food products or surfaces in the food industry; and, 3-the overall ecology of the food chain (17).

### **Acute Toxicity**

Foodborne illness outbreaks, a significant public health concern, caused over 400,000 fatalities globally in 2010 and have taken a heavy toll on livestock production and trade. Toxicological risks to consumers from antibiotic residues in food-producing animals represent an important one. Antibiotics can elicit immediate and chronic adverse effects in humans, as well as favour the emergence of antimicrobial resistance. The human population is exposed to veterinary antibiotics through contaminated food products (e.g., milk, meat, and eggs) consumed on a daily basis (17). Legislative initiatives worldwide urgently call for better knowledge of their pharmacology, toxicological properties, and epidemiological relevance. The risk of acute toxicity depends on the amount of hazardous substances to which an individual is exposed. From the investigations in animal models, guidance values and other information on antibiotic toxicity and exposure pathways are available. Therefore, a crucial aspect of the evaluation of the potential risks due to the

presence of antibiotic residues in food-producing animals relates to the characterization of their toxicity in human subjects. There are three principal conditions for acute toxicity, namely, clinical manifestations appear shortly after an adverse change is triggered; reversible effects often remain even if the change is not getting worse; and only one single exposition is needed. Such damaging effects, their dose ranges, the duration in susceptible populations, and other additional information (18).

### **Chronic Health Effects**

Antibiotic residues in food-producing animals may have long-term health effects on humans. The organs most frequently affected are the kidneys, liver, brain, and reproductive organs. Although the concentration is usually low, chronic exposure can lead to progressive, subclinical impacts. At concentrations too low to have a direct effect, residues can act synergistically with other contaminants. Because residues accumulate in the food chain, considerations of a single product are insufficient. The relationship between dose and effect varies between species, necessitating the evaluation of human exposure. Broader exposure assessment is needed when multiple animal products are consumed (19).

Chronic exposure to antibiotic residues in animal-derived products is of increasing concern. Potential effects include allergenic responses, mutations, alterations of the intestinal microbiome, and the emergence of multi-resistant pathogenic germs. Exposure above a defined threshold increases the risk of adverse effects (20).

### **Development of Antimicrobial Resistance**

The widespread use of antimicrobials in food-producing animals is known to contribute to the selective pressure driving the development of resistant bacterial strains: residues of these agents, detected in the gastrointestinal tract of humans, have been shown to facilitate the emergence of resistant strains and to reduce the therapeutic efficacy of critically important antimicrobials; non-human environmental reservoirs additionally provide an avenue for transmission to humans. Such occurrences are evidenced in food products, water, and various materials along the food supply chain and pose an ecological risk, as residues in faeces upon disposal can perpetuate the selection of resistance within the food chain (21,22). For most active ingredients used in food animals, the vast majority of resistance mechanisms linked to their residues in humans and the relevant transmission routes remain unidentified (23,24).

### **Analytical Methods for Detection of Residues**

Antibiotic residues are a global concern, and robust analytical methods for their determination are essential to monitor compliance with product specifications (25).

Antimicrobials have a wide variety of structures and chemical properties. Public health concern over residues of antibiotics in food is real, as these compounds can pose an acute risk by virtue of their inherent pharmacological activity or can impact consumer health owing to their ability to select for resistant pathogens that can be transferred from animals to

humans. Antibiotics used for disease treatment and control in food-producing animals (including aquaculture) must be precisely regulated, as the incorrect use or overuse of these drugs can lead to their persistence in, and the contamination of, food products (26). The identification of hazardous substances and the assessment of their toxicological impact on human health are essential to safeguarding food safety.

### **Regulatory Frameworks and Compliance**

The production and consumption of food products derived from food-producing animals are tightly linked with the potential presence of antibiotic residues in such products. Antibiotic residues in food products can represent pharmacologically active above-threshold concentrations of an antimicrobial substance in animal-derived products. Pharmacokinetic processes such as absorption, distribution, metabolism, and excretion ultimately govern the formation of such residues. Furthermore, humans can be exposed to these veterinary antibiotic residues through the consumption of contaminated foodstuffs designated for human use (27,28).

Antibiotics are frequently administered to food-producing animals for therapeutic, prophylactic, or growth promotion purposes. Sensitivity to antibiotic residues in food, whether acquired naturally or through non-therapeutic exposure, constitutes a serious public health concern (28).

Traces of  $\beta$ -lactams, tetracyclines, macrolides, sulfonamides, and fluoroquinolones have already been observed (28). When these substances reside at concentrations above the established safety threshold, they trigger issues beyond merely safety, including the choice of restricted medicines or the withdrawal of specific foods from distribution.

### **Risk Assessment Approaches**

An overall risk assessment considers various aspects of risk, including hazard identification (linking hazard to adverse effect), exposure assessment (linking environmental concentrations to intake), toxicological characterization (linking intake to likelihood of effect), uncertainty analysis (quantifying uncertainty in the above steps), and risk characterization (consolidating outputs of the above analyses with a description of uncertainties). Probabilistic approaches quantify uncertainty and produce overall risk estimates under varying exposure (e.g., route, concentration, and frequency) and take into account co-exposures (29,30). Scenario-based approaches evaluate the impact of particular interventions, continue to be used widely, and can readily incorporate explicitly qualitative information. Risk communication illustrations include safety alerts, consumer information sheets, trade advice documents, and awareness-raising materials (31,32).

### **Mitigation Strategies in Animal Husbandry**

Regular veterinary oversight to inform and validate the appropriate use of antibiotics in animals and adherence to established withdrawal times are essential to minimizing residue. Given the potential toxicity of residues,

veterinary guidance is particularly important in cases where an antibiotic has been used contrary to label instructions (33,34).

North American poultry farmers have benefited from vaccination programs targeting common diseases; similar programs exist in other sectors. Implementation of improved sanitation practices has successfully reduced ponding or pooling of contaminated water in floor-space feedlots and reduced disease in established flocks (35,36).

Alternative therapies such as bacteriophages and probiotics have been proposed as mechanisms to decrease the likelihood of high-level infections requiring treatment with growth-promoting or disease-controlling antibiotics (37).

Additional strategies include maximization of farm occupancy in free-range systems, which reduces the introduction of antibiotic-resistant strains, and a more gradual approach to the expansion of new production systems. Other online resources offer guidance on combining the recommendations outlined above with management of water quality, feed formulation, biosecurity, animal-health monitoring, and prevention of cross-communication between animal populations (38).

### **Public Health Implications and Policy Considerations**

Antibiotic residues in food-producing animals pose a significant public health risk that necessitates policy interventions at both national and international levels. Consumers worldwide are constantly exposed to such residues through the food chain, which raises important questions about both food safety and food supply chain integrity. In this context, “residue” refers to leftover quantities of pharmacologically active substances (the active moiety) and/or biotransformation products following the use of veterinary drugs in animals (39). These substances can adversely affect human health, and unequal access to safe food has ethical implications that are unacceptable in light of international human rights treaties. Addressing these policy considerations at an early stage ensures that attention is given to the social and geopolitical aspects of antibiotic contamination of animal-derived foods (39).

Antibiotic residues in food-producing animals also raise equity concerns for several reasons. First and foremost, equitable access to safe food is compromised where, on the one hand, antibiotic residues in food of animal origin are rampant and, on the other hand, food security has not been achieved. Second, together with injustices in wealth distribution and variations in negotiation capacities, the lack of harmonization in national food safety standards affects international trade and, consequently, the affordability of food items in import-dependent countries. Moreover, low-income households are more likely to seek food from dubious sources at retail markets where compliance with food safety standards is less likely. Food from animals raised in unregulated settings, whether domestically or abroad, is more likely to be contaminated. Finally, the emergence of antibiotic-resistant bacteria is disproportionately affecting poor countries, further limiting access to effective curing agents and increasing reliance on antibiotics in food production. These dimensions call for public health messaging that does not further

marginalize at-risk populations while staying clear of dictating the adoption of specific regulatory measures (38,39).

### **Knowledge Gaps and Future Research**

Contemporary literature presents substantial literature on the pharmacology, residues, and toxicological risks of antibiotics used in food-producing animals; however, critical knowledge gaps persist. Fundamental pharmacokinetic data regarding many active substances, particularly concerning the formation of by-products and the metabolites generated during the biotransformation process, remains insufficient and needs to be addressed as a priority. It is also vital to assess how the simultaneous presence of other environmental contaminants influences the kinetics of antibiotic residues and their metabolites, as well as to analyse at-risk population exposure to these substances through the food chain. Progress in analytical chemistry permits the detection of multi-residues by means of advanced methodologies capable of characterizing an extensive list of substances and their metabolites (40,41). Although risk characterization in regard to concentration levels is often carried out in scientific circles, public authorities have refrained from undertaking probabilistic modeling to characterize the hazard-to-exposure relationships pertaining to food contaminants in a systemic and comprehensive manner. Efforts aimed at estimating how risk perception varies across socio-economic and educational strata have received scant attention (42). The full scope of the antimicrobial resistance phenomenon lies beyond documented facts; systematic characterization of the modes and routes of entry of resistant bacteria into the human food chain has not yet been undertaken. Neither has research elucidating how existing resistance interferes with the efficaciousness of critical therapeutic classes aimed at specific priority groups in human medicine. Further, the determinants governing the proliferation of residues within the environment throughout the various stages of the agricultural cycle from post-treatment to disposal of animal waste have yet to be explored (43,44).

### **Conclusion**

Antibiotic residues originating from veterinary use in food-producing animals remain an important public health concern. These residues can persist in meat, milk, eggs, and other animal-derived products, leading to human exposure and contributing to the emergence and spread of antimicrobial resistance (AMR). Recent evidence indicates increasing detection rates of antibiotic residues in food products, particularly in regions with inadequate surveillance and regulatory control. Exposure to such residues may cause adverse health effects, including allergic reactions, toxicity, and disruption of normal microbiota. To minimize these risks, prudent antibiotic use in veterinary practice is essential. Key preventive measures include prescribing antibiotics only when necessary, strict adherence to withdrawal periods, implementation of effective farm hygiene and biosecurity measures, and strengthening residue monitoring programs. Enhanced regulation and surveillance are crucial to reduce antibiotic contamination in the food chain and to preserve the effectiveness of antimicrobial agents.

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