Journal of Natural Science Review

Vol. 3, No. 1, 2025
https://kujnsr.com
e-ISSN: 3006-7804

Residue and Human Risk: A Reassessment of Aminoglycoside Residues in Edible Tissues

Farid Ahmad Tanin

Kabul University, Department of Clinical Pharmacy, Faculty of Pharmacy, Afghanistan

✉E-mail: faridtanin@yahoo.com (corresponding author)

ABSTRACT

Aminoglycosides are a group of antibiotics widely used in both human and veterinary medicine, primarily for the treatment of bacterial infections. These drugs, including gentamicin, neomycin, and tobramycin, are poorly absorbed when taken orally and are therefore primarily administered via injection, although oral formulations are also available for the treatment of certain enteral infections. The primary concern with the use of aminoglycosides in veterinary medicine, especially in food-producing animals, is the potential risk for drug residues in products such as meat, milk, and eggs, staples of the human diet. Antibiotic residues can be harmful to humans, potentially causing adverse effects or contributing to antimicrobial resistance (AMR). However, the pharmacokinetics of aminoglycosides, particularly their limited absorption when ingested orally, raise significant questions about the justification for current withdrawal times. Since these drugs are poorly absorbed by the gastrointestinal tract, the risk of residue accumulation capable of producing adverse effects in consumers is minimal. The aim of this review is to investigate whether current withdrawal times for aminoglycosides, particularly when residues are ingested orally by humans, are scientifically justified. The review evaluates the pharmacokinetic profiles, regulatory guidelines, and the associated risks of drug residues from oral exposure. The findings suggest that the risk of residue-induced adverse effects is negligible, as oral aminoglycosides are poorly absorbed and primarily act locally within the gastrointestinal system. Therefore, the review argues that current withdrawal times may be unnecessary and need to be reevaluated. Further research on residue persistence in food products following oral administration is necessary to optimize withdrawal guidelines.

ARTICLE INFO

Article history:

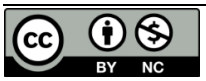
Received: February 8, 2025
Revised: March 17, 2025
Accepted: March 26, 2025

Keywords:

Aminoglycosides; Drug residues; Food safety; Pharmacokinetics; Toxicity risks; Withdrawal Periods

To cite this article: Tanin, F. A. (2025). Residue and Human Risk: A Reassessment of Aminoglycoside Residues in Edible Tissues. *Journal of Natural Science Review*, *3*(1), 15-29. DOI: https://doi.org/10.62810/jnsr.v3i1.187

Link to this article: https://kujnsr.com/JNSR/article/view/187



INTRODUCTION

Veterinary drug residues in food products are indeed a significant concern for food safety and public health. The presence of these residues can lead to various issues in humans (Arsène et al., 2022). Exposure to high levels of drug residues can lead to toxic effects, depending on the

pharmacological properties of the drug (Colopi et al., 2024). For example, some drugs can accumulate in some organs such as the liver or kidneys, potentially causing cellular damage (Beyene, 2015). Residues of certain anti-inflammatory drugs (e.g., phenylbutazone) have been linked to blood disorders and other toxicological risks (Worboys & Toon, 2018).

Prolonged exposure to antibiotic residues in food may contribute to the development of resistant bacteria (Menkem et al., 2019). Antibiotics can exert selective pressure on microbial populations, favoring the growth of resistant strains (Tello et al., 2012). Over time, resistant bacteria in the gut microbiota may transfer resistance genes to pathogenic bacteria via mechanisms such as horizontal gene transfer (McInnes et al., 2020). This process can compromise the efficacy of antibiotic treatments for bacterial infections, posing a significant public health challenges (Mancuso et al., 2021). The issue is particularly concerning in foods like meat, milk, and eggs, which are susceptible to contamination during production if withdrawal periods are not properly followed (Kan & Meijer, 2007).

Certain individuals may develop allergic reactions to drug residues present in food (Herago, 2021). While rare, these reactions can range from mild hypersensitivity symptoms (e.g., skin rash) to severe anaphylactic responses (Bumbăcea et al., 2024).

Residues of antibiotics in food, even at low levels, can disrupt the delicate balance of the human gut microbiota (Ben et al., 2019). The gut microbiota plays a critical role in digestion, immune function, and metabolic health (Vernocchi et al., 2020). Antibiotic residues can reduce microbial diversity, promoting dysbiosis (an imbalance of gut bacteria) and associated health issues such as inflammatory bowel disease, obesity, and caused weak immune responses (Dudek-Wicher et al., 2018). This disruption is especially significant with broad-spectrum antibiotics that target a wide range of bacteria (Avis et al., 2021).

The extent to which these residues affect human health depends on several factors. Pharmacokinetic aspects of the drug such as absorption, distribution, metabolism, and excretion determine whether drug residues reach target organs in biologically active forms (Beyene, 2015). Drugs with low oral bioavailability (e.g., aminoglycosides) are less likely to cause systemic effects, whereas lipophilic drugs may be absorbed more readily and accumulate in fatty tissues (Porter et al., 2007).

Another important factor determining the risk associated with drug residues is the dose and duration of exposure (Boobis et al., 2017). The frequency and amount of contaminated food consumption play a crucial role in determining health risks (Mohammed & Shehasen, 2020). Occasional exposure to low residue levels may pose minimal risks, but chronic exposure, especially to drugs with cumulative toxicity, can have significant long-term effects. Foods from animals treated repeatedly with Veterinary drugs or where withdrawal periods were not observed pose higher risks (Wassenaar, 2005).

Aminoglycosides are a class of broad-spectrum antibiotics used primarily in the treatment of bacterial infections in both human and Veterinary medicine (Van Duijkeren et

al., 2019). Aminoglycosides are bactericidal antibiotics primarily used mainly to treat severe infections caused by aerobic Gram-negative bacteria (Pagkalis et al., 2011).

Chemically, the aminoglycoside antibiotics such as streptomycin, dihydrostreptomycin, kanamycin, gentamicin, tobramycin, amikacin, and neomycin are large molecules characterized by numerous amino acid groups, making them highly basic polycations. At physiological pH, they remain highly ionized due to their polarity, which influences their shared pharmacokinetic properties. Aminoglycosides are highly cationic and polar in nature which restricts their ability to cross biological membranes (Bailey et al., 2013)

They consist of a hexose nucleus with amino sugars attached via glycosidic linkages, classifying them as aminocyclitols or aminoglycosidic aminocyclitols (Darlow et al., 2021).

Aminoglycosides exert their effect by penetrating bacterial cells, a process enhanced when combined with beta-lactam antibiotics, which disrupt bacterial cell wall synthesis (Adeniyi ADEFEGHA, 2019). Aerobic Gram-negative bacteria actively transport aminoglycosides into the cell through an oxygen-dependent mechanism , where the cationic aminoglycosides bind to negatively charged lipopolysaccharides in the bacterial membrane, displacing divalent cations such as Ca^{2+} and Mg^{2+} (Webster & Shepherd, 2023). This interaction alters membrane permeability and facilitates antibiotic entry. Once inside, aminoglycosides irreversibly bind to the 30S ribosomal subunit, causing genetic code misreading and disrupting protein synthesis (Barnhill et al., 2012). These changes compromise membrane integrity, leading to further antibiotic uptake, additional damage, and eventual bacterial cell death (Kohanski et al., 2010).

Oral rout is the most used rout for drug administration (Raihan et al., 2024) but for some reasons such as absorption problems. Aminoglycosides, including gentamicin, neomycin, and tobramycin, are typically administered parenterally (by injection), as they are poorly absorbed when taken orally (Bhattacharjee et al., 2023).

In Veterinary medicine, aminoglycosides are used to treat systemic and localized infections in livestock and poultry, especially in cases of respiratory infections, wound infections, and gastrointestinal infections (Page & Gautier, 2012).

Besides having beneficial therapeutic effects, aminoglycosides have some adverse effects (Arunvikram et al., 2014), despite which they remain critical for treating severe Gram-negative and some gram positive infections in human as well as in Veterinary medicine including food animal medicine (Table 1). Aminoglycosides used in food producing animals leads to prolonged drug residues, which is why their off-label use in mentioned animals is strongly discouraged (Rana et al., 2019).

Table 1. *Overview of aminoglycosides, their applications in human and veterinary medicine, and key notes on their usage).*

Aminoglycoside	Human Use	Veterinary Use	Notes
Gentamicin	Treats serious infections (e.g., sepsis, respiratory, and skin infections) (Karunarathna, 2024).	Treats infections in livestock, pets, and aquaculture (Van Duijkeren et al., 2019).	Widely used in both fields.
Amikacin	Used against multidrug-resistant infections (e.g., Multidrug-resistant tuberculosis) (Chiang et al., 2019).	Treats severe infections in horses and companion animals (Isgren, 2022).	Effective in cases with resistance concerns.
Neomycin	skin infections, bowel preparation (Arezzo et al., 2021).	Prophylactic use in livestock (Cangiano et al., 2023).	High local effectiveness with minimal systemic absorption.
Streptomycin	Historically used for tuberculosis; less common now due to resistance (Rocha et al., 2021).	Treats specific bacterial infections in livestock mainly in combination with penicillin (Tufa et al., 2021).	Often replaced in human medicine by newer antibiotics.
Dihydrostreptomycin	Not used.	Veterinary-only for bacterial infections in animals (Herago, 2021).	Analog of streptomycin optimized for veterinary use.
Apramycin	Not used.	Treats enteric infections in livestock (e.g., cattle) (Herrero-Fresno et al., 2016).	Primarily for Gram-negative bacteria.
Spectinomycin	Not commonly used; has some applications as a second-line treatment (Scherman et al., 2014).	Treats enteric infections in animals (Bergwerff, 1998).	Veterinary antibiotic with limited human applications.

Withdrawal period (also known as withdrawal times, withholding times, clearance times), refers to the period after administration of medication last dose to a food producing animal (Toutain, 2010) (Table 2) during which milk, eggs, or meat from them cannot be sold and consumed because of risk of drug residue toxicological concern (Desa & Jimma, 2020). After this time, the levels of drug residues in the animal body decrease to safe limits (Passantino & Russo, 2008). Antibiotics in food animals can leave residues in meat if withdrawal periods are not followed (Tadesse & Tadesse, 2017).

Table 2. *Aminoglycosides some withdrawal times in food producing animals.*

Animal Species	Drug	Withdrawal Period/Days	Route of Administration	Reference
Cattle	Dihydrostreptomycin	10 days	Oral	(Jalal et al., 2015)
Cattle	Dihydrostreptomycin	30 days	Injection	(Jalal et al., 2015)

Cattle	Streptomycin	2 days	Oral	(Gehring et al., 2005)
Cattle	Neomycin	1 day	Oral	(Gehring et al., 2005)
Sheep and Goat	Dihydrostreptomycin	30 days	Injection	(Jalal et al., 2015)
Sheep and Goat	Neomycin	2 days	Oral	(Gehring et al., 2005)
Chickens	Streptomycin	4 days	Oral	(Gehring et al., 2005)
Chickens	Gentamicin	35 days	Subcutaneous	(Gehring et al., 2005)

Reviewing the literature shows that residues of these antibiotics in meat, milk, and eggs pose risks to human health, including allergic reactions, ototoxicity, nephrotoxicity, neurotoxicity and the potential for AMR development (Pancu et al., 2021). To minimize these risks, regulatory agencies like the Food and Drug Administration (FDA), European Medicines Agency (EMA), and Codex Alimentarius have set maximum residue limits (MRLs) and withdrawal times for drugs used in food-producing animals (Canton et al., 2021). Withdrawal times are the minimum period that must pass between the last administration of a drug and the harvesting of meat, milk, or eggs to ensure that drug residues do not exceed safe limits for human consumption (Concordet & Toutain, 1997).

However, the justification for such withdrawal times for aminoglycosides residues is unclear, since oral aminoglycosides are poorly absorbed in the gastrointestinal tract and are largely excreted through the feces (Almeida et al., 2014), so there is minimal risk of these drugs entering systemic circulation and distributing to organs in which they me produce adverse effects. This leads to the central research question for this review: Are current withdrawal times for aminoglycosides scientifically justified, particularly when residues in food products are ingested orally?

The current research gap lies in the limited studies addressing the pharmacokinetics and residue persistence of oral aminoglycosides. Thus, the primary objective of this review is to explore whether the withdrawal periods for aminoglycosides are scientifically justified, especially considering their minimal absorption and limited risk of residue accumulation in animal origin food.

MATERIALS AND METHOD

A comprehensive literature search was conducted using databases such as PubMed, Scopus, Google Scholar, and Web of Science (Shah et al., 2017). Search terms included: aminoglycosides, residue persistence, withdrawal times, antimicrobial resistance, and food safety. The search focused on most related studies (Snyder, 2019) that examined the pharmacokinetics, residue levels, toxicity risks and regulatory considerations related aminoglycosides used in food producing animals as well as in human.

Inclusion criteria were studies discussing aminoglycoside use in Veterinary settings, particularly oral formulations, as well as research examining withdrawal times and drug residues in animal origin foods. Data on pharmacokinetics and antimicrobial resistance in human beings were also included.

RESULTS

The central theme of this review is whether withdrawal times for oral aminoglycosides are warranted, considering the poor absorption of these drugs in the gastrointestinal tract and the minimal risk of residues in edible tissues or animal origin food. The findings show that Veterinary drug residues in food can pose significant health risks, including organ damage, antimicrobial resistance, allergic reactions, and disruption of gut microbiota. While regulatory agencies have established withdrawal times to mitigate these risks, the rationale for applying them to oral aminoglycosides remains unclear. Given their minimal systemic impact and fecal excretion, reevaluating current withdrawal guidelines for these drugs could be warranted.

Aminoglycosides are a class of broad-spectrum antibiotics primarily used to treat severe Gram-negative bacterial infections in both human and veterinary medicine. Drugs with low oral bioavailability, such as aminoglycosides, are less likely to cause systemic effects, whereas lipophilic drugs may accumulate in fatty tissues.

Withdrawal periods, the time required after drug administration to ensure drug residues in meat, milk, or eggs fall below safe limits, are critical for minimizing health risks. Current withdrawal times for aminoglycosides vary depending on the drug, species, and route of administration. Regulatory agencies have established maximum residue limits and withdrawal times to mitigate these risks.

The justification for current withdrawal times for aminoglycosides is unclear, particularly for oral formulations. Oral aminoglycosides are poorly absorbed in the gastrointestinal tract and are largely excreted in feces, minimizing systemic exposure.

DISCUSSION

The risks associated with veterinary drug residues, particularly aminoglycosides, highlight the importance of scientifically justified withdrawal periods. Current guidelines may not fully account for the poor oral absorption and minimal systemic exposure of aminoglycosides, necessitating further research into their pharmacokinetics and residue persistence. Optimizing withdrawal times will ensure food safety while minimizing unnecessary restrictions on the food production industry.

The following sections provide an in-depth discussion of the pharmacokinetics, untoward effects, regulatory guidelines, and the implications for food safety. The risk of aminoglycoside residues in edible tissues primarily relates to injectable forms, where these drugs are absorbed into the bloodstream and distributed throughout the animal's body (Adeniyi Adefegha, 2019).

Pharmacokinetics of Oral Aminoglycosides in human

Being highly polar cations, aminoglycosides are known for their poor absorption from the gastrointestinal tract resulting to a very low bioavailability. These drugs remain intact in the intestine and are excreted in the feces. This means that when oral aminoglycosides are administered or residues taken by food, the majority of the drug stays in the gastrointestinal tract, where it exerts its effects locally, often in the intestinal canal. Only a small fraction of the drug enters systemic circulation, significantly reducing the potential for accumulation in tissues that they may produce adverse effects.

Untoward Effects

Aminoglycosides, especially in elderly, can cause toxicity via prolonged exposure at high concentrations in specific organs due to their accumulation in cellular compartments like lysosomes or binding to critical cellular structures (Paterson et al., 1998).

Ototoxicity: Several drugs including aminoglycosides have ototoxic potential (Tanin., 2024). Accumulation of aminoglycosides in the perilymph and endolymph of the inner ear may cause hearing and balance damage (Hutchin & Cortopassi., 1994). Drug interaction with cochlear (Jiang et al., 2017) and vestibular sensory hair cells, may lead to disrupting ionic balance and leading to cellular degeneration (Rogers & Petersen., 2011). Formation of an iron-aminoglycoside complex promotes reactive oxygen species (ROS) production (Zhang et al., 2021), causing oxidative stress and permanent damage to sensory hair cells and auditory neurons (Zhang et al., 2021). Cochlear toxicity may lead to high-frequency hearing loss, tinnitus and eventual progression to lower frequencies (Skarzynska et al., 2020). Vestibular toxicity can cause vertigo, nausea, ataxia, chronic labyrinthitis and difficulty coordinating movements (Edlow & Newman-Toker, 2015). Damage is largely irreversible as cochlear and vestibular hair cells cannot regenerate (Zheng & Zuo., 2017).

Ototoxicity requires the systemic distribution of aminoglycosides, where the drug accumulates in the inner ear fluids (perilymph and endolymph) and induces oxidative damage to sensory cells (Jiang et al., 2017). Without systemic absorption, aminoglycosides cannot reach inner ear tissues, thus ototoxicity will not manifest (Rivetti et al., 2023).

This minimal systemic absorption means that oral aminoglycosides are unlikely to reach levels in bloodstream that would pose a significant risk and suggests that the withdrawal times for these formulations may be excessively long, as their pharmacokinetics do not support the same concerns over residue accumulation with other antibiotics (Lees & Toutain, 2012).

Nephrotoxicity: Uptake and retention of aminoglycosides in proximal tubular cells through megalin-mediated endocytosis in the renal cortex may cause nephrotoxicity (Nagai et al., 2025). Aminoglycoside Interference with lysosomal function, mitochondrial activity, and phospholipid metabolism, leads to tubular cell damage and induces brush border enzymuria, proteinuria, and impaired tubular concentrating ability (Kaloyanides & Pastoriza-munoz, 1980).

Affected proximal tubules of nephrons cause gradual rise in serum creatinine levels, proteinuria, non-oliguric renal insufficiency (Dobrek, 2023). It rarely progresses to severe tubular necrosis; typically reversible due to tubular cell regeneration (Mattie et al., 1989).

Nephrotoxicity depends on systemic aminoglycosides accumulating in the renal proximal tubular cells, where they cause mitochondrial and lysosomal damage (Humes., 1988). Ingested drug residue remain confined to the gastrointestinal (GI) tract and do not reach the kidneys, so eliminating the risk of nephrotoxicity.

Neuromuscular blockade: Inhibition of acetylcholine release from presynaptic nerve terminals may lead to reduction of postsynaptic acetylcholine receptor sensitivity at the neuromuscular junction and respiratory paralysis (Humes, 1988). This effect involves inhibition of acetylcholine release and postsynaptic receptor sensitivity at the neuromuscular junction, which depends on systemic availability of aminoglycosides (Krenn et al., 2020). Lack of systemic absorption precludes the drug from affecting neuromuscular function, preventing this rare but severe effect.

Antimicrobial resistance: Antimicrobial resistance (AMR) refers to the ability of microorganisms, such as bacteria, viruses, fungi, or parasites, to resist the effects of drugs that once killed them or inhibited their growth(Abushaheen et al., 2020). Aminoglycosides play a significant role in the development of AMR within both Veterinary (Caneschi et al., 2023) and human medicine (Brinkac et al., 2017). Their use, particularly in food-producing animals, contributes to resistance that can affect enteric flora (intestinal microbiota) in humans (Jaimee & Halami, 2016).

Other Effects: Aminoglycoside caused hypersensitivity is rare and likely mediated by immune responses to drug or impurities in formulations (Childs-Kean et al., 2019). Rash, fever and anaphylaxis may occur. Hypersensitivity reactions occur when aminoglycosides act as antigens in systemic circulation, provoking an immune response (Sánchez-borges et al., 2013). In order to produce an effect, drugs, including aminoglycosides, must be absorbed from the gastrointestinal tract and reach the site of action. Since residues do not cross the GI barrier, they do not enter the circulation and therefore cannot trigger immune-mediated reactions (Ma et al., 2018).

Residues in the GI tract primarily act locally without penetrating systemic circulation. The GI environment limits their interaction with sensitive tissues like the ear, kidney, or neuromuscular systems. Residues are either degraded in the digestive system or eliminated in feces, preventing systemic exposure and subsequent untoward effects. This explains why aminoglycoside residues in food pose no clinical risk to humans when ingested, as systemic absorption, a prerequisite for their toxic effects, which is absent in this case.

Regulatory Guidelines and Withdrawal Times

Agencies such as the FDA and EMA establish strict maximum residue limits (MRLs) and mandatory withdrawal periods for aminoglycoside-containing animal products (Zad et al.,

2023). These requirements are intended to minimize public health risks but do not account for the negligible human systemic exposure following oral ingestion (WHO, 2015).

Regulatory guidelines primarily focus on safeguarding consumers from potential drug residues in food products, assuming systemic absorption and risk of toxicity (Sundram et al., 2024). In these guidelines and several studies, the poor absorption of aminoglycosides in humans is often overlooked, leading to unnecessarily recommendations on their use in animals (Mesfin et al., 2024).

Given the emerging evidence on the minimal absorption of oral aminoglycosides (Jana & Deb, 2006), it is crucial for regulatory bodies to reevaluate the current withdrawal times for these drugs. Specifically, withdrawal times should be shortened or eliminated. Reevaluation should be guided based on evidence-based pharmacokinetic data.

Risk associated with residues of non-absorbed antibiotics like aminoglycosides are very low than absorbed antibiotics (Table 3). This is because they largely remain confined to the GI tract and do not contribute to systemic exposure or adverse effects in humans. However, their localized effects on the gut microbiota still necessitate proper regulatory oversight to ensure food safety.

Any adverse effects of aminoglycoside residues would most likely occur locally in the GI tract, potentially altering gut flora. However, these effects are often negligible at residue levels found in food.

While aminoglycosides generally pose a lower risk due to their lack of absorption, it is still critical to monitor and regulate residues. High concentrations of aminoglycoside residues in the gut might influence gut microbiota, contributing to localized resistance or minor GI disturbances. Regulatory standards (MRLs) help ensure that residue levels in food are low enough to prevent even minor risks.

Table 3. *Risk stratification through comparing systemically administered aminoglycosides and orally ingested residues from animal-origin food.*

Factor	Systemically Administered Aminoglycosides	Oral Ingestion of Residues in Food of Animal Origin
Absorption	Fully absorbed into the bloodstream via intravenous or intramuscular routes, leading to systemic distribution.	Minimal or no absorption from the gastrointestinal (GI) tract, as residues do not enter systemic circulation.
Risk of Ototoxicity	High—Aminoglycosides accumulate in ear fluids (perilymph and endolymph), causing cochlear (auditory) and vestibular (balance) damage (Jiang et al., 2017).	Very low or none—Residues that do not enter systemic circulation cannot reach the inner ear tissues, preventing ototoxicity.
Risk of Nephrotoxicity	High—Accumulation in renal cells causes cellular damage, leading to renal impairment, which is dose- and duration-dependent (Lopez-Novoa et al., 2011).	Very low or none—Since there is no systemic absorption, residues in the GI tract do not accumulate in the kidneys.

Risk of Neuromuscular Blockade	Moderate—Aminoglycosides can interfere with neuromuscular transmission, causing a curare-like blockade, especially in patients with conditions like myasthenia gravis (Krenn et al., 2020).	Very low or none—Absence of systemic absorption means no neuromuscular blockade.
Risk of Hypersensitivity	Low to moderate—Potential for allergic reactions, including anaphylaxis and rash, as the drug is systemically available (Dragostin et al., 2022).	Very low or none—Due to limited systemic absorption, immune responses are unlikely to be triggered by residues.

CONCLUSION

Systemically administered aminoglycosides pose significant risks of ototoxicity, nephrotoxicity, neuromuscular blockade, and hypersensitivity due to their complete absorption into systemic circulation. These risks are highly dose- and duration-dependent, particularly in vulnerable populations such as the elderly or those with renal impairment. On the other hand, the ingestion of aminoglycoside residues from animal-derived food products is generally safe, with negligible risk, as these residues are not absorbed through the gastrointestinal tract. Consequently, they do not enter systemic circulation and are unlikely to cause adverse effects typically associated with aminoglycoside toxicity. The primary concern regarding these residues is their potential contribution to the development of antimicrobial resistance (AMR) in human enteric flora. Current withdrawal times for oral aminoglycosides may not be justified, given the limited systemic absorption of these drugs. Pharmacokinetic evidence suggests that oral aminoglycosides are poorly absorbed in the gastrointestinal tract, further reducing the likelihood of drug residues in edible tissues.

RECOMMENDATIONS

Regulatory agencies should consider reassessing withdrawal guidelines, particularly for oral formulations, to align with these scientific findings. Further research into the pharmacokinetics and residue persistence of oral aminoglycosides in food-producing animals is essential for optimizing withdrawal guidelines and ensuring food safety. The ultimate goal is to safeguard food safety without imposing unnecessary withdrawal periods, which could adversely affect both the food production industry and public health. Additionally, to strengthen the scientific basis for withdrawal times in veterinary medicine, there is a clear need to evaluate the impact of low-dose aminoglycoside exposure on the development of antimicrobial resistance in food systems.

Conflict of Interest: The author(s) claimed no conflict of interest.

REFERENCES

Abushaheen, M. A., Fatani, A. J., Alosaimi, M., Mansy, W., George, M., Acharya, S., Rathod, S., Divakar, D. D., Jhugroo, C., & Vellappally, S. (2020). Antimicrobial resistance,

mechanisms and its clinical significance. *Disease-a-Month*, *66*(6), 100971. https://doi.org/DOI: 10.1016/j.disamonth.2020.100971

Adeniyi, A. S. (2019). Antibiotics and Drug Pharmacology. *Acta Scientific Pharmaceutical Sciences*, *3*(11), 43–49. https://doi.org/10.31080/asps.2019.03.0424

Almeida, A., Duarte, S., Nunes, R., Rocha, H., Pena, A., & Meisel, L. (2014). Human and veterinary antibiotics used in Portugal-A ranking for ecosurveillance. *Toxics*, *2*(2), 188–225. https://doi.org/10.3390/toxics2020188

Arezzo, A., Mistrangelo, M., Bonino, M. A., Salusso, P., Forcignanò, E., Vettoretto, N., Botteri, E., Cillara, N., Ottonello, R., Testa, V., De Rosa, F. G., Corcione, S., Passera, R., & Morino, M. (2021). Oral neomycin and bacitracin are effective in preventing surgical site infections in elective colorectal surgery: a multicentre, randomized, parallel, single-blinded trial (COLORAL-1). *Updates in Surgery*, *73*(5), 1775–1786. https://doi.org/10.1007/s13304-021-01112-5

Arsène, M. M. J., Davares, A. K. L., Viktorovna, P. I., Andreevna, S. L., Sarra, S., Khelifi, I., & Sergueïevna, D. M. (2022). The public health issue of antibiotic residues in food and feed: Causes, consequences, and potential solutions. *Veterinary World*, *15*(3), 662–671. https://doi.org/10.14202/vetworld.2022.662-671

Arunvikram, K., Mohanty, I., Sardar, K. K., Palai, S., Sahoo, G., & Patra, R. C. (2014). Adverse drug reaction and toxicity caused by commonly used antimicrobials in canine practice. *Veterinary World*, *7*(5), 299–305. https://doi.org/10.14202/vetworld.2014.299-305

Avis, T., Wilson, F. X., Khan, N., Mason, C. S., & Powell, D. J. (2021). Targeted microbiome-sparing antibiotics. *Drug Discovery Today*, *26*(9), 2198–2203. https://doi.org/10.1016/j.drudis.2021.07.016

Bailey, J., Oliveri, A., & Levin, E. (2013). New developments in aminoglycoside therapy and ototoxicity. *Bone*, *23*(1), 1–7. https://doi.org/10.1016/j.heares.2011.05.008.New

Barnhill, A. E., Brewer, M. T., & Carlson, S. A. (2012). Adverse effects of antimicrobials via predictable or idiosyncratic inhibition of host mitochondrial components. *Antimicrobial Agents and Chemotherapy*, *56*(8), 4046–4051. https://doi.org/10.1128/AAC.00678-12

Ben, Y., Fu, C., Hu, M., Liu, L., Wong, M. H., & Zheng, C. (2019). Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: A review. *Environmental Research*, *169*(July 2018), 483–493. https://doi.org/10.1016/j.envres.2018.11.040

Bergwerff, A. A. (1998). HPLC determination of residues of spectinomycin in various tissue types from husbandry animals. *Analyst*, *123*(10), 2139–2144. https://doi.org/10.1039/a804511i

Beyene, T. (2015). Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. *Journal of Veterinary Science & Technology*, *07*(01),

1–7. https://doi.org/10.4172/2157-7579.1000285

Bhattacharjee, A., Chakraborty, A., Chaulya, N. C., & Mukhopadhyay, G. (2023). Advances in in vivo Non-invasive Delivery of Gentamicin. *Indian Journal of Pharmaceutical Education and Research*, *57*(3), 648–657. https://doi.org/10.5530/ijper.57.3.79

Boobis, A., Cerniglia, C., Chicoine, A., Fattori, V., Lipp, M., Reuss, R., Verger, P., & Tritscher, A. (2017). Characterizing chronic and acute health risks of residues of veterinary drugs in food: latest methodological developments by the joint FAO/WHO expert committee on food additives. *Critical Reviews in Toxicology*, *47*(10), 885–899. https://doi.org/10.1080/10408444.2017.1340259

Brinkac, L., Voorhies, A., Gomez, A., & Nelson, K. E. (2017). The Threat of Antimicrobial Resistance on the Human Microbiome. *Microbial Ecology*, *74*(4), 1001–1008. https://doi.org/10.1007/s00248-017-0985-z

Bumbăcea, R. S., Udrea, M. R., Ali, S., & Bojincă, V. C. (2024). Balancing Benefits and Risks: A Literature Review on Hypersensitivity Reactions to Human G-CSF (Granulocyte Colony-Stimulating Factor). *International Journal of Molecular Sciences*, *25*(9). https://doi.org/10.3390/ijms25094807

Caneschi, A., Bardhi, A., Barbarossa, A., & Zaghini, A. (2023). The Use of Antibiotics and Antimicrobial Resistance in Veterinary Medicine, a Complex Phenomenon: A Narrative Review. *Antibiotics*, *12*(3). https://doi.org/10.3390/antibiotics12030487

Cangiano, L. R., Ipharraguerre, I. R., Guan, L. L., Buss, L. N., Amorin-Hegedus, R., Chirivi, M., Contreras, G. A., & Steele, M. A. (2023). Prophylactic feeding of neomycin to Holstein calves alters gut microbiota, bile acid metabolism, and expression of genes involved in immunometabolic regulation. *Frontiers in Microbiology*, *14*(August), 1–14. https://doi.org/10.3389/fmicb.2023.1210142

Canton, L., Lanusse, C., & Moreno, L. (2021). Rational pharmacotherapy in infectious diseases: Issues related to drug residues in edible animal tissues. *Animals*, *11*(10), 1–32. https://doi.org/10.3390/ani11102878

Chiang, C. Y., Van Deun, A., Trébucq, A., Piubello, A., Schwoebel, V., & Rieder, H. L. (2019). Multidrug-resistant tuberculosis. *The Lancet*, *394*(10195), 299. https://doi.org/10.1016/S0140-6736(19)30046-7

Childs-Kean, L. M., Shaeer, K. M., Varghese Gupta, S., & Cho, J. C. (2019). Aminoglycoside Allergic Reactions. *Pharmacy*, *7*(3), 124. https://doi.org/10.3390/pharmacy7030124

Colopi, A., Guida, E., Cacciotti, S., Fuda, S., Lampitto, M., Onorato, A., Zucchi, A., Balistreri, C. R., Grimaldi, P., & Barchi, M. (2024). Dietary Exposure to Pesticide and Veterinary Drug Residues and Their Effects on Human Fertility and Embryo Development: A Global Overview. *International Journal of Molecular Sciences*, *25*(16). https://doi.org/10.3390/ijms25169116

Concordet, D., & Toutain, P. L. (1997). The withdrawal time estimation of veterinary drugs: A non-parametric approach. *Journal of Veterinary Pharmacology and Therapeutics*, *20*(5), 374–379. https://doi.org/10.1046/j.1365-2885.1997.00077.x

Darlow, C. A., da Costa, R. M. A., Ellis, S., Franceschi, F., Sharland, M., Piddock, L., Das, S., & Hope, W. (2021). Potential Antibiotics for the Treatment of Neonatal Sepsis Caused by Multidrug-Resistant Bacteria. *Pediatric Drugs*, *23*(5), 465–484. https://doi.org/10.1007/s40272-021-00465-z

Desa, Y. M. and G., & Jimma. (2020). *Public Health Importance of Veterinary Drug Residues in Food Animals*. *15*(1), 39–44. https://doi.org/10.5829/idosi.ajh.2020.01.11

Dobrek, L. (2023). A Synopsis of Current Theories on Drug-Induced Nephrotoxicity. *Life*, *13*(2). https://doi.org/10.3390/life13020325

Dragostin, I., Dragostin, O. M., Lisă, E. L., Stefan, S. C., Zamfir, A. S., Diaconu, C., & Zamfir, C. L. (2022). Drugs frequently involved in inducing hypersensitivity reactions. *Drug and Chemical Toxicology*, *45*(2), 617–624. https://doi.org/10.1080/01480545.2020.1746331

Dudek-Wicher, R. K., Junka, A., & Bartoszewicz, M. (2018). The influence of antibiotics and dietary components on gut microbiota. *Przeglad Gastroenterologiczny*, *13*(2), 85–92. https://doi.org/10.5114/pg.2018.76005

Edlow, J. A., & Newman-Toker, D. E. (2015). Medical and Nonstroke Neurologic Causes of Acute, Continuous Vestibular Symptoms. *Neurologic Clinics*, *33*(3), 699–716. https://doi.org/10.1016/j.ncl.2015.04.002

Gehring, R., Haskell, S. R., Payne, M. A., Craigmill, A. L., Webb, A. I., & Riviere, J. E. (2005). Aminoglycoside residues in food of animal origin. *Journal of the American Veterinary Medical Association*, *227*(1), 63–66. https://doi.org/10.2460/javma.2005.227.63

Herago, T. (2021). Drug Residues in Foods of Animal Origin and Their Impact on Human Health: Review. *Food Science and Quality Management*, *108*, 13–21. https://doi.org/10.7176/fsqm/108-02

Herrero-Fresno, A., Zachariasen, C., Hansen, M. H., Nielsen, A., Hendriksen, R. S., Nielsen, S. S., & Olsen, J. E. (2016). Apramycin treatment affects selection and spread of a multidrug-resistant Escherichia coli strain able to colonize the human gut in the intestinal microbiota of pigs. *Veterinary Research*, *47*(1), 1–10. https://doi.org/10.1186/s13567-015-0291-z

Humes, H. D. (1988). Aminoglycoside nephrotoxicity. *Kidney International*, *33*(4), 900–911. https://doi.org/10.1038/ki.1988.83

Hutchin, T., & Cortopassi, G. (1994). Proposed molecular and cellular mechanism for aminoglycoside ototoxicity. *Antimicrobial Agents and Chemotherapy*, *38*(11), 2517–2520. https://doi.org/10.1128/AAC.38.11.2517

Isgren, C. M. (2022). Improving clinical outcomes via responsible antimicrobial use in horses.

Equine Veterinary Education, *34*(9), 482–492. https://doi.org/10.1111/eve.13502

Jaimee, G., & Halami, P. M. (2016). Emerging resistance to aminoglycosides in lactic acid bacteria of food origin—an impending menace. *Applied Microbiology and Biotechnology*, *100*(3), 1137–1151. https://doi.org/10.1007/s00253-015-7184-y

Jalal, H., Para, P. A., Ganguly, S., Gogai, M., Bhat, M. M., Praveen, P. K., & Bukhari1, and S. A. (2015). CHEMICAL RESIDUES IN MEAT AND MEAT PRODUCTS: A REVIEW. *Wjpls.Org*, *1*(3), 149–159. http://wjpls.org/download/article/24022018/1519795554.pdf

Jana, S., & Deb, J. K. (2006). Molecular understanding of aminoglycoside action and resistance. *Applied Microbiology and Biotechnology*, *70*(2), 140–150. https://doi.org/10.1007/s00253-005-0279-0

Jiang, M., Karasawa, T., & Steyger, P. S. (2017). Aminoglycoside-induced cochleotoxicity: A review. *Frontiers in Cellular Neuroscience*, *11*(October), 1–14. https://doi.org/10.3389/fncel.2017.00308

Kaloyanides, G. J., & Pastoriza-munoz, E. (1980). Aminoglyco side nephrotoxicity. *Kidney International*, *18*(5), 571–582. https://doi.org/10.1038/ki.1980.175

Kan, C. A., & Meijer, G. A. L. (2007). The risk of contamination of food with toxic substances present in animal feed. *Animal Feed Science and Technology*, *133*(1–2), 84–108. https://doi.org/10.1016/j.anifeedsci.2006.08.005

Karunarathna, I. (2024). *The Clinical Use of Gentamicin : Indications , Mechanism of Action , and Key Considerations*. *August*. https://doi.org/10.13140/RG.2.2.24754.00969

Kohanski, M. A., Dwyer, D. J., & Collins, J. J. (2010). How antibiotics kill bacteria: From targets to networks. *Nature Reviews Microbiology*, *8*(6), 423–435. https://doi.org/10.1038/nrmicro2333

Krenn, M., Grisold, A., Wohlfarth, P., Rath, J., Cetin, H., Koneczny, I., & Zimprich, F. (2020). Pathomechanisms and Clinical Implications of Myasthenic Syndromes Exacerbated and Induced by Medical Treatments. *Frontiers in Molecular Neuroscience*, *13*(August). https://doi.org/10.3389/fnmol.2020.00156

Lees, P., & Toutain, P. (2012). *The role of pharmacokinetics in veterinary drug residues*. https://doi.org/10.1002/dta.1374

Ma, W., Yang, L., & He, L. (2018). Overview of the detection methods for equilibrium dissociation constant KD of drug-receptor interaction. *Journal of Pharmaceutical Analysis*, *8*(3), 147–152. https://doi.org/10.1016/j.jpha.2018.05.001

Mancuso, G., Midiri, A., Gerace, E., & Biondo, C. (2021). Pathogens-10-01310-V2.Pdf. *Pathogens*, *10*(1310), 1–14.

Mattie, H., Craig, W. A., & Pechere, J. C. (1989). *Review Determinants of efficacy and toxicity of aminoglycosides*. 281–293.

McInnes, R. S., McCallum, G. E., Lamberte, L. E., & van Schaik, W. (2020). Horizontal transfer of antibiotic resistance genes in the human gut microbiome. *Current Opinion in Microbiology*, *53*, 35–43. https://doi.org/10.1016/j.mib.2020.02.002

Menkem, Z. E., Ngangom, B. L., Tamunjoh, S. S. A., & Boyom, F. F. (2019). Antibiotic residues in food animals: Public health concern. *Acta Ecologica Sinica*, *39*(5), 411–415. https://doi.org/10.1016/j.chnaes.2018.10.004

Mesfin, Y. M., Mitiku, B. A., & Tamrat Admasu, H. (2024). Veterinary Drug Residues in Food Products of Animal Origin and Their Public Health Consequences: A Review. *Veterinary Medicine and Science*, *10*(6). https://doi.org/10.1002/vms3.70049

Mohammed, A. S., & Shehasen, M. Z. (2020). Street Food Consumption and Associated Health Risk. *International Journal of Research Studies in Agricultural Sciences*, *6*(7). https://doi.org/10.20431/2454-6224.0607002

Nagai, J., Tanaka, H., Nakanishi, N., Tanaka, H., Nakanishi, N., Murakami, T., & Takano, M. (2025). *Role of megalin in renal handling of aminoglycosides*. 1–2.

Page, S. W., & Gautier, P. (2012). Use of antimicrobial agents in livestock. *OIE Revue Scientifique et Technique*, *31*(1), 145–188. https://doi.org/10.20506/rst.31.1.2106

Pagkalis, S., Mantadakis, E., Mavros, M. N., Ammari, C., & Falagas, M. E. (2011). Pharmacological considerations for the proper clinical use of aminoglycosides. *Drugs*, *71*(17), 2277–2294. https://doi.org/10.2165/11597020-000000000-00000

Pancu, D. F., Scurtu, A., Macasoi, I. G., Marti, D., Mioc, M., Soica, C., Coricovac, D., Horhat, D., Poenaru, M., & Dehelean, C. (2021). *Antibiotics : Conventional Therapy and Natural Compounds with Antibacterial Activity — A Pharmaco-Toxicological Screening*. https://doi.org/DOI: 10.3390/antibiotics10040401

Passantino, A., & Russo, C. (2008). Maximum residue levels of veterinary medicines in relation to food safety: European community legislation and ethical aspects. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit*, *3*(4), 351–358. https://doi.org/10.1007/s00003-008-0369-x

Paterson, D. L., Robson, J. M. B., & Wagener, M. M. (1998). Risk factors for toxicity in elderly patients given aminoglycosides once daily. *Journal of General Internal Medicine*, *13*(11), 735–739. https://doi.org/10.1046/j.1525-1497.1998.00224.x

Porter, C. J. H., Trevaskis, N. L., & Charman, W. N. (2007). Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs. *Nature Reviews Drug Discovery*, *6*(3), 231–248. https://doi.org/10.1038/nrd2197

Raihan, R., Wafa, A., Zhakfar, A. M., & Sudhakar CK. (2024). Oral Disintegrating Films: A Review. *Journal of Natural Science Review*, *2*(2), 60–74. https://doi.org/10.62810/jnsr.v2i2.42

Rana, M. S., Lee, S. Y., Kang, H. J., & Hur, S. J. (2019). Reducing veterinary drug residues in

animal products: A review. *Food Science of Animal Resources*, *39*(5), 687–703. https://doi.org/10.5851/kosfa.2019.e65

Rivetti, S., Romano, A., Mastrangelo, S., Attin, G., Maurizi, P., & Ruggiero, A. (2023). *Aminoglycosides-Related Ototoxicity : Mechanisms , Risk Factors , and Prevention in Pediatric Patients*. *June*, 1–21. https://doi.org/doi: 10.3390/ph16101353

Rocha, D. M. G. C., Viveiros, M., Saraiva, M., & Osório, N. S. (2021). The neglected contribution of streptomycin to the tuberculosis drug resistance problem. *Genes*, *12*(12). https://doi.org/10.3390/genes12122003

Rogers, C., & Petersen, L. (2011). Aminoglycoside-induced balance deficits: A review of vestibulotoxicity. *South African Family Practice*, *53*(5), 419–424. https://doi.org/10.1080/20786204.2011.10874126

Sánchez-borges, M., Thong, B., Blanca, M., Felipe, L., Ensina, C., González-díaz, S., Greenberger, P. A., Jares, E., Jee, Y., Kase-tanno, L., Khan, D., Park, J., Pichler, W., Romano, A., José, M., & Jaén, T. (2013). *Hypersensitivity reactions to non beta-lactam antimicrobial agents , a statement of the WAO special committee on drug allergy*. 1–23. https://doi.org/doi: 10.1186/1939-4551-6-18

Scherman, S., Vaddady, P. K., Zheng, Z., Qi, J., Akbergenov, R., Das, S., Madhura, D. B., Rathi, C., Trivedi, A., Villellas, C., Boshoff, H. I., Gonzalez-juarrero, M., Meibohm, B., & Erik, C. (2014). *HHS Public Access*. *20*(2), 152–158. https://doi.org/10.1038/nm.3458.Spectinamides

Shah, S. R. U., Mahmood, K., & Hameed, A. (2017). Review of google scholar, web of science, and scopus search results: The case of inclusive education research. *Library Philosophy and Practice*, *2017*(1).

Skarzynska, M., Król, B., & Czajka, L. (2020). Ototoxicity As a Side-Effect of Drugs: Literature Review. *Journal of Hearing Science*, *10*(2), 9–19. https://doi.org/10.17430/jhs.2020.10.2.1

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. *Journal of Business Research*, *104*(July), 333–339. https://doi.org/10.1016/j.jbusres.2019.07.039

Sundram, P., Lloyd, C., & Eri, R. (2024). Addressing residue and resistance in food animals: a policy imperative in Southeast Asia. *International Journal of Food Science and Technology*, 6746–6757. https://doi.org/10.1111/ijfs.17063

Tadesse, T., & Tadesse, T. (2017). *Public Health Impacts of Antibiotic Residues in Foods of Animal Origin: A Review*. *7*(10), 6–11. www.iiste.org

Tanin, F. A. (2024). *Understanding Adverse Drug Effects and the Clinical Pharmacist ' s Role in Their Management*. *2*(4), 1–35.

Tello, A., Austin, B., & Telfer, T. C. (2012). Selective pressure of antibiotic pollution on

bacteria of importance to public health. *Environmental Health Perspectives*, *120*(8), 1100–1106. https://doi.org/10.1289/ehp.1104650

Toutain, P. L. (2010). How to extrapolate a withdrawal time from an EHSLC published detection time: A Monte Carlo simulation appraisal. *Equine Veterinary Journal*, *42*(3), 248–254. https://doi.org/10.1111/j.2042-3306.2010.00028.x

Tufa, T. B., Guta, A., Tufa, T. B., Beyi, A. F., & Regassa, F. (2021). Efficacy of different brands of penicillin-streptomycin against Staphylococcus aureus: the clinicians' myths and the realities (Preprints). *Research Square*.

Van Duijkeren, E., Schwarz, C., Bouchard, D., Catry, B., Pomba, C., Baptiste, K. E., Moreno, M. A., Rantala, M., Ružauskas, M., Sanders, P., Teale, C., Wester, A. L., Ignate, K., Kunsagi, Z., & Jukes, H. (2019). The use of aminoglycosides in animals within the EU: Development of resistance in animals and possible impact on human and animal health: A review. *Journal of Antimicrobial Chemotherapy*, *74*(9), 2480–2496. https://doi.org/10.1093/jac/dkz161

Vernocchi, P., Chierico, F. Del, & Putignani, L. (2020). Gut microbiota metabolism and interaction with food components. *International Journal of Molecular Sciences*, *21*(10). https://doi.org/10.3390/ijms21103688

Wassenaar, T. M. (2005). Use of antimicrobial agents in veterinary medicine and implications for human health. *Critical Reviews in Microbiology*, *31*(3), 155–169. https://doi.org/10.1080/10408410591005110

Webster, C. M., & Shepherd, M. (2023). A mini-review: environmental and metabolic factors affecting aminoglycoside efficacy. *World Journal of Microbiology and Biotechnology*, *39*(1), 1–13. https://doi.org/10.1007/s11274-022-03445-8

WHO. (2015). *Guidance document for WHO monographers and reviewers evaluating veterinary drug residues in food*. 6.

Worboys, M., & Toon, E. (2018). Phenylbutazone (Bute, PBZ, EPZ): one drug across two species. *History and Philosophy of the Life Sciences*, *40*(2), 1–24. https://doi.org/10.1007/s40656-018-0191-4

Zad, N., Tell, L. A., Ampadi, R., Xu, X., Riviere, J. E., Baynes, R., Lin, Z., Maunsell, F., Davis, J., & Jaberi-douraki, M. (2023). Development of machine learning algorithms to estimate maximum residue limits for veterinary medicines. *Food and Chemical Toxicology*, *179*(February), 113920. https://doi.org/10.1016/j.fct.2023.113920

Zhang, L., Du, Z., & Gong, S. (2021). Mitochondrial Dysfunction and Sirtuins: Important Targets in Hearing Loss. *Neural Plasticity*, *2021*. https://doi.org/10.1155/2021/5520794

Zheng, F., & Zuo, J. (2017). Cochlear hair cell regeneration after noise-induced hearing loss : Does regeneration follow development ? *Hearing Research*, *349*, 182–196. https://doi.org/10.1016/j.heares.2016.12.011