Antibacterial Drug Residues in Small Ruminant Edible Tissues and Milk: A Literature Review of Commonly Used Medications in Small Ruminants

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Simple Summary: This review is a summary of published studies that contain drug residue depletion data for edible tissues and milk following treatment of sheep and goats. The information is separated by antibiotic class for ease of comparison between studies. This summary is useful for understanding medication residue depletion following extra-label drug use and can be used to help estimate withdrawal intervals in order to help protect the human food chain.

Abstract: This review provides a summary of extracted data from the published literature that contains drug residue depletion data for edible tissues and milk following treatment of sheep and goats. Out of 20,234 records obtained during the initial search, data from 177 records were included in this review. The data is separated by antibiotic class for ease of comparison between studies. Extracted data includes the active ingredient, dosing information, animal health status, analytical method and limits of detection, tolerance and maximum residue limit information, and time frames relative to residue absence or detection. This information is useful for understanding drug residue depletion profiles following extra-label use and for estimating withdrawal intervals, in order to protect the human food chain.

Keywords: small ruminant; sheep; goat; milk; edible tissue; antibiotic drug residue

1. Introduction

Drinking water and availability of food for both humans and animals are affected by climate change that lowers rainfall and an increasing world population, especially in semi-arid climates [1]. Small ruminants present a unique opportunity for developing nations, specifically in developing nations that are in semi-arid climates, due to their multi-purpose use (meat, milk and fibers), lower production cost compared to large ruminants, and tolerance to low rainfall and hot climates [1].

According to data from the Food and Agriculture Organization of the United Nations (FAO), the number of sheep and goats worldwide has increased from approximately 1.4 billion head combined (1 billion sheep, ~400 million goats) in 1961 to approximately 2.3 billion head combined (~1.2 billion sheep, ~1.1 billion goats) in 2019 [2]. Between 2014 and 2019, the largest producers of sheep meat worldwide were China, Australia, New Zealand, Turkey and Algeria, whereas during this same time period, the largest producers of goat meat worldwide were China, India, Pakistan, Nigeria and Bangladesh.

In the United States, sheep and goats are considered minor species by the Food and Drug Administration (FDA) [3]; however, sheep are considered major species while goats are considered minor species by the European Medicines Agency (EMA) Committee for Medicinal Products for Veterinary Use [4]. In the United States, there is a “severe shortage of approved new animal drugs for use in minor species” [5].
The Food Animal Residue Avoidance and Depletion Program (FARAD) is a United States Department of Agriculture (USDA)-funded program with a mission to provide veterinary practitioners with scientifically based withdrawal interval recommendations following extra-label drug use or chemical/pesticide contamination in food-producing species. FARAD call submission data for small ruminants indicates a steady increase in the number of withdrawal interval request submissions from 2015 to 2019, with a steep increase in the number of submissions in 2020 (2015 = 435 submissions for sheep, 223 for goats; 2019 = 343 submissions for sheep, 710 for goats; 2020 = 595 submissions for sheep, 1401 for goats). The most commonly requested drug categories include antibiotics, anthelmintics, and non-steroidal anti-inflammatory drugs (NSAIDs). This data reflects the increasing numbers of backyard or hobby-farm environments, where the food-products are consumed by the family keeping the sheep or goats. Given the limited FDA-approved medications for use in sheep or goats, drugs are commonly prescribed in an extra-label manner which is legalized by the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) [6].

Given the importance of sheep and goats as commodity groups worldwide, the purpose of this review is to summarize research studies investigating antibiotic medication use in small ruminants with respect to the potential for drug residues to be present in small ruminant meat and milk products. Due to the large volume of published literature in small ruminants, this review only includes antibacterial medications; however, a second review will be completed incorporating anthelmintics and other medication classes not included here. It is important to note that residue depletion times referenced in the text are based on data from scientific studies. Normal industry practice to withdraw feed 8 to 12 h prior to processing the animals in order to minimize fecal contamination [7] may not have occurred in scientific research studies examining a zero day withdrawal. In addition, the residue depletion times listed in this manuscript are dependent on the sensitivity of the analytical method utilized in the study. Summaries of drug residue studies, drug approvals, tolerances (in the United States), and maximum residue limits (MRLs; in the European Union) have been provided in the tables for the reader’s convenience. If available, FDA-approved medications for use in sheep and goats should be utilized according to directions and labeled withdrawal times adhered to in order to guarantee human food safety.

2. Materials and Methods

2.1. Search Strategy

A systematic literature search was conducted using various databases and compared to publications included FARAD Program’s literature database. The aim of the search was to collect milk and edible tissue residue data for antibiotics that had been administered to small ruminants. Published literature between 1926 and 2021 was searched using PubMed, Cab Direct, Scopus, and Web of Science. Search terms and key words included: “sheep”, “goat(s)”, “small ruminants”, “caprine”, “ovine”, “drug absorption”, “clearance”, “drug residue(s)”, “pharmacokinetics”, “metabolic clearance rate”, “intestinal absorption”, “bioavailability”, “biological availability”, “metabolism”.

2.2. Screening Results

For systematic screening, search results were imported into the Covidence online platform (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia) and duplicate results were removed by the Covidence software. Initially, the 20,234 “Titles and Abstracts” were screened by one reviewer (EDR or CED) for relevancy and categorized as ‘yes’, ‘no’, or ‘maybe’ using predetermined inclusion and exclusion criteria. The category of ‘maybe’ was used for trials that did not explicitly state the inclusion or exclusion criteria in the abstract and thus required further review of the full text. Inclusion criteria were as follows: in vivo sheep or goat drug trial; drug or metabolite concentration data and time point in tissue and/or milk; drug dose, route of administration, and dosing frequency stated. Exclusion criteria were as follows: any animal not a sheep or goat; in vitro study; concentration or residue data for non-drug substances (pesticide,
toxin, vitamins) or drugs of abuse; drug plasma or serum concentrations only; dose of drug, route of administration, and dosing frequency missing. After initial screening for exclusion criteria, 1769 ‘yes’ and ‘maybe’ results moved to a ‘Full Text’ screening by one reviewer (EDR, KLM, or CED). These records were further excluded or included based on the above criteria and a reason was assigned. Records were excluded due to: not being a study (e.g., review, short communication, corrigendum; \( n = 128 \)), not being able to verify text (e.g., full text not available from lenders worldwide, abstract only from proceedings, text unable to be translated; \( n = 141 \)), being the wrong patient population/study design (e.g., not in live animals, in live animals other than small ruminants, etc.; \( n = 84 \)), chemical product of study was a non-drug substance (\( n = 10 \)), matrices under study did not consist of tissues or milk (\( n = 1076 \)), and lack of specific concentration versus time presented in the paper (\( n = 60 \)). A total of 270 records met the complete inclusion criteria. Figure 1 displays a flowchart representation of the screening process completed in this literature search.

![Figure 1](schematic-diagram.png)

Figure 1. Schematic diagram of the process for three independent evaluators to assess published manuscripts and the numerical outcome of each step. The ultimate goal was to curate manuscripts with tissue and milk residue data from live sheep and goat antibacterial drug studies.

For comparison, the FARAD database returned 832 records for both sheep and goats; however, 78 records were removed from the review due to incorrect matrices (i.e., plasma or serum data only). Ultimately, only 177 records met the complete inclusion criteria.

3. Data Extraction and Presentation (Antibiotic Drug Classes, Residue Detection, and Analytical Methods)

The published literature presenting tissue and milk residue data for antibiotics used in sheep and goats is presented in the Tables below and is categorized by antibiotic class. Tolerances or maximum residue limits are presented for FDA-approvals and EMA-approvals, respectively. The basic analytical method is described, with a focus on the limit of detection and limit of quantitation, alongside the dosing regimen for each study. Animal health status and additional information are also included, since variations in health- or lactation-status may affect drug residue depletion. Finally, two columns are included to indicate when residues were last detected. The column titled ‘Last sampling time point for which residues WERE detected (post-last treatment)’ refers the last sampling point when residues were detected based on the study sampling protocol. This is in contrast to the column titled ‘Sampling time point when NO residues were detected (post-last treatment)’ which refers to the last sampling point when residues were not detected based on the study sampling protocol.
protocol. Instances where a greater than symbol (“>”) is utilized refers to situations where residues were still detected at the last sampling time point of the study protocol.

Data for the summarized studies includes analytical methods since it is important to consider how those methods impact the sensitivity of drug residue detection and how the analytical limits of detection compare to tolerances or MRLs. Newer analytical methods can detect drug residues at lower concentrations than historical microbiological bioassays or colorimetric testing, resulting in a greater number of days with detectable drug residues. In contrast, studies using less sensitive methods, having higher limits of detection, may have found shorter periods with detectable drug residues upon withdrawal of the drug. Readers are cautioned to keep the sensitivity of the analytical methods in mind when evaluating the data presented within this review, as well as the fact that most of the studies were completed in healthy animals. It is also important to note that US products approved for use in small ruminants should be used according to the FDA-approved label directions. The FDA-approved label withdrawal time should take precedent above any of the data summarized in this paper.

When considering antibiotic drug classes, it is important to remember that the World Health Organization (WHO) classifies antibiotics into categories based on their place in therapy for some infections in human medicine. These categories include critically important, highly important and important [8]. Some critically important antibiotics are then sub-divided by priority if they are considered sole or limited therapy for some infections in human medicine [8]. Some cephalosporins (third, fourth and fifth generations), quinolones, macrolides are classified as highest priority critically important antibiotics for human health. Aminoglycosides, some cephalosporins (first and second generations) are classified as high priority critically important antibiotics. Amphenicols, some penicillins (antipseudomonal, aminopenicillins with and without beta-lactamase inhibitors, amidinopenicillins, anti-staphylococcal, narrow spectrum), sulfonamides and tetracyclines are classified as highly important antibiotics for human health by the WHO.

3.1. Aminoglycosides

Aminoglycosides (amikacin, apramycin, dihydrostreptomycin, gentamicin, tobramycin, neomycin, streptomycin) are concentration dependent, bactericidal antibiotic agents produced from Streptomyces spp. and Micromonospora spp. Aminoglycosides act by irreversibly binding to the 30s subunit of the bacterial ribosome thereby inhibiting protein synthesis. Their spectrum of activity includes mostly Gram-negative bacteria, with some mycobacteria and staphylococci coverage. Transmission of Enterococcus spp., Enterobacteriaceae (including E. coli), and Mycobacterium spp. can occur from non-human sources and potentially result in human infection. Therefore, the appropriate use of aminoglycosides in food animal species is essential to maintain human safety.

Aminoglycosides are generally not well absorbed from the gastrointestinal tract [9], unless there is damage to the intestinal mucosa. When administered parenterally, aminoglycosides are rapidly and completely absorbed. Elimination of aminoglycosides is primarily renally, which may result in persistent residues in the kidneys. In most published studies in sheep and goats, residues in renal tissue exceeded the duration of the study [10–17]. In humans, aminoglycosides are poorly excreted into breastmilk [18]. This may also be the case for sheep and goats as a few studies have shown short duration of residue detection in milk following IV and IM administration [19–26].

In the United States, the only aminoglycoside FDA-approved for use in small ruminants is neomycin sulfate. However, the EMA has approved streptomycin/dihydrostreptomycin and kanamycin for sheep, while also extending MRLs from other species for gentamicin and neomycin. Table 1 shows the published literature that provides data for edible tissue or milk residues of aminoglycosides following treatment of sheep and goats.
Table 1. Aminoglycoside residues in milk or edible tissue samples from sheep or goats following treatment.

| Analyte | Species; Breed; Age; # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment)* | Health Status | Additional Information | Source/ Year |
|---------|-------------------------------------------------|----------------|------------------|-----|-----|---------------------------|--------------------------|------------|--------|-------------------------------|-----------------------------------------------|-------------|------------------------|--------------|
| Amikacin | Goat; Baladi; 2-3 years; n = 5 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | 0.2 ppm | IV | 7.5 mg/kg Amikacin sulfate | 1 | Milk | 4 h (0.22 ppm) | 6 h | Healthy | Mid-lactation; Milked 2 × [19] | 1999 |
| Amikacin | Goat; NS; 1-2-2 years; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | 0.1 ppm | NS | IM | 10 mg/kg Amikacin sulfate | 1 | Milk | 5 h (NS) | 6 h | Healthy | Lactating [20] | 2001 |
| Amikacin | Sheep; crossbred; 2-4 years; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | 0.19 ppm | IV | 7.5 mg/kg Amikacin sulfate | 1 | Milk | 9.5 h (0.85 ppm §) | >3 day | Healthy | Lactating; Milked 2 × /day [21] | 2004 |
| Apramycin | Goat; Saanen; adult; n = 10 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | 0.1 ppm | IV | 20 mg/kg Apramycin sulfate | 1 | Milk | 10 h (0.12 ppm §) | >50 h | Healthy | Early Lactation [22] | 1995 |
| Apramycin | Sheep; Awassi; adult; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | 0.1 ppm | IM | 10 mg/kg Apramycin sulfate | 1 | Milk | 720 min (0.15 ppm §) | 1440 min | Diseased-Mastitis | Mid-lactation [22] | 1995 |
| Apramycin | Sheep; Awassi; adult; n = 10 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | 0.1 ppm | IV | 20 mg/kg Apramycin sulfate | 1 | Milk | 6 h (0.11 ppm §) | 8 h | Healthy | Mid-lactation [22] | 1995 |
| Apramycin | Sheep; NS; Lambs; n = 12 study; n = 3/time pt | US Tol: Not established. EMA MRL: Not established. | HPLC | 901 ppb | NS | PO | 10 mg/kg Apramycin daily | 3 | Liver, Kidney, Muscle, Fat, Liver, Kidney, Muscle, Fat | Liver: 300 ppb, Kidney: 304 ppb, Muscle: 124 ppb, Fat: 42 ppb | Liver: 300 ppb, Kidney: 304 ppb, Muscle: 124 ppb, Fat: 42 ppb | Healthy | NS [19] | 1999 |

*Sampling time point when no residues were detected (post-last treatment) varies depending on species, age, and health status.
Table 1. Cont.

| Analyte                      | Species; Breed; Age; # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOQ | LOD | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/ Year |
|------------------------------|--------------------------------------------------|----------------|------------------|-----|-----|-------------------------|--------------------------|-------------|--------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------|------------------------|---------------|
| Apramycin                    | Goat; NS; Adult; NS                               | US Tol: Not established. EMA MRL: Not established | NS    | NS   | NS | IM                      | 20 mg/kg Apramycin        | 1            | Milk   | 10 h (NS)                                                          | 12 h (NS)                                                      | Healthy     | Dry off period (mean 0.3) 1.4 days 50 (range 25–156) days; 1 tube per gland before drying off; Sample collected after kidding | [23] 2000   |
| Dihydro-streptomycin         | Goat; NS; Adults; n = 220                         | US Tol: Not established. EMA MRL: Not established. | Bioassay | 0.13 ppm | 0.15 ppm | IMM                    | 300,000 IU Procaine benzyl-penicillin; 100 mg dihydro-streptomycin; 100 mg nafcillin | 1 | Milk | 6 days post kidding (≥0.2 ppm) | 7 days post kidding | Healthy | Healthy | Dry off period (mean 112 days (range 85–225 days); 1 tube per gland before drying off; Sample collected after lambing | [19] 1995   |
| Dihydro-streptomycin         | Sheep; Lacaune; adult; n = 8                      | US Tol: Not established. EMA established MRL: 200 ppb (milk). | Bioassay | 0.02 ppm | NS | IMM                    | 300,000 IU Procaine benzyl-penicillin; 100 mg dihydro-streptomycin; 100 mg nafcillin | 1 | Milk | 3 days (0.02 ppm 5) | 4 days | Healthy | Healthy | Dry off period (mean 112 days (range 85–225 days); 1 tube per gland before drying off; Sample collected after lambing | [19] 1995   |
| Dihydro-streptomycin         | Sheep; Awassi; adult; n = 3                       | US Tol: Not established. EMA established MRL: 200 ppb (milk). | Bioassay | NS | NS | IV                     | 20 mg/kg Dihydro-streptomycin (radio-labeled) then 10 mg/kg for 4 doses 45 min interval | 5 | Milk | 24 h (0.20 ppm 6) | 36 h | Healthy | Lactating; Milked 2×/day | [24] 1973   |
| Analyte | Species; Breed; Age; # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/ Year |
|---------|-------------------------------------------------|----------------|-----------------|-----|-----|-------------------------|-------------------------|-------------|--------|-------------------------------------------------|-------------------------------------------------|-------------|---------------------|--------------|
| Dihydrostreptomycin | Sheep; NS; NS; n = 22 study | US Tol: Not established. EMA established MRL: 300 ppb (liver, muscle, fat); 1000 ppb (kidney). | Bioassay | 0.5 ppm | NS | IM | 10 mg/kg Dihydrostreptomycin combined w/ 10,000 IU procaine penicillin-G daily | 5 | Kidney | 28 days (0.5 ppm) | >28 days | Healthy | NS | [11] 1995 |
| Dihydrostreptomycin | Sheep; Awassi; Adult; n = 2 | US Tol: Not established. EMA established MRL: 200 ppb (milk). | Bioassay | NS | NS | IM | 20 mg/kg Dihydrostreptomycin (radio-labeled) | 1 | Milk | 12 h (0.22 ppm) | 24 h | Healthy | Disease-mastitis | Lactating | [29] 1974 |
| Dihydrostreptomycin | Sheep; NS; NS; n = 8 | US Tol: Not established. EMA established MRL: 300 ppb (liver, muscle, fat); 1000 ppb (kidney); 200 ppb (milk). | HPLC | NS | 50 ppb | IM | 10 mg/kg Dihydrostreptomycin combined with benzyl-penicillin daily | 3 | Milk | <LOQ @ 14 days | 14 days | Healthy | NS | [25] 2005 |
| Dihydrostreptomycin | Sheep; Suffolk & Suffolk/Cheviot; Adult; n = 8 | US Tol: Not established. EMA established MRL: 200 ppb (milk). | HPLC | 0.02 ppm | 0.05 ppm | IM | 10 mg/kg Dihydrostreptomycin combined w/ procaine penicillin daily | 3 | Milk | 48 h (0.06 ppm) | 80 h | Healthy | Lactating | Milked; 2×/day | [26] 2002 |
| Dihydrostreptomycin | Sheep; NS; NS; n = 12 study; n = 4/time pt | US Tol: Not established. EMA established MRL: 300 ppb (liver, muscle, fat); 1000 ppb (kidney). | HPLC | NS | 400 ppb | IM | 10 mg/kg Dihydrostreptomycin combined w/ benzyl-penicillin daily | 3 | Liver | <LOQ @ 14 days | 14 days | Healthy | NS | [30] 2000 |
| Dihydrostreptomycin | Sheep; NS; NS; n = 12 study; n = 4/time pt | US Tol: Not established. EMA established MRL: 300 ppb (liver, muscle, fat); 1000 ppb (kidney). | HPLC | NS | 400 ppb | IM | 10 mg/kg Dihydrostreptomycin combined w/ procaine penicillin daily | 3 | Liver | <LOQ @ 14 days | 14 days | Healthy | NS | [31] 1998 |
| Analyte | Species; Breed; Age; # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/ Year |
|---------|-------------------------------------------------|----------------|------------------|-----|-----|-------------------------|--------------------------|------------|--------|-------------------------------------------------|-------------------------------------------------|----------------|----------------------|--------------|
| Gentamicin | Sheep; mixed breed; adult; n = 7 | US Tol: Not established. EMA established MRL in all mammalian food producing species: 750 ppb (kidney). | Bioassay | NS | NS | IV | 4 mg/kg Gentamicin | 1 | Kidney | biopsy | 28 days (9.9 ppm) | 35 days | Healthy | NS | 1985 |
| Gentamicin | Sheep; Suffolk; adult; n = 9 study; n = 3/time pt | US Tol: Not established. EMA established MRL in all mammalian food producing species: 750 ppb (kidney); 30 ppb (muscle). | Immunoassay | 0.01 ppm | NS | IM | 3 mg/kg Gentamicin sulfate at 8 h intervals | 2 | Kidney | IM | 15 days (0.0 ppm) | >15 days | Healthy | NS | 1985 |
| Gentamicin | Sheep; Suffolk; adult; n = 12 study; n = 3/time pt | US Tol: Not established. EMA established MRL in all mammalian food producing species: 250 ppb (liver); 750 ppb (kidney); 50 ppb (muscle, fat). | Immunoassay | 0.01 ppm | NS | IM | 18 mg/kg Gentamicin sulfate | 1 | Liver | IM | 12 days (0.31 ppm) | >12 days | Healthy | NS | 1986 |
| Gentamicin | Sheep; western range; adult; n = 4 | US Tol: Not established. EMA established MRL in all mammalian food producing species: 750 ppb (kidney). | Immunoassay | 0.04 ppm | NS | IM | 3 mg/kg Gentamicin sulfate at 12 h intervals | 20 | Kidney | IM | 77 days (87.71 ppm) | >77 days | NS | NS | 1988 |
| Kanamycin | Sheep; Bergamo; adult; n = 12 study; n = 3/time pt | US Tol: Not established. EMA established MRL: 600 ppb (liver); 2500 ppb (kidney); 100 ppb (muscle). | Bioassay | NS | NS | IM | 20 mg/kg Kanamycin | 1 | Liver | IM | 3 days (2.2 ppm) | 6 days | NS | NS | 1991 |
Table 1. Cont.

| Analyte | Species; Breed; Age; # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/ Year |
|----------|-----------------------------------------------|----------------|------------------|-----|-----|-------------------------|-------------------------|------------|----------------|-------------------------------------------------|-------------------------------------------------|----------|-----------------------|-------------|
| Neomycin | Goat; NS; NS; n = 18 study; n = 4/time pt      | US Tol: 3600 ppb (liver); 7200 ppb (kidney) | Bioassay NS 0.5 ppm | POMW | 22 mg/kg Neomycin sulfate daily | 14 | Liver Kidney Muscle Fat | ND @ 12 h | ND @ 12 h | 12 h | >96 h | Healthy NS | [15] 1996 |
| Neomycin | Goat; NS; NS; n = 20 study; n = 5/time pt      | US Tol: 3600 ppb (liver); 7200 ppb (kidney) | Bioassay NS 0.5 ppm | PO  | 22 mg/kg Neomycin sulfate daily | 14 | Liver Kidney Muscle Fat | ND @ 12 h | ND @ 12 h | 12 h | >96 h | Healthy NS | [16] 2000 |
| Neomycin | Goat; NS; NS; n = 20 study; n = 4/time pt      | US Tol: 3600 ppb (liver); 7200 ppb (kidney) | NS NS 0.5 ppm | POMW | 22 mg/kg Neomycin sulfate daily | 14 | Liver Kidney Muscle Fat | ND @ 12 h | ND @ 12 h | 12 h | >96 h | Healthy NS | [17] 1995 |
| Neomycin | Sheep; NS; NS; n = 18 study; n = 4/time pt     | US Tol: 3600 ppb (liver); 7200 ppb (kidney) | Bioassay NS 0.5 ppm | POMW | 22 mg/kg Neomycin sulfate daily | 14 | Liver Kidney Muscle Fat | ND @ 12 h | ND @ 12 h | 12 h | >96 h | Healthy NS | [15] 1996 |
| Neomycin | Sheep; NS; NS; n = 20 study; n = 5/time pt     | US Tol: 3600 ppb (liver); 7200 ppb (kidney) | Bioassay NS 0.5 ppm | POMW | 22 mg/kg Neomycin sulfate daily | 14 | Liver Kidney Muscle Fat | ND @ 12 h | ND @ 12 h | 12 h | >96 h | Healthy NS | [16] 2000 |
| Neomycin | Sheep; NS; NS; n = 20 study; n = 4/time pt     | US Tol: 3600 ppb (liver); 7200 ppb (kidney) | Bioassay NS 0.5 ppm | POMW | 22 mg/kg Neomycin sulfate daily | 14 | Liver Kidney Muscle Fat | ND @ 12 h | ND @ 12 h | 12 h | >96 h | Healthy NS | [17] 1995 |
Table 1. Cont.

| Analyte | Species; Breed; Age; # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/ Year |
|---------|--------------------------------------------------|----------------|------------------|-----|-----|-------------------------|-------------------------|------------|--------|------------------------------------------------------------|---------------------------------------------------------------|------------|----------------------|---------------|
| Neomycin | Sheep; NS; NS; n = 20 study, n = 4/time point, 3600 ppb (liver), 7200 ppb (kidney), 1200 ppb (muscle); EMA extrapolated to all food-producing species: 5500 ppb (liver), 9000 ppb (kidney), 500 ppb (muscle, fat) | NS NS 0.5 ppm POMW | 22 mg/kg Neomycin sulfate daily | 14 | Liver Kidney Muscle Fat | ND @ 1 day 1 day (male) (1.26 ppm) 3 days (female) (0.45 ppm) 7 days (male) | Not detected | Healthy NS [34] 1996 |
| | Sheep; NS; NS; n = 4 | HS LC NS 50 ppb IM | 10 mg/kg Streptomycin combined w/ dihydro-streptomycin daily | 3 | Milk | 48 h (0.07 ppm) | 60 h | Healthy Lactating, Milked 2×/day [25] 2005 |
| | Sheep; Suffolk & Suffolk/Cheviot; adult; n = 9 | HS LC N 0.02 ppm 0.05 ppb† 0.05 ppm IM | 10 mg/kg Streptomycin combined w/ dihydro-streptomycin daily | 3 | Milk | 48 h (0.07 ppm) | 60 h | Healthy Milked 2×/day [26] 2002 |
| | Sheep; NS; NS; NS | HS LC N 0.02 ppm 0.05 ppb† 0.05 ppm IM | 10 mg/kg Streptomycin daily | 3 | Liver Kidney Muscle Fat Inj. Site | 2 days (655 ppb) >2 days | 2 days (914 ppb) >2 days 2 days | Healthy NS [30] 2000 |

† Manuscript states limit of quantitation as 0.05 ppb; however, the limit of detection is in parts per million, therefore it is likely an error and should be interpreted as 0.05 parts per million. # = number. * Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. Abbreviations: 2×/day: twice daily. LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. MRL: Maximum residue limit. ND: Not detected. NS: Not specified. Routes of Administration: IMM = intramammary, IM = intramuscular, IV = intravenous, PO = per os, POMF = per os as medicated feed, POMW = per os as medicated water, SC = subcutaneous. § Data points manually extracted using scanning software (Webplot digitizer or UnScanIt 7.0). Units: s = seconds, min = minutes, h = hours, ppt = parts per trillion, ppb = parts per billion, ppm = parts per million.
3.2. Amphenicols

Amphenicols (chloramphenicol, florfenicol, thiamphenicol) are broad-spectrum antibiotics. These antibiotics are typically bacteriostatic agents that act by inhibiting microbial protein synthesis by binding to the 50s bacterial ribosomal subunit. Amphenicols are broad-spectrum against many aerobic and anaerobic Gram-positive and Gram-negative bacteria.

Little pharmacokinetic data is available following the use of amphenicols in sheep or goats. The limited data available in goats shows that florfenicol and thiamphenicol residues do enter the milk after intramuscular and intravenous administration, however tissue data was not available [35,36]. In one study, thiamphenicol concentrations were higher in the mammary gland that was frequently stripped compared to the gland that was not [35].

In the United States, there are no amphenicol products FDA-approved for use in sheep or goats. Chloramphenicol is prohibited from use in food producing animals in several countries including the United States, European Union, and Canada [6,37,38] due to the risk of blood dyscrasias, such as aplastic anemia and bone marrow suppression, in humans. Table 2 summarizes the published literature evaluating edible tissue or milk residues of amphenicols following treatment of sheep and goats.
Table 2. Amphenicol residues in milk or edible tissue samples from sheep or goats following treatment.

| Analyte          | Species, Breed, Age; # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matris         | Last Sampling Time Point (Past-Last Treatment When Residues WERE Detected) | Sampling Time Point When NO Residues Were Detected (Past-Last Treatment) | Health Status | Additional Information | Source/ Year |
|------------------|--------------------------------------------------|----------------|-------------------|-----|-----|--------------------------|--------------------------|------------|----------------|---------------------------------------------------------------------------|---------------------------------------------------------------|----------------|------------------------|------------|
| Chloramphenicol  | Sheep; Awassi; adult; n = 2                       | US Tol: Not established. EMA MRL: Not established. | Chemically       | NS  | NS  | IM                        | 50 mg/kg Chloramphenicol  | 1          | Milk           | 26 h (1.68 ppm §)          | >26 h                                                       | Healthy        |                       | [39] 1973    |
|                   |                                                  |                | Bioassay         | NS  | NS  | IM                        | 50 mg/kg Chloramphenicol  | 1          | Milk           | 26 h (2.02 ppm §)          | >26 h                                                       | Healthy        | Lactating              | [41] 1973    |
|                   | Radio-activity                                  |                |                  | NS  | NS  | IM                        | 50 mg/kg Chloramphenicol (radilabeled) | 1          | Milk           | 13 h (NS)                                                   | >13 h                                                       | Healthy        |                       | [42] 1990    |
| Chloramphenicol   | Sheep; Awassi; adult; n = 1                      | US Tol: Not established. EMA MRL: Not established. | Bioassay         | NS  | NS  | IV                        | 50 mg/kg Chloramphenicol sodium succinate then 12.5 mg/kg for 2 doses at 90 min interval | 3          | Milk           | 24 h (0.65 ppm §)          | 36 h                                                        | Healthy        | Lactating, Milked 2x/day | [41] 1973    |
|                   | Radio-activity                                  |                |                  | NS  | NS  | IV                        | 50 mg/kg Chloramphenicol sodium succinate then 12.5 mg/kg for 2 doses at 90 min interval | 3          | Milk           | 48 h (0.81 ppm §)          | 60 h                                                        | Healthy        |                       |             |
| Chloramphenicol   | Sheep; Awassi; Adult; n = 2                      | US Tol: Not established. EMA MRL: Not established. | Bioassay         | NS  | NS  | IM                        | 50 mg/kg Chloramphenicol   | 1          | Milk           | 56 h (0.85 ppm §)          | >56 h                                                       | Healthy        | Lactating              | [39] 1974    |
|                   | Radio-activity                                  |                |                  | NS  | NS  | IM                        | 50 mg/kg Chloramphenicol (radilabeled) | 1          | Milk           | 56 h (0.2 ppm §)           | >56 h                                                       | Healthy        |                       | [39] 1974    |
| Chloramphenicol   | Sheep; Rouge de L’Ouest; adult; n = 11 study; n = 3 & 2/time pt | US Tol: Not established. EMA MRL: Not established. | HPLC             | 2 ppb | NS  | IM                        | 30 mg/kg Chloramphenicol   | 1          | Liver           | 24 h (0.35 ppm §)          | >38 h                                                      | Healthy        |                       | [40] 1990    |
|                   |                                                  |                |                  |      |     |                           |                           |            | Kidney          | 206 h (0.76 ppm §)         | >38 h                                                      | Healthy        |                       |             |
|                   |                                                  |                |                  |      |     |                           |                           |            | Muscle          | 206 h (2.13 ppm §)         | >38 h                                                      | Healthy        |                       |             |
|                   |                                                  |                |                  |      |     |                           |                           |            | Inj. Site       | 206 h (4.33 ppm §)         | >38 h                                                      | Healthy        |                       |             |
| Chloramphenicol   | Sheep; Awassi; adult; n = 2                      | US Tol: Not established. EMA MRL: Not established. | Bioassay         | NS  | NS  | IV                        | 30 mg/kg Chloramphenicol sodium succinate | 1          | Milk           | NS                         | NS                                                         | Healthy        | Lactating, Milked 2x/day | [41] 1975    |
### Table 2. Cont.

| Analyte | Species, Breed, Age, # of Animals per Time Point | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|---------|-------------------------------------------------|----------------|------------------|-----|-----|-------------------------|--------------------------|-----------|--------|-------------------------------------------------|-------------------------------------------------|-------------|---------------------|------------|
| Florfenicol amine | Sheep; Polypay; NS; n = 25 study; n = 5/time pt | US Tol: Not established. EMA MRL by extension from bovine to ovine: 3000 ppb (liver); 300 ppb (kidney); 200 ppb (muscle). | HPLC | NS | NS | SC | 40 mg/kg Florfenicol daily | 3 | Liver | 40 days (1.99 ppm) | >40 days | NS | NS | [42] 2006 |
| Florfenicol amine | Sheep; mixed breed; 6–7 months; n = 26 study; n = 5/time pt | US Tol: Not established. EMA MRL by extension from bovine to ovine: 3000 ppb (liver); 300 ppb (kidney); 200 ppb (muscle). | HPLC | NS | | | 40 mg/kg Florfenicol daily | 3 | Liver | 40 days (NS) | >40 days | Healthy | NS | [43] 2008 |
| Thiamphenicol | Sheep; crossbred; adult; n = 16 study; n = 4/time pt | US Tol: Not established. EMA MRL by extension from bovine to ovine: 50 ppb (liver, kidney, muscle, fat, milk). | HPLC | 5 ppb | 21 ppb | IM | 30 mg/kg Thiamphenicol daily | 5 | Liver | ND # 4 days | 4 days | Healthy | NS | [44] 2000 |
| Chloramphenicol | Goat; Does; 9–12 months; n = NS | US Tol: Not established. EMA MRL: Not established. | Colorimetric | NS | NS | IM | | | | | | | | |
| Chloramphenicol | Goat; NS/Adult; n = 2 | US Tol: Not established. EMA MRL: Not established. | HPLC | 5 ppb | | IM | | | | | | | | |
| Thiamphenicol | Goat; Saanen & crossbred; adult; n = 6 | US Tol: Not established. EMA MRL by extension from bovine to ovine: 50 ppb (liver, kidney, muscle, fat, milk). | HPLC | NS | NS | IV | 50 mg/kg Thiamphenicol | 1 | Milk | 12 h (4.02 ppm 5) | >12 h | Healthy | Late Lactation | [35] 1991 |
| Florfenicol | Goat; Saanen & crossbred; adult; n = 10 | US Tol: Not established. EMA MRL: Not established. | HPLC | NS | NS | IV | 25 mg/kg Florfenicol | 1 | Milk | 8 h (0.21 ppm 5) | >8 h | Healthy | Mid-Lactation | [36] 1991 |

5 Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # = number. *Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. Abbreviations: 2×/day: twice daily. LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. MRL: Maximum residue limit. ND: Not detected. NS: Not specified. Routes of Administration: IMM = intramammary, IM = intramuscular, IV = intravenous, PO = per os, POMF = per os as medicated feed, SC = subcutaneous. Units: s = seconds, min = minutes, h = hours, ppb = parts per billion, ppm = parts per million.
3.3. *Penicillin and Penicillin-Derivatives*

Penicillins (penicillin G procaine, penicillin G benzathine) and penicillin-derivatives (amoxicillin, ampicillin, cloxacillin, dicloxacillin, nafcillin) are bactericidal antibiotics that act by inhibiting cell wall synthesis. These antibiotics display a broad spectrum of activity against many Gram-positive and Gram-negative bacteria, including anaerobic bacteria.

Amoxicillin and ampicillin show limited milk penetration or accumulation, even when the blood-milk barrier is altered in cases of mastitis [47,48]. However, beta-lactam products labeled for intramammary administration in cattle can result in very high antibiotic concentrations within the small ruminant udder due to the differences in both body and udder size [49,50]. Consequently, intramammary administration of cattle-labeled products to small ruminants can lead to persistent residues present in the milk and require extended withdrawal intervals beyond the labeled withdrawal times for cattle [49,51–54]. In the United States, penicillin G procaine is FDA-approved for use in sheep via intramuscular administration. In the EU, MRLs have been extended from bovine species to all ruminants for nafcillin.

Due to the potential for allergic reactions to penicillin and penicillin-derivatives in humans, caution must be exhibited to ensure food-products from small ruminants do not contain traces of penicillins [55,56]. Table 3 summarizes the published literature evaluating edible tissue or milk residues of beta-lactams or penicillins following treatment of sheep and goats.
## Table 3. Penicillin and penicillin-derivative residues in milk or edible tissue samples from sheep or goats following treatment.

| Analyte | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOQ | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|---------|-----------------------------------|---------------|------------------|-----|-----|--------------------------|-------------------------|-----------|--------|---------------------------------------------------------------|---------------------------------------------------------------|----------------|------------------------|------------|
| Amoxicillin | Sheep; Texel; adult; n = 12 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IM | 10 mg/kg Amoxicillin sodium | 1 | Milk | 500 min (0.03 ppm §) | >500 min | Healthy & Diseased-mastitis | Lactating | [47] 1979 |
| Amoxicillin | Goats; Saanen; adult; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | 0.001 ppm | NS | IMM | 200 mg Amoxicillin trihydrate; 50 mg potassium clavulanate; 50 mg prednisolone combo product at 8 h intervals | 3 | Milk | 5 days (0.07 ppm §) | >5 days | Healthy | Lactating; Milked 2 × /day; 1 syringe / gland | [40] 1989 |
| Amoxicillin | Sheep; Texel; adult; n = 12 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IM | 10 mg/kg Amoxicillin trihydrate | 1 | Milk | 500 min (0.06 ppm §) | >500 min | Healthy & Diseased-mastitis | Lactating | [47] 1979 |
| Amoxicillin | Sheep; Friesland; adult; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | 0.001 ppm | NS | IMM | 200 mg Amoxicillin trihydrate; 50 mg potassium clavulanate; 50 mg prednisolone combo product at 8 h intervals | 3 | Milk | 7 days (0.03 ppm §) | >7 days | Healthy | Lactating; Milked 2 × /day; 1 syringe / gland | [51] 1989 |
| Amoxicillin | Sheep; Comisana; adult; n = 10 | US Tol: Not established. EMA MRL: Not established. HPLC | 1.5 ppb | 2.5 ppb | IM | 12.5 mg/kg Amoxicillin trihydrate (long acting) | 1 | Milk | 132 h (1.5 ppb) | 6 days | Healthy | Lactating; Milked 2 × /day | [57] 2002 |
| Amoxicillin | Sheep; domestic dairy breed; adult; n = 10 | US Tol: Not established. EMA MRL: Not established. | Bioassay | 3 ppb | 4 ppb | IMM w/ IM | 200 mg Amoxicillin trihydrate; 50 mg potassium clavulanate; 50 mg prednisolone combo product (IMM) at 12 h intervals co-administered with 140 mg/35 mg per ml amoxicillin trihydrate/clavulanic acid (IM) at 24 h intervals | | Milk | 192 h (4.5 ppb) | >192 h | Diseased-mastitis | Lactating; 1 syringe/gland | [52] 2009 |
| Amoxicillin | Sheep; crossbred; NS; n = 36 study; n = 4/time pt Dairy type; adult; n = 20 | US Tol: Not established. EMA MRL: Not established. LC-MS | 5.8 ppb | 25.6 ppb | IM | 7 mg/kg Amoxicillin 7 daily | 5 | Liver | NS | 48 h | NS | Healthy | NS | [46] 2012 |
| Amoxicillin | | | | NS | NS | NS | 7 mg/kg Amoxicillin 7 daily | 5 | Muscle | NS | 48 h | NS | Healthy | NS | [46] 2012 |
| Amoxicillin | | | | NS | NS | NS | 7 mg/kg Amoxicillin 7 daily | 5 | Fat | NS | 48 h | NS | Healthy | NS | [46] 2012 |
| | | | | NS | NS | NS | 7 mg/kg Amoxicillin 7 daily | 5 | Inj. Site | NS | 48 h | NS | Healthy | NS | [46] 2012 |
| | | | | NS | NS | NS | 7 mg/kg Amoxicillin 7 daily | 5 | Liver | NS | 48 h | NS | Healthy | NS | [46] 2012 |
| Amoxicillin | Sheep; Texel; adult; n = 12 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IM | 10 mg/kg Ampicillin sodium | 1 | Milk | 8 h (0.01 ppm §) | >8 h | Healthy | Diseased-mastitis | Lactating | [47] 1979 |
### Table 3. Cont.

| Analyte        | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues Were Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status              | Additional Information                      | Source/Year |
|----------------|-----------------------------------|---------------|-------------------|-----|-----|--------------------------|--------------------------|-------------|--------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------|------------------------------------------------|-------------|
| Ampicillin     | Goats; Saanen; adult; n = 24 study | US Tol: Not established. EMA MRL: Not established. | HPLC            | 1.5 ppb | 2.2 ppb | IM                        | 15 mg/kg Amoxicillin † (long acting) at 72 hour interval | 2           | Milk    | 168 h (6.0 ppb) | 193 h                               | Healthy       | Mid-lactation; Milked 2 × /day              | [34] 2010    |
| Ampicillin     | Sheep; Texel; adult; n = 12       | US Tol: Not established. EMA MRL: Not established. | Bioassay         | NS     | NS    | IM                        | 10 mg/kg Ampicillin trihydrate | 1           | Milk    | 12 h (0.04 ppm§) | >12 h                              | Healthy       | Diseased-mastitis                           | [47] 1979    |
| Ampicillin     | Sheep; NS; adult; n = 4           | US Tol: Not established. EMA MRL: Not established. | Bioassay         | NS     | NS    | IM                        | 250,000 IU Ampicillin trihydrate | 1           | Milk    | 72 h (0.11 ppm) | 96 h                               | NS            | Lactating; Half syringe per gland            | [93] 1977    |
| Cloxacillin    | Goats; Saanen; adult; n = 8       | US Tol: Not established. EMA MRL: Not established. | Bioassay         | 0.02 ppm | NS    | IM                        | 200 mg Cloxacillin at 48 h intervals | 3           | Milk    | 13 h (0.15 ppm§) | >13 h                              | Healthy       |                               | [52] 1984    |
| Dicloxacillin  | Sheep; Sarda; 2–3.5 years; n = 4 | US Tol: Not established. EMA MRL: Not established. | HPLC             | NS     | 0.02 ppm | IM                        | 100 mg/half Dicloxacillin at 12 h intervals | 3           | Milk    | 60 h (0.109 ppm) | 72 h                               | Healthy       | Lactating; High production; Milked 2 × /day | [56] 2000    |
| Nafcillin      | Goats; NS; Adults; n = 220        | US Tol: Not established. EMA MRL: Not established. | Bioassay         | 0.012 ppm | 0.015 ppm | IM                        | 300,000 IU Procaine benzylpenicillin; 100 mg dihydrostreptomycin; 100 mg nafcillin | 1           | Milk    | NS | 3 days | Healthy | Dry off period (mean 61.0 ± 14.3 days SD (range 23–156 days); 1 tube per gland before drying off; Sample collected after kidding | [27] 1995    |
| Nafcillin      | Sheep; Lacaune; adult; n = 8      | US Tol: Not established. EMA MRL: Not established. | Bioassay         | 0.02 ppm | NS    | IM                        | 300,000 IU Procaine benzylpenicillin; 100 mg dihydrostreptomycin; 100 mg nafcillin | 1           | Milk    | ND | 2 days | Healthy | Dry off period (mean 112 days (range 95–222 days); 1 tube per gland before drying off; Sample collected after kidding | [28] 1995    |
| Pen-ethamate   | Goats; NS; Adult; n = 2           | US Tol: Not established. EMA MRL: Not established. | Bioassay         | NS     | NS    | IM                        | 200,000 IU Penethamate (oil) 200,000 IU Penethamate (aqueous) | 1           | Milk    | 1 day (0.004 U/mL) | 1 day                               | NS            | Lactating                                | [98] 1966    |
| Penicillin     | Sheep; Awassi; Adult; n = 2       | US Tol: Not established. EMA MRL: Not established. | Bioassay         | NS     | NS    | IM                        | 20 mg/kg Penicillin † | 1           | Milk    | 12 h (0.02 ppm§) | 1 day                               | Healthy       | Diseased-mastitis                           | [29] 1974    |
### Table 3. Cont.

| Analyte          | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|------------------|-----------------------------------|---------------|-------------------|-----|-----|------------------------|-------------------------|------------|--------|--------------------------------------------------------------------------|------------------------------------------------------------------------|---------------|------------------------|-------------|
| **Penicillin**   | Goats; NS; Adult; n = 2           | US Tol: Not established. EMA MRL: Not established. | Busaway          | NS  | NS  | IM                     | 200,000 IU Procaine penicillin (oil) | 1          | Milk   | 1 day (0.010 U/mL)                                                       | >1 day                                                  | Lactating    | Dry off period (mean 61.0 ± 14.3 days (range 23–156 days) 1 tube per gland before drying off. Sample collected after kidding | [98] 1966 |
|                  |                                   |               |                   |     |     |                        | 200,000 IU Procaine penicillin (aqueous) | 1          | Milk   | 12 h (0.012 U/mL)                                                       | 1 day                                                 |               | Early & mid-lactation; Milked 2x/day, 1 syringe per gland                  | [96] 1984 |
|                  |                                   |               |                   |     |     |                        | 500,000 IU Procaine penicillin (oil) | 1          | Milk   | 1 day (0.017 U/mL)                                                      | >1 day                                                |               |                                                                     | [86] 1996 |
|                  |                                   |               |                   |     |     |                        | 500,000 IU Procaine penicillin (aqueous) | 1          | Milk   | 1 day (0.02 U/mL)                                                      | >1 day                                                 |               |                                                                     |             |
| **Penicillin**   | Goats; dairy type; 2-7 years; n = 10 | US Tol: Not established. EMA MRL: Not established. | Busaway          | 0.002 IU/mL | 0.004 IU/mL | IMM                  | 300,000 IU Procaine benzylpenicillin, 100 mg dihydro-streptomycin, 100 mg nafcillin combo product | 1          | Milk   | 7 days Healthy                                                          | 4 days                                                | Healthy      | Dry off period (mean 112 days (range 85–223 days) 1 tube per gland before drying off. Sample collected after lambing | [28] 1995 |
|                  |                                   |               |                   |     |     |                        | 100,000 IU Procaine G penicillin at 12 h intervals | 3          | Milk   | 60 h (0.49 ppm §)                                                      | >60 h                                                 |               |                                                                     | [61] 2010 |
| **Penicillin**   | Sheep; NS; n = 2                  | US Tol: Zero. EMA MRL: Not established. | LC-MS            | 0.005 ppm | NS  | IM                    | 1500 mg Benzylpenicillin daily | 5          | Liver   | 2 days (0.24 ppm)                                                      | >2 days                                                | Healthy      |                                                                     |             |
|                  |                                   |               |                   |     |     |                        | Kidney Muscle | 2 days (0.07 ppm)                                                    | >2 days                                               | NS           |                                                                     | [95] 1996 |
| **Penicillin**   | Sheep; Lacaune; adult; n = 8      | US Tol: Zero. EMA MRL: Not established. | Busaway          | 0.016 ppm | NS  | IMM                   | 300,000 IU Procaine benzylpenicillin, 100 mg dihydro-streptomycin, 100 mg nafcillin | 1          | Milk   | 3 days (0.01 ppm §)                                                   | 4 days                                                | Healthy      |                                                                     |             |
| **Penicillin**   | Sheep; NS; 14-17 months; n = 10/1 study; n = 0/2 time pt | US Tol: Zero. EMA MRL: Not established. | Busaway          | 0.0125 ppm | NS  | IM                    | 3000 IU/lt Penicillin G penicillin daily | 4          | Liver   | NS                                                            | 9 days                                                | Healthy      |                                                                     |             |
|                  |                                   |               |                   |     |     |                        | Kidney Muscle | NS                                                            | 9 days                                               | NS           |                                                                     |             |
|                  |                                   |               |                   |     |     |                        | Fat | NS                                                            | 9 days                                               | NS           |                                                                     | [61] 2010 |
|                  |                                   |               |                   |     |     |                        | Inj. Site | NS                                                            | 9 days                                               | NS           |                                                                     |             |
| **Penicillin**   | Sheep; Awassi; adult; n = 3       | US Tol: Zero. EMA MRL: Not established. | Busaway          | NS  | NS  | IV                     | 20 mg/kg Penicillin †, then 10 mg/kg for 4 doses 45 min interval | 5          | Milk   | 26 h (0.01 ppm §)                                                     | 48 h                                                  | Healthy      | Lactating; Milked 2x/day                                                | [24] 1973 |
| **Penicillin**   | Sheep; Sardinian; Adult; n = 5     | US Tol: Zero. EMA MRL: Not established. | Radioactivity    | NS  | NS  | IV                     | 20 mg/kg Penicillin † (radiolabeled), then 10 mg/kg for 4 doses 45 min interval | 5          | Milk   | 9 h (0.10 ppm §)                                                     | 10 h                                                  | Healthy      |                                                                     |             |
| **Penicillin**   | Sheep; domestic dairy breed; adult; n = 10 | US Tol: Zero. EMA MRL: Not established. | HPLC             | 2.6 ppb | 8.8 ppb | IM                    | 24 mg/kg Penicillin G sodium | 1          | Milk   | 8 days (0.01 ppm)                                                     | > 9 days                                               | NS           | Lactating; Milked 2x/day                                                | [50] 1998 |
| **Penicillin**   | Sheep; domestic dairy breed; adult; n = 10 | US Tol: Zero. EMA MRL: Not established. | Busaway          | 3 ppb | 4 ppb | IMM co-administered w/IM | 1,000,000 IU Benzyloxycarbonyl penicillin (IM) daily co-administered with 250,000 IU benzylpenicillin (IM) at 24 h intervals | 5          | Milk   | 192 h (8.9 ppm)                                                   | 192 h                                                 | Diseased     | Lactating; 1 syringe/gland                                               | [12] 2009 |

Salt form unclear or not stated in article. § = number. * Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. † Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). Abbreviations: 2x/day: twice daily. LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. MRL: Maximum residue limit. ND: Not detected. NS: Not specified. Routes of Administration: IMM = intramammary, IM = intramuscular, IV = intravenous, PO = per os, POMF = per os as medicated feed, SC = subcutaneous. Units: s = seconds, min = minutes, h = hours, ppb = parts per billion, ppm = parts per million, mL = milliliter.
3.4. Cephalosporins

Cephalosporins (first-generation: cephapirin, cefacetrile, cephalothin, cephradine, cephalaxin; second-generation: cefonicid; third-generation: ceftazidime, ceftiofur, ceftriaxone; fourth-generation: cefquinome, cefepime) are beta-lactam antibiotics divided into five ‘generations’ based on the spectrum of activity (first-generation cephalosporins are active against Gram-positive bacteria but not Gram-negative bacteria, while each consecutive generation has increased activity against Gram-negative bacteria with decreased Gram-positive activity). In the United States, cephalosporins are permitted to be used in an extra-label manner in minor species, such as sheep and goats, unlike major food producing species (cattle, swine, chickens & turkeys).

In general, cephalosporins have low penetration into milk [62–66] with variable pharmacokinetic parameters and slower milk depletion in mastitic animals [67,68]. Cephalexin exhibited a nearly double terminal serum elimination half-life in ewes compared to cattle, in addition to increased concentrations of cephalexin residues [69]. Cephapirin exhibited a longer presence of residues in goat samples compared to cattle when used for mastitis treatment [70].

Ceftiofur sodium (Naxcel®) is currently the only FDA-approved cephalosporin for use in sheep and goats with a 0 day meat and milk withdrawal time. Pharmacokinetic parameters of both intravenous and intramuscular ceftiofur sodium are found to be similar between sheep and goats when administered at the same dose [71]. Table 4 summarises the published literature evaluating edible tissue or milk residues of cephalosporins following treatment of sheep and goats.
**Table 4. Cephalosporin residues in milk or edible tissue samples from sheep or goats following treatment.**

| Analyte      | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues Were Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|--------------|----------------------------------|---------------|-------------------|-----|-----|--------------------------|--------------------------|------------|--------|-----------------------------------------------|-----------------------------------------------|---------------|-----------------------|-------------|
| Cefepime     | Goat; NS; Adult; n = 10           | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS  | NS  | IV                        | 20 mg/kg Cefepime         | 1          | Milk   | 12 h (0.27 ppm)                             | >12 h                                    | Healthy     | Lactating: Milked 2x/day | [62] 2004   |
| Cefepime     | Goat; NS; 1 year; n = 5           | US Tol: Not established. EMA MRL: Not established. | HPLC    | 1.15 ppm | 3.49 ppm | IM                      | 20 mg/kg Cefepime         | 1          | Milk   | 12 h (0.25 ppm)                             | >12 h                                    | Healthy     | Lactating: Milked 1x/day | [7] 2010    |
| Cefonicid    | Goat; Montanara-Granadina; 2–4 years; n = 6 | US Tol: Not established. EMA MRL: Not established. | HPLC    | 500 ppb | 790 ppb  | IV                        | 10 mg/kg Cefonicid sodium | 1          | Milk   | <LOQ @ 1 h                                  | 1 h                                      | Healthy     | Lactating: Milked 1x/day | [63] 2020   |
| Cef-quinome  | Goat; Zaraibi; 30–36 months; n = 5 | US Tol: Not established. EMA MRL: Not established. | HPLC    | 0.006 ppm | 0.027 ppm | IV                        | 3 mg/kg Cefquinome sulfate | 1          | Milk   | 48 h (0.01 ppm)                             | >2 days                                   | Healthy     | Lactating: Milked 1x/day | [67] 2019   |
| Cef-quinome  | Goat; Zaraibi; 30–36 months; n = 5 | US Tol: Not established. EMA MRL: Not established. | IMM     | 0.006 ppm | 0.027 ppm | IM                        | 75 mg Cefquinome sulfate | 1          | Milk   | 120 h (0.01 ppm)                           | >120 h                                  | Healthy     | Early & mid-lactating: 1 full tube per gland | [64] 2019   |
| Cef-tazidime | Goat; Creole; Adult; n = 1        | US Tol: Not established. EMA MRL: Not established. | Bioassay | 0.125 ppm | 0.3 ppm  | IM                        | 10 mg/kg Cefotaxime       | 1          | Milk   | 12 h (0.02 ppm)                             | >12 h                                   | Healthy     | Lactating: Milked 2x/day | [7] 2011    |
| Ceftriaxone  | Goat; Alpine & Alpine-Saanen; 4 years; n = 6 | US Tol: 100 ppb (milk). EMA MRL: extrapolated from bovine to all mammalian species 100 ppb (milk). | HPLC    | NS  | 0.05 ppm | IV                        | 2.2 mg/kg Ceftriaxone sodium | 1          | Milk   | 24 h (NS)                                   | 2 days                                  | Healthy     | Lactating: Milked 2x/day | [7] 1994    |
| Ceftriaxone  | Sheep; NS; Adult; n = 9           | US Tol: 100 ppb (milk). EMA MRL: extrapolated from bovine to all mammalian species 100 ppb (milk). | HPLC    | NS  | NS    | IM                        | 2 mg/kg Ceftriaxone sodium daily | 5          | Milk   | <LOQ @ 12 h                                | 12 h                                    | Healthy     | Lactating                 | [7] 2006    |
| Ceftriaxone  | Goat; mixed dairy type; 28 months; n = 5 | US Tol: 100 ppb (milk). EMA MRL: extrapolated from bovine to all mammalian species 100 ppb (milk). | LC-MS   | NS  | 20 ppb | IM                        | 125 mg Ceftriaxone hydrochloride sodium | 2          | Milk   | 72 h (37 ppm)                               | 4 days                                  | Healthy     | Milk: Early lactation: Milked 2x/day Left udder half infused | [7] 2015    |
| Ceftriaxone  | Goat; Dairy type; 1.5–2 years; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS  | NS    | IV                        | 20 mg/kg Ceftriaxone sodium | 1          | Milk   | 2 h (0.11 ppm)                              | 2.5 h                                   | Healthy     | Lactating                 | [61] 2013   |
### Table 4. Cont.

| Analyte | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information Source/Year |
|---------|----------------------------------|---------------|-------------------|-----|-----|-------------------------|--------------------------|-------------|--------|--------------------------------|---------------------------------|----------------|----------------------------------|
| Ceftriaxone | Goat; NS; 2–2.5 years; n = 10 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | 0.2 ppm | IV | 20 mg/kg Ceftriaxone 20 mg/kg Ceftriaxone | 1 | Milk | 8 h (0.36 ppm) 10 h | 10 h | Healthy Lactating | [60] 2005 |
| Ceftriaxone | Sheep; native breed; 2–5 years; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | 0.1 ppm | IV | 20 mg/kg Ceftriaxone 20 mg/kg Ceftriaxone | 1 | Milk | 10 h (0.22 ppm) 12 h | 12 h | Healthy Lactating | [75] 2006 |
| Ceph-acetrile | Sheep; Texel; adult; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IM | 12 mg/kg Benzathinecephalothin | 1 | Milk | 24 h (NS) >1 day | 24 h | Healthy Lactating | [76] 2005 |
| Cephalexin | Goat; NS; 1 year; n = 2 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IM | 10 mg/kg Cephalexin | 1 | Milk | 8 h (0.46 ppm) >8 h | Healthy | Late lactation | [77] 1998 |
| Cephalexin | Sheep; Awassi; adult; n = 10 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IM | 10 mg/kg Cephalexin | 1 | Milk | 8 h (0.19 ppm) >12 h | Healthy | Early lactation; Restricted diet | [78] 1996 |
| Cephalothin | Goat; Creole; adult; n = 20 | US Tol: Not established. EMA MRL: Not established. | HPLC | 0.01 ppm | NS | IV | 50 mg/kg Cephalothin | 1 | Milk | 12 h (0.31 ppm) >8 h | Healthy | Early lactation; Balanced diet | [79] 1986 |
| Cephapirin | Goat; French Alpine; 1–7 years; n = 20 | US Tol: Not established. EMA MRL: Not established. | HPLC | 0.01 ppm | NS | IV | 200 mg Cephapirin at 12 h intervals | 1 | Milk | 6 h (0.08 ppm) >8 h | Healthy | Early lactation; Restricted diet | [80] 2007 |
| Cephradine | Goat; dairy type; 2–7 years; n = 10 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IMM | 200 mg Sodium cephradine at 12 h intervals | 2 | Milk | ND > 192 h 8 days | Healthy | Early lactation; Milked 2 × /day | [81] 1986 |
| Cephradine | Goat; NS; adult; n = 4 | US Tol: Not established. EMA MRL: Not established. | Spectrophotometrically | 0.2 ppm | NS | IMM | 50 mg/kg Cephradine 30 mg/kg Cephradine at 12 h intervals | 1 | Milk | 8 h (1.55 ppm) 12 h | Healthy and Diseased | Lactating | [82] 1994 |

§ Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # = number. * Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. Abbreviations: 1 × /day: once daily. 2 × /day: twice daily. LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. MRL: Maximum residue limit. ND: Not detected. NS: Not specified. Routes of Administration: IMM = intramammary, IM = intramuscular, IV = intravenous, SC = subcutaneous. Units: s = seconds, min = minutes, h = hours, ppb = parts per billion, ppm = parts per million.
3.5. Fluoroquinolones/Quinolones

Fluoroquinolones (ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, levofloxacin, marbofloxacin, moxifloxacin, norfloxacin, orbifloxacin, pefloxacin, sarafloxacin) are broad-spectrum antibiotics that exhibit concentration-dependent bactericidal activity via inhibition of DNA gyrase in bacterial cells. As a drug class, fluoroquinolones exhibit a high lipid solubility, low protein binding, high bioavailability (especially after parenteral administration) and large volumes of distribution in most species, including small ruminants [81–95]. Due to the importance of fluoroquinolones to human health, fluoroquinolones are prohibited from extra-label drug use in food-producing species in the United States.

Studies suggest that the pharmacokinetics of fluoroquinolones change during lactation due to the increased elimination of the drug from serum [88,96]. Additionally, multiple fluoroquinolones extensively penetrate into milk, with some drugs in the class exhibiting up to a 10× higher concentration in milk compared to plasma or serum [88,96–98]. This variation can be useful in mastitis cases since these drugs can accumulate in the milk at concentrations above the MIC for a sustained period of time [96,97,99].

In the United States, there are no fluoroquinolones FDA-approved for use in small ruminants, and due to the stipulations outlined by AMDUCA in the CFR, fluoroquinolones are prohibited from extra-label use in food-producing species [6]. In the European Union, flumequine is the only approved fluoroquinolone for use in sheep, while MRLs have been extended from bovine species to all food-producing species for enrofloxacin. Table 5 summarizes the published literature evaluating edible tissue or milk residues of quinolones following treatment of sheep and goats.
| Analyte     | Species, Breed, Age, # of Animals | Tolerance/ MRL                                                                 | Analytical Method | LOQ | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/ Year |
|-------------|----------------------------------|-------------------------------------------------------------------------------|-------------------|-----|-----|-------------------------|----------------------------|------------|-----------------|---------------------------------------------------------------|-----------------------------------------------------------------------|----------------|------------------------|-------------|
| Ciprofloxacin | Goats; Nil, adult; n = 6          | US Tol: Prohibited. EMA MRL: Not established.                              | Bioassay          | 0.05 ppm | NS | IV                        | 4 mg/kg Ciprofloxacin       | 1          | Milk           | 24 h (0.07 ppm)                                            | 30 h                                                      | Healthy | Lactating              | [61] 2014   |
| Ciprofloxacin | Goats; Baladi; 30-36 months; n = 5 | US Tol: Prohibited. EMA MRL: Not established.                              | Bioassay          | 0.01 ppm | NS | IV                        | 5 mg/kg Ciprofloxacin       | 1          | Milk           | 10 h (0.11 ppm)                                            | 18 h                                                      | Healthy | Lactating              | [62] 1998   |
| Danofloxacin | Goats; Murciano-Granadina; 1.5–3 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 0.005 ppm | 0.005 ppm | SC                        | 6 mg/kg Danofloxacin       | 1          | Milk           | 36 h (0.01 ppm)                                            | 48 h                                                      | Healthy | Lactating              | [63] 2007   |
| Danofloxacin | Sheep; Manchega; 2–4 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 0.005 ppm | 0.005 ppm | SC                        | 6 mg/kg Danofloxacin       | 1          | Milk           | 36 h (0.02 ppm)                                            | 48 h                                                      | Healthy | Lactating              | [64] 2007   |
| Danofloxacin | Sheep; Assaf, adult; n = 12       | US Tol: Prohibited. EMA MRL: Not established.                              | Bioassay          | 0.04 ppm | NS | IV                        | 1.25 mg/kg Danofloxacin     | 1          | Milk           | 24 h (0.07 ppm)                                            | >1 day                                                     | Healthy | Mal-lactating          | [65] 2007   |
| Danofloxacin | Sheep; Assaf; 2–3 years; n = 5    | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 4 ppb     | 5 ppb                      | IM                        | 1.25 mg/kg co-administered with 0.2 mg/kg tetramethrin | 1          | Milk           | 24 h (0.07 ppm)                                            | >4 h                                                      | Healthy | Mal-lactating          | [66] 2011   |
| Danofloxacin | Sheep; Assaf; 2–3 years; n = 6    | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 4 ppb     | 5 ppb                      | IM                        | 1.25 mg/kg Danofloxacin     | 1          | Milk           | 24 h (0.08 ppm)                                            | >4 h                                                      | Healthy | Mal-lactating          | [67] 2013   |
| Danofloxacin | Sheep; Assaf; 2–3 years; n = 6    | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 100 ppb   | 1                      | IM                        | 1.25 mg/kg Danofloxacin     | 1          | Milk           | 24 h (0.03 ppm)                                            | >4 h                                                      | Healthy | Mal-lactating          | [68] 2013   |
| Danofloxacin | Sheep; Assaf, adult; n = 6        | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 19 ppb    |                      | IM                        | 1.25 mg/kg Danofloxacin standard diet | 1          | Milk           | 24 h (0.05 ppm)                                            | >24 h                                                     | Healthy | Mal-lactating          | [69] 2016   |
| Difloxacin   | Goats; Mastiano-Granadina; 4-5 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 10 ppb    |                      | IV                        | 5 mg/kg Difloxacin          | 1          | Milk           | 40 h (0.02 ppm)                                            | 72 h                                                      | Healthy | Lactating              | [70] 2010   |
| Difloxacin   | Goats; Mastiano-Granadina; 4-5 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                              | HPLC              | 10 ppb    |                      | SC                        | 5 mg/kg Difloxacin          | 1          | Milk           | 36 h (0.02 ppm)                                            | 48 h                                                      | Healthy | Lactating              | [71] 2011   |
### Table 5. Cont.

| Analyte | Species, Breed, Age, # of Animals | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues Were Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment)* | Health Status | Additional Information | Source/ Year |
|---------|---------------------------------|----------------|------------------|-----|-----|-------------------------|----------------------------|-------------|--------|---------------------------------------------------------------|---------------------------------------------------------------|----------------|--------------------------|--------------|
| Enrofloxacin | Goats; Sham; 2-3 years; n = 10 | US Tol: Prohibited; EMA MRL extension from bovine to all food producing species: 100 ppb (milk) | Bioassay | NS | 0.02 ppm | IV | 5 mg/kg Enrofloxacin co-administered with 7.5 mg/kg albendazole PO | 1 | Milk | 24 h (0.06 ppm) | 36 h | Healthy | Lactating | 2005 |
| | | | | | | IV | 5 mg/kg Enrofloxacin co-administered with 7.5 mg/kg albendazole PO | 1 | Milk | 24 h (0.11 ppm) | 24 h | | | |
| | | | | | | IM | 5 mg/kg Enrofloxacin co-administered with 7.5 mg/kg albendazole PO | 1 | Milk | 36 h (0.08 ppm) | 48 h | | | |
| | | | | | | IM | 5 mg/kg Enrofloxacin | 1 | Milk | 24 h (0.16 ppm) | 36 h | | | |
| | Goats; Montano-Granadina; 2.5-3.5 years; n = 6 | US Tol: Prohibited; EMA MRL extension from bovine to all food producing species: 100 ppb (milk) | HPLC | NS | NS | SC | 5 mg/kg Enrofloxacin | 1 | Milk | NS | NS† | Healthy | Lactating | 2009 |
| | | | | | | IV | 5 mg/kg Enrofloxacin (long acting) | 1 | Milk | NS | NS‡ | | | |
| | | | | | | SC | 5 mg/kg Enrofloxacin (long acting) | 1 | Milk | NS | NS§ | | | |
| | Goats; Neo-natal | US Tol: Prohibited; EMA MRL extension from bovine to all food producing species: 100 ppb (milk) | HPLC | NS | 10 ppb | PO | 7.5 mg/kg Enrofloxacin | 1 | Milk | 30 h (0.08 ppm) | 36 h | | | |
| | | | | | | | 5 mg/kg Enrofloxacin | 1 | Milk | 36 h (0.02 ppm) | 48 h | | | |
| | | | | | | | | | | | | | | |
| | Sheep; Neo-natal | US Tol: Prohibited; EMA MRL by extension from bovine to ovine: 200 ppb (liver, 200 ppb (kidney)); 100 ppb (muscle, fat) | HPLC | NS | 10 ppb | PO | 7.5 mg/kg Enrofloxacin | 1 | Milk | 24 h (0.03 ppm †) | 24 h (0.15 ppm †) | >24 h | | Healthy | Lactating | 1998 |
| | | | | | | | | | | | | | | | |
| | Sheep; crossbred; 2-4 years; n = 6 | US Tol: Prohibited; EMA MRL extension from bovine to all food producing species: 100 ppb (milk) | Bioassay | NS | 0.019 ppm | IV | 2.5 mg/kg Enrofloxacin | 1 | Milk | 24 h (0.09 ppm †) | >24 h | Healthy | Lactating; Milked 2×/day | 2005 |
| | | | | | | IM | 2.5 mg/kg Enrofloxacin | 1 | Milk | 24 h (0.05 ppm †) | >24 h | Healthy | Lactating; Milked 2×/day | 2006 |
| | Sheep; Assid; 2-3 years; n = 12 | US Tol: Prohibited; EMA MRL extension from bovine to all food producing species: 100 ppb (milk) | HPLC | NS | NS | IM | 2.5 mg/kg Enrofloxacin co-administered with 14 mg/kg gentamycin IM | 1 | Milk | 24 h (0.09 ppm †) | >24 h | Healthy | Lactating; Milked 2×/day | 2005 |
Table 5. Cont.

| Analyte     | Species, Breed, Age; # of Animals | Tolerance/ MRL                                                   | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment When Residues Were Detected) | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|-------------|-----------------------------------|-----------------------------------------------------------------|-------------------|-----|-----|-------------------------|-------------------------|------------|--------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------|------------------------|-------------|
| Ibafloxacin | Goats; Murciano-Granadina; 3–4 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                   | HPLC NS           | 0 ppb | IV  | 15 mg/kg Ibafloxacin     | 1 Milk                  | 6 h (0.05 ppm §) | 12 h | Healthy Lactating                                                                 | [89] 2007                                                                 |                |                        |             |
| Levofloxacin | Goats; NS; 3–5 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                   | Bioassay NS       | 0.05 ppm | IV | 4 mg/kg Levofloxacin hemihydrate | 1 Milk                 | 36 h (0.06 ppm §) | 48 h | Healthy Lactating                                                                 | [90] 2009                                                                 |                |                        |             |
| Marbofloxacin | Goats; Anglo-nubian; 3–5 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                   | HPLC NS           | 0.025 ppm | IV | 5 mg/kg Marbofloxacin   | 1 Milk                  | 36 h (0.06 ppm §) | 48 h | Healthy Lactating                                                                 | [91] 2017                                                                 |                |                        |             |
| Moxifloxacin | Goats; Murciano-Granadina; 3–4 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                   | HPLC NS           | 0 ppb | IV  | 2.5 mg/kg Moxifloxacin   | 1 Milk                  | 24 h (0.05 ppm §) | >24 h | Healthy Mid-lactation                                                                 | [92] 1997                                                                 |                |                        |             |
| Norfloxacin | Sheep; crossbred; adult; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                   | HPLC NS           | 0.07 ppm | IV | 25 mg/kg Norfloxacin nitrate | 1 Milk                  | 24 h (10 ppm)  | >24 h | Healthy Lactating                                                                 | [109] 2001                                                                 |                |                        |             |
| Oritrifloxacin | Goats; Murciano-Granadina; 3–4 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                   | HPLC 20 ppb       | 25 ppb | SC  | 2.5 mg/kg Oritrifloxacin | 1 Milk                  | 12 h (0.05 ppm §) | 24 h | Healthy Lactating                                                                 | [107] 2007                                                                 |                |                        |             |
| Oritrifloxacin | Sheep; Barky; 4–6 years; n = 6 | US Tol: Prohibited. EMA MRL: Not established.                   | Bioassay NS       | 0.04 ppm | IM | 2.5 mg/kg Oritrifloxacin | 1 Milk                  | 24 h (0.06 ppm §) | 48 h | Healthy Lactating                                                                 | [94] 2009                                                                 |                |                        |             |
| Pefloxacin | Goats; Egyptian; 2 years; n = 5 | US Tol: Prohibited. EMA MRL: Not established.                   | Bioassay NS       | 0.025 ppm | IV | 10 mg/kg Pefloxacin     | 1 Milk                  | 10 h (0.1 ppm) | 12 h | Healthy Lactating                                                                 | [95] 2002                                                                 |                |                        |             |
Table 5. Cont.

| Analyte          | Species, Breed, Age, # of Animals | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | # of Doses | Last Sampling Time Point (Post-Last Treatment) When Residues Were Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/ Year |
|------------------|-----------------------------------|----------------|-------------------|-----|-----|-------------------------|------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------|-------------|------------------------|--------------|
| Flumequine       | **Sheep** US Tol: Not established, EMA established MRL: 300 ppb (liver), 300 ppb (kidney), 50 ppb (muscle, fat, skin). | HPLC NS 10 ppb IM | 12 mg/kg Flumequine for first dose, then 6 mg/kg at 12 h intervals | 10  | Muscle | 7-OH: 78 h (13.8 ppb) Flu: 78 h (100 ppb) | **Liver** 100 ppb | Flu: >78 h | Flu: >78 h | **NS** NS | [109] 1997 |
|                  |                                   |                |                   |     |                  | 7-OH: 36 h (43.5 ppb) Flu: >78 h | **Kidney** 100 ppb | Flu: >78 h | 7-OH: >78 h | **NS** NS | [109] 1997 |
|                  |                                   |                |                   |     |                  | 7-OH: 30 h (13.5 ppb) Flu: >78 h | **Fat** 100 ppb | Flu: >90 h | 7-OH: >78 h | **NS** NS | [109] 1997 |
|                  |                                   |                |                   |     |                  | 7-OH: 0.018 ppm IV 2.5 mg/kg | **Int. Site** 100 ppb | Flu: >78 h | 7-OH: >78 h | **NS** NS | [109] 1997 |
|                  |                                   |                |                   |     |                  | 7-OH: 0.018 ppm IV 2.5 mg/kg | Enrolbactam | Flu: >78 h | 7-OH: >78 h | **NS** NS | [109] 1997 |
| 7-Hydroxy-       | **Sheep; NS; NS; 300 ppb (liver), | HPLC NS 5 ppb IM | 12 mg/kg Flumequine for first dose, then 6 mg/kg at 12 h intervals | 6   | Muscle | 7-OH: 78 h (10 ppb) Flu: 78 h (13.5 ppb) | **Liver** 100 ppb | Flu: >78 h | 7-OH: >78 h | **Healthy** NS | [109] 1998 |
| flumequine       | 300 ppb (kidney), 50 ppb (muscle, fat, skin). |                |                   |     |                  | 7-OH: 30 h (13.5 ppb) Flu: >78 h | **Kidney** 100 ppb | Flu: >78 h | 7-OH: >78 h | **Healthy** NS | [109] 1998 |
|                  |                                   |                |                   |     |                  | 7-OH: 30 h (13.5 ppb) Flu: >78 h | **Muscle** 100 ppb | Flu: >78 h | 7-OH: >78 h | **Healthy** NS | [109] 1998 |
|                  |                                   |                |                   |     |                  | 7-OH: 0.018 ppm IV 2.5 mg/kg | **Fat** 100 ppb | Flu: >78 h | 7-OH: >78 h | **Healthy** NS | [109] 1998 |

$^6$ Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # = number. $^5$ Enrofloxacin parent half-life reported = 2.74 h; Ciprofloxacin metabolite half-life = 4.79 h. $^1$ Intravenous half-life reported= 5.39 h. $^2$ Subcutaneous half-life reported= 14.85 h. $^3$ Enro; Enrofloxacin. $^4$ Cipro; Ciprofloxacin. $^*$ Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. $^1$ LOD and LOQ values should be confirmed with authors; however, they are reported as published. Abbreviations: 1 ×/day: once daily. 2 ×/day: twice daily. 7-OH: 7-hydroxyflumequine. LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. FLU: flumequine. MRL: Maximum residue limit. NS: Not specified. Routes of Administration: IM = intramuscular, IV = intravenous, PO = per os, SC = subcutaneous. Units: s = seconds, min = minutes, h = hours, ppb = parts per billion, ppm = parts per million.
3.6. Macrolides

Macrolides (erythromycin, gamithromycin, spiramycin, tilmicosin, tulathromycin and tylosin) are a group of bacteriostatic compounds that bind to the 50S bacterial ribosomal subunit inhibiting bacterial protein synthesis and cell growth [110]. These antibiotics are effective against Mycoplasma spp. and Gram-positive organisms, and less effective against Gram-negative organisms.

Penetration into tissues, milk and blood are shown to be relatively quick with high systemic availability [111]. Macrolides show good penetration and distribution into the udder. In particular, tilmicosin and tulathromycin have been shown to have persistent drug residues in the milk [112–117], thus they are not recommended for use in lactating animals. Erythromycin, spiramycin and tylosin also exhibit good udder penetration, but result in shorter withdrawal intervals [29,60,111,118–122]. Some small ruminant macrolide pharmacokinetic parameters (absorption, volume of distribution and elimination) were found to be similar to those reported in cattle [111,112,116,123,124].

In the United States, the only FDA-approved macrolide for use in sheep is tilmicosin; however, this approval specifically excludes lactating sheep. Therefore, no tolerance has been established for milk. In the European Union, multiple macrolides are approved for use in small ruminants: gamithromycin and tilmicosin in sheep, and tulathromycin in both sheep and goats. Additionally, MRLs have been extended from other species for erythromycin, tilmicosin (in goats) and tylosin. Table 6 summarizes the published literature evaluating edible tissue or milk residues of macrolides following treatment of sheep and goats.
| Analyte | Species; Breed Age; # of Animals | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues WERE Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/ Year |
|---------|---------------------------------|----------------|------------------|-----|-----|-------------------------|--------------------------|------------|--------|-------------------------------------------------|-------------------------------------------------|------------------|------------------------|--------------|
| Erythromycin | Goat; dairy type; 2–7 years; n = 10 | US Tol: Not established. EMA MRL by extension from bovine to all food producing species: 40 ppb (milk) | Bioassay | NS | NS | IM | 300 mg Erythromycin at 12 h intervals | 3 | Milk | 24 h (0.05 ppm §) | 36 h | Healthy | Early & mid-lactation; Milked 2x/day, Whole tub per gland | NW | 1984 |
| Erythromycin | Goat; NS; adult; n = 6 | US Tol: Not established. EMA MRL by extension from bovine to all food producing species: 40 ppb (milk) | Bioassay | NS | 0.024 ppm | IV IM | 10 mg/kg Erythromycin. 15 mg/kg Erythromycin. | 1 | Milk | 12 h (0.14 ppm §) | >12 h | Healthy | Early lactation | [221] | 2007 |
| Erythromycin | Sheep; NS; 3–4 years; n = 6 | US Tol: Not established. EMA MRL by extension from bovine to all food producing species: 40 ppb (milk) | Bioassay | NS | 0.039 ppm | IV IM SC | 10 mg/kg Erythromycin. | 1 | Milk | 12 h (0.14 ppm §) | 24 h | Healthy | Lactating | [111] | 2007 |
| Erythromycin | Sheep; NS; NS; n = 20 study; n = 4/time pt | US Tol: Not established. EMA established MRL: 200 ppb (liver, kidney, muscle, fat). | Bioassay | NS | Liver: 250 ppb Kidney: 250 ppb Muscle: 200 ppb Fat: 200 ppb Inj Site: 200 ppb | IM | 10 mg/kg Erythromycin daily | 5 | Liver | 1 day (1.22 ppm) | 3 days | Healthy | | NS | 2000 |
| | | | | | | Kidney | 1 day (0.77 ppm) | 3 days | | | | | | |
| | | | | | Muscle | 1 day (0.42 ppm) | 3 days | | | | | | |
| | | | | | Fat | ND | 1 day | | | | | | |
| | | | | | Inj Site | 15 days (0.37 ppm) | >15 days | | | | | | |
| | | | | | Liver | 1 days (0.41 ppm) | 3 days | | | | | | |
| | | | | | Kidney | 1 days (0.09 ppm) | 3 days | | | | | | |
| | | | | | Muscle | 1 days (0.07 ppm) | 3 days | | | | | | |
| | | | | | Fat | ND | 1 day | | | | | | |
| | | | | | Inj Site | 6 days (0.40 ppm) | 9 days | | | | | | |
**Table 6. Cont.**

| Analyte     | Species; Breed Age; # of Animals | Tolerance/ MRL | Analytical Method | LOD | LDQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/ Year |
|-------------|----------------------------------|----------------|-------------------|-----|-----|-------------------------|-------------------------|-------------|--------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------|------------------------|-------------|
| Gamithromycin | Sheep; Merino; 5–6 months; n = 9 study; n = 3/time pt | US Tol: Not established. EMA MRL: Not established. | LS-MC | NS | 10 ppb | SC | 6 mg/kg Gamithromycin | 1 | Skin | 10 days (276 ppb) | >10 days | Healthy | NS | [29] 2014 |
| Gamithromycin | Sheep; NS; 7 months; n = 35 study; n = 5/time pt | US Tol: Not established. EMA established MRL: 300 ppb (liver); 200 ppb (kidney); 50 ppb (muscle & fat). | LS-MC | NS | NS | SC | 5 mg/kg Gamithromycin | 1 | Liver | NS | NS | Healthy | NS | [26] 2016 |
| Spirotonycin | Sheep; Awassi; adult; n = 1 | US Tol: Not established. EMA MRL: Not established. | Bioassay Radioactivity | NS | NS | IV | 20 mg/kg Spirotonycin adipate | 1 | Milk | 60 h (2.78 ppm §) | >96 h | Healthy | Lactating; Milked 2×/day | [24] 1973 |
| Spirotonycin | Sheep; Awassi; Adult; n = 2 | US Tol: Not established. EMA MRL: Not established. | Bioassay Radioactivity | NS | NS | IM | 20 mg/kg Spirotonycin adipate | 1 | Milk | 56 h (2.40 ppm §) | >56 h | Healthy | Diseased-mastitis | [25] 1974 |
| Tilmicosin | Goats; NS; 2.5–3 years; n = 5 | US Tol: Not established. EMA MRL by extention from ovine to all food producing species: 40 ppb (milk). | Bioassay | 10 ppb | NS | SC | 10 mg/kg Tilmicosin | 1 | Milk | 11 days (0.04 ppm §) | 12 days | Healthy | Early lactation | [13] 1997 |
| Tilmicosin | Sheep; Barki; 2–3 years; n = 5 | US Tol: Not established. EMA MRL: 40 ppb (milk). | Bioassay | 0.1 ppm | SC | 10 mg/kg Tilmicosin phosphate | 1 | Milk | 8 days (0.08 ppm §) | >8 days | Healthy | Mid-lactation | [127] 1999 |
| Tilmicosin | Sheep; Suffolk crossed; adult; n = 4 | US Tol: Not established. EMA MRL: 40 ppb (milk). | HPLC | 50 ppm | NS | SC | 10 mg/kg Tilmicosin | 1 | Milk | 11 days (48 ppb) | >11 days | NS | Early & mid-lactation; Milked 2×/day | [23] 1994 |
### Table 6. Cont.

| Analyte | Species; Breed Age; # of Animals | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues Were Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/ Year |
|---------|----------------------------------|----------------|-------------------|-----|-----|-------------------------|-------------------------|------------|--------|-------------------------------------------------|-------------------------------------------------|-------------|------------------------|--------------|
| Tilmicosin | Sheep; Beulah Cross; 10–11 weeks; n = 14 study (slaughter 4 time pts) | Radioactivity | NS | NS | SC | 20 mg/kg Tilmicosin phosphate (radiolabeled) | 1 | Liver | 28 days (2.7 ppm) | >28 days | Healthy | | | |
| | | | | | | | Muscle | 28 days (1.55 ppm) | >28 days | | | |
| | | | | | | | Fat | 28 days (0.26 ppm) | >28 days | | | |
| | | | | | | | Inj. Site | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Liver | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Inj. Site | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Kidney | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Muscle | 7 days (193.5 ppm) | >21 days | | | |
| | | | | | | | Fat | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Inj. Site | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Kidney | 28 days (121.8 ppm) | >28 days | | | |
| | | | | | | | Liver | 56 days (81 ppb) | >56 days | | | |
| | | | | | | | Muscle | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Inj. Site | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Kidney | 21 days (7 ppm) | >28 days | | | |
| | | | | | | | Liver | 28 days (0.26 ppm) | >28 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Inj. Site | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Kidney | 56 days (81 ppb) | >56 days | | | |
| | | | | | | | Liver | 35 days (89 ppb) | >35 days | | | |
| | | | | | | | Fat | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Inj. Site | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Kidney | 28 days (121.8 ppm) | >28 days | | | |
| | | | | | | | Liver | 56 days (81 ppb) | >56 days | | | |
| | | | | | | | Muscle | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Inj. Site | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Kidney | 21 days (7 ppm) | >28 days | | | |
| | | | | | | | Liver | 28 days (0.26 ppm) | >28 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |

**Source/ Year**

[113] 1997

**Additional Information**

Healthy

**Health Status**

Healthy

**Tilmicosin**

| Analyte | Species; Breed Age; # of Animals | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues Were Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/ Year |
|---------|----------------------------------|----------------|-------------------|-----|-----|-------------------------|-------------------------|------------|--------|-------------------------------------------------|-------------------------------------------------|-------------|------------------------|--------------|
| Tilmicosin | Sheep; NS; lambs; n = 12 study; n = 3/time pt | Radioactivity | NS | NS | SC | 20 mg/kg Tilmicosin phosphate (radiolabeled) | 1 | Liver | 28 days (2.7 ppm) | >28 days | Healthy | | | |
| | | | | | | | Muscle | 28 days (1.55 ppm) | >28 days | | | |
| | | | | | | | Fat | 28 days (0.26 ppm) | >28 days | | | |
| | | | | | | | Inj. Site | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Liver | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Inj. Site | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Kidney | 28 days (0.55 ppm) | >28 days | | | |
| | | | | | | | Muscle | 7 days (193.5 ppm) | >21 days | | | |
| | | | | | | | Fat | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Inj. Site | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Kidney | 28 days (121.8 ppm) | >28 days | | | |
| | | | | | | | Liver | 56 days (81 ppb) | >56 days | | | |
| | | | | | | | Muscle | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Inj. Site | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Kidney | 21 days (7 ppm) | >28 days | | | |
| | | | | | | | Liver | 28 days (0.26 ppm) | >28 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Inj. Site | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Kidney | 56 days (81 ppb) | >56 days | | | |
| | | | | | | | Liver | 35 days (89 ppb) | >35 days | | | |
| | | | | | | | Fat | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Inj. Site | 7 days (77 ppm) | >7 days | | | |
| | | | | | | | Kidney | 28 days (121.8 ppm) | >28 days | | | |
| | | | | | | | Liver | 56 days (81 ppb) | >56 days | | | |
| | | | | | | | Muscle | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Inj. Site | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Kidney | 21 days (7 ppm) | >28 days | | | |
| | | | | | | | Liver | 28 days (0.26 ppm) | >28 days | | | |
| | | | | | | | Fat | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Inj. Site | <LOQ @ 14 days | 14 days | | | |
| | | | | | | | Kidney | 56 days (81 ppb) | >56 days | | | |
| | | | | | | | Liver | 35 days (89 ppb) | >35 days | | | |
Table 6. Cont.

| Analyte       | Species; Breed Age; # of Animals | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/ Year |
|---------------|----------------------------------|----------------|-------------------|-----|-----|-------------------------|--------------------------|------------|--------|---------------------------------------------------------------------------|---------------------------------------------------------------------|--------------|------------------------|--------------|
| Tilmicosin    | Sheep; Suffolk crossbred; Adult; n = 4 | US Tol: Not established. EMA established MRL: 50 ppb (milk). | HPLC | NS | 50 ppb | SC | 10 mg/kg Tilmicosin | 1 | Milk | 15 days (0.3 ppm) | >15 days | Healthy | Early lactation | [114] 2008 |
| Tulathromycin | Goats; Boer; 5-7 months; n = 16 study; n = 4/time pt | US Tol: Not established. EMA established MRL: 450 ppb (muscle); 250 ppb (liver); 540 ppb (liver); 1800 ppb (kidney). | UPLC | 0.7 ppb | 2 ppb | SC | 2.5 mg/kg Tulathromycin at 7-day interval | 2 | Liver | 20 days (0.79 ppm) | >20 days | Healthy | NS | [123] 2012 |
| Tulathromycin | Goats; Mixed; 7-8 weeks; n = 6 | US Tol: Not established. EMA established MRL: 450 ppb (muscle); 250 ppb (liver); 540 ppb (liver); 1800 ppb (kidney). | LC-MS | Liver: 0.75 ppm | Kidney: 0.29 ppm | Muscle: 0.24 ppm | 2.5 mg/kg Tulathromycin | 1 | Liver | <LOD @ 14 days | 14 days | Healthy | Juveniles | |
| | | | | | | | | | | | | | | | |
| Tulathromycin | Goats; Mixed; 7-8 months; n = 30 study; n = 4/time pt | US Tol: Not established. EMA established MRL: 450 ppb (muscle); 250 ppb (liver); 540 ppb (liver); 1800 ppb (kidney). | LC-MS | Liver: 0.75 ppm | Kidney: 0.29 ppm | Muscle: 0.24 ppm | 2.5 mg/kg Tulathromycin | 1 | Liver | <LOD @ 14 days | 14 days | Healthy | Juveniles | |
| | | | | | | | | | | | | | | | |
| Tulathromycin | Mixed; 2-3 weeks; n = 12 | US Tol: Not established. EMA established MRL: 450 ppb (muscle); 250 ppb (liver); 540 ppb (liver); 1800 ppb (kidney). | LC-MS | Liver: 0.75 ppm | Kidney: 0.29 ppm | Muscle: 0.24 ppm | 2.5 mg/kg Tulathromycin at 7-day interval | 3 | Muscle | <LOD @ 7 days | 7 days | Healthy | Juveniles | NS [124] 2012 |
### Table 6. Cont.

| Analyte     | Species; Breed Age; # of Animals | Tolerance/ MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/ Year |
|-------------|----------------------------------|----------------|------------------|-----|-----|------------------------|--------------------------|------------|--------|--------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------|------------------------|----------------|
| Tulathromycin | Goats; dairy type; 2–5 years; n = 8 | US Tol: Not established. EMA MRL: Not established. | HPLC | 1.8 ppb | 5.0 ppb | SC | 2.5 mg/kg Tulathromycin | 1 | Milk | 45 days (2 ppb) >45 days | Healthy | Lactating; Milked 2x/day | [115] 2016 |
| | Goats; NS; 30–36 months; n = 5 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IM | 2.5 mg/kg Tulathromycin | 1 | Milk | 19 days (0.08 ppm §) >19 days | Healthy | Lactating | [116] 2012 |
| | Goats; dairy type; 1–7 years; n = 8 | US Tol: Not established. EMA MRL: Not established. | LS-MS | 1.8 ppb | 5.0 ppb | SC | 2.5 mg/kg Tulathromycin at 7-day interval | 2 | Milk | 56 days (0.3 ppm) >61 days | Healthy | Lactating; Milked 2x/day | [117] 2016 |
| Tulathromycin | Sheep; NS; NS; n = 30 study; n = 3/time pt | US Tol: Not established. EMA established MRL: 450 ppb (muscle); 250 ppb (liver); 3400 ppb (kidney). | LS-MC | NS | | | 2.5 mg/kg Tulathromycin | 1 | Liver | 35 days (0.3 ppm) >42 days | Healthy | NS | [130] 2015 |
| | | | | | Liver: 300 ppb | | | | | | | | | |
| | | | | Kidney: 200 ppb | | | | | | | | | |
| | | | | Muscle: 50 ppb | | | | | | | | | |
| | | | | Fat: 50 ppb | | | | | | | | [Inj Site: 50 ppb] | |
| | | | | IM | | | | | | | | | |
| | Tylosin | Goats; NS; adult; n = 5 | US Tol: Not established. EMA MRL by extension from bovine to all food producing species: 50 ppb (milk). | Bioassay | NS | NS | IV | 15 mg/kg Tylosin | 1 | Milk | 24 h (0.6 ppm) >24 h | Healthy | Lactating | [118] 1991 |
| | | | | IM | 15 mg/kg Tylosin | 1 | Milk | 24 h (1.7 ppm) >24 h | Healthy | Lactating | [118] 1991 |
| | | | | | | | | | | | | | |
| | Tylosin | Sheep; Awassi; adult; n = 3 | US Tol: Not established. EMA MRL by extension from bovine to all food producing species: 50 ppb (milk). | Bioassay | NS | NS | IM | 20 mg/kg Tylosin | 1 | Milk | 26 h (1.80 ppm) >26 h | Healthy | Diseased-mastitis | Lactating; Milked 2x/day | [119] 1973 |
| | | | | | | | | | | | | | |
| | Tylosin | Sheep; Merinos; adult; n = 7 | US Tol: Not established. EMA MRL by extension from bovine to all food producing species: 50 ppb (milk). | HPLC | NS | NS | IM | 10 mg/kg Tylosin | 5 | Milk | 26 h (10.9 ppm) >48 h | Healthy | Lactating; Milked 2x/day | [120] 2011 |

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* § Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # = number. ‡ Liver HL reported= 5.48 days; Kidney HL reported = 4.22 days; Muscle HL = 2.55 days; Fat HL reported = 2.62 days; Injection site core = 4.43 days; Injection site ring = 2.39 days. † Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. Abbreviations: 2x/day: twice daily. LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. MRL: Maximum residue limit. ND: Not detected. NS: Not specified. Routes of Administration: IMM = intramammary, IM = intramuscular, IV = intravenous, SC = subcutaneous. Units: s = seconds, min = minutes, h = hours, ppb = parts per billion, ppm = parts per million.
3.7. Sulfonamides

Sulfonamides (sulfadiazine, sulfadimethoxine, sulfamethoxazole, sulfachlorpyrazine) are bacteriostatic antibacterial medications that compete with para-aminobenzoic acid disrupting folic acid synthesis. They are active against Gram-positive and Gram-negative bacteria and protozoa.

One study administered sulfonamides in both normal and mastitic ewes. Sulfonamide concentrations were found to be much higher in the mastitic ewe milk, which the authors attributed in part to the increase in milk pH of mastitic milk [131]. Another study found that some sulfonamides are found in the milk in higher concentrations than blood, whereas others (sulfathiazole, sulfadimidine, sulfadiazine and sulfacetamide) are found in the milk in lower concentrations than blood [132].

Due to the potential for allergic reactions to sulfonamides, caution must be exhibited to ensure food-products from small ruminants do not contain traces of sulfonamides [133,134]. In the US, extra-label use of sulfonamides is prohibited in dairy cattle 20 months of age and older, due to allergic potential of affected milk and increased violative residues.

In the United States, there are no sulfonamide products FDA-approved for use in small ruminants, whereas there are some sulfonamide active ingredients with established milk MRLs for small ruminants in the EU. Table 7 summarizes the published literature evaluating edible tissue or milk residues of sulfonamides following treatment of sheep and goats.
### Table 7. Sulfonamide residues in milk or edible tissue samples from sheep or goats following treatment.

| Analyte                | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|------------------------|-----------------------------------|---------------|-------------------|-----|-----|-------------------------|--------------------------|------------|--------|------------------------------------------------------------------------|---------------------------------------------------------------|--------------|------------------------|-------------|
| Sulfadimethoxine       | Goat; NS; adult; n = 5             | US Tol: Not established. EMA MRL: Not established. | Colorimetrically | NS  | NS  | PO                      | 286 mg/kg sulfadimethoxine | 1          | Milk   | 2 days (NS)                                                            | 3 days                                                      | Healthy     | Lactating              | [135] 2016 |
| Sulfanilamide          | Goat; NS; Adult; n = 1             | US Tol: Not established. EMA established MRL: 100 ppm (milk). | Spectrometric   | NS  | NS  | IMM                    | 1000 mg Sulfanilamide     | 1          | Milk   | 4 days (143 ppm)                                                      | >4 days                                                     | Healthy     | Lactating; Single gland | [132] 1958 |
| Sulfacetamide          | Goat; NS; Adult; n = 1             | US Tol: Not established. EMA established MRL: 100 ppm (milk). | Spectrometric   | NS  | NS  | IMM                    | 1000 mg Sulfacetamide     | 1          | Milk   | 4 days (2520 ppm)                                                     | >4 days                                                     | Healthy     | Lactating; Single gland | [132] 1958 |
| Sulfanilamide          | Sheep; NS; adult; n = 7            | US Tol: Not established. EMA MRL: Not established. | Bioassay        | NS  | NS  | IV PO                  | 150 mg/kg Sulfanilamide  PO at 12 h intervals | 8          | Liver   | 8 days (79 ppm)                                                       | >8 days                                                     | Healthy     | NS                     | [136] 1977 |
| Sulfmethoxy-pyridazine | Sheep; NS; adult; n = 7            | US Tol: Not established. EMA MRL: Not established. | Bioassay        | NS  | NS  | PO                     | 35 mg/kg Sulfamethoxy-pyridazine once then 25 mg/kg Sulfamethoxy-pyridazine daily | 4          | Liver   | 8 days (55 ppb)                                                       | >8 days                                                     | Healthy     | NS                     | [136] 1977 |
| Sulfathiazole          | Sheep; mixed; lambs; n = 15 study; n = 3/time pt | US Tol: Not established. EMA MRL: Not established. | Spectrometric   | NS  | NS  | IV                     | 72 mg/kg Sodium sulfathiazole | 1          | Liver   | 1 day (0.12 ppm ④)                                                   | >1 day                                                      | Healthy     | NS                     | [137] 1977 |
| Sulfamerazine          | Sheep; mixed; 22 months; n = 13 study; n = 3/time pt | US Tol: Not established. EMA MRL: Not established. | HPLC            | NS  | 0.1 ppm | PO                     | 132 mg/kg Sulfamerazine once, then 66 mg/kg at 12 h intervals | 6          | Liver   | 5 days (0.11 ppm)                                                     | 7 days                                                     | Healthy     | NS                     | [138] 1972 |
Table 7. Cont.

| Analyte       | Species; Breed; Age; # of Animals | Tolerance/MRL | Analysis Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/ Year |
|---------------|-----------------------------------|---------------|-----------------|-----|-----|-------------------------|--------------------------|------------|--------|--------------------------------------------------------------------------------|---------------------------------------------------------------|---------------|------------------------|--------------|
| Sulfa-merazine | Sheep; NS; adult; n = 12          | US Tol: Not established. EMA MRL: 100 ppm (milk). | Spectrographic | NS  | NS  | PO                       | 100 mg/kg Sulfamerazine  | 1          | Milk   | 2 days (3.7 ppm)                                                              | >2 days                                      | Healthy       | Lactating; Full dose/gland | [139]        |
|               |                                   |               |                 |     |     | IV                       | 100 mg/kg Sulfamerazine  | 1          | Milk   | 1 day (5.0 ppm)                                                               | 2 days                                       |               |                        |              |
|               |                                   |               |                 |     |     | IM                       | 100 mg/kg Sulfamerazine  | 1          | Milk   | 1 days (4.2 ppm)                                                              | 2 days                                       |               |                        |              |
|               |                                   |               |                 |     |     | IMM                      | 500 mg Sulfamerazine     | 1          | Milk   | 12 min (428 ppm)                                                             | >12 min                                      |               |                        |              |
| Sulfa-        | Goat; West African Dwarf; 1 year;   | US Tol: Not established. EMA MRL: Not established. | Spectrographic | 0.05 ppm | NS | IM                       | 100 mg/kg Sulfadimidine  | 1          | Liver  | 30 days (5.29 ppm)                                                           | >30 days                                      | Healthy       | NS                      | [133]        |
| methazine     | n = 20 study; n = 1/time point     |               |                 |     |     |                           |                          |            | Kidney | 30 days (3.84 ppm)                                                           | >30 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Muscle | 30 days (2.01 ppm)                                                           | >30 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Fat     | 30 days (4.84 ppm)                                                            | >30 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Liver   | 30 days (5.33 ppm)                                                            | >30 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Kidney  | 30 days (4.79 ppm)                                                            | >30 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Muscle  | 30 days (1.38 ppm)                                                            | >30 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Fat     | 30 days (4.53 ppm)                                                            | >30 days                                      |               |                        |              |
| Sulfa-        | Sheep; Targhee/Rambouillet; lambs; n = 16 study; n = 2/time pt | US Tol: Not established. EMA MRL: Not established. | Spectrographic | NS  | NS  | IV                       | 107.25 mg/kg Sodium sulfamethazine | 1 | Liver | 4 days (0.11 ppm)                                                            | >4 days                                      | Healthy       | NS                      | [134]        |
| methazine     |                                   |               |                 |     |     |                           |                          |            | Kidney | 4 days (0.14 ppm)                                                            | >4 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Muscle | 4 days (0.09 ppm)                                                            | >4 days                                      |               |                        |              |
|               |                                   |               |                 |     |     |                           |                          |            | Fat     | 4 days (0.05 ppm)                                                            | >4 days                                      |               |                        |              |
### Table 7. Cont.

| Analyte | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|---------|-----------------------------------|---------------|-------------------|-----|-----|-------------------------|--------------------------|------------|--------|------------------------------------------------------------------|-------------------------------------------------|-------------|------------------------|-------------|
| Sulfa-<br>methazine† | Sheep; crossbred; 2–3 years; <br>n = 25 study; <br>n = 5/time pt | US Tol: Not established. <br>EMA MRL: Not established. | HPLC | NS | 0.1 ppm | PO | 391 mg/kg Sulfamethazine | 1 | Liver | 4 days (0.3 ppm) | 8 days | Healthy | NS | [140] 1991 |
| | | | | | | | | | Kidney | 4 days (0.25 ppm) | 8 days | | | |
| | | | | | | | | | Muscle | 4 days (0.2 ppm) | 8 days | | | |
| | | | | | | | | | Fat | ND | 4 days | | | |
| Sulfa-<br>methazine† | Sheep; crossbred; adult; n = 10 | US Tol: Not established. <br>EMA Established MRL: 100 ppb (milk). | Spectro-<br>metric | NS | NS | PO | 15,000 mg Sulfamethazine | 1 | Milk | 1 day (NS) | >1 day | Healthy | | |
| | | | | | | | | | Milk | 2 days (NS) | >2 days | Healthy | | |
| | | | | | | | | | Milk | 2 days (NS) | >2 days | Healthy | | |
| | | | | | | | | | Milk | 2 days (NS) | >2 days | Healthy | | |
| | | | | | | | | | Milk | >53 h (NS) | >53 h | Diseased-mastitis | Lactating | [131] 1965 |

Note: * Denotes that residues were detected only at the last sampling time point.

† Indicates that the analyte is a sulfa-methazine.
### Table 7. Cont.

| Analyte       | Species; Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point (Post-Last Treatment) * | Health Status | Additional Information | Source/Year |
|---------------|-----------------------------------|---------------|-------------------|-----|-----|--------------------------|---------------------------|-------------|--------|-----------------------------------------------------------------------------|-------------------------------|-------------|------------------------|-------------|
| Sulfa-methazine† | Sheep; NS; NS; NS | NS NS NS PO | 107.25 mg/kg Sulfamethazine | 1 | Liver Kidney Muscle Fat | 2 days (0.1 ppm §) >2 days | Healthy NS | [141] 1978 |
| Sulfa-methazine† | Sheep; Suffolk; NS; n = 2; n = 1/time pt | Radioactivity NS NS NS PO | 100 mg/kg Sulfamethazine (radiolabeled) | 1 | Liver Kidney Muscle | 2 days (10 ppm) >2 days | Healthy NS | [142] 1983 |
| Sulfa-methazine† | Sheep; Balady; 2–4 years; n = 9 study; n = 3/time pt | NS NS NS IM | 0.1 mg/kg Sulfadimidine | 1 | Liver Kidney Muscle | 4 h (20 ppm) >4 h | Healthy NS | [143] 1980 |
| Sulfadiazine | Sheep; Balady; 2–4 years; n = 9 study; n = 3/time pt | NS NS NS IM | 0.1 mg/kg Sulfadiazine | 1 | Liver Kidney Muscle | 4 h (25 ppm) >4 h | Healthy NS | [143] 1980 |

§ Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # Number. † Sulfa-methazine and sulfadimidine are the same chemical/active ingredient. * Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. Abbreviations: LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. MRL: Maximum residue limit. NS: Not specified. Routes of Administration: IMM = intramammary, IM = intramuscular, IV = intravenous, PO = per os. Units: s = seconds, min = minutes, h = hours, ppb = parts per billion, ppm = parts per million.
3.8. Tetracyclines

Tetracyclines (chlortetracycline, doxycycline oxytetracycline, tetracycline) are broad-spectrum antibiotics that act by inhibiting the 30S bacterial ribosomal subunit thus inhibiting protein synthesis. They are active against Gram-positive and Gram-negative bacteria, as well as some atypical mycobacteria and protozoa [144–146].

In oxytetracycline- and chlortetracycline-treated animals, milk production decreased 15% [147]. Infusion of drug into one half of the udder resulted in diffusion of low concentrations into the untreated udder half [147].

Following intramammary infusion of chlortetracycline, residues were detected for a shorter time in goat milk compared to cow milk; however, parenteral chlortetracycline administration results in similar milk residue depletion between goats and cows [122].

In the United States, there are multiple tetracycline approvals for both sheep and goats: chlortetracycline (mediated feed for sheep), oxytetracycline (sheep) and tetracycline (sheep and goats; only topical administration for goats). In the EU, MRLs have been determined for chlortetracycline, oxytetracycline and tetracycline in all food-producing species. Table 8 summarizes the published literature evaluating edible tissue or milk residues of tetracyclines following treatment of sheep and goats.
Table 8. Tetracycline residues in milk or edible tissue samples from sheep or goats following treatment.

| Analyte   | Species/Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matris | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|-----------|---------------------------------|---------------|------------------|-----|-----|-------------------------|--------------------------|------------|-------|------------------------------------------------|-------------------------------------------------------------|--------------|-------------------|------------|
| Chlortetra-cycline | Sheep; Chios & Friesian; adult; n = 4 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | Bioassay | NS | NS | IM | 25 mg/kg Chlortetra-cycline hydrochloride | 1 | Milk | 72 h (0.1 ppm) | | Healthy | Lactating; Only right 1/2 of udder infused. | [147] 1982 |
|         | Sheep; NS; lambs; NS | US Tol: 6000 ppb (liver); 12,000 ppb (kidney, fat); 2000 ppb (muscle). EMA established MRL for all food producing species: 100 ppb (liver); 100 ppb (kidney), 200 ppb (muscle). | NS | NS | Liver: 0.05 ppm Kidney: 0.025 ppm Muscle: 0.027 ppm Fat: 0.027 ppm | POMF | 50 mg/kg Chlortetra-cycline daily | 42 | Liver | 0 days (0.11 ppm) | 2 days (0.06 ppm) | 2 days (0.03 ppm) | ND | 2 days | Healthy | NS | 1996 |
| Chlortetra-cycline | Sheep; NS; lambs; NS | US Tol: 6000 ppb (liver); 12,000 ppb (kidney, fat); 2000 ppb (muscle). EMA established MRL for all food producing species: 100 ppb (liver); 100 ppb (kidney), 200 ppb (muscle). | NS | NS | Liver: 0.05 ppm Kidney: 0.025 ppm Muscle: 0.027 ppm Fat: 0.027 ppm | POMF | 50 mg/kg Chlortetra-cycline daily co-admin with 50 mg/kg sulfamethazine daily | 42 | Liver | 0 days (0.21 ppm) | 6 days (0.05 ppm) | 0 days (0.04 ppm) | ND | 4 days | Healthy | NS | 1996 |
|         | Goat; NS; adult; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IV | 5 mg/kg Doxy-cycline hydrochloride | 1 | Milk | 48 h (0.12 ppm) | >2 days | Healthy | Lactating | | [149] 1989 |
| Doxy-cycline | Goat; NS; 1.5-2 years; n = 6 | US Tol: Not established. EMA MRL: Not established. | Bioassay | NS | NS | IV | 5 mg/kg Minocycline hydrochloride | 1 | Milk | 36 h (0.11 ppm) | 2 days | Healthy | Lactating | | [150] 1999 |
| Mino-cycline | Sheep; mixed breed; NS; n = 24, study; n = 4/time pt | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | Bioassay | 0.5 ppm | NS | IM | 20 mg/kg Oxytetracycline | 1 | Milk | 72 h (NS) | >3 days | Healthy | Early lactation | | [151] 1982 |
| Oxytetra-cycline | Sheep; mixed breed; NS; n = 24, study; n = 4/time pt | US Tol: 6000 ppb (liver); 12,000 ppb (kidney, fat); 2000 ppb (muscle). EMA established MRL for all food producing species: 100 ppb (milk). | Bioassay | HPLC | Liver: 85 ppb Kidney: 42 ppb Muscle: 65 ppb Fat: 45 ppb | IM | 19.8 mg/kg Oxytetracycline (long acting) | 1 | Muscle | 14 days | 14 days | Healthy | NS | NS | [152] 1997 |
Table 8. Cont.

| Analyte       | Species, Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matric | Last Sampling Time Point (Post-Last Treatment) | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) | Health Status | Additional Information | Source/Year |
|---------------|----------------------------------|---------------|-------------------|-----|-----|-------------------------|--------------------------|------------|--------|---------------------------------------------|-------------------------------------------------|----------------|---------------------------|-------------|
| **Oxytetracycline** | Sheep; Sardinian; adult; n = 5 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | HPLC | 5.2 ppb | 17.5 ppb | IM | 20 mg/kg Oxytetracycline | 1 | Milk | 7 days (0.1 ppm §) | >7 days [153] | NS | Lactating, Milked 2 × /day | 1999 |
| **Oxytetracycline** | Sheep; mixed breed; NS; n = 24 study; n = 4/time pt | US Tol: 8000 ppb (liver); 12,000 ppb (kidney, fat); 2000 ppb (muscle). EMA established MRL for all food producing species: 150 ppb (liver); 500 ppb (kidney); 100 ppb (muscle). | HPLC | NS | Liver: 5 ppb | IM | 20 mg/kg Oxytetracycline (long acting) | 1 | Liver | 7 days (52 ppb) | >14 days | 14 days | Healthy | NS [154] | 2000 |
| **Oxytetracycline** | Sheep; NS; 16 months; n = 2 study; n = 1/time pt | US Tol: 8000 ppb (liver); 12,000 ppb (kidney, fat); 2000 ppb (muscle). EMA established MRL for all food producing species: 150 ppb (liver); 500 ppb (kidney); 100 ppb (muscle). | LC-MS | Liver Ocy: 15.3 ppb | Liver 4-Epi †: 16.6 ppb | IM | 30 mg/kg Oxytetracycline daily | 5 | Muscle | 7 days (272.8 ppb) | >7 days | 4-Epis †: 4 h (217.8 ppb) | 4-Epis †: 2 days | Healthy | NS [155] | 2008 |
| **4-epi-Oxytetracycline** | Sheep; desert; 9–12 months; n = 12; study; n = 4/time pt | US Tol: 8000 ppb (liver); 12,000 ppb (kidney, fat); 2000 ppb (muscle). EMA established MRL for all food producing species: 150 ppb (liver); 500 ppb (kidney); 100 ppb (muscle). | LC-MS | Liver Ocy: 15.3 ppb | Liver 4-Epi †: 16.6 ppb | IM | 30 mg/kg Oxytetracycline daily | 5 | Muscle | 7 days (272.8 ppb) | >7 days | 4-Epis †: 4 h (217.8 ppb) | 4-Epis †: 2 days | Healthy | NS [156] | 2000 |

### Source References
- [153](#)
- [154](#)
- [155](#)
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- [158](#)
### Table 8. Cont.

| Analyte | Species/Breed; Age; # of Animals | Tolerance/MRL | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues WERE Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/Year |
|---------|---------------------------------|---------------|-------------------|-----|-----|-------------------------|--------------------------|-----------|--------|-----------------------------------------------|-----------------------------------------------|---------------|------------------------|-------------|
| Oxytetracycline | Sheep; Chios; 16 months; n = 30 study; n = 5/time pt | US Tol: 6000 ppb (liver), 12,000 ppb (kidney, fat), 2000 ppb (muscle) | EMA established MRL for all food producing species: 300 ppb (liver), 600 ppb (kidney), 100 ppb (muscle). | LC-MS | NS | IM | 20 mg/kg Oxytetracycline daily | 5 | Muscle | Kidney | 50 ppb | Kidney | 50 ppb | Liver: 30 ppb | Liver | Oxy: 4 days [0.05 ppm] | 4-Epi †: 2 days [0.05 ppm] | Healthy | NS | [146] 2009 |
| 4-epi-Oxytetracycline | Goat; Saanen; adult; n = 8 | US Tol: Not established. | | HPLC | NS | IM | 20 mg/kg Oxytetracycline (long acting) | 1 | Milk | 7.5 days (60 ppm) | 14 days | Healthy | Lactating; Milked 2 ×/day | [137] 2000 |
| Oxytetracycline | Goat; mixed breed; NS; n = 32 | US Tol: Not established. | | HPLC | NS | NS | 20 mg/kg Oxytetracycline (long acting) | 1 | Fat | 7 days (385 ppb) | >14 days | Healthy | Lactating; Milked 2 ×/day | [143] 2002 |
| Oxytetracycline | Goat; Canary Island; adult; n = 5 | US Tol: Not established. | | HPLC | NS | IM | 20 mg/kg Oxytetracycline (long acting) | 1 | Milk | 178 h (0.46 ppm) | >178 h | Healthy | Lactating; Milked 2 ×/day | [160] 1995 |
| Oxytetracycline | Goat; Saanen; adult; n = 8 | US Tol: Not established. | | HPLC | NS | IM | 15 mg/kg Oxytetracycline daily | 4 | Milk | 100 h (0.46 ppm) | >300 h | Healthy | Lactating; Milked 2 ×/day | [139] 1994 |
| Oxytetracycline | Goat; Canary Island; adult; n = 5 | US Tol: Not established. | | HPLC | NS | IM | 15 mg/kg Oxytetracycline daily | 4 | Milk | 96 h (0.46 ppm) | >96 h | Healthy | Lactating; Milked 2 ×/day | [160] 1995 |
| Oxytetracycline | Goat; Saanen; adult; n = 8 | US Tol: Not established. | | LC-MS | 15 ppb | 50 ppb | 20 mg/kg Oxytetracycline | 1 | Milk | 180 h (0.46 ppm) | 8 days | Healthy | Lactating; Milked 2 ×/day | [161] 2002 |
| Analyte     | Species, Breed; Age; # of Animals | Tolerance/MRL                          | Analytical Method | LOD | LOQ | Route of Administration | Dose & Active Ingredient | # of Doses | Matrix | Last Sampling Time Point (Post-Last Treatment) When Residues Were Detected | Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) * | Health Status | Additional Information | Source/Year |
|-------------|----------------------------------|----------------------------------------|-------------------|-----|-----|--------------------------|--------------------------|------------|--------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------|------------------------|-------------|
| Oxytetracycline | Goat, Nubian, Alpine & LaMancha, adult; n = 15 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | HPLC              | NS  | NS  | IM                       | 426 mg Oxytetracycline hydrochloride per half at 12 h intervals | 3          | Milk   | 96 h (0.02 ppm §)                                                      | 108 h                                                    | Healthy      | Early & mid-lactation; Milkted 2 ×/day; 1 tube/ mammary gland | [60] 1984 |
| Oxytetracycline | Goat, Murciano-Granadina, adult; n = 5 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | HPLC              | NS  | NS  | IM                       | 20 mg/kg Oxytetracycline chloride at 48 h interval | 1          | Milk   | 2 days (0.25 ppm §)                                                     | >2 days                                                  | Healthy      | Healthy                | [162] 2001 |
| Oxytetracycline | Goat; NS; 2-7 years; n = 10 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | Bioassay           | NS  | NS  | IM                       | 426 mg Oxytetracycline hydrochloride per half at 12 h intervals | 3          | Milk   | 96 h (0.02 ppm §)                                                      | 108 h                                                    | Healthy      | Early & mid-lactation; Milkted 2 ×/day; 1 tube/ mammary gland | [60] 1984 |
| Tetracycline   | Sheep, Awassi; Adult; n = 2 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | Bioassay           | NS  | NS  | IM                       | 20 mg/kg Tetracycline                         | 1          | Milk   | 48 h (0.08 ppm §)                                                      | >2 days                                                  | Healthy      | Diseased-mastitis       | [20] 1974 |
| Tetracycline   | Sheep, Awassi; adult; n = 4 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | Radioactivity      | NS  | NS  | IM                       | 20 mg/kg Tetracycline (radiolabeled)           | 1          | Milk   | 48 h (0.14 ppm §)                                                      | >2 days                                                  | Healthy      | Diseased-mastitis       | [20] 1974 |
| Tetracycline   | Goat, Canary Island; adult; n = 5 | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | HPLC              | NS  | NS  | IM                       | 15 mg/kg Tetracycline                         | 4          | Milk   | 96 h (0.01 ppm)                                                       | >96 h                                                   | Healthy      | Lactating; Milkted 2 ×/day | [100] 1995 |
| Tetracycline   | Goat; NS, adult; NS              | US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk). | HPLC              | NS  | NS  | IM                       | 15 mg/kg Tetracycline daily                   | 4          | Milk   | 100 h (0.01 ppm)                                                      | >100 h                                                   | Healthy      | Lactating               | [139] 1994 |

§ Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). n = number. 4-epi-Oxytetracycline Metabolite. * Projected time for which residues could still be detected based on study protocol for sample collection time points and sample concentration results. Authors caution readers to critically evaluate these publications to estimate when full residue depletion might occur. Abbreviations: 2 ×/day: twice daily. LOD: Limit of detection. LOQ: Limit of quantification. EMA: European Medicines Agency. MRL: Maximum residue limit. ND: Not detected. NS: Not specified. Routes of Administration: IMM = intramammary, IM = intramuscular, IV = intravenous, PO = per os, POMF = per os as medicated feed, SC= subcutaneous. Units: s = seconds, min = minutes, h = hours, ppb = parts per billion, ppm = parts per million.
4. Conclusions

The judicious use of medications and drug residue avoidance is an important topic in animal agriculture and for veterinarians treating animals that provide food for humans. Although there are numerous published studies that describe drug residues in sheep and goat meat and milk, they are scattered throughout the primary literature. In this review, these studies are compiled, and data extracted for easy reference to help facilitate a comprehensive overview of the scientific data, with respect to drug residues in edible tissues and milk from sheep and goats for antibiotics used in small ruminant practice.

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Abbreviations

AMDUCA Animal Medicinal Drug Use Clarification Act of 1994
CFR Code of Federal Regulations
EMA European Medicines Agency
FAO Food and Agriculture Organization of the United Nations
FARAD Food Animal Residue Avoidance and Depletion Program
FDA Food and Drug Administration
MIC Minimum inhibitory concentration
MRL Maximum residue limit
NSAIDs Non-steroidal anti-inflammatory drugs
USDA United States Department of Agriculture
WHO World Health Organization

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