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Review

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

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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.

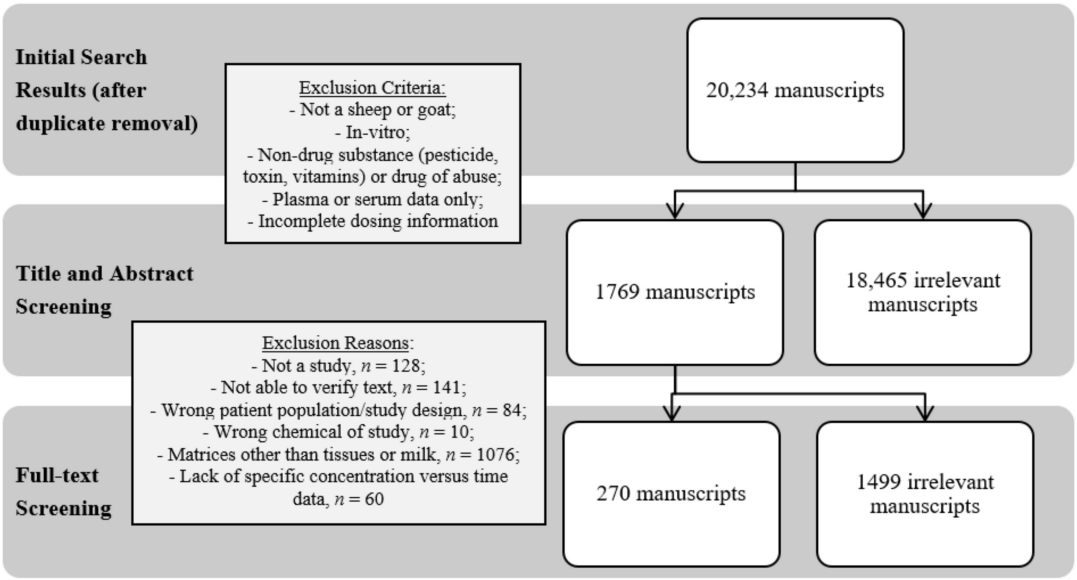

Figure 1. Schematic diagram of the process for three independent evaluators to assess published manuscripts and the numerical outcome of each step. The ultimate goal was to curate manuscripts with tissue and milk residue data from live sheep and goat antibacterial drug studies.

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. 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 Admin-istration	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 Informa-tion	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
						IM	7.5 mg/kg Amikacin sulfate	1	Milk	6 h (0.21 ppm)	8 h			
Amikacin	Goat; NS; 1.5–2 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 §)	>1 day	Healthy	Lactating; Milked 2×/day	[21] 2004
						IM	7.5 mg/kg Amikacin sulfate	1	Milk	9.5 h (0.21 ppm §)	>1 day			
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 §)	>10 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.	Bioassay	500 ppb	NS	PO	10 mg/kg Apramycin daily	3	Liver	ND@1 day	1 day	Healthy	NS	[10] 1999
									Kidney	21 days (1730 ppb)	35 days			
									Muscle	ND@1 day	1 day			
									Fat	21 days (960 ppb)	28 days			
	NS; Lambs; n = 20 study; n = 4/time pt		HPLC	Liver: 368 ppb	Liver: 2500 ppb	PO	10 mg/kg Apramycin daily	5	Liver	30 days (700 ppb)	>30 days			
				Kidney: 394 ppb	Kidney: 2500 ppb				Kidney	30 days (1700 ppb)	>30 days			
				Muscle: 124 ppb	Muscle: 500 ppb				Muscle	ND @ 6 days	6 days			
				Fat: 42 ppb	Fat: 500 ppb				Fat	ND @ 6 days	6 days			

Table 1. *Cont.*

Analyte	Species; Breed; Age; # of Animals per Time Point	Tolerance/ MRL	Analytical Method	LOD	LOQ	Route of Admin-istration	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 Informa-tion	Source/ Year
Apramycin	Goat; NS; Adult; NS	US Tol: Not established. EMA MRL: Not established.	NS	NS	NS	IM IV	20 mg/kg Apramycin 20 mg/kg Apramycin	1 1	Milk Milk	10 h (NS) 12 h (NS)	12 h >12 h	NS	NS	[23] 2000
Dihydro-strepto-mycin	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-strepto-mycin; 100 mg nafcillin	1	Milk	6 days post kidding (≥0.2 ppm)	7 days post kidding	Healthy	Dry off period (mean 61.0 ± 4.3 days SD (range 23–156 days); 1 tube per gland before drying off. Sample collected after kidding	[27] 1995
Dihydro-strepto-mycin	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 §)	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
Dihydro-strepto-mycin	Sheep; Awassi; adult; *n* = 3	US Tol: Not established. EMA established MRL: 200 ppb (milk).	Bioassay Radio-activity	NS NS	NS NS	IV IV	20 mg/kg Dihydro-streptomycin (radio-labeled) then 10 mg/kg for 4 doses 45 min interval	5 5	Milk Milk	24 h (0.20 ppm §) 8 h (1.83 ppm §)	36 h 10 h	Healthy	Lactating; Milked 2×/day	[24] 1973

Table 1. *Cont.*

Analyte	Species; Breed; Age; # of Animals per Time Point	Tolerance/ MRL	Analytical Method	LOD	LOQ	Route of Admin-istration	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 Informa-tion	Source/ Year
Dihydro-strepto-mycin	Sheep; NS; NS; *n* = 22 study *n* = 4/time pt	US Tol: Not established. EMA established MRL: 500 ppb (liver, muscle, fat); 1000 ppb (kidney).	Bioassay	0.5 ppm	NS	IM	10 mg/kg Dihydro-streptomycin combined w/ 10,000 IU procaine penicillin-G daily	5	Kidney	28 days (0.8 ppm)	>28 days	Healthy	NS	[11] 1995
									Muscle	14 days (0.07 ppm)	21 days			
									Inj. Site	28 days (0.2 ppm)	>28 days			
Dihydro-strepto-mycin	Sheep; Awassi; Adult; *n* = 2	US Tol: Not established. EMA established MRL: 200 ppb (milk).	Bioassay	NS	NS	IM	20 mg/kg Dihydro-streptomycin (radio-labeled)	1	Milk	12 h (0.22 ppm §)	24 h	Healthy	Lactating	[29] 1974
									Milk	48 h (0.11 ppm §)	56 h	Disease-mastitis		
			Radio-activity	NS	NS	IM			Milk	48 h (0.75 ppm §)	>48 h	Healthy		
									Milk	12 h (0.42 ppm §)	24 h	Disease-mastitis		
Dihydro-strepto-mycin	Sheep; NS; NS; *n* = 12 study; *n* = 4/ time pt NS; Adult; *n* = 8	US Tol: Not established. EMA established MRL: 500 ppb (liver, muscle, fat); 1000 ppb (kidney); 200 ppb (milk).	NS	NS	NS	IM	10 mg/kg Dihydro-streptomycin combined with benzyl-penicillin daily	3	Liver	<400 ppb @ 14 days	14 days	Healthy	NS	[25] 2005
									Kidney	<400 ppb @ 14 days	14 days			
									Muscle	<400 ppb @ 14 days	14 days			
									Fat	<400 ppb @ 14 days	14 days			
									Inj. Site	18 days (0.58 ppm)	28 days			
			HPLC	NS	50 ppb	IM	10 mg/kg Dihydro-streptomycin sulfate combined with 10 mg/kg streptomycin daily	3	Milk	48 h (0.06 ppm)	60 h	Healthy	Lactating	
Dihydro-strepto-mycin	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 Dihydro-streptomycin combined with 10 mg/kg streptomycin daily	3	Milk	48 h (0.06 ppm)	60 h	Healthy	Lactating; Milked 2×/day	[26] 2002
Dihydro-strepto-mycin	Sheep; NS; NS; *n* = 12 study; *n* = 4/time pt	US Tol: Not established. EMA established MRL: 500 ppb (liver, muscle, fat); 1000 ppb (kidney).	NS	NS	400 ppb	IM	10 mg/kg Dihydro-streptomycin combined w/ benzyl-penicillin daily	3	Liver	<LOQ @ 14 days	14 days	Healthy	NS	[30] 2000
									Kidney	<LOQ @ 14 days	14 days			
									Muscle	<LOQ @ 14 days	14 days			
									Fat	<LOQ @ 14 days	14 days			
									Inj. Site	18 days (0.584 ppm)	28 days			
Dihydro-strepto-mycin	Sheep; NS; NS; *n* = 12 study; *n* = 4/time pt	US Tol: Not established. EMA established MRL: 500 ppb (liver, muscle, fat); 1000 ppb (kidney).	HPLC	NS	400 ppb	IM	10 mg/kg Dihydro-streptomycin combined w/ procaine penicillin daily	3	Liver	<LOQ @ 14 days	14 days	Healthy	NS	[31] 1998
									Kidney	<LOQ @ 14 days	14 days			
									Muscle	<LOQ @ 14 days	14 days			
									Fat	<LOQ @ 14 days	14 days			
									Inj. Site	18 days (0.584 ppm)	28 days			

Table 1. *Cont.*

Analyte	Species; Breed; Age; # of Animals per Time Point	Tolerance/ MRL	Analytical Method	LOD	LOQ	Route of Admin-istration	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 Informa-tion	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	[32] 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); 50 ppb (muscle).	Immuno-assay	0.01 ppm	NS	IM	3 mg/kg Gentamicin sulfate at 8 h intervals	2	Kidney	15 days (20.0 ppm §)	>15 days	Healthy	NS	[12] 1985
									Muscle	15 days (0.21 ppm §)	>15 days			
									Heart	15 days (0.64 ppm §)	>15 days			
Gentamicin	Sheep; Suffolk; adult; $n = 12$ study; $n = 3$/time pt	US Tol: Not established. EMA Established MRL in all mammalian food producing species: 200 ppb (liver); 750 ppb (kidney); 50 ppb (muscle, fat).	Immuno-assay	0.01 ppm	NS	IM	2 mg/kg Gentamicin sulfate	1	Liver	12 days (0.31 ppt)	>12 days	Healthy	NS	[13] 1986
									Kidney	12 days (2.74 ppt)	>12 days			
									Muscle	12 days (0.2 ppt)	>12 days			
									Inj. Site	12 days (0.15 ppt)	>12 days			
							6 mg/kg Gentamicin sulfate	1	Liver	12 days (1.5 ppt)	>12 days			
									Kidney	12 days (5.15 ppt)	>12 days			
									Muscle	12 days (0.002 ppt)	>12 days			
									Inj. Site	12 days (0.02 ppt)	>12 days			
							18 mg/kg Gentamicin sulfate	1	Liver	12 days (4.0 ppt)	>12 days			
									Kidney	12 days (9.23 ppt)	>12 days			
									Muscle	12 days (0.14 ppt)	>12 days			
									Inj. Site	12 days (0.53 ppt)	>12 days			
							2 mg/kg Gentamicin sulfate at 8 h intervals	9	Liver	12 days (4.02 ppt)	>12 days			
									Kidney	12 days (9.74 ppt)	>12 days			
									Muscle	12 days (0.04 ppt)	>12 days			
									Inj. Site	12 days (2.49 ppt)	>12 days			
							6 mg/kg Gentamicin sulfate daily	3	Liver	12 days (3.12 ppt)	>12 days			
									Kidney	12 days (10.0 ppt)	>12 days			
									Muscle	12 days (0.14 ppt)	>12 days			
									Inj. Site	12 days (5.03 ppt)	>12 days			
Gentamicin	Sheep; western range; adult; $n = 4$	US Tol: Not established. EMA established MRL in all mammalian food producing species: 750 ppb (kidney).	Immuno-assay	0.04 ppm	NS	IM	3 mg/kg Gentamicin sulfate at 12 h intervals	20	Kidney (biopsy)	77 days (9.71 ppm)	>77 days	NS	NS	[14] 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	3 days (2.2 ppm)	6 days	NS	NS	[33] 1991
									Kidney	10 days (8.31 ppm)	14 days			
									Muscle	ND @ 3 days	3 days			

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);1200 ppb (muscle); 7200 ppb (fat). EMA MRL extrapolated to all food producing species: 5500 ppb (liver); 9000 ppb (kidney); 500 ppb (muscle, fat).	Bioassay	NS	0.5 ppm	POMW	22 mg/kg Neomycin sulfate daily	14	Liver Kidney Muscle Fat	ND @ 12 h 96 h (0.6 ppm) ND @ 12 h ND @ 12 h	12 h >96 h 12 h 12 h	Healthy	NS	[15] 1996
Neomycin	Goat; NS; NS; *n* = 20 study; *n* = 5/time pt	US Tol: 3600 ppb (liver); 7200 ppb (kidney); 1200 ppb (muscle); 7200 ppb (fat). EMA MRL extrapolated to all food producing species: 5500 ppb (liver); 9000 ppb (kidney); 500 ppb (muscle, fat).	Bioassay	NS	500 ppb	POMW	20 mg/kg Neomycin sulfate daily	14	Liver Kidney Muscle Fat	ND @ 12 h 96 h (700 ppb) ND @ 12 h ND @ 12 h	12 h >96 h 12 h 12 h	Healthy	NS	[16] 2000
Neomycin	Goat; NS; NS; *n* = 20 study, *n* = 4/time pt	US Tol: 3600 ppb (liver); 7200 ppb (kidney); 1200 ppb (muscle); 7200 ppb (fat). EMA MRL extrapolated to all food producing species: 5500 ppb (liver); 9000 ppb (kidney); 500 ppb (muscle, fat).	Bioassay	NS	0.5 ppm	PO	22 mg/kg Neomycin sulfate daily	14	Liver Kidney Muscle Fat	ND @ 12 h 96 h (0.7 ppm) ND @ 12 h ND @ 12 h	12 h >96 h 12 h 12 h	Healthy	NS	[17] 1995
Neomycin	Goat; NS; NS; *n* = 20 study, *n* = 4/time pt	US Tol: 3600 ppb (liver); 7200 ppb (kidney); 1200 ppb (muscle); 7200 ppb (fat). EMA MRL 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 @ 12 h 96 h (0.57 ppm) ND @ 12 h ND @ 12 h	12 h >96 h 12 h 12 h	Healthy	NS	[34] 1996
Neomycin	Sheep; NS; NS; *n* = 18 study; *n* = 4/time pt	US Tol: 3600 ppb (liver); 7200 ppb (kidney); 1200 ppb (muscle); 7200 ppb (fat). EMA MRL extrapolated to all food producing species: 5500 ppb (liver); 9000 ppb (lidney); 500 ppb (muscle, fat).	Bioassay	NS	0.5 ppm	POMW	22 mg/kg Neomycin sulfate daily	14	Liver Kidney Kidney Muscle Fat	ND @ 1 day 1 day (female) (1.28 ppm) 3 days (male) (0.45 ppm) ND @ 1 day ND @ 1 day	1 day 3 days (female) 7 days (male) 1 day 1 day	Healthy	NS	[15] 1996
Neomycin	Sheep; NS; NS; *n* = 20 study; *n* = 5/time pt	US Tol: 3600 ppb (liver); 7200 ppb (kidney); 1200 ppb (muscle); 7200 ppb (fat). EMA MRL extrapolated to all food producing species: 5500 ppb (liver); 9000 ppb (kidney); 500 ppb (muscle, fat).	Bioassay	NS	500 ppb	POMW	20 mg/kg Neomycin sulfate daily	14	Liver Kidney Muscle Fat	ND @ 1 day 3 days (522 ppb) ND @ 1 day ND @ 1 day	1 day 7 days 1 day 1 day	Healthy	NS	[16] 2000
Neomycin	Sheep; NS; NS; *n* = 20 study, *n* = 4/time pt	US Tol: 3600 ppb (liver); 7200 ppb (kidney); 1200 ppb (muscle); 7200 ppb (fat). EMA MRL extrapolated to all food producing species: 5500 ppb (liver); 9000 ppb (kidney); 500 ppb (muscle, fat).	Bioassay	NS	0.5 ppm	PO	22 mg/kg Neomycin sulfate daily	14	Liver Kidney Muscle Fat	ND @ 1 day 3 days (522 ppb) ND @ 1 day ND @ 1 day	1 day 7 days 1 day 1 day	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 pt	US Tol: 3600 ppb (liver); 7200 ppb (kidney); 1200 ppb (muscle); 7200 ppb (fat). EMA MRL 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 Kidney Muscle Fat	ND @ 1 day 1 day (female) (1.28 ppm) 3 days (male) (0.45 ppm) ND @ 1 day ND @ 1 day	1 day 3 days (female) 7 days (male) 1 day 1 day	Healthy	NS	[34] 1996
Strepto-mycin	Sheep; NS; NS; n = 4	US Tol: Not established. EMA established MRL: 200 ppb (milk).	HPLC	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
Strepto-mycin	Sheep; Suffolk & Suffolk/Cheviot; adult; n = 8	US Tol: Not established. EMA established MRL: 200 ppb (milk).	HPLC	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
Strepto-mycin	Sheep; NS; NS; NS	US Tol: Not established. EMA established MRL: 500 ppb (liver, muscle, fat); 1000 ppb (kidney).	HPLC	NS	200 ppb	IM	10 mg/kg Streptomycin daily	3	Liver Kidney Muscle Fat Inj. Site	2 days (655 ppb) 2 days (914 ppb) ND @ 2 days ND @ 2 days 2 days (1373 ppb)	>2 days >2 days 2 days 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 use 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 Admin-istration	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
Chloram-phenicol	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	Lactating	[39] 1973
									Milk	26 h (1.82 ppm §)	>26 h	Diseased-mastitis		
			Bioassay	NS	NS	IM	50 mg/kg Chloramphenicol	1	Milk	26 h (1.02 ppm §)	>26 h	Healthy		
									Milk	26 h (1.54 ppm §)	>26 h	Diseased-mastitis		
			Radio-activity	NS	NS	IM	50 mg/kg Chloramphenicol (radiolabeled)	1	Milk	13 h (NS)	>13 h	Healthy		
									Milk	13 h (NS)	>13 h	Diseased-mastitis		
Chloram-phenicol	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	[24] 1973
			Radio-activity	NS	NS	IV	50 mg/kg Chloramphenicol (radiolabeled) then 12.5 mg/kg for 2 doses at 90 min interval	3	Milk	48 h (0.81 ppm §)	60 h			
Chloram-phenicol	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; Milked 2×/day	[29] 1974
									Milk	56 h (1.28 ppm §)	>56 h	Diseased-mastitis		
			Radio-activity	NS	NS	IM	50 mg/kg Chloramphenicol (radiolabeled)	1	Milk	56 h (0.2 ppm §)	>56 h	Healthy		
									Milk	56 h (0.18 ppm §)	>56 h	Diseased-mastitis		
Chloram-phenicol	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 ppb §)	336 h	NS	NS	[40] 1990
									Kidney	336 h (0.76 ppb §)	>336 h			
									Muscle	336 h (2.13 ppb §)	>336 h			
									Inj. Site	336 h (4.18 ppb §)	>336 h			
Chloram-phenicol	Sheep; Awassi; adult; *n* = 2	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IV	50 mg/kg Chloramphenicol sodium succinate	1	Milk	NS	NS	Healthy	Lactating; Milked 2×/day	[41] 1975

Table 2. *Cont.*

Analyte	Species; Breed; Age; # of Animals per Time Point	Tolerance/ MRL	Analytical Method	LOD	LOQ	Route of Admin-istration	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
									Kidney	40 days (0.17 ppm)	>40 days			
									Muscle	40 days (0.08 ppm)	>40 days			
									Fat	40 days (0.01 ppm)	>40 days			
									Inj. Site	40 days (0.15 ppm)	>40 days			
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	Liver: 0.32 ppm	SC	40 mg/kg Florfenicol daily	3	Liver	40 days (NS)	>40 days	Healthy	NS	[43] 2008
					Kidney: 0.1 ppm				Kidney	40 days (NS)	>40 days			
					Muscle: 0.05 ppm				Muscle	40 days (NS)	>40 days			
					Fat: 0.04 ppm				Fat	40 days (NS)	>40 days			
					Inj. Site: 0.05 ppm				Inj. Site	40 days (NS)	>40 days			
Thiam-phenicol	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
									Kidney	4 days (40.2 ppb)	8 days			
									Muscle	<LOD @ 4 days	4 days			
									Fat	4 days (342.5 ppb)	8 days			
Chloram-phenicol	Goat; Desi; 9–12 months; *n* = NS	US Tol: Not established. EMA MRL: Not established.	Colorimetric	NS	NS	IM	10 mg/kg Chloramphenicol	1	Milk	24 h (2.16 ppm)	2 days	Healthy	Lactating	[45] 1983
						IM	30 mg/kg Chloramphenicol	1	Milk	96 h (3.33 ppm)	>4 days	Healthy		
Chloram-phenicol	Goat; NS; Adult; *n* = 2	US Tol: Not established. EMA MRL: Not established.	HPLC	5 ppb	NS	IM	600 mg Chloram-phenicol	1	Milk	8 h (0.077 ppm)	1 day	Healthy	Lactating	[46] 1980
						IMM	600 mg Chloram-phenicol	1	Milk	24 h (0.026 ppm)	32 h	Healthy		
Thiam-phenicol	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 (4.92 ppm §)	>12 h	Healthy	Late lactation	[35] 1991
						IM	50 mg/kg Thiamphenicol	1	Milk	12 h (4.90 ppm §)	>12 h	Healthy		
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 §)	>8 h	Healthy	Mid-lactation	[36] 1991
						IM	25 mg/kg Florfenicol	1	Milk	8 h (0.11 ppm §)	>8 h	Healthy		

§ 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	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
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; 10 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	[49] 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; 10 mg prednisolone combo product at 8 h intervals	3	Milk	7 days (0.003 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, 10 mg prednisolone combination product (IMM) at 12 h intervals co-administered with 140 mg/35 mg per mL amoxicillin trihydrate/ clavulanic acid (IM) at 24 h intervals	5 (IMM); 2(IM)	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 Amoxicilllin ‡ daily	5	Liver Kidney Muscle Fat Inj. Site	NS NS NS NS 64 days (25.6 ppb)	48 h 48 h 48 h 48 h >64 days	Healthy	NS	[48] 2012
			NS	NS	NS	IM	7 mg/kg Amoxicilllin ‡ daily	5	Milk	120 h (2.09 ppb)	>120 h	Healthy	Lactating; Milked 2×/day	
Ampicillin	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 (0.03 §) 10 h (0.03 §)	>8 h >10 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.	HLPC	1.5 ppb	2.2 ppb	IM	15 mg/kg Amoxicilllin † (long acting) at 72 h interval	2	Milk	168 h (6.0 ppb)	180 h	Healthy	Mid-lactation; Milked 2×/day	[54] 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 (0.1 ppm §)	>12 h >12 h	Healthy Diseased-mastitis	Lactating	[47] 1979
Ampicillin	Sheep; NS; adult; *n* = 4	US Tol: Not established. EMA MRL: Not established.	NS	NS	NS	IMM	250,000 IU Ampicillin trihydrate	1	Milk	72 h (0.11 ppm)	96 h	NS	Lactating; Half syringe per gland	[58] 1977
Cloxacillin	Goats; Saanen; adult; *n* = 8	US Tol: Not established. EMA MRL: Not established.	Bioassay	0.02 ppm	NS	IMM	200 mg Cloxacillin at 48 h intervals	3	Milk	13 h (0.15 ppm§)	>13 h	Healthy	Late lactation; Milked 2×/day. Only one half/gland treated.	[53] 1984
Diclox-acillin	Sheep; Sarda; 2–3.5 years; *n* = 4	US Tol: Not established. EMA MRL: Not established.	HPLC	NS	0.02 ppm	IMM	100 mg/half Dicloxacillin at 12 h intervals.	3	Milk	60 h (0.029 ppm) 72 h (0.026 ppm)	72 h 84 h	Healthy Healthy	Lactating, High production; Milked 2x/day Lactating, Low production; Milked 2×/day	[50] 2000
Nafcillin	Goats; NS; Adults; *n* = 220	US Tol: Not established. EU MRL by extension from bovine to all ruminants: 30 ppb (milk).	Bioassay	0.012 ppm	0.015 ppm	IMM	300,000 IU Procaine benzylpenicillin; 100 mg dihydro-streptomycin; 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 by extension from bovine to all ruminants: 30 ppb (milk).	Bioassay	0.02 ppm	NS	IMM	300,000 IU Procaine benzylpenicillin; 100 mg dihydrostreptomycin; 100 mg nafcillin	1	Milk	ND	2 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
Pen-ethamate	Goats; NS; Adult; *n* = 2	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IM IM	200,000 IU Penethamate (oil) 200,000 IU Penethamate (aqueous) 500,000 IU Penethamate (oil) 500,000 IU Penethamate (aqueous)	1 1	Milk Milk Milk Milk	1 day (0.004 U/mL) 12 h (0.075 U/mL) 1 day (0.04 U/mL) 1 day (0.2 U/mL)	>1 day 1 day >1 day >1 day	NS	Lactating	[59] 1966
Penicillin	Sheep; Awassi; Adult; *n* = 2	US Tol: Not established. EMA MRL: Not established.	Bioassay Radioactivity Bioassay Radioactivity	NS NS NS NS	NS NS NS NS	IM IM	20 mg/kg Penicillin † 20 mg/kg Benzylpenicillin-14C	1 1	Milk Milk Milk Milk	12 h (0.02 ppm §) 56 h (0.03 ppm §) 48 h (0.01 ppm §) 12 h (0.02 ppm §)	1 day >56 h 56 h 1 day	Healthy Diseased-mastitis Healthy Diseased-mastitis	Lactating	[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.	Bioassay	NS	NS	IM	200,000 IU Procaine penicillin (oil)		Milk	1 day (0.008 U/mL)	>1 day	NS	Lactating	[59] 1966
							200,000 IU Procaine penicillin (aqueous)	1	Milk	12 h (0.012 U/mL)	1 day			
						IM	500,000 IU Procaine penicillin (oil)	1	Milk	1 day (0.07 U/mL)	>1 day			
							500,000 IU Procaine penicillin (aqueous)		Milk	1 day (0.02 U/mL)	>1 day			
Penicillin	Goats; NS; Adults; *n* = 217	US Tol: Not established. EMA MRL: Not established.	Bioassay	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	NS	7 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
Penicillin	Goats; dairy type; 2–7 years; *n* = 10	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IMM	100,000 IU Penicillin G procaine at 12 h intervals	3	Milk	60 h (0.49 ppm §)	>60 h	Healthy	Early & mid-lactation; Milked 2x/day; 1 syringe per gland	[60] 1984
Penicillin	Sheep; NS; NS; *n* = 2	US Tol: Zero. EMA MRL: Not established.	LC-MS	0.005 ppm	NS	IM	1500 mg Benzylpenicillin daily	3	Liver	2 days (0.24 ppm)	>2 days	NS	NS	[56] 1996
									Kidney	2 days (0.87 ppm)	>2 days			
									Muscle	2 days (0.02 ppm)	>2 days			
Penicillin	Sheep; Lacaune; adult; *n* = 8	US Tol: Zero. EMA MRL: Not established.	Bioassay	0.006 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	Dry off period (mean 112 days (range 85–223 days); 1 tube per gland before drying off. Sample collected after lambing	[28] 1995
Penicillin	Sheep; NS; 14–17 months; *n* = 10 study; *n* = 10/time pt	US Tol: Zero. EMA MRL: Not established.	Bioassay	0.0125 ppm	NS	IM	3000 IU/lb Penicillin G procaine daily	4	Liver	NS	9 days	Healthy	NS	[61] 2010
									Kidney	NS	9 days			
									Muscle	NS	9 days			
									Fat	NS	9 days			
									Inj. Site	NS	9 days			
Penicillin	Sheep; Awassi; adult; *n* = 3	US Tol: Zero. EMA MRL: Not established.	Bioassay	NS	NS	IV	20 mg/kg Penicillin †, then 10 mg/kg for 4 doses 45 min interval	5	Milk	36 h (0.01 ppm §)	48 h	Healthy	Lactating; Milked 2×/day	[24] 1973
			Radioactivity	NS	NS	IV	20 mg/kg Penicillin † (radiolabeled) then 10 mg/kg for 4 doses 45 min interval	5	Milk	8 h (0.08 ppm §)	10 h			
Penicillin	Sheep; Sardinian; Adult; *n* = 5	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)	> 8 days	NS	Lactating; Milked 2×/day	[55] 1998
						IMM	24 mg/kg Penicillin G sodium	1	Milk	7 days (0.001 ppm)	8 days			
Penicillin	Sheep; domestic dairy breed; adult; *n* = 10	US Tol: Zero. EMA MRL: Not established.	Bioassay	3 ppb	4 ppb	IMM co-admin w/IM	1,000,000 IU Benzylpenicillin (IMM) daily co- administered with 250,000 IU benzylpenicillin (IM) at 24 h intervals.	5 (IMM) 2 (IM)	Milk	192 h (9.9 ppb)	>192 h	Diseased	Lactating; 1 syringe/gland	[52] 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: 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, mL = milliliter.

3.4. Cephalosporins

Cephalosporins (first-generation: cephapirin, cefacetrile, cephalothin, cephradine, cephalexin; 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 summarizes 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 Admini-stration	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 (0.17 ppm)	>12 h	Healthy	Lactating; Milked 2×/day	[62] 2004
						IM	20 mg/kg Cefepime	1	Milk	12 h (0.25 ppm)	>12 h			
Cefepime	Goat; NS; 1 year; *n* = 5	US Tol: Not established. EMA MRL: Not established.	HPLC	1.15 ppb	3.49 ppm	IM	50 mg/kg Cefepime	1	Milk	4 h (5.14 ppm§)	> 4 h	Healthy	Lactating	[72] 2010
Cefonicid	Goat; Muriano-Granadina; 2–4 years; *n* = 6	US Tol: Not established. EMA MRL: Not established.	HPLC	500 ppb	750 ppb	IV	10 mg/kg Cefonicid sodium	1	Milk	<LOQ @ 1 h	1 h	Healthy	Lactating; Milked 1×/day	[63] 2020
						IM	10 mg/kg Cefonicid sodium	1	Milk	<LOQ @ 1 h	1 h			
						SC	10 mg/kg Cefonicid sodium	1	Milk	<LOQ @ 1 h	1 h			
						SC	20 mg/kg Cefonicid sodium	1	Milk	<LOQ @ 1 h	1 h			
Cef-quinome	Goat; Zaraibi; 30–36 months; *n* = 5	US Tol: Not established. EMA MRL: Not established.	Bioassay	0.009 ppm	0.027 ppm	IV	3 mg/kg Cefquinome sulfate	1	Milk	48 h (0.02 ppm §)	>2 days	Healthy	Lactating; Milked 1×/day	[67] 2015
			HPLC	0.006 ppm	0.017 ppm				Milk	48 h (0.01 ppm §)	>2 days			
			Bioassay	0.009 ppm	0.027 ppm	IV	3 mg/kg Cefquinome sulfate	1	Milk	48 h (0.02 ppm §)	>2 days	Diseased-Mastitis		
			HPLC	0.006 ppm	0.017 ppm				Milk	48 h (0.02 ppm §)	>2 days			
Cef-quinome	Goat; Zaraibi; 30–36 months; *n* = 5	US Tol: Not established. EMA MRL: Not established.	HPLC	0.006 ppm	0.018 ppm	IMM	75 mg Cefquinome sulfate	1	Milk	120 h (0.01 ppm §)	>120 h	Healthy	Early & mid-lactating; 1 full tube per gland 1 full tube into single infected udder half	[68] 2019
						IMM	75 mg Cefquinome sulfate	1	Milk	96 h (0.01 ppm §)	120 h	Diseased-Mastitis		
Cef-tazidime	Goat; Creole; Adult; *n* = 6	US Tol: Not established. EMA MRL: Not established.	Bioassay	0.125 ppm	0.3 ppm	IV	10 mg/kg Ceftazidime	1	Milk	12 h (0.52 ppm §)	>12 h	Healthy	Lactating; Milked 2x/day	[73] 2011
						IM	10 mg/kg Ceftazidime	1	Milk	12 h (0.54 ppm §)	>12 h			
Ceftiofur	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 Ceftiofur sodium	1	Milk	24 h (NS)	2 days	Healthy	Lactating; Milked 2×/day	[71] 1994
						IM	2.2 mg/kg Ceftiofur sodium daily	5	Milk	24 h (NS)	2 days			
Ceftiofur	Sheep; NS; Adult; *n* = 9	US Tol: 100 ppb (milk). EMA MRL by extension from bovine to ovine: 100 ppb (milk).	HPLC	NS	NS	IM	2 mg/kg Ceftiofur sodium daily	5	Milk	<LOQ @ 12 h	12 h	Healthy	Lactating	[74] 2006
Ceftiofur	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	IMM	125 mg Ceftiofur hydrochloride daily	2	Milk	72 h (37 ppb)	4 days	Healthy	Mid- & late lactation; Milked 2×/day. Left udder half infused.	[75] 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	[64] 2013

Table 4. *Cont.*

Analyte	Species; Breed; Age; # of Animals	Tolerance/MRL	Analytical Method	LOD	LOQ	Route of Admini-stration	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	1	Milk	8 h (0.36 ppm)	10 h	Healthy	Lactating	[65] 2005
						IM	20 mg/kg Ceftriaxone	1	Milk	10 h (0.26 ppm)	12 h			
Ceftriaxone	Sheep; native breed; 2–3 years; *n* = 6	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	0.1 ppm	IV	10 mg/kg Ceftriaxone	1	Milk	10 h (0.22 ppm)	12 h	Healthy	Lactating; Milked 2×/day	[76] 2006
						IM	10 mg/kg Ceftriaxone	1	Milk	12 h (0.19 (ppm)	24 h			
Ceph-acetrile	Sheep; Texel; adult; *n* = 6	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IM	12 mg/kg Benzathine cephacetrile	1	Milk	24 h (NS)	>1 day	Healthy	Lactating	[66] 1977
Cephalexin	Goat; NS; 1 year; *n* = 2	US Tol: Not established. EMA MRL: Not established.	HPLC	0.165 ppm	NS	IM	10 mg/kg Cephalexin	1	Milk	72 h (0.07 ppm §)	>3 days	NS	Lactating	[77] 2019
Cephalexin	Sheep; Awassi; adult; *n* = 10	US Tol: Not established. EMA MRL: Not established.	Bioassay	0.1 ppm	NS	IM	10 mg/kg Cephalexin	1	Milk	8 h (0.46 ppm §)	>8 h	Healthy	Late lactation	[69] 1988
Ceph-alothin	Goat; Creole; adult; *n* = 20	US Tol: Not established. EMA MRL: Not established.	HPLC	0.01 ppm	NS	IV	10 mg/kg Cephalothin	1	Milk	12 h (0.31 ppm §)	>12 h	Healthy	Lactating; Milked 2x/day	[78] 2004
Ceph-alothin	Goat; Creole; adult; *n* = 22 study; groups of 8, 8 and 6	US Tol: Not established. EMA MRL: Not established.	HPLC	0.01 ppm	NS	IV	20 mg/kg Cephalothin	1	Milk	6 h (0.08 ppm §)	8 h	Healthy	Early lactation; Restricted diet	[79] 2007
						IV	20 mg/kg Cephalothin	1	Milk	8 h (0.28 ppm §)	10 h		Early lactation; Restricted diet + additional energy	
						IV	20 mg/kg Cephalothin	1	Milk	12 h (0.12 ppm §)	14 h		Early lactation; Balanced diet	
Cephapirin	Goat; French Alpine; 1–7 years; *n* = 20	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IMM	200 mg Cephapirin at 12 h intervals	2	Milk	ND @ 192 h	8 days	Healthy	Mid-lactation; 1 full tube into R half udder	[70] 1986
						IMM	200 mg Cephapirin at 12 h intervals	3	Milk	ND @ 192 h	8 days			
Cephapirin	Goat; dairy type; 2–7 years; *n* = 10	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IMM	200 mg Sodium cephapirin at 12 h intervals	2	Milk	48 h (0.03 ppm §)	60 h	Healthy	Early & mid- lactation; Milked 2×/day; 1 full tube into each gland	[60] 1984
Cephradine	Goat; NS; adult; *n* = 4	US Tol: Not established. EMA MRL: Not established.	Spectrophoto-metrically	0.2 ppm	NS	IM	10 mg/kg Cephradine	1	Milk	8 h (1.55 ppm)	12 h	Healthy and Diseased	Lactating	[80] 1994
						IM	10 mg/kg Cephradine at 12 h intervals	3	Milk	8 h (1.28 ppm)	12 h			
						IM	10 mg/kg Cephradine at 12 h intervals	5	Milk	8 h (3.02 ppm)	12 h			
						IM	10 mg/kg Cephradine at 12 h intervals	7	Milk	8 h (2.78 ppm)	12 h			
						IM	10 mg/kg Cephradine at 12 h intervals	9	Milk	8 h (3.02 ppm)	12 h			

§ 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.

Table 5. Fluoroquinolone 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
Ciprofloxacin	Goats; NS; 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	[81] 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	[82] 1998
						IM	5 mg/kg Ciprofloxacin	1	Milk	10 h (0.07 ppm)	18 h			
						IM	5 mg/kg Ciprofloxacin daily	5	Milk	3 days (0.07 ppm)	4 days			
Danofloxacin	Goats; Murciano-Granadina; 1.5–3 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	0.005 ppm	0.015 ppm	SC	6 mg/kg Danofloxacin	1	Milk	36 h (0.01 ppm §)	48 h	Healthy	Mid-lactation; Milked 2×/day	[83] 2007
Danofloxacin	Sheep; Manchega; 2–4 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	0.005 ppm	0.015 ppm	SC	6 mg/kg Danofloxacin	1	Milk	36 h (0.02 ppm §)	48 h	Healthy	Mid-lactation; Milked 2×/day	[83] 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 (0.1 ppm §)	>1 day	Healthy	Mid-lactation	[99] 1997
						IM	1.25 mg/kg Danofloxacin	1	Milk	24 h (0.07 ppm §)	>1 day			
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	1	Milk	24 h (0.07 ppm §)	>24 h	Healthy	Mid-lactation; Milked 2×/day	[96] 2011
						IM	1.25 mg/kg co-administered with 0.2 mg/kg ivermectin	1	Milk	24 h (0.09 ppm §)	>24 h			
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 §)	>24 h	Healthy	Mid-lactation; Milked 2×/day	[97] 2013
						IM	1.25 mg/kg Danofloxacin + soy diet	1	Milk	24 h (0.1 ppm §)	>24 h			
						IM	1.25 mg/kg Danofloxacin + Gen-daid (isoflavones)	1	Milk	24 h (0.03 ppm §)	>24 h			
Danofloxacin	Sheep; Assaf; 2–3 years; *n* = 6	US Tol: Prohibited EMA MRL: Not established.	HPLC	NS	100 ppb	IM	1.25 mg/kg Danofloxacin	1	Milk	24 h (0.03 ppm §)	>24 h	Healthy	Mid-lactation; Milked 2×/day	[100] 2013
						IM	1.25 mg/kg Danofloxacin co-administered with 1 mg/kg IV triclabendazole	1	Milk	24 h (0.25 ppm §)	>24 h			
Danofloxacin	Sheep; Assaf; adult; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	NS	19 ppb	IM	1.25 mg/kg Danofloxacin standard diet	1	Milk	24 h (0.05 ppm §)	> 24 h	Healthy	Mid-lactation; Milked 2×/day	[101] 2018
						IM	1.25 mg/kg Danofloxacin w/ 10% flaxseed diet	1	Milk	24 h (0.04 ppm §)	>24 hr			
						IM	1.25 mg/kg Danofloxacin w/ 15% flaxseed diet	1	Milk	24 h (0.05 ppm §)	> 24 h			
Difloxacin	Goats; Murciano-Granadina; 4–5 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	NS	10 ppb	IV	5 mg/kg Difloxacin	1	Milk	48 h (0.02 ppm §)	72 h	Healthy	Lactating; Milked 1×/day	[102] 2010
						SC	5 mg/kg Difloxacin	1	Milk	36 h (0.02 ppm §)	48 h			
						SC	15 mg/kg Difloxacin (long acting)	1	Milk	144 h (0.59 ppm §)	>144 h			
Difloxacin	Goats; Murciano-Granadina; 4–5 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established	HPLC	NS	10 ppb	SC	15 mg/kg Difloxacin (long acting)	1	Milk	144 h (0.07 ppm §)	>144 h	Healthy	Lactating; Milked 1x/day	[84] 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	1	Milk	24 h (0.06 ppm)	36 h	Healthy	Mid-lactation; Milked 2x/day	[85] 2003
						IV	5 mg/kg Enrofloxacin co-administered with 7.5 mg/kg albendazole PO	1	Milk	12 h (0.11 ppm)	24 h			
						IM	5 mg/kg Enrofloxacin	1	Milk	36 h (0.08 ppm)	48 h			
						IM	5 mg/kg Enrofloxacin co-administered with 7.5 mg/kg albendazole PO	1	Milk	24 h (0.16 ppm)	36 h			
Enrofloxacin Ciprofloxacin	Goats; Murciano-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 ǂ	Healthy	Lactating	[103] 2009
Enrofloxacin	Goats; Murciano-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	IV	5 mg/kg Enrofloxacin	1	Milk	NS	NS ‡	Healthy	Lactating	[86] 2009
						SC	5 mg/kg Enrofloxacin (long acting)	1	Milk	NS	NS ♀			
Enrofloxacin	Goats; NS; 1.5–2 years; *n* = 6	US Tol: Prohibited. EMA MRL extension from bovine to all food producing species: 100 ppb (milk).	Bioassay	0.01 ppm	NS	SC	5 mg/kg Enrofloxacin	1	Milk	30 h (0.08 ppm)	36 h	Healthy	Lactating	[87] 2009
						SC	5 mg/kg Enrofloxacin SC, pretreated with 70 mg/kg probenecid PO	1	Milk	36 h (0.02 ppm)	48 h			
Enrofloxacin Ciprofloxacin	Sheep; NS; Neo-natal	US Tol: Prohibited. EMA MRL by extension from bovine to ovine: 300 ppb (liver); 200 ppb (kidney); 100 ppb (muscle, fat).	HPLC	NS	10 ppb	PO	7.5 mg/kg Enrofloxacin	1	Liver	NS	Enro ~: 16 days Cipro ≈: 16 days	Healthy	NS	[104] 1998
									Kidney	NS	Enro ~: 16 days Cipro ≈: 16 days			
									Muscle	NS	Enro ~: 16 days Cipro ≈: 16 days			
									Fat	NS	Enro ~: 16 days Cipro ≈: 16 days			
Enrofloxacin	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	0.018 ppm	IV	2.5 mg/kg Enrofloxacin	1	Milk	24 h (0.13 ppm §)	>24 h	Healthy	Lactating; Milked 2×/day	[88] 2003
						IM	2.5 mg/kg Enrofloxacin	1	Milk	24 h (0.15 ppm §)	>24 h			
Enrofloxacin	Sheep; Assaf; 2–3 years; *n* = 12	US Tol: Prohibited. EMA MRL extension from bovine to all food producing species: 100 ppb (milk).	HPLC	NS	NS	IV	2.5 mg/kg Enrofloxacin	1	Milk	24 h (0.09 ppm §)	> 24 h	Healthy	Mid-lactation; Milked 2×/day	[98] 2006
						IV	2.5 mg/kg Enrofloxacin co-administered with 0.8 mg/kg genistein IM	1	Milk	24 h (0.05 ppm §)	> 24 h			
						IV	2.5 mg/kg Enrofloxacin co-administered with 2 mg/kg albendazole IV	1	Milk	24 h (0.06 ppm §)	> 24 h			

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	10 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 (0.04 ppm §)	48 h	Healthy	Lactating	[90] 2009
						IM	4 mg/kg Levofloxacin hemihydrate	1	Milk	36 h (0.06 ppm §)	48 h			
Marbo-floxacin	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
						IM	5 mg/kg Marbofloxacin	1	Milk	36 h (0.07 ppm §)	48 h			
Marbo-floxacin	Sheep; Assaf; adult; *n* = 15	US Tol: Prohibited. EMA MRL: Not established.	Bioassay	0.05 ppm ^	0.04 ppm ^	IV	2.5 mg/kg Marbofloxacin	1	Milk	24 h (0.05 ppm §)	>24 h	Healthy	Mid-lactation	[92] 1997
						IM	2.5 mg/kg Marbofloxacin	1	Milk	24 h (0.23 ppm §)	> 24 h			
Moxifloxacin	Goats; Murciano-Granadina; 3–4 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	NS	10 ppb	IV	5 mg/kg Moxifloxacin	1	Milk	32 h (0.01 ppm §)	48 h	Healthy	Lactating	[93] 2006
						SC	5 mg/kg Moxifloxacin	1	Milk	32 h (0.05 ppm §)	48 h			
Moxifloxacin	Goats; Murciano-Granadina; 3–4 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	NS	10 ppb	IM	5 mg/kg Moxifloxacin	1	Milk	32 h (0.01 ppm §)	48 h	Healthy	Lactating	[105] 2007
Norfloxacin	Sheep; crossbred; adult; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	0.07 ppm	NS	IV	25 mg/kg Norfloxacin nicotinate	1	Milk	24 h (10 ppm)	>24 h	Healthy	Lactating	[106] 1994
Orbifloxacin	Goats; Murciano-Granadina; 5–6 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	HPLC	20 ppb	25 ppb	IV	2.5 mg/kg Orbifloxacin	1	Milk	12 h (0.04 ppm §)	24 h	Healthy	Lactating	[107] 2007
						SC	2.5 mg/kg Orbifloxacin	1	Milk	24 h (0.03 ppm §)	36 h			
						IM	2.5 mg/kg Orbifloxacin	1	Milk	12 h (0.05 ppm §)	24 h			
Orbifloxacin	Sheep; Barky; 4–6 years; *n* = 6	US Tol: Prohibited. EMA MRL: Not established.	Bioassay	NS	0.04 ppm	IV	2.5 mg/kg Orbifloxacin	1	Milk	24 h (0.09 ppm §)	30 h	Healthy	Lactating	[94] 2009
						IM	2.5 mg/kg Orbifloxacin	1	Milk	30 h (0.06 ppm §)	48 h			
Pefloxacin	Goats; Egyptian; 2 years; *n* = 5	US Tol: Prohibited. EMA MRL: Not established.	Bioassay	NS	0.078 ppm	IV	10 mg/kg Pefloxacin	1	Milk	10 h (0.1 ppm)	12 h	Healthy	Lactating	[95] 2002
						IM	10 mg/kg Pefloxacin	1	Milk	10 h (0.1 ppm)	12 h			

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
Flumequine 7-Hydroxy-flumequine	Sheep	US Tol: Not established. EMA established MRL: 100 ppb (liver); 300 ppb (kidney); 50 ppb (muscle, fat, skin).	HPLC	NS	100 ppb	IM	12 mg/kg Flumequine for first dose, then 6 mg/kg at 12 h intervals	10	Liver	Flu: 78 h (13.8 ppb) 7-OH: 48 h(10.24 ppb)	Flu: >78 h 7-OH: 60 h	NS	NS	[108] 1997
									Kidney	Flu: 78 h (38.6 ppb) 7-OH: 78 h (4.5 ppb)	Flu: >78 h 7-OH: >78 h			
									Muscle	Flu: 78 h (9.0 ppb) 7-OH: 18 h (15.3 ppb)	Flu: >78 h 7-OH: 30 h			
									Fat	Flu: 78 h (52.5 ppb) 7-OH: ND @ 18 h	Flu: >78 h 7-OH: 18 h			
									Inj. Site	Flu: 90 h (10 ppb) 7-OH: 30 h (13.5 ppb)	Flu: >90 h 7-OH: 42 h			
Flumequine	Sheep; NS; NS; n = 20 study; n = 4/time pt	US Tol: Not established. EMA established MRL: 100 ppb (liver); 300 ppb (kidney); 50 ppb (muscle, fat, skin).	HPLC	NS	5 ppb	IM	12 mg/kg Flumequine for first dose, then 6 mg/kg at 12 h intervals	6	Liver	78 h (19.3 ppb)	>78 h	Healthy	NS	[109] 1998
									Kidney	78 h (62.5 ppb)	>78 h			
									Muscle	78 h (12.4 ppb)	>78 h			
									Fat	78 h (171.9 ppb)	>78 h			

§ Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # = number. † Enrofloxacin parent half-life reported = 2.74 h; Ciprofloxacin metabolite half-life = 4.79 h. ‡ Intravenous half-life reported= 5.39 h. º Subcutaneous half-life reported= 14.85 h. ~ Enro: Enrofloxacin. ≈ 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. ^ 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

Marcolides (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.

Table 6. Macrolide 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
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	IMM	300 mg Erythromycin at 12 h intervals	3	Milk	24 h (0.05 ppm Ŝ)	36 h	Healthy	Early & mid-lactation; Milked 2x/day, Whole tube per gland	[60] 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 1	Milk Milk	12 h (0.14 ppm Ŝ) 12 h (0.24 ppm Ŝ)	>12 h >12 h	Healthy	Early lactation	[121] 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 10 mg/kg Erythromycin 10 mg/kg Erythromycin	1 1 1	Milk Milk Milk	12 h (0.14 ppm Ŝ) 12 h (0.16 ppm Ŝ) 24 h (0.05 ppm Ŝ)	24 h 24 h >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 Kidney Muscle Fat Inj. Site	1 day (1.22 ppm) 1 days (0.77 ppm) 1 day (0.42 ppm) ND 15 days (0.37 ppm)	3 days 3 days 3 days 1 day >15 days	Healthy	NS	[110] 2000
			LS-MC	NS	100 ppb	IM	10 mg/kg Erythromycin daily	5	Liver Kidney Muscle Fat Inj. Site	1 days (0.41 ppm) 1 days (0.59 ppm) 1 days (0.27 ppm) ND 6 days (0.46 ppm)	3 days 3 days 3 days 1 day 9 days	Healthy		

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
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	[125] 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	6 mg/kg Gamithromycin	1	Liver Kidney Muscle Fat Inj. Site	NS ‡ NS ‡ NS ‡ NS ‡ NS ‡	NS ‡ NS ‡ NS ‡ NS ‡ NS ‡	Healthy	NS	[126] 2016
Spiramycin	Sheep; Awassi; adult; *n* = 1	US Tol: Not established. EMA MRL: Not established.	Bioassay Radio-activity	NS NS	NS NS	IV IV	20 mg/kg Spiramycin adipate 20 mg/kg Spiramycin (radiolabeled)	1 1	Milk Milk	60 h (2.78 ppm §) 60 h (3.61 ppm §)	>96 h >96 h	Healthy	Lactating; Milked 2×/day	[24] 1973
Spiramycin	Sheep; Awassi; Adult; *n* = 2	US Tol: Not established. EMA MRL: Not established.	Bioassay Radio-activity Bioassay Radio-activity	NS NS NS NS	NS NS NS NS	IM IM	20 mg/kg Spiramycin adipate 20 mg/kg Spiramycin (radiolabeled)	1 1	Milk Milk Milk Milk	56 h (2.40 ppm §) 56 h (3.61 ppm §) 56 h (1.79 ppm §) 56 h (1.92 ppm §)	>56 h >56 h >56 h >56 h	Healthy Diseased-mastitis	Lactating; Milked 2x/day	[29] 1974
Tilmicosin	Goats; NS; 2.5–3 years; *n* = 5	US Tol: Not established. EMA MRL by extension from ovine to all food producing species: 40 ppb (milk).	Bioassay	10 ppb	NS	SC	10 mg/kg Tilmicosin	1	Milk	11 days (0.16 ppm §)	12 days	Healthy	Early lactation	[112] 1997
Tilmicosin	Sheep; Barki; 2–3 years; *n* = 5	US Tol: Not established. EMA established MRL: 40 ppb (milk).	Bioassay	NS	0.1 ppm	SC	10 mg/kg Tilmicosin phosphate	1	Milk	8 days (0.04 ppm §)	>8 days	Healthy	Mid-lactation	[127] 1999
Tilmicosin	Sheep; Suffolk crossbred; adult; *n* = 4	US Tol: Not established. EMA established MRL: 40 ppb (milk).	HPLC	50 ppb	NS	SC	10 mg/kg Tilmicosin	1	Milk	11 days (46 ppb)	>11 days	NS	Early & mid-lactation; Milked 2x/day	[128] 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)	US Tol: 1200 ppb (liver); 100 ppb (muscle). EMA established MRL: 1000 ppb (liver & kidney); 50 ppb (muscle & fat).	Radio-activity	NS	NS	SC	20 mg/kg Tilmicosin phosphate (radiolabeled)	1	Liver	28 days (2.7 ppm)	>28 days	Healthy	NS	[129] 2002
									Kidney	28 days (0.55 ppm)	>28 days			
									Muscle	28 days (1.35 ppm)	>28 days			
									Fat	28 days (0.26 ppm)	>28 days			
									Inj. Site	28 days (6.51 ppm)	>28 days			
	NS; NS; *n* = 16 & 4 slaughter time pts		HPLC	50 ppb	NS	SC	20 mg/kg Tilmicosin phosphate	1	Liver	28 days (160 ppb)	>28 days	Healthy		
									Kidney	28 days (73 ppb)	>28 days			
									Muscle	7 days (193.5 ppb)	21 days			
									Fat	3 days (73 ppb)	7 days			
									Inj. Site	28 days (121.8 ppb)	>28 days			
	Scottish Blackface; 6 months; *n* = 24 study; *n* = 4/time pt		HPLC	NS	50 ppb	SC	30 mg/kg Tilmicosin phosphate	1	Liver	56 days (81 ppb)	>56 days	Healthy		
									Kidney	42 days (51 ppb)	56 days			
									Muscle	<LOQ @ 14 days	14 days			
									Fat	<LOQ @ 14 days	14 days			
									Inj. Site	56 days (81 ppb)	>56 days			
	Swaledale; NS; *n* = 28 study; *n* = 4/tme pt		HPLC	NS	50 ppb	SC	10 mg/kg Tilmicosin phosphate	1	Liver	35 days (59 ppb)	42 days	Healthy		
									Kidney	21 days (73 ppb)	28 days			
									Muscle	<LOQ @ 14 days	14 days			
									Fat	<LOQ @ 14 days	14 days			
									Inj. Site	28 days (80 ppb)	35 days			
Tilmicosin	Sheep; NS; lambs; *n* = 12 study; *n* = 3/time pt	US Tol: 1200 ppb (liver); 100 ppb (muscle). EMA established MRL: 50 ppb (muscle & fat); 1000 ppb (liver & kidney).	Radio-activity	NS	NS	SC	20 mg/kg Tilmicosin phosphate (radiolabeled)	1	Liver	28 days (2.7 ppm)	>28 days	Healthy	NS	[113] 1997
									Kidney	28 days (0.55 ppm)	>28 days			
									Muscle	28 days(<0.26 ppm)	>28 days			
									Fat	28 days (<1.2 ppm)	>28 days			
									Inj. Site	28 days (1.32 ppm)	>28 days			
	NS; lambs; *n* = 12 study; *n* = 3/time pt		HPLC	NS	0.05 ppm	SC	20 mg/kg Tilmicosin phosphate	1	Liver	28 days (0.16 ppm)	>28 days	Healthy		
									Kidney	28 days (0.06 ppm)	>28 days			
									Muscle	7 days (0.19 ppm)	21 days			
									Fat	7 days (<0.05 ppm)	7 days			
									Inj. Site	28 days (0.12 ppm)	>28 days			
	Swaledale; NS; *n* = 28 study; *n* = 4/time pt		LC	NS	0.05 ppm	SC	10 mg/kg Tilmicosin phosphate	1	Liver	21 days (0.07 ppm)	28 days	Healthy	NS	
									Kidney	21 days (0.07 ppm)	28 days			
									Muscle	ND @ 14 days	14 days			
									Fat	<LOQ @ 14 days	14 days			
									Inj. Site	28 days (0.08 ppm)	35 days			
	NS; adult; *n* = 4		HPLC	NS	0.05 ppm	SC	10 mg/kg Tilmicosin phosphate	1	Milk	10 days (0.06 ppm)	14 days	Healthy	Lactating	

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 (fat); 5400 ppb (liver);1800 ppb (kidney).	UPLC	0.7 ppb	2 ppb	SC	2.5 mg/kg Tulathromycin at 7-day interval	2	Liver Kidney Muscle Fat	20 days (0.78 ppm)) 20 days (0.44 ppm) 5 days (0.46 ppm) 10 days (0.17 ppm)	>20 days >20 days 10 days 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 (fat); 5400 ppb (liver); 1800 ppb (kidney).	LC-MS	Liver: 0.75 ppm Kidney: 0.29 ppm Muscle: 0.24 ppm Fat: 0.14 ppm Inj. Site: 0.24 ppm	Liver: 1.91 ppm Kidney: 1.66 ppm Muscle: 0.69 ppm Fat: 0.61 ppm Inj. Site: 0.69 ppm	SC	2.5 mg/kg Tulathromycin	1	Liver Kidney Muscle Fat Inj. Site	<LOD @ 14 days <LOD @ 14 days <<LOD @ 14 days <LOD @ 14 days 35 days (0.25 ppm)	14 days 14 days 14 days 14 days >35 days	Healthy Juveniles	NS	[124] 2012
	Mixed; 5–6 months; *n* = 30 stdy; *n* = 6/time pt					SC	2.5 mg/kg Tulathromycin	1	Liver Kidney Muscle Fat Inj. Site	12 days (1.18 ppm) 48 days (0.31 ppm) 5 days (0.24 ppm) 12 days (0.15 ppm) 18 days (1.27 ppm)	18 days >48 days 12 days 18 days 27 days	Healthy Market-age		
	Mixed; 2–3 weeks; *n* = 12					SC	2.5 mg/kg Tulathromycin at 7-day interval	3	Liver Kidney Muscle Fat Inj. Site	7 days (0.7 ppm) <LOD @ 7 days <LOD @ 7 days <LOD @ 7 days 7 days (8.76 ppm)	>7 days >7 days >7 days >7 days >7 days	Healthy Juveniles		
						SC	7.5 mg/kg Tulathromycin at 7-day interval	3	Liver Kidney Muscle Fat Inj. Site	7 days (3.4 ppm) 7 days (1.65 ppm) 7 days (0.65 ppm) 7 days (0.36 ppm) 7 days (17.9 ppm)	>7 days >7 days >7 days >7 days >7 days	Healthy Juveniles		
						SC	12.5 mg/kg Tulathromycin at 7-day interval	3	Liver Kidney Muscle Fat Inj. Site	7 days (4.87 ppm) 7 days (3.28 ppm) 7 days (1.33 ppm) 7 days (0.65 ppm) 7 days (24.4 ppm)	>7 days >7 days >7 days >7 days >7 days	Healthy Juveniles		

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 2×/day	[115] 2016
Tulathromycin	Goats; NS; 30–36 months; *n* = 5	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IV	2.5 mg/kg Tulathromycin	1	Milk	19 days (0.08 ppm §)	>19 days	Healthy	Lactating	[116] 2012
						IM	2.5 mg/kg Tulathromycin	1	Milk	19 days (0.1 ppm §)	>19 days			
Tulathromycin	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	58 days (0.5 ppb)	61 days	Healthy	Lactating; Milked 2×/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 (fat); 5400 ppb (liver); 1800 ppb (kidney).	LS-MC	NS	Liver: 300 ppb	IM	2.5 mg/kg Tulathromycin	1	Liver	35 days (0.3 ppm)	42 days	Healthy	NS	[130] 2015
					Kidney: 200 ppb				Kidney	21 days (0.2 ppm)	28 days			
					Muscle; 50 ppb				Muscle	21 days (0.05 ppm)	28 days			
					Fat: 50 ppb				Fat	14 days (0.05 ppm)	21 days			
					Inj. Site: 50 ppb				Inj. Site	49 days (0.15 ppm)	>49 days			
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 tartrate	1	Milk	24 h (0.6 ppm)	>24 h	Healthy	Lactating	[118] 1991
						IM	15 mg/kg Tylosin tartrate	1	Milk	24 h (1.7 ppm)	>24 h			
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	Lactating; Milked 2x/day	[119] 1973
									Milk	26 h (0.67 ppm)	>26 h	Diseased-mastitis		
Tylosin	Sheep; Merino; 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	36 h (30.9 ppb)	48 h	Healthy	Lactating; Milked 2×/day	[120] 2001

§ 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 = 2.82 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: 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.

3.7. Sulfonamides

Sulfonamides (sulfadiazine, sulfadimethoxine, sulfamethoxazole, sulfachlorpyrazine) are bacteriostatic antibacterial medications that complete 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 ppb (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 ppb (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 IV once then 100 mg/kg sulfanilamide PO at 12 h intervals	8	Liver Kidney Muscle	8 days (79 ppm) 8 days (119 ppm) 8 days (50 ppm)	>8 days >8 days >8 days	Healthy	NS	[136] 1977
Sulfamethoxypyridazine	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 Kidney Muscle	8 days (55 ppb) 8 days (115 ppb) 8 days (41 ppb)	>8 days >8 days >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 Kidney Muscle Fat	1 day (0.12 ppm §) 1 days (0.11 ppm §) 16 h (0.27 ppm §) 16 h (0.26 ppm §)	>1 day >1 day 1 day 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 Kidney Muscle Fat	5 days (0.11 ppm) 5 days (0.07 ppm) 7 days (0.12 ppm) 7 days (0.05 ppm)	7 days 7 days 10 days >7 days	Healthy	NS	[138] 1972

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
Sulfamerazine	Sheep; NS; adult; $n = 12$	US Tol: Not established. EMA established MRL: 100 ppb (milk).	Spectrometric	NS	NS	PO	100 mg/kg Sulfamerazine	1	Milk	2 days (3.7 ppm)	>2 days	Healthy	Lactating; Full dose/ gland	[139] 1978
						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			
Sulfamethazine †	Goat; West African Dwarf; 1 year; $n = 20$ study; $n = 1$/time point	US Tol: Not established. EMA MRL: Not established.	Spectrometric	0.05 ppm	NS	IM	100 mg/kg Sulfadimidine	1	Liver	30 days (5.29 ppm)	>30 days	Healthy	NS	[133] 2018
									Kidney	30 days (3.84 ppm)	>30 days			
									Muscle	30 days (2.01 ppm)	>30 days			
									Fat	30 days (4.84 ppm)	>30 days			
						IM	100 mg/kg Sulfadimidine co-admin w/5 mg/kg piroxicam	1	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			
Sulfamethazine †	Sheep; Targhee/ Rambouillet; lambs; $n = 16$ study; $n = 2$/time pt	US Tol: Not established. EMA MRL: Not established.	Spectrometric	NS	NS	IV	107.25 mg/kg Sodium sulfamethazine	1	Liver	4 days (0.11 ppm)	>4 days	Healthy	NS	[134] 1977
									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
Sulfamethazine †	Sheep; crossbred; 2–3 years; *n* = 25 study; *n* = 5/time pt	US Tol: Not established. EMA MRL: Not established.	HPLC	NS	0.1 ppm	PO	391 mg/kg Sulfamethazine	1	Liver Kidney Muscle Fat	4 days (0.3 ppm) 4 days (0.25 ppm) 4 days (0.2 ppm) ND	8 days 8 days 8 days 4 days	Healthy	NS	[140] 1991
Sulfamethazine †	Sheep; crossbred; adult; *n* = 10	US Tol: Not established. EMA Established MRL: 100 ppb (milk).	Spectrometric	NS	NS	PO	15,000 mg Sulfamethazine	1	Milk	1 day (NS)	>1 day	Healthy	Lactating	[131] 1965
						PO	15,000 mg Sulfamethazine at 12 h interval	2	Milk	2 days (NS)	>2 days	Healthy		
						PO	15,000 mg Sulfamethazine at 16 h interval	2	Milk	2 days (NS)	>2 days	Healthy		
						PO	15,000 mg Sulfamethazine at 22 h interval	2	Milk	2 days (NS)	>2 days	Healthy		
						PO	15,000 mg Sulfamethazine at 24 h interval	2	Milk	2 days (NS)	>2 days	Healthy		
						PO	15,000 mg Sulfamethazine at 25 h interval	2	Milk	53 h (NS)	>53 h	Diseased-mastitis		
						PO	15,000 mg Sulfamethazine first dose, 10,000 mg second dose at 24 h interval	2	Milk	2 days (NS)	>2 days	Healthy		
						PO	15,000 mg Sulfamethazine first dose, 7000 mg second dose at 24 h interval	3	Milk	2 days (NS)	>2 days	Healthy		
						PO	15,000 mg Sulfamethazine first dose, 7000 mg second dose at 22 h interval	3	Milk	78 h (NS)	>78 h	Diseased-mastitis		
						PO	15,000 mg Sulfamethazine first 2 doses at 13 h interval, 7000 mg third dose at 23 h interval	3	Milk	74 h (NS)	>74 h	Diseased-mastitis		

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
						PO	15,000 mg Sulfamethazine first 2 doses at 13 h interval, 7000 mg third dose at 22 h interval	3	Milk	83 h (NS)	>83 h	Diseased-mastitis		
						PO	18,000 mg first dose, 6000 mg second dose at 17 h interval then 19 h interval	3	Milk	80 h (NS)	>80 h	Diseased-mastitis		
						PO	18,000 mg Sulfamethazine first dose, 6000 mg at 24 h intervals	4	Milk	96 h (NS)	>96 h	Diseased-mastitis		
Sulfamethazine †	Sheep; NS; NS; NS	US Tol: Not established. EMA MRL: Not established.	NS	NS	NS	PO	107.25 mg/kg Sulfamethazine	1	Liver Kidney Muscle Fat	2 days (0.1 ppm §) 2 days (0.23 ppm §) 2 days (0.15 ppm §) 36 h (0.16 ppm §)	>2 days >2 days >2 days 2 days	Healthy	NS	[141] 1978
Sulfamethazine †	Sheep; Suffolk; NS; *n* = 2; *n* = 1/time pt	US Tol: Not established. EMA MRL: Not established.	Radioactivity	NS	NS	PO	100 mg/kg Sulfamethazine (radiolabeled)	1	Liver Kidney Muscle	2 days (10 ppm) 2 days (22 ppm) 2 days (3 ppm)	>2 days >2 days >2 days	Healthy	NS	[142] 1983
Sulfamethazine †	Sheep; Balady; 2–4 years; *n* = 9 study; *n* = 3/time pt	US Tol: Not established. EMA MRL: Not established.	NS	NS	NS	IM	0.1 mg/kg Sulfadimidine	1	Liver Kidney Muscle	4 h (20 ppm) 4 h (198 ppm) 4 h (11 ppm)	>4 h >4 h >4 h	Healthy	NS	[143] 1980
Sulfadiazine	Sheep; Balady; 2–4 years; *n* = 9 study; *n* = 3/time pt	US Tol: Not established. EMA MRL: Not established.	NS	NS	NS	IM	0.1 mg/kg Sulfadiazine	1	Liver Kidney Muscle	4 h (25 ppm) 4 h (40 ppm) 4 h (13 ppm)	>4 h >4 h >4 h	Healthy	NS	[143] 1980

§ Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # Number. † Sulfamethazine 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 (medicated 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	Matrix	Last Sampling Time Point (Post-Last Treatmnet) When Residues WERE Detected	Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) *	Health Status	Additional Information	Source/ Year
Chlortetracycline	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 IMM	25 mg/kg Chlortetracycline hydrochloride 426 mg Chlortetracycline hydrochloride in right half of udder.	1 1	Milk Milk	72 h (0.1 ppm) 120 h (R udder) (0.28 ppm) 38 h (L udder) (0.09 ppm)	>72 h >120 h (R udder) 48 h (L udder)	Healthy	Lactating; Only right $\frac{1}{2}$ of udder infused.	[147] 1982
Chlortetracycline	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: 300 ppb (liver); 600 ppb (kidney); 100 ppb (muscle).	NS	NS	Liver: 0.03 ppm Kidney: 0.028 ppm Muscle: 0.027 ppm Fat: 0.025 ppm	POMF	50 mg/kg Chlortetracycline daily	42	Liver Kidney Muscle Fat	0 days (0.11 ppm) 2 days (0.06 ppm) 0 days (0.03 ppm) ND	2 days 4 days 2 days 0 days	Healthy	NS	[148] 1996
Chlortetracycline	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: 300 ppb (liver); 600 ppb (kidney); 100 ppb (muscle).	NS	NS	Liver: 0.03 ppm Kidney: 0.028 ppm Muscle: 0.027 ppm Fat: 0.025 ppm	POMF	50 mg/kg Chlortetracycline co-admin with 50 mg/kg sulfamethazine daily	42	Liver Kidney Muscle Fat	0 days (0.21 ppm) 6 days (0.05 ppm) 0 days (0.04 ppm) ND	4 days 8 days 4 days 0 days	Healthy	NS	[148] 1996
Doxy-cycline	Goat; NS; adult; *n* = 6	US Tol: Not established. EMA MRL: Not established.	Bioassay	NS	NS	IV	5 mg/kg Doxycycline hydrochloride	1	Milk	48 h (0.12 ppm §)	>2 days	Healthy	Lactating	[149] 1989
Mino-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
Oxytetracycline	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 IMM	30 mg Oxytetracycline hydrochloride 420 mg Oxytetracycline hydrochloride in right half of udder	1 1	Milk Milk	38 h (0.7 ppm) 110 h (R udder) (0.58 ppm) 14 h (L udder) (1.22 ppm	48 h 120 h (R udder) 24 h (L udder)	Healthy	Lactating; Only right $\frac{1}{2}$ of udder infused.	[147] 1982
Oxytetracycline	Sheep; Awassi; adult; *n* = 8	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
Oxytetracycline	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: 300 ppb (liver); 600 ppb (kidney); 100 ppb (muscle).	HPLC	NS	Liver: 85 ppb Kidney: 42 ppb Muscle: 45 ppb Fat: 45 ppb	IM	19.8 mg/kg Oxytetracycline (long acting)	1	Liver Kidney Muscle Fat Inj. Site	NS NS NS NS NS	14 days 14 days 14 days 14 days 14 days	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	Matrix	Last Sampling Time Point (Post-Last Treatmnet) When Residues WERE Detected	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	IMM	20 mg/kg Oxytetracycline	1	Milk	7 days (0.1 ppm §)	>7 days	NS	Lactating; Milked 2×/day	[153] 1999
						IM	20 mg/kg Oxytetracycline	1	Milk	7 days (4.15 ppm §)	>7 days			
Oxytetracycline	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: 300 ppb (liver); 600 ppb (kidney); 100 ppb (muscle).	HPLC	NS	Liver: 85 ppb Kidney: 42 ppb Muscle: 45 ppb; Fat: 45 ppb	IM	20 mg/kg Oxytetracycline (long acting)	1	Liver Kidney Muscle Fat Inj. Site	7 days (52 ppb) 14 days (65 ppb) 7 days (49 ppb) 7 days (88 ppb) 14 days (59 pb)	14 days >14 days 14 days 14 days >14 days	Healthy	NS	[154] 2000
Oxytetracycline 4-epi-Oxytetracycline	Sheep; NS; 16 months; *n* = 2 study; *n* = 1/ 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	Liver Oxy: 15.3 ppb Liver 4-Epi †: 16.6 ppb Kidney Oxy: 15.7 ppb Kidney 4-Epi †: 17.5 ppb Muscle Oxy: 12.4 ppb Muscle 4-Epi †: 13.9 ppb Fat Oxy: 12.4 ppb Fat 4-Epi †: 14.1 ppb Inj. Site Oxy: 12.4 ppb Inj. Site 4-Epi †: 13.9 ppb	Liver Oxy: 50 ppb Liver 4-Epi †: 50 ppb Kidney Oxy: 50 ppb Kidney 4-Epi †: 50 ppb Muscle Oxy: 50 ppb Muscle 4-Epi †: 30 ppb Fat Oxy: 50 ppb Fat 4-Epi †: 30 ppb Inj. Site Oxy: 30 ppb Inj. Site 4-Epi †: 30 ppb	IM	10 mg/kg Oxytetracycline daily	5	Liver Kidney Muscle Fat Inj. Site	Oxy: 2 days (272.8 ppb) 4-Epi †: 4 h (217.8 ppb) Oxy: 2 days (1342.4 ppb) 4-Epi †: 2 days (55 ppb) Oxy: 2 days (73.6 ppb) 4-Epi †: 4 h (34.2 ppb) Oxy: 4 h (3610.7 ppb) 4-Epi †: <LOQ @ 4 h Oxy: 2 days (763.2 ppb) 4-Epi†: 2 days (34.5 ppb)	Oxy: >2 days 4-Epi †: 2 days Oxy: >2 days 4-Epi †: >2 days Oxy: >2 days 4-Epi †: 2 days Oxy: 2 days 4-Epi †: 4 h Oxy: >2 days 4-Epi †: >2 days	Healthy	NS	[155] 2008
Oxytetracycline	Sheep; Chios; 3 years; *n* = 20	US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk).	LC-MS	NS	20 ppb	IM	10 mg/kg Oxytetracycline daily	5	Milk	7 days (33.2 ppb)	8 days	Healthy	Lactating; Milked 2×/day	[156] 2008
Oxytetracycline	Sheep; Comisana; adult; *n* = 8	US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk).	HPLC	NS	NS	IM	20 mg/kg Oxytetracycline (long acting)	1	Milk	7.5 days (50 ppb)	8 days	Healthy	Lactating; Milked 2×/day	[157] 2000
Oxytetracycline	Sheep; desert; 9–12 months; *n* = 12/ study; *n* = 4/time pt	US Tol: 6000 ppb (liver);12,000 ppb (kidney, fat); 2000 ppb (muscle). EMA establsihed MRL for all food producing species: 300 ppb (liver); 600 ppb (kidney); 100 ppb (muscle).	Bioassay	NS	NS	IM	5000 mg/kg Oxytetracycline (long acting) daily	5	Liver Kidney Muscle Inj. Site	10 days (1.51 ppm) 10 days (6.7 ppm) 10 days (70.87 ppm) 10 days (1227.7 ppm)	>10 days >10 days >10 days >10 days	NS	NS	[158] 2007

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 Treatmnet) When Residues WERE Detected	Sampling Time Point When NO Residues Were Detected (Post-Last Treatment) *	Health Status	Additional Information	Source/ Year
Oxytetracycline 4-epi-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	Liver: 50 ppb Kidney: 50 ppb Muscle: 30 ppb Fat: 30 ppb Inj. Site: 30 ppb	IM	10 mg/kg Oxytetracycline daily	5	Liver Kidney Muscle Fat Inj. Site	Oxy: 6 days (0.05 ppm) 4-Epi †: 2 days (0.05 ppm) Oxy: 9 days (0.08 ppm) 4-Epi †: 4 days (0.05 ppm) Oxy: 4 days (0.04 ppm) 4-Epi †: 2 days (0.04 ppm) Oxy: 0 days (2.7 ppm) 4-Epi †:<LOQ @ 0 days Oxy: 9 days (0.04 ppm) 4-Epi †: 2 days (0.062 ppm)	Oxy: 9 days 4-Epi †: 4 days Oxy: 12 days 4-Epi †: 6 days Oxy: 6 days 4-Epi †: 4 days Oxy: 2 days 4-Epi †: 0 days Oxy: 12 days 4-Epi †: 4 days	Healthy	NS	[146] 2009
Oxytetracycline	Goat; Saanen; adult; *n* = 8	US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk).	HPLC	NS	NS	IM	20 mg/kg Oxytetracycline (long acting)	1	Milk	7.5 days (60 ppb)	8 days	Healthy	Lactating; Milked 2×/day	[157] 2000
Oxytetracycline	Goat; mixed breed; NS; *n* = 32 Mixed breed; adult; *n* = 10	US Tol: 6000 ppb (liver); 12,000 ppb (kidney, fat); 2000 ppb (muscle); Not approved (milk). EMA established MRL for all food producing species: 300 ppb (liver); 600 ppb (kidney); 100 ppb (muscle); 100 ppb (milk).	Bioassay HPLC	0.1 ppm 0.15 ppm	NS	IM IM SC	20 mg/kg Oxytetracycline (long acting) 20 mg/kg Oxytetracycline (long acting) 20 mg/kg Oxytetracycline (long acting)	1 1 1	Liver Kidney Muscle Fat Inj. Site Milk Milk	7 days (385 ppb) 7 days (376 ppb) 7 days (246 ppb) 96 h (236 ppb) 14 days (1129 ppb) 178 h (0.03 ppm) 178 h (0.05 ppm)	14 days 14 days 14 days 7 days >14 days >178 h >178 h	Healthy Healthy	Lactating; Milked 2×/day Lactating; Milked 2×/day	[145] 2002
Oxytetracycline	Goat; Saanen; adult; *n* = 8	US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk).	Bioassay	0.25 ppm	NS	IMM	426 mg Oxytetracycline per half daily	3	Milk	5 h (0.50 ppm §)	>5 h	Healthy	Lactating; Milked 2×/day	[53] 1984
Oxytetracycline	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 Oxytetracycline daily	4	Milk	100 h (0.46 ppm)	>100 h	Healthy	Lactating	[159] 1994
Oxytetracycline	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 Oxytetracycline	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. EMA established MRL for all food producing species: 100 ppb (milk).	LC-MS	15 ppb	50 ppb	IM	20 mg/kg Oxytetracycline	1	Milk	180 h (60 ppb)	8 days	Healthy	Lactating; Milked 2×/day	[161] 2002

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 Treatmnet) 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	17.6 mg/kg Oxytetracycline at 48 h interval	2	Milk	96 h (87 ppb)	>96 h	Healthy	Mid-lactation; Milked 2×/day	[144] 2015
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	IV	20 mg/kg Oxytetracycline chlorhydrate	1	Milk	2 days (0.25 ppm §)	>2 days	Healthy	Lactating; Milked 1×/day	[162] 2001
						IM	20 mg/kg Oxytetracycline chlorhydrate	1	Milk	3 days (0.36 ppm §)	>3 days			
						IM	20 mg/kg Oxytetracycline dehydrate (Long Acting)	1	Milk	3 days (0.27 ppm §)	>3 days			
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	IMM	426 mg Oxytetracycline hydrochloride per half at 12 h intervals	3	Milk	96 h (0.02 ppm §)	108 h	Healthy	Early & mid-lactation; Milked 2×/day; 1 tube/ mammary gland	[60] 1984
Tetra-cycline	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	Lactating; Milked 2×/day	[29] 1974
										48 h (0.04 ppm §)	>2 days	Diseased-mastitis		
			Radio-activity	NS	NS	IM	20 mg/kg Tetracycline (radiolabeled)	1	Milk	48 h (0.14 ppm §)	>2 days	Healthy		
										48 h (0.2 ppm §)	>2 days	Diseased-mastitis		
Tetra-cycline	Sheep; Awassi; adult; $n = 4$	US Tol: Not established. EMA established MRL for all food producing species: 100 ppb (milk).	Bioassay	NS	NS	IV	20 mg/kg Tetracycline hydrochloride (radiolabeled), then 5 mg/kg for 2 doses at 90 min interval	1	Milk	60 h (0.70 ppm §)	4 days	Healthy	Lactating; Milked 2×/day	[24] 1973
			Radio-activity	NS	NS					60 h (0.12 ppm §)	4 days			
Tetra-cycline	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 (0.91 ppm)	>96 h	Healthy	Lactating; Milked 2×/day	[160] 1995
Tetra-cycline	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 (0.91 ppm)	>100 h	Healthy	Lactating	[159] 1994

§ Data points manually extracted use scanning software (Webplot digitizer or UnScanIt 7.0). # = 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

References

1. Akinmoladun, O.F.; Muchenje, V.; Fon, F.N.; Mpendulo, C.T. Small Ruminants: Farmers' Hope in a World Threatened by Water Scarcity. *Animals* **2019**, *9*, 456. [CrossRef] [PubMed]
2. Food and Agriculture Organization of the United Nations. FAOSTAT. 2022. Available online: https://www.fao.org/faostat/en/#compare (accessed on 22 November 2021).
3. Food and Drug Administration. *Minor Use/Minor Species*; Food and Drug Administration: Spring, MD, USA, 2022.
4. European Medicines Agency. *Guideline on Safety and Residue Data Requirements for the Establishment of Maximum Residue Limits in Minor Species*; European Medicines Agency: Amsterdam, The Netherlands, 2022.
5. Congress of the United States. *Minor Use and Minor Species Animal Health Act of 2004*; Congress of the United States: Washington, DC, USA, 2004.
6. Food and Drug Administration. *Title 21, Chapter I, Subchapter E, Part 530: Extralabel Drug Use in Animals*; Food and Drug Administration: Silver Spring, MD, USA, 2022.
7. Northcutt, J.K. Preslaughter factors affecting poultry meat quality. In *Poultry Meat Processing*; Woodhead Publishing: Cambridge, UK, 2000.
8. World Health Organization. *Critically Important Antimicrobials for Human Medicine 6th Revision*; World Health Organization: Geneva, Switzerland, 2018.
9. Riviere, J.E.; Craigmill, A.L.; Sundlof, S.F. Aminoglycosides. In *Handbook of Comparative Pharmacokinetics and Residues of Veterinary Antimicrobials*; CRC Press: Boca Raton, FL, USA, 1991.

10. European Medicines Agency Committee for Veterinary Medicinal Products. *Apramycin Summary Report (2)*; European Medicines Agency Committee for Veterinary Medicinal Products: Amsterdam, The Netherlands, 1999; Volume 526, pp. 1–8.
11. Heitzman, R. Dihydrostreptomycin Streptomycin. *Residues Some Vet. Drugs Anim. Foods* **1995**, *41*, 17–29.
12. Brown, S.; Riviere, J.; Coppoc, G.; Hinsman, E.; Carlton, W.; Steckel, R. Single intravenous and multiple intramuscular dose pharmacokinetics and tissue residue profile of gentamicin in sheep. *Am. J. Vet. Res.* **1985**, *46*, 69–74. [PubMed]
13. Brown, S.; Coppoc, G.; Riviere, J. Effects of dose and duration of therapy on gentamicin tissue residues in sheep. *Am. J. Vet. Res.* **1986**, *47*, 2373–2379. [PubMed]
14. Brown, S.; Baird, A. Evaluation of renal gentamicin depletion kinetic properties in sheep, using serial percutaneous biopsies. *Am. J. Vet. Res.* **1988**, *49*, 2056–2059.
15. The Upjohn Company. *NADA 011-315 Neomycin 325/Neomix Ag 325 Soluble Powder—Supplemental Approval (Date of Approval: 3 April 1996)*; FOI—Neomix- NADA 011-315; The Upjohn Company: Hastings, MI, USA, 1996; pp. 1–3.
16. European Medicines Agency Committee for Veterinary Medicinal Products. *Neomycin Summary Report (2)*; EMEA/MRL/730/00-Final; European Medicines Agency Committee for Veterinary Medicinal Products: Amsterdam, The Netherlands, 2000; Volume 730, pp. 1–8.
17. Livingston, R.C. Neomycin. *Residues Some Vet. Drugs Anim. Foods* **1995**, *41*, 57–67.
18. National Library of Medicine. *Drugs and Lactation Database (LactMed)*; National Library of Medicine: Bethesda, MD, USA, 2006.
19. El-Sooud, K.A. Pharmacokinetics of amikacin in lactating goats. *Zent. Vet. A* **1999**, *46*, 239–246. [CrossRef]
20. Agrawal, A.; Singh, S.; Jayachandran, C. Pharmacokinetics of amikacin in goats after single intramuscular administration. *Indian J. Pharmacol.* **2001**, *33*, 374.
21. Haritova, A.; Lashev, L. Pharmacokinetics of amikacin in lactating sheep. *Vet. Res. Commun.* **2004**, *28*, 429–435. [CrossRef]
22. Ziv, G.; Kurtz, B.; Risenberg, R.; Glickman, A. Serum and milk concentrations of apramycin in lactating cows, ewes and goats. *J. Vet. Pharmacol. Ther.* **1995**, *18*, 346–351. [CrossRef]
23. El-Gendi, A.Y.; Amer, A.M.; Azooz, H.A. Disposition kinetics and milk residues of apramycin in goats. In Proceedings of the European Association of Veterinary Pharmacology and Toxicology 8th Congress, Jerusalem, Israel, 30 July–3 August 2000.
24. Ziv, G.; Bogin, E.; Shani, J.; Sulman, F.G. Distribution and blood-to-milk transfer of labeled antibiotics. *Antimicrob. Agents Chemother.* **1973**, *3*, 607–613. [CrossRef]
25. European Medicines Agency Committee for Veterinary Medicinal Products. *Dihydrostreptomycin (Extrapolation to All Ruminants) Summary Report (4)*; EMEA/CVMP/211249/2005-Final; European Medicines Agency Committee for Veterinary Medicinal Products: Amsterdam, The Netherlands, 2005; Volume 211249, pp. 1–5.
26. Friedlander, L.G.; Stephany, R.W. Dihydrostreptomycin and Streptomycin Addendum. *Residues Some Vet. Drugs Anim. Foods* **2002**, *41*, 37–41.
27. Lohuis, J.; Poutrel, B.; Cremoux, R.; Parez, V.; Aguer, D. Milk residues of penicillin, nafcillin and dihydrostreptomycin in dairy goats postpartum treated with Nafpenzal N8 at drying-off. In Proceedings of the Residues of Antimicrobial Drugs and Other Inhibitors in Milk, Kiel, Germany, 28–31 August 1995.
28. Lohuis, J.; Berthelot, X.; Cester, C.; Parez, V.; Aguer, D. Pharmacokinetics and milk residues of penicillin, nafcillin and dihydrostreptomycin in dairy sheep treated with nafpenzal DC at drying-off. In Proceedings of the Residues of Antimicrobial Drugs and Other Inhibitors in Milk, Kiel, Germany, 28–31 August 1995.
29. Ziv, G.; Bogin, E.; Shani, J.; Sulman, F. Penetration of radioactive-labeled antibiotics from blood serum into milk in normal and mastitic ewes. *Ann. Rech. Vét.* **1974**, *5*, 15–28.
30. European Medicines Agency Committee for Veterinary Medicinal Products. *Streptomycin and Dihydrostreptomycin Summary Report (2)*; EMEA/MRL/728/00-Final; European Medicines Agency Committee for Veterinary Medicinal Products: Amsterdam, The Netherlands, 2000; Volume 728, pp. 1–7.
31. Heitzman, R.J. Dihydrostreptomycin/Streptomycin Addendum. *Residues Some Vet. Drugs Anim. Foods* **1998**, *41*, 39–44.
32. Toutain, P.; De Pomyers, H.; Larrieu, G.; Periquet, B.; More, J. An in vivo model for pharmacokinetic studies in the kidney. *J. Pharmacol. Methods* **1985**, *14*, 1–11. [CrossRef]
33. Andreini, G.; Pignattelli, P. Kanamycin blood levels and residues in domestic animals. *Vet. Milano* **1972**, *21*, 51–72.
34. Pfizer, Inc. *ANADA 200-046 Neomycin Sulfate Soluble Powder 325 g/lb—Supplemental Approval (3 April 1996)*; FOI—Neomycin ANADA 200-046; Pfizer: New York, NY, USA, 1996; pp. 1–3.
35. Lavy, E.; Ziv, G.; Glickman, A. Single-dose pharmacokinetics of thiamphenicol in lactating goats. *Acta Vet. Scand. Suppl.* **1991**, *87*, 99–102.
36. Lavy, E.; Ziv, G.; Soback, S.; Glickman, A.; Winkler, M. Clinical pharmacology of florfenicol in lactating goats. *Acta Vet. Scand. Suppl.* **1991**, *87*, 133–136.
37. Government of Canada. *Questions and Answers on Health Canada's Policy on Extra-Label Drug Use (ELDU) in Food-Producing Animals*; Government of Canada: Ottowa, ON, Canada, 2009.
38. European Food Safety Authority. *Scientific Opinion on Chloramphenicol in Food and Feed*; European Food Safety Authority: Parma, Italy, 2014. [CrossRef]
39. Ziv, G.; Bogin, E.; Sulman, F. Blood and milk levels of chloramphenicol in normal and mastitic cows and ewes after intramuscular administration of chloramphenicol and chloramphenicol sodium succinate. *Zent. Vet. Reihe A* **1973**, *20*, 801–811. [CrossRef]

40. Dagorn, M.; Guillot, P.; Sanders, P. Pharmacokinetics of chloramphenicol in sheep after intravenous, intramuscular and subcutaneous administration. *Vet. Q.* **1990**, *12*, 166–174. [CrossRef]
41. Ziv, G. Pharmacokinetics of antimycoplasma antibiotics in dairy cows and ewes. In Proceedings of the 8th International Meeting of Diseases in Cattle, Milan, Italy, 9–13 September 1974; pp. 80–92.
42. Wetzlich, S.E.; Lane, V.M.; Craigmill, A.L. Tissue residue depletion after multiple subcutaneous administration of florfenicol to sheep. In Proceedings of the European Association of Veterinary Pharmacology and Toxicology 10th Congress, Turin, Italy, 17–22 September 2006; Volume 29, pp. 154–155.
43. Lane, V.M.; Villarroel, A.; Wetzlich, S.; Clifford, A.; Taylor, I.; Craigmill, A. Tissue residues of florfenicol in sheep. *J. Vet. Pharmacol. Ther.* **2008**, *31*, 178–180. [CrossRef]
44. Wells, R.J. Thiamphenicol; Addendum to the thiamphenicol residue monograph prepared by the 47th meeting of the Committee and published in FAO Food and Nutrition Paper 41/9, Rome 1996. *Residues Some Vet. Drugs Anim. Foods* **2000**, *41*, 119–128.
45. Roy, B.; Banerjee, N. Distribution of chloramphenicol in goat blood and milk after intramuscular administration. *Indian J. Anim. Sci.* **1983**, *53*, 847–849.
46. Wal, J.-M.; Peleran, J.-C.; Bories, G.F. High performance liquid chromatographic determination of chloramphenicol in milk. *J. Assoc. Off. Anal. Chem.* **1980**, *63*, 1044–1048. [CrossRef]
47. Ziv, G.; Nouws, J. Serum and milk concentrations of ampicillin and amoxycillin in ruminants. *Refuah Vet.* **1979**, *36*, 104–110.
48. Ramos, F.; Boison, J.; Friedlander, L.G. Amoxicillin. *Residues Some Vet. Drugs Anim. Foods* **2012**, 1–35. Available online: https://www.fao.org/fileadmin/user_upload/vetdrug/docs/12-2012-amoxicillin.pdf (accessed on 7 August 2022).
49. Buswell, J.; Knight, C.; Barber, D. Antibiotic persistence and tolerance in the lactating goat following intramammary therapy. *Vet. Rec.* **1989**, *125*, 301–303. [CrossRef]
50. Roncada, P.; Tomasi, L.; Stracciari, G.; Ermini, L.; Strocchia, A. Milk depletion of dicloxacillin residues in cows and sheep following intramammary administration. *J. Vet. Pharmacol. Ther.* **2000**, *23*, 237–241. [CrossRef] [PubMed]
51. Buswell, J.; Barber, D. Antibiotic persistence and tolerance in the lactating sheep following a course of intramammary therapy. *Br. Vet. J.* **1989**, *145*, 552–557. [CrossRef]
52. Pengov, A.; Kirbis, A. Risks of antibiotic residues in milk following intramammary and intramuscular treatments in dairy sheep. *Anal. Chim. Acta* **2009**, *637*, 13–17. [CrossRef] [PubMed]
53. Hill, B.; Jagusch, K.; Rajan, L.; Kidd, G. Antibiotic residues in goats milk following intramammary treatment. *N. Z. Vet. J.* **1984**, *32*, 130–131. [CrossRef]
54. Ferrini, A.M.; Trenta, S.; Mannoni, V.; Rosati, R.; Coni, E. Depletion of long-acting ampicillin in goat milk following intramuscular administration. *J. Agric. Food Chem.* **2010**, *58*, 12199–12203. [CrossRef]
55. Boatto, G.; Cerri, R.; Pau, A.; Palomba, M.; Pintore, G.; Denti, M.G. Monitoring of benzylpenicillin in ovine milk by HPLC. *J. Pharm. Biomed. Anal.* **1998**, *17*, 733–738. [CrossRef]
56. Gee, H.-E.; Ho, K.-B.; Toothill, J. Liquid chromatographic determination of benzylpenicillin and cloxacillin in animal tissues and its application to a study of the stability at –20 °C of spiked and incurred residues of benzylpenicillin in ovine liver. *J. AOAC Int.* **1996**, *79*, 640–644. [CrossRef]
57. Longo, F.; Cozzani, R.; Santis, L.d.; Boselli, C.; Rosati, R.; Fagiolo, A.; Cinquina, A. Amoxicillin detection in milk using screening tests and liquid chromatography after administration to lactating sheep. *Riv. Sci. Dell'alimentazione* **2002**, *31*, 313–319.
58. Chaleva, E.; Dincheva, E. Ampicillin tolerance and content in the mammary gland of lactating cows and sheep. *Vet. Med. Nauk.* **1977**, *14*, 73–78.
59. Edwards, S. Penicillin levels in the milk following intramuscular injection. *Vet. Rec.* **1966**, *78*, 583–585. [CrossRef]
60. Long, P.; Heavner, J.; Ziv, G.; Geleta, J.; Nepote, K. Depletion of antibiotics from the mammary gland of goats. *J. Dairy Sci.* **1984**, *67*, 707–712. [CrossRef]
61. Norbrook Laboratories, Ltd. *Freedom of Information Summary, Supplemental New Animal Drug Application, NADA 065-010. Norocillin (Penecillin G Procaine Injectable Suspension) Cattle, Sheep, Swine, and Horses; To Revise the Currently Approved Formulation to Include Lecithin as a Surfactant*; FOI—Norocillin NADA 065-010; Norbrook Laboratories, Ltd.: Newry, UK, 2010; pp. 1–27.
62. Rule, R.; Lacchini, R.; Mordujovich, P.; Antonini, A. Evaluation of cefepime kinetic variables and milk production volume in goats. *Arq. Bras. Med. Vet. Zootec.* **2004**, *56*, 116–118. [CrossRef]
63. Badillo, E.; Escudero, E.; Hernandis, V.; Galecio, J.S.; Marín, P. Pharmacokinetics of cefonicid in lactating goats after intravenous, intramuscular and subcutaneous administration, and after a long-acting formulation for subcutaneous administration. *J. Vet. Pharmacol. Ther.* **2020**, *43*, 50–56. [CrossRef]
64. Yadav, K.; Jayachandran, C.; Singh, M.; Jha, H.; Sinha, S. Kinetics of intravenously administered ceftriaxone in lactating goat. *Indian J. Anim. Sci.* **2013**, *70*, 163–165.
65. Ismail, M. Pharmacokinetics, urinary and mammary excretion of ceftriaxone in lactating goats. *J. Vet. Med. Ser. A* **2005**, *52*, 354–358. [CrossRef]
66. Ziv, G.; Nouws, J. Clinical pharmacology of cephacetrile in ruminants. *Zent. Vet. Reihe B* **1977**, *24*, 798–811. [CrossRef]
67. El Badawy, S.; Amer, A.; Kamel, G.; Eldeib, K.; Constable, P. Comparative pharmacokinetics using a microbiological assay and high performance liquid chromatography following intravenous administration of cefquinome in lactating goats with and without experimentally induced Staphylococcus aureus mastitis. *Small Rumin. Res.* **2015**, *133*, 67–76. [CrossRef]

68. El Badawy, S.A.; Amer, A.M.; Kamel, G.M.; Eldeib, K.M.; Constable, P.D. Pharmacokinetics and pharmacodynamics of intramammary cefquinome in lactating goats with and without experimentally induced Staphylococcus aureus mastitis. *J. Vet. Pharmacol. Ther.* **2019**, *42*, 452–460. [CrossRef]
69. Soback, S.; Ziv, G.; Bor, A.; Shapira, M. Pharmacokinetics of cephalexin glycinate in lactating cows and ewes. *Zent. Vet. Reihe A* **1988**, *35*, 755–760.
70. Wetzel, R.K.; Stayer, P.A.; Wildman, E.E.; Randy, H.A. Depletion of cephapirin in goat's milk following intramammary infusion. *J. Dairy Sci.* **1986**, *69*, 245.
71. Courtin, F.; Wetzlich, S.; Gustafson, C.; Craigmill, A. Pharmacokinetics and milk residues of ceftiofur and metabolites in dairy goats. In Proceedings of the European Association of Veterinary Pharmacology and Toxicology 6th Congress, Edinburgh, UK, 7–11 August 1994; pp. 81–82.
72. El-Rabbat, N.A.; Abdel-Wadood, H.M.; Sayed, M.; Mousa, H.S. High-performance liquid chromatographic determination and pharmacokinetic study of cefepime in goat plasma and milk after pre-column derivatization with Hg (I). *J. Sep. Sci.* **2010**, *33*, 2599–2609. [CrossRef]
73. Rule, R.; Villagra, S.; Barrena, P.; Lacchini, R.; Reynaldni, F.J. Pharmacokinetics of ceftazidime administered to lactating and non-lactating goats. *J. S. Afr. Vet. Assoc.* **2011**, *82*, 219–223. [CrossRef]
74. European Medicines Agency Committee for Veterinary Medicinal Products. *Ceftiofur (Extension to Ovine and Extrapolation to All Mammalian Species) Summary Report (4)*; European Medicines Agency Committee for Veterinary Medicinal Products: Amsterdam, The Netherlands, 2006; Volume 80785, pp. 1–3.
75. Garrett, E.; Dirikolu, L.; Grover, G. Milk and serum concentration of ceftiofur following intramammary infusion in goats. *J. Vet. Pharmacol. Ther.* **2015**, *38*, 569–574. [CrossRef]
76. Goudah, A.; Shin, H.; Shim, J.; El-Aty, A.A. Characterization of the relationship between serum and milk residue disposition of ceftriaxone in lactating ewes. *J. Vet. Pharmacol. Ther.* **2006**, *29*, 307–312. [CrossRef] [PubMed]
77. Rageh, A.H.; Abdel-Rahim, S.A.; Askal, H.F.; Saleh, G.A. Hydrophilic-interaction planar chromatography in ultra-sensitive determination of α-aminocephalosporin antibiotics. Application to analysis of cefalexin in goat milk samples using modified QuEChERS extraction technique. *J. Pharm. Biomed. Anal.* **2019**, *166*, 421–434. [CrossRef] [PubMed]
78. Rule, R.; Cordiviola, C.; Vita, M.; Lacchini, R. Correlations between milk production and kinetic variables in milk of cephalothin administered to lactating goats. *Vet. Med.* **2004**, *49*, 370. [CrossRef]
79. Rule, R.; Lacchini, R.; Román, A.G.; Antonini, A.; de Buschiazzo, P. Influence of feed type on the pharmacokinetics of cephalothin administered to lactating goats. *Arch. Zootec.* **2007**, *56*, 807–815.
80. El-Sayed, M.; Atef, M.; El-Komy, A. Disposition kinetics of cephradine in normal and Escherichia coli infected goats. *Dtsch. Tierarztl. Wochenschr.* **1994**, *101*, 56–60.
81. Singh, C.S.; Singh, S.D.; Singh, M.K.; Jayachandran, C. Disposition kinetics and distribution of ciprofloxacin in biological fluids of goats after intravenous administration. *Indian J. Anim. Sci.* **2001**, *71*, 635–637.
82. El-Banna, H.; El-Sooud, K.A. Disposition kinetics of ciprofloxacin in lactating goats. *Dtsch. Tierarztl. Wochenschr.* **1998**, *105*, 35–38.
83. Escudero, E.; Cárceles, C.; Fernandez-Varon, E.; Marin, P.; Benchaoui, H. Pharmacokinetics of danofloxacin 18% in lactating sheep and goats. *J. Vet. Pharmacol. Ther.* **2007**, *30*, 572–577. [CrossRef]
84. Escudero, E.; Marín, P.; Cárceles, C.M.; Ramírez, M.J.; Fernández-Varón, E. Pharmacokinetic and milk penetration of a difloxacin long-acting poloxamer gel formulation with carboxy-methylcellulose in lactating goats. *Vet. J.* **2011**, *188*, 92–95. [CrossRef]
85. El-Sooud, K.A. Influence of albendazole on the disposition kinetics and milk antimicrobial equivalent activity of enrofloxacin in lactating goats. *Pharmacol. Res.* **2003**, *48*, 389–395. [CrossRef]
86. Marin, P.; Escudero, E.; Fernandez-Varon, E.; Espuny, A.; Titos, J.; Hernandis, V.; Carceles, C. Pharmacokinetics and milk penetration of an enrofloxacin long-acting poloxamer 407 gel formulation in lactating goats. *J. Vet. Pharamcol. Ther.* **2009**, *32*, 195–196.
87. Narayan, J.P.; Kumar, N.; Jha, H.; Jayachandran, C. Effect of probenecid on kinetics of enrofloxacin in lactating goats after subcutaneous administration. *Indian J. Exp. Biol.* **2009**, *47*, 53–56.
88. Haritova, A.; Lashev, L.; Pashov, D. Pharmacokinetics of enrofloxacin in lactating sheep. *Res. Vet. Sci.* **2003**, *74*, 241–245. [CrossRef]
89. Marín, P.; Cárceles, C.M.; Escudero, E.; Fernández-Varón, E. Pharmacokinetics and milk penetration of ibafloxacin after intravenous administration to lactating goats. *Can. J. Vet. Res.* **2007**, *71*, 74.
90. Goudah, A.; Abo-El-Sooud, K. Pharmacokinetics, urinary excretion and milk penetration of levofloxacin in lactating goats. *J. Vet. Pharmacol. Ther.* **2009**, *32*, 101–104. [CrossRef]
91. Lorenzutti, A.; Litterio, N.; Himelfarb, M.; Zarazaga, M.D.P.; Andrés, M.S.; De Lucas, J. Pharmacokinetics, milk penetration and PK/PD analysis by Monte Carlo simulation of marbofloxacin, after intravenous and intramuscular administration to lactating goats. *J. Vet. Pharmacol. Ther.* **2017**, *40*, 629–640. [CrossRef]
92. Shem-Tov, M.; Ziv, G.; Glickman, A.; Saran, A. Pharmacokinetics and penetration of marbofloxacin from blood into the milk of cows and ewes. *J. Vet. Med. Ser. A* **1997**, *44*, 511–519. [CrossRef]
93. Fernández-Varón, E.; Villamayor, L.; Escudero, E.; Espuny, A.; Cárceles, C.M. Pharmacokinetics and milk penetration of moxifloxacin after intravenous and subcutaneous administration to lactating goats. *Vet. J.* **2006**, *172*, 302–307. [CrossRef]

94. Goudah, A.; Cho, H.J.; Shin, H.C.; Shim, J.H.; Regmi, N.L.; Shimoda, M.; Abd El-Aty, A.M. Pharmacokinetics and milk distribution characteristics of orbifloxacin following intravenous and intramuscular injection in lactating ewes. *J. Vet. Pharmacol. Ther.* **2009**, *32*, 338–344. [CrossRef]
95. El-Aty, A.M.A.; Goudah, A. Some pharmacokinetic parameters of pefloxacin in lactating goats. *Vet. Res. Commun.* **2002**, *26*, 553–561. [CrossRef]
96. Real, R.; Egido, E.; Pérez, M.; Gonzalez-Lobato, L.; Barrera, B.; Prieto, J.; Alvarez, A.; Merino, G. Involvement of breast cancer resistance protein (BCRP/ABCG2) in the secretion of danofloxacin into milk: Interaction with ivermectin. *J. Vet. Pharmacol. Ther.* **2011**, *34*, 313–321. [CrossRef] [PubMed]
97. Perez, M.; Otero, J.A.; Barrera, B.; Prieto, J.G.; Merino, G.; Alvarez, A.I. Inhibition of ABCG2/BCRP transporter by soy isoflavones genistein and daidzein: Effect on plasma and milk levels of danofloxacin in sheep. *Vet. J.* **2013**, *196*, 203–208. [CrossRef] [PubMed]
98. Pulido, M.M.; Molina, A.J.; Merino, G.; Mendoza, G.; Prieto, J.G.; Alvarez, A.I. Interaction of enrofloxacin with breast cancer resistance protein (BCRP/ABCG2): Influence of flavonoids and role in milk secretion in sheep. *J. Vet. Pharmacol. Ther.* **2006**, *29*, 279–287. [CrossRef] [PubMed]
99. Shem-Tov, M.; Ziv, G.; Glickman, A.; Saran, A. Pharmacokinetics and penetration of danofloxacin from the blood into the milk of ewes. *Vet. Res.* **1997**, *28*, 571–579.
100. Barrera, B.; González-Lobato, L.; Otero, J.A.; Real, R.; Prieto, J.G.; Álvarez, A.I.; Merino, G. Effects of triclabendazole on secretion of danofloxacin and moxidectin into the milk of sheep: Role of triclabendazole metabolites as inhibitors of the ruminant ABCG2 transporter. *Vet. J.* **2013**, *198*, 429–436. [CrossRef]
101. Otero, J.A.; García-Mateos, D.; Alvarez-Fernández, I.; García-Villalba, R.; Espín, J.C.; Álvarez, A.I.; Merino, G. Flaxseed-enriched diets change milk concentration of the antimicrobial danofloxacin in sheep. *BMC Vet. Res.* **2018**, *14*, 14. [CrossRef]
102. Marín, P.; Escudero, E.; Fernández-Varón, E.; Ramírez, M.; Cárceles, C. Pharmacokinetics and milk penetration of difloxacin after a long-acting formulation for subcutaneous administration to lactating goats. *J. Dairy Sci.* **2010**, *93*, 3056–3064. [CrossRef]
103. Fernandez-Varon, E.; Escudero, E.; Marin, P.; Titos, J.; Espuny, A.; Carceles, C. Pharmacokinetics and milk penetration of enrofloxacin and its metabolite ciprofloxacin after subcutaneous administration to lactating goats. *J. Vet. Pharmacol. Ther.* **2009**, *32*, 196–197.
104. European Medicines Agency Committee for Veterinary Medicinal Products. *Enrofloxacin (Extension to Sheep, Rabbits and Lactating Cows) Summary Report (3)*; EMEA/MRL/389/98-Final; European Medicines Agency Committee for Veterinary Medicinal Products: Amsterdam, The Netherlands, 1998; Volume 389, pp. 1–5.
105. Cárceles, C.M.; Villamayor, L.; Escudero, E.; Marín, P.; Fernández-Varón, E. Pharmacokinetics and milk penetration of moxifloxacin after intramuscular administration to lactating goats. *Vet. J.* **2007**, *173*, 452–455. [CrossRef]
106. Soback, S.; Gips, M.; Bialer, M.; Bor, A. Effect of lactation on single-dose pharmacokinetics of norfloxacin nicotinate in ewes. *Antimicrob. Agents Chemother.* **1994**, *38*, 2336–2339. [CrossRef]
107. Marín, P.; Escudero, E.; Fernández-Varón, E.; Cárceles, C. Pharmacokinetics and milk penetration of orbifloxacin after intravenous, subcutaneous, and intramuscular administration to lactating goats. *J. Dairy Sci.* **2007**, *90*, 4219–4225. [CrossRef]
108. Delmas, J.; Chapel, A.; Gaudin, V.; Sanders, P. Pharmacokinetics of flumequine in sheep after intravenous and intramuscular administration: Bioavailability and tissue residue studies. *J. Vet. Pharmacol. Ther.* **1997**, *20*, 249–257. [CrossRef]
109. Francis, P.G.; Wells, R.J. Flumequine. *Residues Some Vet. Drugs Anim. Foods* **1998**, *41*, 59–70.
110. European Medicines Agency Committee for Veterinary Medicinal Products. *Erythromycin Summary Report (2)*; EMEA/MRL/720/99-Final; European Medicines Agency Committee for Veterinary Medicinal Products: Amsterdam, The Netherlands, 2000; Volume 720, pp. 1–8.
111. Goudah, A.; Sher Shah, S.; Shin, H.; Shim, J.; Abd El-Aty, A. Pharmacokinetics and mammary residual depletion of erythromycin in healthy lactating ewes. *J. Vet. Med. Ser. A* **2007**, *54*, 607–611. [CrossRef]
112. Ramadan, A. Pharmacokinetics of tilmicosin in serum and milk of goats. *Res. Vet. Sci.* **1997**, *62*, 48–50. [CrossRef]
113. MacNeil, J.D. Tilmicosin. *Residues Some Vet. Drugs Anim. Foods* **1997**, *41*, 106–118.
114. Xu, S.; Arnold, D. Tilmicosin: Addendum to tho monographs prepared by the 47th meeting of the Committee and published in the FAO Food and Nutrition paper 41/9. *Residues Some Vet. Drugs Anim. Foods* **2008**, *41*, 1–37.
115. Grismer, B.; Rowe, J.D.; Carlson, J.; Wetzlich, S.; Tell, L.A. Pharmacokinetics of tulathromycin in plasma and milk samples after a single subcutaneous injection in lactating goats (C apra hircus). *J. Vet. Pharmacol. Ther.* **2014**, *37*, 205–208. [CrossRef]
116. Amer, A.; Constable, P.; Goudah, A.; El Badawy, S. Pharmacokinetics of tulathromycin in lactating goats. *Small Rumin. Res.* **2012**, *108*, 137–143. [CrossRef]
117. Lin, Z.; Cuneo, M.; Rowe, J.D.; Li, M.; Tell, L.A.; Allison, S.; Carlson, J.; Riviere, J.E.; Gehring, R. Estimation of tulathromycin depletion in plasma and milk after subcutaneous injection in lactating goats using a nonlinear mixed-effects pharmacokinetic modeling approach. *BMC Vet. Res.* **2016**, *12*, 258. [CrossRef]
118. Atef, M.; Youssef, S.; Atta, A.; El-Maaz, A. Disposition of tylosin in goats. *Dtsch. Tierarztl. Wochenschr.* **1991**, *98*, 451–453. [CrossRef]
119. Ziv, G.; Sulman, F.G. Serum and milk concentrations of spectinomycin and tylosin in cows and ewes. *Am. J. Vet. Res.* **1973**, *34*, 329–333.
120. Nagy, J.; Popelka, P.; Sokol, J.; Turek, P.; Neuschl, J. The excretion of tylosin residues in ewes milk after its experimental administration. *Folia Vet.* **2001**, *45*, 196–198.

121. Ambros, L.; Montoya, L.; Kreil, V.; Waxman, S.; Albarellos, G.; Rebuelto, M.; Hallu, R.; Andres, M.S. Pharmacokinetics of erythromycin in nonlactating and lactating goats after intravenous and intramuscular administration. *J. Vet. Pharmacol. Ther.* **2007**, *30*, 80–85. [CrossRef]
122. Ziv, G. Concentrations and residues of antibiotics in the milk of goats after parenteral and intramammary administration. In Proceedings of the Symposium Internacional de Ordeno Mecanico de Pequenos Rumiantes, Valladolid, Spain; 1984; pp. 513–528.
123. Romanet, J.; Smith, G.W.; Leavens, T.L.; Baynes, R.E.; Wetzlich, S.E.; Riviere, J.E.; Tell, L.A. Pharmacokinetics and tissue elimination of tulathromycin following subcutaneous administration in meat goats. *Am. J. Vet. Res.* **2012**, *73*, 1634–1640. [CrossRef]
124. Clothier, K.A.; Leavens, T.; Griffith, R.W.; Wetzlich, S.E.; Baynes, R.E.; Riviere, J.E.; Tell, L.A. Tulathromycin assay validation and tissue residues after single and multiple subcutaneous injections in domestic goats (Capra aegagrus hircus). *J. Vet. Pharmacol. Ther.* **2012**, *35*, 113–120. [CrossRef]
125. Kellermann, M.; Huang, R.A.; Forbes, A.B.; Rehbein, S. Gamithromycin plasma and skin pharmacokinetics in sheep. *Res. Vet. Sci.* **2014**, *97*, 199–203. [CrossRef]
126. European Medicines Agency Committee for Veterinary Medicinal Products. *European Public MRL Assessment Report (EPMAR) Gamithromycin (All Ruminants Except Bovine Species.)12 December 2016*; EMA/CVMP/454092/2016; European Medicines Agency Committee for Veterinary Medicinal Products EPMAR: Amsterdam, The Netherlands, 2016; Volume 454092, pp. 1–11.
127. Atef, M.; El-Sooud, K.A.; Nahed, E.; Tawfik, M. Elimination of tilmicosin in lactating ewes. *Dtsch. Tierarztl. Wochenschr.* **1999**, *106*, 291–294.
128. Parker, R.; Patel, R.; Mclaren, I.; Francis, P. Residues of tilmicosin in milk of sheep after subcutaneous administration. In Proceedings of the European Association for Veterinary Pharmacology and Toxicology, Edinburgh, UK, 7–11 August 1994; pp. 226–227.
129. Elanco Animal Health. *Freedom of Information Summary; Micotil 300 Injection (tilmicosin phosphate)*; Supplement to NADA 140-929; Date of Approval: 4 September 2002; FOI—Micotil NADA 140-929; Elanco Animal Health: Greenfield, IN, USA, 2002; pp. 1–14.
130. European Medicines Agency Committee for Veterinary Medicinal Products. *European Public MRL Assessment Report (EPMAR) Tulathromycin (Ovine and Caprine Species) 23 February 2015*; EMA/CVMP/131462/2014; European Medicines Agency Committee for Veterinary Medicinal Products EPMAR: Amsterdam, The Netherlands, 2015; Volume 131462, pp. 1–11.
131. Tunnicliff, E.; Swingle, K. Sulfonamide concentrations in milk and plasma from normal and mastitic ewes treated with sulfamethazine. *Am. J. Vet. Res.* **1965**, *26*, 920–927.
132. Rasmussen, F. Mammary excretion of sulphonamides. *Acta Pharmacol. Toxicol.* **1958**, *15*, 139–148. [CrossRef]
133. Akogwu, E.; Saganuwan, S.; Onyeyili, P. Effects of piroxicam on tissue distribution of sulfadimidine in west African dwarf male and female goats. *Hum. Exp. Toxicol.* **2018**, *37*, 61–68. [CrossRef] [PubMed]
134. Bevill, R.; Sharma, R.; Meachum, S.; Wozniak, S.; Bourne, D.; Dittert, L. Disposition of sulfonamides in food-producing animals: Concentrations of sulfamethazine and its metabolites in plasma, urine, and tissues of lambs following intravenous administration. *Am. J. Vet. Res.* **1977**, *38*, 973–977. [PubMed]
135. Jha, H.; Banerjee, N. A note on distribution of sulphadimethoxine in blood, milk and urine of goats. *Indian J. Anim. Sci.* **1977**, *47*, 496–497.
136. Yndestad, M.; Underdal, B. Residues of Sulfadimidine/Sulfanilamide and Sulfamethoxypyridazine in Sheep Tissue. *Acta Vet. Scand.* **1977**, *18*, 15–22. [CrossRef] [PubMed]
137. Bevill, R.F.; Koritz, G.D.; Dittert, L.W.; Bobrne, D.W. Disposition of sulfonamides in food-producing animals V: Disposition of sulfathiazole in tissue, urine, and plasma of sheep following intravenous administration. *J. Pharm. Sci.* **1977**, *66*, 1297–1300. [CrossRef]
138. Righter, H.F.; Worthington, J.M.; Mercer, H.D. Tissue residue depletion of sulfamerazine in sheep. *J. Agric. Food Chem.* **1972**, *20*, 876–878. [CrossRef]
139. Atef, M. Half-life, volume of distribution and acetylation of sulphamerazine in sheep. *Zent. Vet. Reihe A* **1978**, *25*, 585–591. [CrossRef]
140. Bulgin, M.; Lane, V.M.; Archer, T.; Baggot, J.; Craigmill, A. Pharmacokinetics, safety and tissue residues of sustained-release sulfamethazine in sheep. *J. Vet. Pharmacol. Ther.* **1991**, *14*, 36–45. [CrossRef]
141. Bevill, R.F. Application of Pharamcokinetics to the Study of Sulfonamide Behavior in Cattle, Sheep, and Swine. In Proceedings of the Symposium of Veterinary Pharmacology and Therapeutics, Baton Rouge, LA, USA, 13–15 March 1978; pp. 75–101.
142. Paulson, G.; Struble, C.; Mitchell, A. Comparative metabolism of sulfamethazine [4-amino-N-(4,6-dimethyl-2-pyrimidinyl) benzenesulfonamide] in the rat, chicken, pig and sheep. In *Mode of Action, Metabolism and Toxicology*; Elsevier: Amsterdam, The Netherlands, 1983; pp. 375–380.
143. Hashem, M.; Tayeb, F.; El-Mekkawi, T. The level of some sulphonamide preparations in tissues and blood of cocks and sheep. *J. Egypt. Vet. Med. Assoc.* **1980**, *40*, 5–11.
144. Attaie, R.; Bsharat, M.; Mora-Gutierrez, A.; Woldesenbet, S. Short communication: Determination of withdrawal time for oxytetracycline in different types of goats for milk consumption. *J. Dairy Sci.* **2015**, *98*, 4370–4376. [CrossRef]
145. Payne, M.; Babish, J.; Bulgin, M.; Lane, M.; Wetzlich, S.; Craigmill, A. Serum pharmacokinetics and tissue and milk residues of oxytetracycline in goats following a single intramuscular injection of a long-acting preparation and milk residues following a single subcutaneous injection. *J. Vet. Pharmacol. Ther.* **2002**, *25*, 25–32. [CrossRef]

146. Fletouris, D.; Papapanagiotou, E. Tissue residue depletion of oxytetracycline after repeated intramuscular administration of Oxysentin 100 in sheep. *J. Vet. Pharmacol. Ther.* **2009**, *32*, 56–61. [CrossRef]
147. Anifantakis, E.M. Excretion rates of antibiotics in milk of sheep and their effect on yogurt production. *J. Dairy Sci.* **1982**, *65*, 426–429. [CrossRef]
148. Wells, R.J. Chlortetracycline. *Residues Some Vet. Drugs Anim. Foods* **1996**, *41*, 31–66.
149. Jha, V.; Jayachandran, C.; Singh, M.; Singh, S. Pharmacokinetic data on doxycycline and its distribution in different biological fluids in female goats. *Vet. Res. Commun.* **1989**, *13*, 11–16. [CrossRef]
150. Jayachandran, C.; Singh, M.; Singh, S.; Jha, H. Pharmacokinetics and distribution of minocydine in different biological fluids of goats after intravenous administration. *Indian J. Anim. Sci.* **2012**, *69*, 304–306.
151. Immelman, A.; Ziv, G. Serum and milk concentrations of oxytetracycline after the administration of a long-acting formulation to sheep. *J. S. Afr. Vet. Assoc.* **1982**, *53*, 199–200.
152. Arndt, T.; Robinson, D.; Holland, R.; Wetzlich, S.; Craigmill, A. Oxytetracycline residues in sheep following im dosing with a long-acting formulation. *J. Vet. Pharmacol. Ther.* **1997**, *20*, 314–315.
153. Boatto, G.; Pau, A.; Palomba, M.; Arenare, L.; Cerri, R. Monitoring of oxytetracycline in ovine milk by high-performance liquid chromatography. *J. Pharm. Biomed. Anal.* **1999**, *20*, 321–326. [CrossRef]
154. Craigmill, A.; Holland, R.; Robinson, D.; Wetzlich, S.; Arndt, T. Serum pharmacokinetics of oxytetracycline in sheep and calves and tissue residues in sheep following a single intramuscular injection of a long-acting preparation. *J. Vet. Pharmacol. Ther.* **2000**, *23*, 345–352. [CrossRef]
155. Fletouris, D.J.; Papapanagiotou, E.P. A new liquid chromatographic method for routine determination of oxytetracycline marker residue in the edible tissues of farm animals. *Anal. Bioanal. Chem.* **2008**, *391*, 1189–1198. [CrossRef] [PubMed]
156. Fletouris, D.J.; Papapanagiotou, E.P.; Nakos, D.S. Liquid chromatographic determination and depletion profile of oxytetracycline in milk after repeated intramuscular administration in sheep. *J. Chromatogr. B* **2008**, *876*, 148–152. [CrossRef] [PubMed]
157. Cinquina, A.L.; Longo, F.; Barchi, D.; Fagiolo, A.; Rosati, R.; Cozzani, R. Comparative pharmacokinetics of oxytetracycline in goat and sheep milk. Residues of Veterinary Drugs in Food. In Proceedings of the European Residue Conference IV, Veldhoven, The Netherlands, 8–10 May 2000; pp. 285–290.
158. Hassan, S.A.A.; Shaddad, S.A.I.; El-Tayeb, L.B.; Omer, M.A.; Al-Nazawi, M.H.; Homeida, A.M. Detection of long-acting oxytetracycline residue levels in tissue of desert sheep following intramuscular injection. *Int. J. Pharmacol.* **2007**, *3*, 299–301.
159. Reja, A.; Gonzalez, R.; Serrano, J.M.; Santiago, D.; Guimera, M.E.; Cano, M. Oxytetracycline and tetracycline residues in goat milk. In Proceedings of the European Associations of Veterinary Pharmacology and Toxicology 6th Congress, Edinburgh, UK, 7–11 August 1994.
160. Reja Sanchez, A.; Gonzalez Pedrajas, R.; Serrano Caballero, J.M.; Santiago Laguna, D. Experimental determination of occurrence of tetracycline and oxytetracycline residues in goat milk. Blood/milk transference rates. *Rev. Toxicol.* **1995**, *12*, 29–34.
161. Cinquina, A.L.; Gianetti, L.; Barchi, D.; Lanzi, S.; Longo, F.; Coresi, A.; Fagiolo, A.; Cozzani, R. Oxytetracycline residues in goat milk. *Obiettivi Doc. Vet.* **2002**, *23*, 37–40.
162. Rule, R.; Moreno, L.; Serrano, J.M.; Garcia Roman, A.; Moyano, R.; Garcia, J. Pharmacokinetics and residues in milk of oxytetracyclines administered parenterally to dairy goats. *Aust. Vet. J.* **2001**, *79*, 492–496. [CrossRef]