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REVIEW ARTICLE

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Drug residues in poultry meat: A literature review of commonly used veterinary antibacterials and anthelmintics used in poultry

Trishna Patel[1] | Tara Marmulak[2] | Ronette Gehring[3] | Maurice Pitesky[4] | Maaike O. Clapham[2] | Lisa A. Tell[2]

[1]William R. Pritchard Veterinary Medical Teaching Hospital, University of California, Davis, California

[2]Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California

[3]Department of Anatomy and Physiology, Institute of Computational Comparative Medicine, Kansas State University, Manhattan, Kansas

[4]Department of Population Health and Reproduction, School of Veterinary Medicine, Cooperative Extension, University of California, Davis, California

Correspondence
Lisa A. Tell, Department of Medicine and Epidemiology, University of California at Davis, One Shields Avenue, Davis, CA 95616.
Email: latell@ucdavis.edu

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Abstract

Poultry meat is widely consumed throughout the world and production practices often include the administration of pharmaceutical products. When appropriate, extra-label drug use of medications is necessary, but scientifically derived drug withdrawal intervals must be observed so that poultry meat is not contaminated with drug residues which could pose health risks to consumers. Over the past decade, there has been increased advocacy for judicious use of antimicrobial drugs for treating food animals. Judicious use of medications is commonly referred to as practices that reduce antibiotic resistance, but also includes residue avoidance. In that light, many investigators have performed scientific studies and have published estimated pharmacokinetic parameters for veterinary medications used in commercial avian species. This manuscript is a review of medication classes that have been studied in poultry (mostly chickens) with an emphasis on drug residue depletion in poultry meat.

KEYWORDS
anthelmintics, antibacterial, chickens, drug residue, poultry

1 | INTRODUCTION

Poultry is the second most widely eaten meat in the world and accounts for about 36% of meat production worldwide (Conway, 2017). The United States (US) has the largest broiler chicken industry in the world and in 2017, approximately 9 billion broiler chickens were produced (National Chicken Council, 2018). In addition to chicken, other poultry meats produced for consumption include turkey and quail, as well as waterfowl such as duck and geese. Historically, veterinary antibacterials and antiparasitics have been used in poultry practice for therapeutic, prophylactic, and/or growth promotion purposes (Reig & Toldra, 2008). With respect to prophylaxis, antibacterials and antiparasitics are used to prevent clinical and subclinical necrotic enteritis and coccidiosis which have been recognized as the most prevalent diseases in poultry (McDevitt, Brooker, Acamovic, & Sparks, 2006; Williams, 2005). Regarding growth promotion, the use of antibacterials for growth promotion has not been allowed in the European Union (EU) since 2006. The use of antibacterials for growth promotion is allowed in the United States. However, since the implementation of Guidance for Industry (GFI) 209 (United States Food and Drug Administration, 2012) and GFI 213 (United States Food and Drug Adminsitration, 2013), the United States (US) Food and Drug Administration (FDA) has executed steps to encourage judicious use of medically important antibacterials (MIA). GFI 209 (www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf) and GFI 213 (https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf) eliminates the use of MIAs for growth promotion. Furthermore, in 2017, the US (Castanon,

2007; Federal Register, 2015) restricted the use of medically important antibiotics in feed to Veterinary Feed Directives (VFD) that require veterinary oversight. A VFD is a written order issued by a veterinarian with a valid veterinary-client-patient-relationship for the use of a VFD drug for therapeutic purposes. In January 2017, VFD legislation became effective in the United States, bringing veterinary oversite to medically important antibacterials intended for use in or on animal feed. As part of the new regulation, extra label use of VFD drugs in major food producing species, such as chickens and turkeys, is not permitted. New Animal Drugs for use in or on animal feed are classified by the FDA as Category I or Category II drugs. Category I drugs do not require a withdrawal period for each major species they are approved for, while Category II drugs require a withdrawal period for at least one major animal species or have a zero residue tolerance due to carcinogenic concerns (United States Food and Drug Administration, 2018). Additionally, beginning in 2018, California legislators took the federal VFD regulations one step further so that any of the over the counter products that contain a medically important antimicrobial drug are now considered prescription and are under the jurisdiction of a licensed veterinarian per Senate Bill 27 (California Senate Bill #27, 2015).

Despite changing regulations, medications can still be used for therapeutic purposes and the residues of veterinary drugs or their metabolites in meat have the potential to cause adverse toxic effects, allergic reactions, or microbiological effects on human gastrointestinal flora (Reig & Toldra, 2008). Therefore, from a safety standpoint, extensive toxicology and pharmacology studies are necessary to demonstrate that consumers will not be exposed to harmful concentrations of medication residues in edible poultry tissues (Donoghue, 2003).

The Food Animal Residue Avoidance and Depletion program (FARAD; previously known as the Food Animal Residue Avoidance Databank) has been serving the veterinary profession for 35 years and is administered by the United States Department of Agriculture. The overarching goal of FARAD (www.farad.org) is to provide veterinary practitioners with current scientific information to facilitate production of foods derived from animal products that are safe for human consumption through prevention of violative drug residues. FARAD provides scientific-based estimates of withdrawal intervals in response to inquiries by veterinarians. In addition, FARAD offers a multitude of resources to help mitigate voilative drug residues including a citation database, VetGRAM (FARAD VetGRAM, 2018; database of Food and Drug Administration (FDA) approved food animal medications), and educational materials (digests, research articles, FARAD perspectives, etc.).

In regards to antibacterial use in the poultry industry, it is important to recognize that there are several that are no longer or are very rarely used in poultry production including the aminocyclitols (e.g. apramycin, spectinomycin) and amphenicols (e.g. florfenicol). Additionally, chloramphenicol is prohibited from use in any food producing species, including poultry. Aminoglycosides including gentamicin, while still in use, are typically only used in the hatchery in ovo or by subcutaneous injection at a day of age and therefore do not pose a risk with respect to residues in meat at processing.

In the United States, poultry are defined as any domesticated bird (chicken, turkeys, ducks, geese, guineas, ratites, or squabs, also termed young pigeons from one to about thirty days of age), whether live or dead. In addition, any migratory waterfowl or game bird, pheasant, partridge, quail, grouse, or pigeon, whether live or dead (United States Public Health Service, 2013) could be considered as poultry. In contrast with the United States, the European Union defines poultry as fowl, turkeys, guinea fowl, ducks, geese, quails, pigeons, pheasants, partridges, and ratites (Ratitae) reared or kept in captivity for breeding, the production of meat or eggs for consumption, or for restocking supplies of game and maximum residue limits are not differentiated between species (Council of the European Union, 1990).

This review summarizes research studies investigating commonly used antibacterials and antiparasitics in the United States with respect to the potential for drug residues to be present in different poultry meat products. It is important to note that residue depletion times referenced in the text are based on data from scientific studies. If available, FDA-approved withdrawal times should always be observed following drug administration in order to guarantee human food safety. In addition, it is a normal industry practice to withdraw feed 8–12 hr prior to processing the birds in order to minimize fecal contamination (Northcutt & Buhr, 2000). However, this practice of feed withdrawal for 8–12 hr 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 (US), and maximum residue levels (EU) have been provided in the tables for the reader's convenience.

2 | ANTIBACTERIALS

2.1 | Fluoroquinolones/Quinolones

Fluoroquinolones (ciprofloxacin, enrofloxacin, danofloxacin, sarafloxacin) are antimicrobial agents that exhibit broad spectrum activity, including activity against Pseudomonas spp. These bactericidal agents act by inhibiting DNA gyrase in bacterial cells. Studies have found a longer elimination half-life for poultry than in mammals (Abd El-Aziz, Aziz, Soliman, & Afify, 1997). Both enrofloxacin and sarafloxacin were historically labeled for use in chickens and turkeys. Attributed to the increase in human infections with antibacterial resistant Campylobacter spp. the FDA withdrew the use of fluoroquinolones in poultry (Cornejo et al., 2011). Sarafloxacin, the first fluoroquinolone approved for use in poultry in the United States was withdrawn in 2001 by the FDA (Federal Register, 2001). Additionally, enrofloxacin was withdrawn by the FDA in 2005 (Federal Register, 2005). However, in the USA, National Antimicrobial Resistance Monitoring System (NARMS) data has shown no change in resistance

trends in *Campylobacter jejuni* isolates from either humans or chickens following the ban of enrofloxacin in poultry (NARMS, 2014).

Within this drug class, drug depletion times for these agents can be different for various reasons. In comparison to ciprofloxacin, danofloxacin shows greater bioavailability following oral and intramuscular administration and has a higher degree of protein binding. These variations may account for the difference in drug elimination for these two agents in broiler chickens (El-Gendi, El-Banna, Abo Norag, & Gaber, 2001). Active metabolites can also account for differences in withdrawal times. Enrofloxacin is metabolized into ciprofloxacin, a pharmacologically active metabolite. Both the parent and metabolites may be found in chicken muscle after treatment with enrofloxacin (Shim, Shen, Kim, Lee, & Kim, 2003). Some studies have found substantial concentrations of the metabolite ciprofloxacin for multiple days after termination of enrofloxacin treatment (Anadón et al., 1995).

The FDA has established muscle as target tissue for residue monitoring in chickens and turkeys, but the regulatory process does not differentiate between edible muscle types in poultry (Reyes-Herrera et al., 2005). There is some evidence that there can be significant differences in fluoroquinolone drug residue deposition between different muscle types (Reyes-Herrera & Donoghue, 2008). One study found that when using both the lowest and highest FDA approved enrofloxacin doses, breast tissue had consistently higher drug concentrations than thigh tissues during the dosing period (Reyes-Herrera et al., 2005). Although enrofloxacin residue concentrations were higher in breast versus thigh tissues in this study, another antibacterial medication may produce higher concentrations in thigh muscle. Therefore, it is important to determine which edible tissue contains the highest residue content when muscle is the target tissue (Reyes-Herrera et al., 2005).

Some studies suggest that fluoroquinolone residues are also found in feathers. This is of concern because feather meal could be a potential source of drug residue that can pass through the food chain when contaminated meal is fed to food-producing animals (San Martín, Cornejo, Iragüen, Hidalgo, & Anadón, 2007). Studies involving flumequine, enrofloxacin and ciprofloxacin showed drug concentrations that remained elevated during and after withdrawal time, which suggests that withdrawal times do not guarantee the absence of drug in chicken nonedible tissue such as feathers (Cornejo et al., 2011). Please refer to Table 1 for further information on fluoroquinolone drug residue studies.

2.2 | Lincosamides

Lincosamides (lincomycin, clindamycin) are antimicrobial agents produced from Streptomyces lincolnensis and show exceptional activity against various gram positive organisms (Hornish, Gosline, & Nappier, 1987). They act by binding to the 50s subunit of bacterial ribosomes and inhibiting protein synthesis. Lincomycin is approved in the United States for broilers only and is used as a feed and water additive in broilers to aid in the prevention and control of coccidiosis, clinical and subclinical necrotic enteritis (Hornish et al., 1987). Based on the FDAs guidance for industry document (GFI #213; https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf) the use of antimicrobial drugs with indications such as "increased rate of weight gain" or "improved feed efficiency" is no longer permissible.

In chickens, liver and kidney tissue contained the highest total concentration of lincomycin drug residue, and liver metabolites were detected and identified as lincomycin sulfoxide, N-demethyl lincomycin, and N-demethyl lincomycin sulfoxide. The concentrations were so low, however, that authors have suggested they should be classified as safe, nontoxic residues, and of no toxicological concern (Hornish et al., 1987). Please refer to Table 2 for further information on lincosamide drug residue studies.

2.3 | Macrolides

Macrolides (erythromycin, roxithromycin, spiramycin, tilmicosin, tylosin) are bacteriostatic antimicrobial agents produced by Streptomyces spp. and are characterized by a macrocyclic lactone ring attached to two or more sugar moieties. They act by binding to the 50s bacterial ribosome and inhibiting protein synthesis and they are particularly useful against intracellular bacterial infections due their lipophilic nature. In mammals, macrolides are metabolized in the liver and the highest tissue concentrations for chickens and turkeys are also found in the liver (Goudah, Abo El Sooud, & Abd El-Aty, 2004). In the United States, only tylosin is approved for use in poultry although licensed poultry veterinarians can use other macrolides as ELDU under the AMDUCA if they are willing to take full responsibility for residues.

The absorption of erythromycin in poultry is highly variable following oral administration (Vermeulen, De Backer, & Remon, 2002). There is literature that suggests that crop flora can impede the absorption of certain macrolide drugs, such as erythromycin (Devriese & Dutta, 1984; Vermeulen et al., 2002). Erythromycin should be given twice daily at a dosage of 30 mg/kg body weight with a 3 day withdrawal time to ensure that the drug is eliminated from the tissues (Goudah et al., 2004).

Roxithromycin can be more effective at lower doses than erythromycin and can be given less frequently, due to the drug's longer elimination half-life and higher plasma levels (Lim, Park, & Yun, 2003). Following oral administration in broilers, the liver was detected to have the highest residual concentration of drug and one study determined withdrawal time to be 7 days after treatment of roxithromycin (Lim et al., 2003). Although roxithromycin is not FDA approved for use in poultry, it can be used in an extralabel manner. Tilmicosin also exhibits a long elimination half-life and residues from the liver persist for up to 9 days in broilers (Zhang et al., 2004) and up to 20 days in turkeys (Fricke et al., 2008) following a 5 day oral course of treatment. Tylosin and spiramycin have been studied in growing chicks and results show that tylosin residues are not detected more rapidly from the liver than spiramycin residues. After withdrawal of dietary tylosin at a dose of 8000 mg kg^{-1} day^{-1} for

TABLE 1 Fluoroquinolone residues in meat following treatment in broilers

Fluoroquinolone	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Ciprofloxacin	US: Prohibited EU: Not approved		HPLC	NS	NS	Oral	10 mg/kg bw	1.25	4	Liver Kidney Muscle	CIPRO:>12[b] Metabolite:>12 CIPRO:12 Metabolite:>12 CIPRO:12 Metabolite:>12	Iturbe, Martínez-Larrañaga, and Anadón (1997)
Ciprofloxacin			Bioassay	NS	NS	Oral	10 mg/kg bw	1.75	4	Liver Kidney Muscle	5 7 1	El-Gendi et al. (2001)
Ciprofloxacin			HPLC	NS	3 μg/kg[c]	Oral	8 mg/kg bw	1.33	3	Liver Kidney Muscle Skin/fat	CIPRO: 10 Metabolite: >10 CIPRO: 10 Metabolite: 10 CIPRO: 10 Metabolite: 10 CIPRO:10 Metabolite: >10	Anadón et al. (2001)
Danofloxacin	US: Prohibited EU: Not approved	EU: 200 μg/kg	Bioassay	NS	NS	Oral	5 mg/kg bw	1.75	4	Liver Kidney Muscle	9 13 1	El-Gendi et al. (2001)
Danofloxacin			Radioassay	NS	NS	Water	25 mg/L drinking water	0.75	5	Liver Kidney Muscle Skin/Fat	>2 >2 >2 >2	Lynch et al. (1994)
			HPLC/F	10 μg/kg	Liver: 10-60 μg/kg Muscle: 25-200 μg/kg Skin/Fat: 25-200 μg/kg	Water	5 mg/kg bw	0.75	3	Liver Muscle Skin/Fat	1.5 1 1	
Enrofloxacin	US: Prohibited EU: Not approved	EU: 100 μg/kg	Microdialysis-LC	NS	ENRO: 0.8 μg/kg CIPRO: 1.0 μg/kg	Oral	11 mg/kg bw	NS	7	Liver Muscle	ENRO: >3[b] CIPRO: >3[d] ENRO: >3 CIPRO: >3	Schneider (2001)

(Continues)

TABLE 1 (Continued)

Fluoroquinolone	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Enrofloxacin			LC-fluorescence-multiple MS	0.3 μg/kg 0.2 μg/kg 0.2 μg/kg 1.5 μg/kg	NS	Water	50 mg/L drinking water	NS	7	Liver Muscle	ENRO: >2 CIPRO:>2 ENRO: >2 CIPRO: 2	Schneider and Donoghue (2002)
Enrofloxacin			Bioassay	NS	NS	Water	25 mg/L drinking water 50 mg/L drinking water	0 0	3 7 3 7	Muscle Muscle Muscle Muscle	>1 >1 >1 >1	Reyes-Herrera et al. (2005)
Enrofloxacin			LC-MS/MS	1.2 μg/kg	NS	IM	10 mg/kg bw	3.75	3	Liver Kidney Muscle and Skin	>9 >9 >9	San Martín et al. (2007)
Enrofloxacin			Bioassay	10 μg/kg[e]	NS	Water	25 mg/L drinking water 50 mg/L drinking water	1 1	3 7 3 7	Muscle Muscle Muscle Muscle	2 2 3 3	Reyes-Herrera and Donoghue (2008)
Enrofloxacin			HPLC-MS/MS	1 μg/kg	2 μg/kg	Oral	10 mg/kg bw (10% formulation) 10 mg/kg bw (16% formulation) 10 mg/kg bw (20% formulation) 10 mg/kg bw (80% formulation)	0 0 0 0	5 5 5 5	Liver Muscle Liver Muscle Liver Muscle Liver Muscle	9 9 9 9 8 8 6 6	San Martín et al. (2010)
Enrofloxacin			Bioassay	NS	NS	Oral	10 mg/kg bw	1.82	5	Liver Kidney Muscle Skin Fat	4 4 2 3 4	Abd El-Aziz et al. (1997)

(Continues)

TABLE 1 (Continued)

Fluoroquinolone	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Enrofloxacin			HPLC	ENRO and CIPRO: 3 μg/kg	NS	Oral	10 mg/kg bw	1.25	4	Liver	ENRO:>12[b]	Anadón et al. (1995)
											CIPRO:>12[d]	
										Kidney	ENRO:12	
											CIPRO:>12	
										Muscle	ENRO:6	
											CIPRO:>12	
										Skin	ENRO:12	
											CIPRO:12	
										Fat	ENRO:6	
											CIPRO:6	
Enrofloxacin			HPLC	1 μg/kg	5 μg/kg	Water	10 mg/kg bw	1	6 hr	Muscle	5	Shim et al. (2003)
Enrofloxacin			Bioassay	20 μg/kg	NS	Oral	10 mg/kg bw	0.25–1.5	1	Liver	>1	Scheer (1987)
										Kidney	>1	
										Muscle	1	
										Skin	>1	
						Oral	2.5 mg/kg bw	0.75	1	Liver	1	
										Kidney	1	
										Muscle	1	
Enrofloxacin			HPLC	NS	NS	Oral	10 mg/kg/day bw	1.25	4	Liver	ENRO:12[b]	Martínez-Lannañaga et al. (1994)
											CIPRO:>12[d]	
										Kidney	ENRO:12	
											CIPRO:>12	
										Muscle	ENRO:12	
											CIPRO:>12	
										Skin	ENRO:12	
											CIPRO:>12	
Enrofloxacin			Radioassay	NS	NS	Oral Gavage	50 mg/kg bw TID	0.75	7	Liver	>1	Bayer Corporation (1996)
										Muscle	>1	
										Skin/Fat	>1	

(Continues)

TABLE 1 (Continued)

Fluoroquinolone	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Flumequine	US: Prohibited EU: Not approved	EU: 400 μg/kg	LC-MS/MS	1.5 μg/kg	2.0 μg/kg	Oral	24 mg/kg bw (10% premix powder)	0	5	Liver	>6	Cornejo et al. (2011)
										Muscle	>6	
							24 mg/kg bw (20% solution)	0	5	Liver	>6	
										Muscle	>6	
							24 mg/kg bw (80% premix powder)	0	5	Liver	>6	
										Muscle	>6	
Marbofloxacin	US: Prohibited EU: Not approved		HPLC	NS	10 μg/kg[c]	Oral	2 mg/kg bw	1.25	3	Liver	>5	Anadón et al. (2002)
										Kidney	>5	
										Muscle	3	
										Skin/Fat	3	
Moxifloxacin	US: Prohibited EU: Not approved		HPLC	NS	10 μg/kg[c]	IM[a]	5 mg/kg bw	1.5	5	Liver	>6	Goudah (2009)
										Kidney	>6	
										Muscle	6	
						Oral	5 mg/kg bw	1.5	5	Liver	>6	
										Kidney	>6	
										Liver	6	
Nalidixic Acid	US: Prohibited EU: Not approved		Bioassay	NS	NS	Oral	25 mg/kg bw BID	0.75	5	Liver	LP:>7; HP:7[f]	Abd El-Aziz, Afify, and Kamel (1995)
										Kidney	LP:>7; HP:7	
										Muscle	LP:>7; HP:7	
Norfloxacin	US: Prohibited EU: Not approved		HPLC	Norfloxacin: 3 μg/kg[c] Metabolites: 5 μg/kg[c]	NS	Oral	8 mg/kg bw	1.25	4	Liver	>12	Anadón, Martínez-Larrañaga, Velez, Díaz, and Bringas (1992)
										Kidney	>12	
										Muscle	Norfloxacin:12 Metabolites:>12	
										Fat	>12	
Norfloxacin			HPLC/F	2.5 μg/kg	NS	Water	175 mg/L drinking water	NS	5	Liver	6	Rolinski, Kowalski, and Wlaz (1997)
										Muscle	>9	
										Gizzard	6	
Olaquindox	US: Prohibited EU: Not approved		HPLC	NS	NS	Oral	20 mg/kg bw	1.33	3	Liver	>14	Anadón, Martínez-Larrañaga, Díaz, Velez, and Bringas (1990)
										Kidney	>14	
										Muscle	>14	

(Continues)

TABLE 1 (Continued)

Fluoroquinolone	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Oxilinic Acid	US: Prohibited EU: Not approved		HPLC	NS	NS	Oral	200 mg/kg bw	1.25	1	Liver Kidney Muscle	8 14 8	Anadón et al. (1990)
Pefloxacin	US: Prohibited EU: Not approved		HPLC	Pefloxacin and Norfloxacin: 30 μg/kg	Pefloxacin and Norfloxacin: 30 μg/kg	Oral	10 mg/kg bw	NS	4	Liver Kidney Muscle Skin/Fat	Pefloxacin and Norfloxacin:5 Pefloxacin and Norfloxacin:5 Pefloxacin:5 Norfloxacin:1 Pefloxacin and Norfloxacin:>10	Pant et al. (2005)
Piromidic Acid	US: Not approved EU: Not Approved		HPLC	NS	NS	Oral	10 mg/kg bw	1.33	3	Liver Muscle Kidney	8 8 8	Anadón et al. (1990)
Sarafloxacin	US: Not approved EU: Approved	EU: 10 μg/kg (skin and fat)	Radioassay	NS	NS	Oral	40 mg/kg bw	0.75	5	Liver Muscle Skin/Fat	>0.25 >0.25 >0.25	Abbott Laboratories (1995)
Sarafloxacin			NS	1 μg/kg[g]	NS	SC	0.094 mg	0	1	Liver Leg Breast	21 14 21	Abbott Laboratories (1996)

Notes. > Indicates that residues were still positive at the last sampling time; NS Indicates not specified in published manuscript.

[a]See Appendix S1 for list of definitions and abbreviations; [b]CIPRO, ciprofloxacin; [c]Published manuscript reported the units for LOD/LOQ as ug/ml; [d]ENRO, enrofloxacin; [e]Published manuscript reported the units for LOD as ppb; [f]Chickens were fed either a High Protein diet (HP) of 26% or a Low Protein diet of 15%; [g]Published manuscript reported the units for LOQ as ppm.

TABLE 2 Lincosamide residues in meat following treatment in broilers

Lincosamide	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Lincomycin	US: Approved EU: Approved	US: Not required EU: 100 μg/kg	Radioassay	NS	5 μg/kg[b]	Water	34 mg/L drinking water	NS	7	Liver Kidney Muscle Skin/Fat	>7 >7 2 7	Hornish et al. (1987)
Lincomycin			Radioassay	5 μg/kg[b]	NS	Water	NS	1	7	Liver Kidney Muscle Skin/Fat	>7 >7 2 7	The Upjohn Company (1990)
Lincomycin			Bioassay	100 μg/kg[b]	NS	Feed	4.4 mg/kg feed[c]	NS	49	Liver Muscle Skin/Fat	0 NS 0 NS 0 NS	Roussel-Uclaf (1989)
Lincomycin			NS	NS	NS	Feed	4.4 mg/kg feed[c]	NS	NS	Liver	0.25	Elanco Animal Health (1998)

Notes. > indicates that residues were still positive at the last sampling time; NS Indicates not specified in published manuscript; 0 NS indicates that a zero day withdrawal was stated in the publication but did not specify how many hours after feed withdrawal.

[a]See Appendix S1 for list of definitions and abbreviations; [b]Published manuscript reported the units for LOD/LOQ as ppm; [c]Published manuscript reported dose as 4 g/ton.

TABLE 3 Macrolide residues in meat following treatment in broilers

Macrolides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Erythromycin	US: Approved EU: Approved	US: 125 μg/kg (edible tissue) EU: 200 μg/kg	Bioassay	NS	30 μg/kg[b]	IM	30 mg/kg bw BID	1.5	3	Liver	>2	Goudah et al. (2004)
										Kidney	>2	
										Muscle	2	
						SC	30 mg/kg bw BID	1.5	3	Liver	2	
										Kidney	2	
										Muscle	2	
						Oral	30 mg/kg bw BID	1.5	3	Liver	>2	
										Kidney	>2	
										Muscle	2	
Roxithromycin	US: Not approved EU: Not approved		LC-MS	1 μg/kg	5 μg/kg	Water	15 mg/L drinking water	NS	7	Liver	10	Lim et al. (2003)
										Kidney	5	
										Muscle	5	
										Skin	5	
										Fat	5	
						Water	60 mg/L drinking water	NS	5	Liver	10	
										Kidney	5	
										Muscle	10	
										Skin	10	
										Fat	5	
Spiramycin	US: Not approved EU: Not approved	EU: 200 μg/kg	Bioassay	450 μg/kg	NS	Feed	1,000 mg/kg feed	10	7	Liver	>12	Yoshida, Kubota et al. (1971)
Spiramycin			Bioassay	NS	NS	Feed	20 mg/kg feed	0	56	Liver	1	Yoshida, Yonezawa et al. (1971)
										Muscle	1	
							500 mg/kg feed	0	56	Liver	7	
										Muscle	1	
							1,000 mg/kg feed	0	56	Liver	>7	
										Muscle	1	

(Continues)

TABLE 3 (Continued)

Macrolides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Tilmicosin	US: Not approved EU: Approved	EU: 75 μg/kg	HPLC	Liver: 25 μg/kg	NS	Water	37,500 mg/L drinking water	0.75	5	Liver	>14	Zhang et al. (2004)
										Kidney	>14	
				Kidney: 25 μg/kg	NS					Muscle	>14	
							75,000 mg/L drinking water	0.75	5	Liver	>14	
				Muscle: 10 μg/kg	NS					Kidney	>14	
										Muscle	>14	
Tylosin	US: Approved EU: Approved	US: 200 μg/kg EU: 100 μg/kg	Bioassay	300 μg/kg	NS	Feed	20 mg/kg feed	0	56	Liver	0 hr	Yoshida, Hoshii et al. (1972)
										Muscle	0 hr	
							250 mg/kg feed	0	56	Liver	0 hr	
										Muscle	0 hr	
							500 mg/kg feed	0	56	Liver	0 hr	
										Muscle	0 hr	
							1,000 mg/kg feed	0	56	Liver	0 hr	
										Muscle	0 hr	
							1,500 mg/kg feed	0	56	Liver	>0	
										Muscle	0 hr	
							2,000 mg/kg feed	0	56	Liver	2	
										Muscle	1	
							8,000 mg/kg feed	0	56	Liver	2	
										Muscle	1	
							8,000 mg/kg feed	0	42	Liver	5	
										Muscle	2	
Tylosin			Bioassay	400 μg/kg	NS	Feed	8,000 mg/kg feed	10	7	Liver	7	Yoshida, Daisaku et al. (1972)

Notes. > indicates that residues were still positive at the last sampling time. NS Indicates not specified in published manuscript.

[a]See Appendix S1 for list of definitions and abbreviations; [b]Published manuscript reported the units for LOQ as ug/ml.

TABLE 4 Sulfonamide residues in meat following treatment in broilers

Sulfonamides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Sulfadimethoxine	US: Approved EU: Not Approved	US: 100 μg/kg (edible tissue)	NS	100 μg/kg[b]	NS	Feed	200 mg/kg feed	0	56	Liver Kidney Muscle Skin	2 1 1 1	Fellig, Westheimer, Walsh, and Marusich (1971)
Ormetoprim	US: Approved EU: Not Approved	US: 100 μg/kg (edible tissue)	NS	100 μg/kg[b]	NS	Feed	200 mg/kg feed	0	56	Liver Kidney Muscle Skin	1 2 1 1	Fellig, Westheimer, Walsh, and Marusich (1971)
Sulfadimethoxine			HPLC and LC-TSP-MS	50 μg/kg	NS	Feed	100 mg/kg feed	0.25	20	Liver Kidney Muscle Skin Gizzard	2 2 2 2 2	Nagata, Saeki, Waki, Kataoka, and Shikano (1994)
Sulfadimethoxine			HPLC	100 μg/kg	NS	Feed	400 mg/kg feed	6	5	Liver Kidney Muscle Fat	>1 >1 >1 1	Furusawa, Mukai, and Ohori (1996)
Sulfadimethoxine			HPLC	50 μg/kg	NS	Oral	200 mg/kg bw	NS	1	Liver Kidney Muscle Skin Fat	5 5 3 10 3	Takahashi et al. (1991)

(Continues)

TABLE 4 (Continued)

Sulfonamides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Sulfadimethoxine			HPLC	50 μg/kg	NS	IV	30 mg/kg bw	NS	1	Skin	1.5	Takahashi et al. (1993)
							100 mg/kg bw	NS	1	Skin	3	
							200 mg/kg bw	NS	1	Skin	7	
						Water	500 mg/L drinking water	NS	5	Skin	7	
							1,000 mg/L drinking water	NS	5	Skin	14	
Sulfadimethoxine			HPLC	100 μg/kg[b]	NS	Feed	400 mg/kg feed	6	5	Liver	SDM: >0.83 metabolite: >0.83	Furusawa (1999)
										Kidney	SDM: >0.83 metabolite: >0.83	
										Muscle	SDM:>0.83 metabolite: 0.83	
										Fat	SDM:>0.83 metabolite: 0.21	
Sulfadimethoxine			HPLC	10 μg/kg	NS	Feed	25 mg/kg feed	0	21	Liver	2	Nagata et al. (1994)
										Muscle	1	
										Fat	1	
										Gizzard	1	
						Feed	50 mg/kg feed	0	21	Liver	2	
										Muscle	1	
										Fat	1	
										Gizzard	1	
							100 mg/kg feed	0	21	Liver	2	
										Muscle	1	
										Fat	1	
										Gizzard	2	

(Continues)

TABLE 4 (Continued)

Sulfonamides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Sulfadimethoxine			HPLC	100 µg/kg[b]	NS	Feed	25 mg/kg feed	0	21	Liver	2	Nagata, Saeki, Ida, and Waki (1992)
										Muscle	1	
										Fat	1	
										Gizzard	1	
							50 mg/kg feed	0	21	Liver	2	
										Muscle	1	
										Fat	1	
										Gizzard	1	
							100 mg/kg feed	0	21	Liver	2	
										Muscle	1	
										Fat	1	
										Gizzard	2	
Sulfadiazine	US: Not approved EU: Not Approved		NS	NS	NS	Oral	200 mg/kg bw	10	1	Liver	0.083	Hashem, Tayeb, and El-Mekkawi (1980)
										Kidney	2	
										Muscle	1.33	
										Gizzard	2	
Sulfadiazine and Trimethoprim	Trimethoprim: EU: Approved	EU: 50 µg/kg	NS	NS	NS	Water	SDA - 33.3 mg/kg bw TMP - 6.7 mg/kg bw	NS	6	Liver	3	De Baere, Croubels, Baert, and De Backer (2000)
										Kidney	3	
										Muscle	3	
Sulfadimidine	US: Not approved EU: Not Approved		NS	NS	NS	Oral	200 mg/kg bw	10	1	Liver	0.33	Hashem et al. (1980)
										Kidney	2	
										Muscle	2	
										Gizzard	2	
Sulfamethazine	US: Approved EU: Not Approved	US: 100 µg/kg (edible tissue)	LSC	1,000 µg/kg[b]	NS	Oral (capsule)	100 mg/kg bw	NS	1	Liver	>8	Paulson, Struble, and Mitchell (1983)
								NS	1	Kidney	8	
								NS	1	Muscle	2	

(Continues)

TABLE 4 (Continued)

Sulfonamides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Sulfamethazine			cFLISA	1.0 μg/kg[c]	NS	Feed	200 mg/kg bw	2	5	Muscle	10	Ding et al. (2006)
							400 mg/kg bw	2	5	Muscle	10	
			HPLC	10 μg/kg[c]	NS	Feed	200 mg/kg bw	2	5	Muscle	5	
							400 mg/kg bw	2	5	Muscle	5	
Sulfamethazine			HPLC	122 dpm (3.0 ng)	183 dpm (4.5 ng)	Oral	274.6 mg/day	NS	6	Liver	>3	Shaikh and Chu (2000)
										Muscle	>3	
Sulfamethazine			NS	0.1 mg/kg[b]	NS	Feed	4,000 mg/kg feed	4	6	Liver	>10	Righter, Worthington, and Mercer (1971)
										Kidney	>10	
										Muscle	10	
										Skin	10	
										Fat	5	
						Feed	1,000 mg/kg feed	4	6	Liver	>10	
										Kidney	10	
										Muscle	5	
										Skin	3	
										Fat	3	
Sulfamethazine (40%)	US: Approved EU: Approved		TLC densitometric	15 μg/kg[d]	NS	Water	400 mg/L drinking water	3	5	Liver	6	Alpharma, Inc. (2006)
Sulfamerazine (40%)				15 μg/kg[d]	NS	Water	400 mg/L drinking water	3	5	Liver	6	Alpharma, Inc. (2006)

(Continues)

TABLE 4 (Continued)

Sulfonamides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Sulfaquinoxaline (20%)				10 μg/kg[d]	NS	Water	400 mg/L drinking water	3	5	Liver	6	Alpharma, Inc. (2006)
Sulfamonomethoxine (SMM)	US: Not approved EU: Not Approved		HPLC	NS	NS	Oral	200 mg/kg bw	1.75-2	1	Liver	>2	Li et al. (1995)
										Kidney	>2	
										Muscle	>2	
Sulfaquinoxaline (SQ)	US: Approved EU: Not Approved	US: 100 μg/kg (edible tissue)	HPLC	NS	NS	Oral	200 mg/kg bw	2	1	Liver	4	Li et al. (1995)
										Kidney	4	
										Muscle	4	
Sulfaquinoxaline			NS	100 μg/kg[d]	NS	Feed	500 mg/kg feed	6–30	12	Liver	>7	Righter, Worthington, Zimmer-man, and Mercer (1970)
										Kidney	>7	
										Muscle	7	
										Skin	>7	
										Fat	>7	
						Feed	250 mg/kg feed	1.25	14	Liver	7	
										Kidney	>7	
										Muscle	>7	
										Skin	>7	
										Fat	5	
						Water	250 mg/L drinking water	1.25	14	Liver	7	
										Kidney	>7	
										Muscle	>7	
										Skin	>7	
										Fat	5	

(Continues)

TABLE 4 (Continued)

Sulfonamides	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Sulfaquinoxaline			Colorimetric	NS	NS	Oral	100 mg/kg bw	1.5-2	5	Liver	5	El-Sayed, Abd El-Aziz, and El-Kholy (1995)
										Kidney	5	
										Thigh	4	
										Breast	5	
										Skin	1	
										Fat	4	
										Gizzard	5	
Sulfaquinoxaline			HPLC	1.2 ng per injection	NS	Feed	80 mg/kg feed	1-1.25	14	Liver	8	Patthy (1983)
										Muscle	8	

Notes. > indicates that residues were still positive at the last sampling time. NS Indicates not specified in published manuscript.

[a]See Appendix S1 for list of definitions and abbreviations; [b]Published manuscript reported the units for LOD as ppm; [c]Published manuscript reported the units for LOD as ng/ml; [d]Published manuscript reported the units for LOD as ppb.

7 days, no residues were detected in the liver after 2 days while residues of spiramycin were detectable in the liver for up to 7 days (Yoshida, Hoshii, Yonezawa, Nakamura, & Yamaoka, 1972). In laying hens, residues from both spiramycin and tylosin are not detected after 7 days, although large individual variations have been observed among the liver content of spiramycin (Yoshida, Daisaku et al., 1972). Please refer to Table 3 for further information on macrolide drug residue studies.

2.4 | Polymyxins

Polymyxins (colistin) are polypeptide antibacterials that are primarily effective against Gram-negative bacteria and are utilized in veterinary medicine as a drug or feed additive. Human exposure to colistin, via parenteral routes of administration, could result in nephrotoxicity, CNS dysfunction, drug fever, and anorexia.

Studies suggest that polymyxins are not absorbed to any extent from the GI tract when administered orally (Zeng et al., 2010). After oral administration in ducks, colistin was not detectable in plasma and tissues, except for the intestines. Following a single intramuscular dose in ducks, the highest colistin concentrations were observed in kidney and the lowest concentrations in muscle. In contrast, colistin was eliminated rapidly in plasma, kidney, and liver, but very slowly in muscle. Since high drug concentrations and a long elimination profile were observed in duck kidney and muscle, these sites could serve as representative tissues in duck for colistin residue monitoring (Zeng et al., 2010).

2.5 | Sulfonamides

Sulfonamides (sulfadimethoxine, sulfaquinoxaline, sulfamethoxazole, sulfachlorpyrazine) are bacteriostatic antibacterial agents that are active against Gram-negative and Gram-positive organisms, as well as protozoa, such as coccidia. They interfere with synthesis of folic acid by competing with para-aminobenzoic acid (PABA) and prevent cellular replication in bacteria (Lebkowska-Wieruszewska & Kowalski, 2010). These agents are approved for use in food-producing animals, but human consumption of sulfonamide contaminated products can cause central nervous system effects, gastrointestinal disturbances, and hypersensitivity reactions (Lebkowska-Wieruszewska & Kowalski, 2010). Sulfonamides exhibit high protein binding in tissues and blood and some sulfonamides are known to have active metabolites. Sulfadimethoxine is metabolized by acetylation and hydroxylation (Furusawa, 1999). Hydroxylation has been suggested as the main metabolic pathway (Nagata & Fukuda, 1994). Hydroxylated metabolites have antibacterial properties, but <40% activity of the parent drug and pharmacological effects seem to be low (Nagata & Fukuda, 1994). Sulfonamide medications are used very rarely in US broiler production because of the high potential for residues. On rare occasions, a sulfadimethoxine + ormethoprim combination is used in a "prestarter feed" for birds under 16 weeks of age to prevent mortality from coccidiosis and

TABLE 5 Tetracycline residues in meat following treatment in broilers

Tetracyclines	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Chlortetracycline	US: Approved EU: Approved	US: 2,000 μg/kg EU: 100 μg/kg	Bioassay	50 μg/kg	NS	Feed	8,000 mg/kg feed	8	7	Liver	3	Yoshida et al. (1973)
Chlortetracycline			Bioassay	25–40 μg/kg	NS	Feed	881.8 mg/kg feed[b] (800 g/ton feed)	2.5	5	Liver	6	Shor, Abbey, and Gale (1968)
										Kidney	>6	
										Muscle	3	
										Fat	1	
							1,322.8 mg/kg of feed[b] (1,200 g/ton feed)	2.5	5	Liver	6	
										Kidney	>6	
										Muscle	6	
										Fat	6	
							1,763.7 mg/kg of feed[b] (1,600 g/ton feed)	2.5	5	Liver	>6	
										Kidney	>6	
										Muscle	6	
										Fat	3	
							2,204.6 mg/kg of feed[b] (2,000 g/ton feed)	2.5	5	Liver	6	
										Kidney	>6	
										Muscle	6	
										Fat	3	
Chlortetracycline			Bioassay	NS	NS	Feed	50 mg/kg feed	2.5-3	70-84	Liver	1	Durbin, DiLorenzo, Randall, and Wilner (1953)
										Muscle	1	
							100 mg/kg feed	2.5-3	70-84	Liver	1	
										Muscle	1	
							200 mg/kg feed twice weekly daily for the last 5 days	2.5-3	70-84	Liver	1	
										Muscle	1	
Chlortetracycline			Bioassay	52 μg/kg	NS	Feed	20 mg/kg feed	0	56	Liver	1	Yoshida, Yonezawa et al. (1971)
										Muscle	1	
							500 mg/kg feed	0	56	Liver	1	
										Muscle	1	
							1,000 mg/kg feed	0	56	Liver	3	
										Muscle	1	

(Continues)

TABLE 5 (Continued)

Tetracyclines	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Chlortetracycline			NS	NS	NS	Water	17 mg/L drinking water	0.5	42	Muscle	7	Amin, Kazemi, Bondari, and Yazdani (1977)
							35 mg/L drinking water	0.5	42	Muscle	7	
							70 mg/L drinking water	0.5	42	Muscle	7	
							105 mg/L drinking water	0.5	42	Muscle	7	
Chlortetracycline			Bioassay	25–5,000 μg/kg[c]	NS	Feed	110.2 mg/kg of feed[b] (100 g/ton feed)	2	6	Liver	0 hr	Broquist and Kohler (1953)
										Muscle	0 hr	
							220.5 mg/kg of feed[b] (200 g/ton feed)	2	6	Liver	1	
										Muscle	2	
							1,102.3 mg/kg of feed[b] (1,000 g/ton feed)	2	6	Liver	1	
										Muscle	2	
Chlortetracycline			Bioassay	25 μg/kg	NS	Feed	881.8 mg/kg feed[b] (800 g/ton feed)	2.5	5	Liver	6	Roche Vitamins Inc. (1998)
										Kidney	>10	
										Muscle	3	
										Fat	1	
Chlortetracycline			NS	25 μg/kg[d]	NS	Feed	220.5 mg/kg[b] (200 g/ton) feed for the first 37 days, followed by 551.2 mg/kg feed[b] (500 g/ton feed)	NS	42	Liver	>7	American Cyanamid Company (1989a)
										Muscle	>7	
										Fat	>7	
										Skin and Fat	>7	
Chlortetracycline			NS	25 μg/kg[d]	NS	Feed	220.5 mg/kg[b] (200 g/ton) feed for the first 37 days, followed by 551.2 mg/kg feed[b] (500 g/ton feed)	NS	42	Liver	>7	American Cyanamid Company (1989b)
										Muscle	>7	
										Fat	>7	
										Skin and Fat	>7	
Chlortetracycline			HPLC	NS	50,000–75,000 μg/kg[c]	Oral	60 mg/kg bw	1.33	5	Kidney	>5	Anadón et al. (2012)
										Muscle	3	
										Liver	5	

(Continues)

TABLE 5 (Continued)

Tetracyclines	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Doxycycline	US: Not approved EU: Approved	EU: 100 μg/kg	HPLC	NS	NS	Oral	20 mg/kg bw	1.25	4	Liver	>5	Anadón et al. (1993)
										Kidney	>5	
										Muscle	>5	
Doxycycline			Bioassay	20 μg/kg[c]	NS	Oral	15 mg/kg bw BID	1.5	5	Liver	7	Atef et al. (2002)
										Kidney	7	
										Muscle	5	
						IM	15 mg/kg bw BID	1.5	5	Liver	7	
										Kidney	7	
										Muscle	5	
Doxycycline			HPLC	25 μg/kg[e]	NS	Oral	20 mg/kg bw	1.25	4	Liver	>5	Anadón et al. (1994)
										Kidney	>5	
										Muscle	>5	
Oxytetracycline	US: Approved EU: Approved	US: 2,000 μg/kg EU: 100 μg/kg	Bioassay	NS	NS	Oral	6 mg/kg bw BID	2-2.5	5	Liver	1	Atef et al. (1986)
										Kidney	1	
										Muscle	0.04	
						IM	6 mg/kg bw BID	2-2.5	5	Liver	1	
										Kidney	1	
										Muscle	1	
Oxytetracycline			Bioassay	180 μg/kg	NS	Feed	2,000 mg/kg feed	0	56	Liver	3	Yoshida et al. (1975)
										Muscle	2	
						Feed	4,000 mg/kg feed	0	56	Liver	>7	
										Muscle	5	
						Feed	4,000 mg/kg feed	0	28	Liver	6	

(Continues)

TABLE 5 (Continued)

Tetracyclines	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Oxytetracycline			Bioassay	80-100 μg/kg	NS	Feed	5.5 mg/kg feed[b] (5 g/ton feed)	0	NS	Liver	0 NS	Luther, Reynolds, McMahan, and Kersey (1953)
										Kidney	0 NS	
										Muscle	0 NS	
						Feed	55.1 mg/kg feed[b] (50 g/ton feed)	0	NS	Liver	0 NS	
										Kidney	0 NS	
										Muscle	0 NS	
						Feed	110.2 mg/kg feed[b] (100 g/ton feed	0	NS	Liver	0 NS	
										Kidney	1	
										Muscle	0 NS	
						Feed	220.5 mg/kg feed[b] (200 g/ton feed)	0	NS	Liver	1	
										Kidney	1	
										Muscle	0 NS	
						Feed	551.2 mg/kg feed[b] (500 g/ton feed)	0	NS	Liver	1	
										Kidney	1	
										Muscle	0 NS	
						Feed	1,102.3 mg/kg feed[b] (1,000 g/ton feed)	0	NS	Liver	1	
										Kidney	3	
										Muscle	1	
						Feed	2,755.8 mg/kg feed[b] (2,500 g/ton feed)	0	NS	Liver	2	
										Kidney	5	
										Muscle	1	
						Feed	5,511.6 mg/kg feed[b] (5,000 g/ton feed)	0	NS	Liver	5	
										Kidney	5	
										Muscle	5	
Oxytetracycline			NS	NS	NS	Feed	27.6, 110.2, 165.3, and 220.5 mg/kg feed[b] (25, 50, 100, 150 and 200 g/ton feed)	0	77	Liver	1	Katz et al. (1973)
								0	77	Kidney	1	
								0	77	Muscle	1	

(Continues)

TABLE 5 (Continued)

Tetracyclines	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Oxytetracycline			NS	NS	NS	Water	17 mg/L drinking water	0.5	42	Muscle	14	Amin et al. (1977)
							35 mg/L drinking water	0.5	42	Muscle	7	
							70 mg/L drinking water	0.5	42	Muscle	14	
							105 mg/L drinking water	0.5	42	Muscle	7	
Oxytetracycline			Bioassay	NS	NS	Water	211.3 mg/L[f] drinking water	2	14	Liver	0.17	Fermenta Animal Health Company (1993)
										Muscle	0 hr	
										Skin/Fat	>0.21	
Oxytetracycline			Bioassay	Liver: 250 µg/kg[d] Kidney, Muscle and Skin/Fat: 150 µg/kg[d]	NS	Feed	551.2 mg/kg feed[b] (500 g/ton feed)	NS	41	Liver	>2	Roussel-Uclaf (1990)
										Kidney	>2	
										Muscle	>2	
										Skin/Fat	>2	
Tetracycline	US: Approved EU: Approved	US: 2,000 µg/kg EU: 100 µg/kg	HPLC-DAD	10.5 µg/kg	20.9 µg/kg	Feed	480 mg/kg feed	0	7	Muscle	>7	De Ruyck, De Ridder, Van Renterghem, and Van Wambeke (1999)
Tetracycline			Bioassay	116–185 µg/kg[d]	NS	Oral	55.1 mg/kg[g] bw	NS	14	Liver	3	Vetri-Tech, Inc (1991)
										Muscle	0.25	
										Skin/Fat	1	
										Fat	0.25	
Tetracycline			**HPLC**	**NS**	**NS**	**Oral**	**100 mg/kg bw**	**1.25**	**4**	Liver	>5	Anadón et al. (1993)
										Kidney	>5	
										Muscle	>5	

Notes. > indicates that residues were still positive at the last sampling time; NS Indicates not specified in published manuscript; 0 NS indicates that a zero day withdrawal was stated in the publication but did not specify how many hours after feed withdrawal.

[a]See Appendix S1 for list of definitions and abbreviations; [b]Published manuscript reported the dose units as g/ton; [c]Published manuscript reported the units for LOD/LOQ as ug/ml; [d]Published manuscript reported the units for LOD as ppm; [e]Published manuscript reported the units for LOD as ng/ml; [f]Published manuscript reported dose as 800 mg/gallon; [g]Published manuscript reported dose as 25 mg/lb.

TABLE 6 Anthelmintic residues in meat following treatment in broilers

Anthelmintics	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Ivermectin	US: Not approved EU: Not Approved		HPLC	0.5 µg/kg	NS	Feed	0.073 mg/kg feed	2	5	Liver	0.5	Keukens, Kan, Van Rhijn, and Van Dijk (2000)
										Muscle	0.5	
							0.52 mg/kg feed	2	5	Liver	0.5	
										Muscle	0.5	
							0.98 mg/kg feed	2	5	Liver	0.5	
										Muscle	0.5	
Ivermectin			HPLC/F	2 µg/kg[b]	NS	Feed	2 mg/kg feed	0	35	Liver	0.5	Miller (1990)
Levamisole	US: Not approved EU: Not Approved		HPLC-UV	NS	NS	Oral	40 mg/kg bw	8	1	Liver	21	El-Kholy and Kemppainen (2005)
										Muscle	21	
										Skin/ Fat	18	
										Fat	21	
Fenbendazole	US: Approved EU: Approved	US: 5,200 µg/kg EU: 500 µg/kg	LC-MS/MS	NS	NS	Oral	5 mg/kg bw	1.5	6	Liver	0.25	Intervet (2015)
Fenbendazole			HPLC/F	NS	25 µg/kg	Water	1 mg/L bw drinking water		5	Liver	>5	Committee for Medicinal Products for Veterinary Use (2013)
										Kidney	>5	
										Muscle	5	
										Skin/ Fat	>5	
Flubendazole	US: Not Approved EU: Approved	EU: 500 µg/kg	HPLC	NS	NS	Feed	60 mg/kg feed	0	7	Liver	7	Committee for Veterinary Medicinal Products (1997)
										Kidney	7	
										Muscle	7	

(Continues)

TABLE 6 (Continued)

Anthelmintics	Approval Status (broilers)	Tolerance/ Maximum Residue Limit[a] (muscle)	Analytical Method	Limit of Detection	Limit of Quantification	Route	Dose	Chicken Age (months)	Treatment Duration (days)	Matrix	Study day from last treatment until residues no longer detected	Source
Flubendazole			Radioassay	10 µg/kg	NS	Feed	30 mg/kg feed	8	7	Liver	>20	Flubendazole (1993)
										Kidney	13	
										Muscle	7	
										Fat	7	
			HPLC	10 µg/kg		Feed	60 mg/kg feed	0	7	Muscle	6	
										Kidney	6	
										Liver	6	

Notes. > indicates that residues were still positive at the last sampling time; NS Indicates not specified in published manuscript.

[a]See Appendix S1 for list of definitions and abbreviations; [b]Published manuscript reported the units for LOD as ppb.

bacterial infections with a 5 day meat withdrawal (United States Food and Drug Administration, 2016).

Many studies have found high drug residues in broiler skin and turkey skin and this is an important public health concern because broiler skin is considered an edible tissue and comprises >10% carcass weight (Righter, Lakata, & Mercer, 1973; Takahashi, Hashizume, Said, & Kido, 1993; Takahashi, Said, Hashizume, & Kido, 1991). Some authors suggest a two compartment model within the skin which could explain the slow drug elimination rates from the skin (Takahashi et al., 1993). Please refer to Table 4 for further information on sulfonamide drug residue studies.

2.6 | Tetracyclines

Tetracyclines (oxytetracycline, chlortetracycline, doxycycline, tetracycline) are broad spectrum antibacterial agents that act by inhibiting the 30s bacterial ribosomal subunits and inhibiting protein synthesis. This class of antibacterials is often used in the treatment of avian infectious diseases, especially in bacterial respiratory tract diseases (Croubels et al., 1998). Tetracycline antibacterials can be administered orally, in medicated feed or water, or by injection. Doxycycline is highly lipophilic and would be expected to distribute widely in the chicken; however, one chicken study found a lower apparent volume of distribution than expected and this may be attributed to higher plasma protein binding, as well as lower gut reabsorption of drug (Anadón et al., 1994). Studies have demonstrated that oxytetracycline displays greater oral bioavailability than doxycycline and tetracycline and oral administration of this drug is acceptable as a feasible route of administration to avoid irritation and tissue damages at the injection site in chickens (Anadón et al., 1993, 1994; Atef, El-Gendi, Youssef, & Amer, 1986). Multiple studies have demonstrated that drug residues from the tetracycline class are completely eliminated upon cooking the meat. Studies have found that cooking meat contaminated with chlortetracycline residues will destroy the residues completely (Yoshida, Yonezawa et al., 1971). One study found that simmering the muscle tissue for one hour destroyed all traces of oxytetracycline activity in the tissue (Katz, Fassbender, & Dowling, 1973).

Some differences in oxytetracycline drug compartments have been found between chicks and adults. Findings suggest that a part of dietary oxytetracycline is deposited in some storage site in the chick's body and authors suggest the most possible storage site may be bone (Yoshida et al., 1975). In contrast, studies in laying hens found that there were no reservoirs of antibacterial activity or release from bone tissue that could be measured by analytical methods used (Katz et al., 1973). Potential drug reservoirs could lead to a difference in withdrawal times between chicks and adults.

Pharmacokinetic differences have been noted between healthy and diseased birds. Aflatoxin B1 experimentally intoxicated birds administered doxycycline via intramuscular and oral routes, had smaller systemic bioavailability percentages compared to nonintoxicated birds (Atef, Youssef, El-Eanna, & El-Maaz, 2002). Results show that distribution values are higher and clearance rates are faster in aflatoxin B1 experimentally intoxicated birds compared with healthy chickens. The authors suggest that the drug could penetrate diseased tissues more efficiently and hypoproteinemia

could lead to decreased protein binding in broilers (Atef et al., 2002). In turkeys infected with Pasteurella multocida, the addition of citric acid significantly increased the fraction of drug absorbed and the rate of absorption (Pollet, Glatz, & Dyer, 1985). It is hypothesized that the ions in tap water may have the ability to inhibit absorption of tetracyclines (Pollet, Glatz, Dyer, & Barnes, 1983; Pollet et al., 1985). Organic acids, such as citric acid, have the ability to bind to divalent cations and prevents the cations from interfering with tetracycline absorption (Pollet et al., 1985). Citric acid has the ability to chelate multivalent cations such as $Ca2+$ and $Mg2+$ and inhibit the formation of insoluble complexes (Boling, Webel, Mavromichalis, Parsons, & Baker, 2000; Maenz, Engele-Schaan, Newkirk, & Classen, 1999; Woyengo, Slominski, & Jones, 2010). By binding the divalent cations the absorption of tetracycline is improved with citric acid and prevents chelation of the drug (Pollet et al., 1983, 1985). The diseased state of turkeys also appeared to increase plasma concentration of chlortetracycline by increasing intestinal permeability and lowering the hepatic and or renal clearance (Pollet et al., 1985).

Potentiation of tetracycline in poultry feeds is commonly achieved by reducing calcium concentration in the feed to prevent chelation of tetracycline and improve drug absorption (Price, Zolli, Atkinson, Collins, & Luther, 1959; Sebree & Roberts, 1957; Waldroup et al., 1981). Tetracycline's are often used in poultry starter diets, therefore reducing the concentration of calcium in diets should only be used for short periods since calcium is essential for growth (Waldroup et al., 1981). Please refer to Table 5 for further information on tetracycline drug residue studies.

2.7 | Anthelmintics

Anthelmintics are a class of agents that exert their effects by either stunning or killing helminthes. Examples of some anthelmintics classes include benzimidazoles, macrocyclic lactones, and imidazothiazoles.

Benzimidazoles (mebendazole, fenbendazole) exert their effects by inhibiting tubulin polymerization and progressively depleting energy reserves and inhibiting excretion of waste products and protective factors from parasite cells (Vercruysse, 2018). In the United States, fenbendazole is the only benzimidazole specifically approved by the FDA for the treatment of helminthiasis (Ascaridia dissimilis and Heterakis gallinarum) in turkeys. Mebendazole appears to be slowly absorbed and peak plasma concentrations are not measurable until 24–48 hr after drug administration (Benard, Burgat-Sacaze, Massat, & Rico, 1986). Studies have found that as long as 15 days after dosing of mebendazole, residues were still measureable in the liver and kidneys (Benard et al., 1986). In contrast, fenbendazole appears to be eliminated more rapidly from the body. A depletion study performed in chickens found that fenbendazole residues were undetectable in plasma 36 hr after cessation of drug administration (Taylor et al., 1993). Metabolites of fenbendazole could be present as residues in meat with sulfoxide and sulfone present 48 and 96 hr after cessation of drug administration (Taylor et al., 1993). One depletion study found that there is a difference in fenbendazole metabolism between chickens and turkeys. The study found that chickens had a higher rate of metabolite production and elimination than turkeys (Short et al., 1988). Please refer to Table 6 for further information on drug residue studies.

3 | CONCLUSION

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 poultry meat, they are scattered throughout the primary literature. In this review, these data are compiled for easy reference and to help facilitate a comprehensive overview of what scientific data, with respect to drug residues in poultry meat, are available for antibacterials and anthelmintics used in the US poultry industry. When evaluating these published studies, it is important to consider the differing analytical methods used and how those methods impact the sensitivity of drug residue detection. 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. It is also important to note that US products approved for use in poultry 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.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Ronette Gehring http://orcid.org/0000-0002-1329-201X
Lisa A. Tell http://orcid.org/0000-0003-1823-7420
Maurice Pitesky http://orcid.org/0000-0003-0084-6404
Maaike O. Clapham http://orcid.org/0000-0003-3272-8955

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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