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Pharmacokinetics of veterinary drugs in laying hens and residues in eggs: a review of the literature

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Poultry treated with pharmaceutical products can produce eggs contaminated with drug residues. Such residues could pose a risk to consumer health. The following is a review of the information available in the literature regarding drug pharmacokinetics in laying hens, and the deposition of drugs into eggs of poultry species, primarily chickens. The available data suggest that, when administered to laying hens, a wide variety of drugs leave detectable residues in eggs laid days to weeks after the cessation of treatment.

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INTRODUCTION

In poultry, antibiotics and antiparasitics are used extensively for disease prevention and treatment. In the United States, antibiotics are also used for growth promotion, although this type of use has been prohibited in the European Union since 2006 (Donoghue, 2003; Castanon, 2007; Companyo *et al.*, 2009). Edible tissues containing veterinary drug residues can pose risks to human health, including direct toxic effects, allergic reactions and increased bacterial resistance to common antibiotics (Botsoglou & Fletouris, 2001; Donoghue, 2003; Companyo *et al.*, 2009).

Drug residues in chicken eggs are of concern because relatively few drugs are labelled for laying hens, although several medications are approved for other production classes of poultry (Hofacre, 2006; Castanon, 2007). Drug residues in eggs may arise when laying hens are mistakenly given medicated feed, when feed is contaminated at the mill during mixing, or when drugs are given off-label (Kennedy *et al.*, 2000; Donoghue, 2003). While a chicken lays an egg roughly every 24 h, each egg takes several days to develop *in vivo*, and some egg components are in existence months before the fully developed and shelled egg containing them is laid (Etches, 1996; Whittow, 2000). Because of the protracted nature of egg development, many weeks may be required following treatment or exposure before eggs are free of drug residues.

It should be noted that some drugs included in this review are prohibited from use in some or all food animals in the US and/or the EU. In the US, extra-label use of fluoroquinolones is prohibited in food animals, and any use of these drugs in a manner not explicitly approved is illegal. If an animal is mistakenly or intentionally treated with a drug that is prohibited from extra-label drug use, then the exposed animal(s) should not enter the food chain unless permission is granted from the proper authorities. In both the US and EU, other drugs, including chloramphenicol, the nitroimidazoles, and nitrofurans, are completely prohibited from use in food animals (Davis *et al.*, 2009; EMEA, 2009). A summary of drugs approved in the US for game bird species has been published (Needham *et al.*, 2007), and a recent update on drugs prohibited from extra-label drug use in the US is available (Davis *et al.*, 2009). EU approval statuses and maximum residue limits for veterinary drugs used in food-producing animals are described in the European Commission Regulation 37/2010 (European Commission, 2009).

Of the three main egg components (yolk, albumen, and shell), the yolk has the longest development time. Precursors to yolk lipoproteins are produced in the liver and transported through circulation to the yolk follicles in the ovary. In an actively laying hen, several follicles at varying developmental stages reside simultaneously in the ovary. Before an egg is laid, the yolk undergoes a stage of rapid growth, in which it increases in size exponentially over 10 days (Etches, 1996). Drugs that deposit in the yolk will rapidly accumulate during this time and can be present in successive eggs for 10 or more days following treatment. Following yolk maturation, the albumen or 'egg white' is laid down over a period of 2–3 h (Whittow, 2000) and can also serve as a residue accumulation site. The egg shell is added after albumen proteins are deposited and diluted with water (Etches, 1996). The egg development process is similar across species of poultry and game birds, although the rates of development vary (Whittow, 2000). A detailed diagram of a chicken egg is shown in Fig. 1.

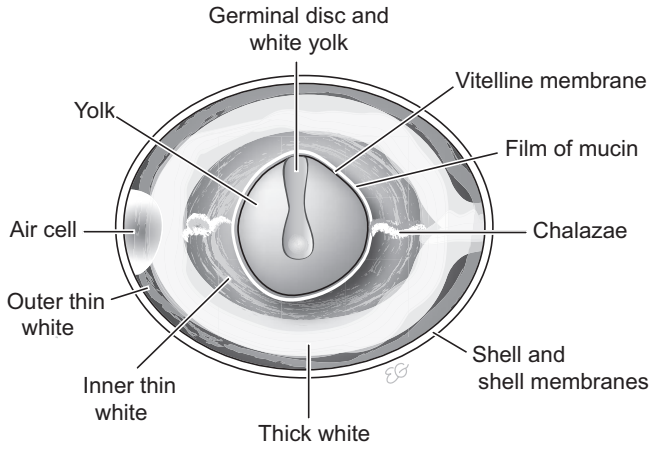

Fig. 1. Detailed illustration of the components of a developing avian egg.

Many drugs deposit preferentially in the yolk or albumen, depending on the drug's physicochemical properties. Some characteristics that effect the distribution of residues are the drug's tendency to bind to plasma proteins, hydrophobicity or hydrophilicity, and the ability to move through different tissue types (Martinez, 1998). However, a drug's kinetic properties cannot always be predicted from its chemical properties (Donoghue, 2005). This review presents a compilation of studies found scattered throughout the literature that address the kinetics of veterinary drugs in laying hens.

OVERVIEW OF THE DRUG CLASSES

Antimicrobials

Aminocyclitols. Aminocyclitols (e.g. spectinomycin and apramycin) are antimicrobial compounds produced by *Streptomyces* and *Micromonospora* spp. (Botsoglou & Fletouris, 2001). Aminocyclitols are effective against gram-negative and some gram-positive bacteria, but not anaerobic bacteria, because their mechanism of action relies on bacteria's oxygen transport system (Dowling, 2006). In poultry, administration is most commonly oral, via the feed or water. A limited number of studies in chickens demonstrate that following oral administration there is little or no absorption of the drugs from the gastrointestinal (GI) tract, and therefore when given orally, aminocyclitols are likely to be effective primarily against GI infections (Bennett *et al.*, 2001). The main excretory pathway following oral administration in mammals is the faeces (Brown & Riviere, 1991). Probably because of poor GI absorption, spectinomycin residues are not found in eggs following oral administration (Table 1). In contrast, orally administered apramycin is found in the egg albumen for several days following treatment (Romvary *et al.*, 1991) (Table 1). This difference between the two aminocyclitols could be attributable to differences in serum protein binding affinity: *in vitro*, chicken serum protein binding of apramycin is 26% (Afifi & Ramadan, 1997), compared with 5–6% for spectinomycin (El-Sayed *et al.*, 1995). In mammals, absorbed apramycin can concentrate in the kidney and persist unchanged for prolonged periods (Botsoglou & Fletouris, 2001).

Aminoglycosides. The aminoglycosides (e.g. streptomycin, neomycin, gentamicin) are antimicrobial compounds produced by *Streptomyces* and *Micromonospora* spp. (Botsoglou & Fletouris, 2001). Like aminocyclitols, aminoglyosides are effective against gram-negative and some gram-positive bacteria, but not anaerobic bacteria (Dowling, 2006), and are not absorbed well from the GI tract (Bennett *et al.*, 2001). The main excretory pathway following oral administration in mammals is the faeces (Brown & Riviere, 1991). Based on the physical properties of aminoglycosides (cationic, with a high degree of polarity), birds most likely also eliminate orally administered aminoglycosides in the faeces, although data specific to birds are lacking. Probably because of the poor GI absorption of aminoglycosides, it is rare to find aminoglycoside residues in eggs following oral administration (Table 1).

When aminoglycosides are given systemically, the main route of elimination in mammals is via the kidneys (Botsoglou & Fletouris, 2001). In mammals and birds, systemic administration of aminoglycosides is complicated by their nephrotoxicity (Botsoglou & Fletouris, 2001). There are no avian-specific data on the pharmacokinetics of systemic aminoglycosides, but as birds and mammals both exhibit aminoglycoside-induced nephrotoxicity, it is likely that elimination occurs via the renal pathway in birds as it does in mammals (Frazier *et al.*, 1995). Systemically administered aminoglycosides are much more bioavailable than when given orally (Abu-Basha *et al.*, 2007a); therefore, residues are more likely to be found in eggs. When administered to laying hens via IM or SC routes, both gentamicin and dihydrostreptomycin were deposited in egg yolk and albumen, with residues persisting for longer periods in the yolk (Roudaut, 1989b; Filazi *et al.*, 2005) (Table 1).

Amphenicols. The amphenicols (e.g. chloramphenicol, thiamphenicol, florfenicol) are broad-spectrum antimicrobials, effective against *Rickettisia* and *Chlamydophila* spp., anaerobic and gram-positive aerobic bacteria, and enteric bacteria (Bishop, 2001). The original source of chloramphenicol was the bacterium *Streptomyces venezualae*. Chloramphenicol is now produced synthetically, and thiamphenicol is a synthetic derivative (Papich & Riviere, 2001). As a result of its potential to cause bone marrow suppression in humans, most countries have restricted or banned the use of chloramphenicol in food animals (Dowling, 2006).

In poultry, amphenicols are given orally in feed or water (Botsoglou & Fletouris, 2001). Following oral administration to chickens, absorption is rapid but incomplete (Anadon *et al.*, 1994a), and the drug is rapidly and thoroughly distributed throughout the body (Anadon *et al.*, 1994a, 2008b). Excretion pathways vary by drug. In most mammalian species studied, chloramphenicol is processed by the liver and excreted in urine and bile (Bennett *et al.*, 2001). The pathways of chloramphenicol elimination have not been described for avian species. However, in chickens, thiamphenicol is eliminated via both the biliary and renal systems (Francis, 1997), and florfenicol is

Table 1. Persistence of residues of aminoglycoside medications in chicken eggs following treatment of laying hens

Aminoglycosides & aminocyclitols	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Dihydrostreptomycin	EU: not approved	None	Bioassay	Y: 3; A: 0.3 mg/kg	NS*	Water	1 g/L (100 mg/kg bw*)	13–18	5	WE: 0	Roudaut (1989b)
	USA: not approved					IM*	100 mg/kg bw	13–18	1	Y: 9; A: 2; WE: >9	
Spectinomycin	EU: not approved	USA: 0 mg/kg	Bioassay	12 mg/kg	NS	Water	0.5 g/L (50 mg/kg bw)	13–18	5	WE: 0	Roudaut (1989b)
	USA: approved		Bioassay	2 mg/kg	NS	Feed	110 mg/kg feed†	NS	7	WE: 0	Cuerpo and Livingston (1994)
							165 mg/kg feed†	NS	7	WE: 0	
							220 mg/kg feed†	NS	7	WE: 0	
Gentamicin	EU: not approved	None	HPLC*	0.01 mg/kg	NS	SC*	10 mg/kg bw‡	7.5	1	Y: 7; A: 3; WE: 7	Filazi *et al.* (2005)
	USA: not approved						25 mg/kg bw‡	7.5	1	Y: 10; A: 4; WE: 10	
							50 mg/kg bw‡	7.5	1	Y: 12; A: 5; WE: 12	
						IM	10 mg/kg bw‡	7.5	1	Y: 7; A: 3; WE: 7	
							25 mg/kg bw‡	7.5	1	Y: 10; A: 4; WE: 10	
Neomycin	EU: approved USA: not approved	EU: 500 μg/kg	Bioassay	Y: 9.6 mg/kg; A: 0.15 mg/kg; WE: 1.2 mg/kg	NS	Water	0.25 g/L (25 mg/kg bw)	13–18	5	WE: 0	Roudaut (1989b)
Apramycin	EU: not approved USA: not approved	None	Bioassay	NS	Y: 0.138; A: 0.049 mg/kg	Water	20 mg/kg bw§	NS	5	Y: 0; A: >10	Romvary *et al.* (1991)
Kanamycin	EU: not approved USA: not approved	None	Bioassay	0.5 mg/kg	NS	Feed	20 mg/kg feed¶	10	7	Y: 0; A: 0	Yoshida *et al.* (1976)
							1000 mg/kg feed¶	10	7	Y: 0; A: 0	
							4000 mg/kg feed¶	10	7	Y: >0; A: 0	
							8000 mg/kg feed¶	10	7	Y: >0; A: 0	
							16 000 mg/kg feed¶	10	7	Y: >7; A: 0	

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †spectinomycin was given with lincomycin. The doses here refer to the amount of spectinomycin only; ‡a veterinary gentamicin formulation containing 50 mg/mL was used; §apramycin in the form of apramycin sulphate was used; ¶kanamycin sulphate was added to feed. The concentrations per kg feed indicate the amount of active compound added.

partly metabolized to florfenicol amine, with significant residues of both parent drug and metabolite found in the liver and kidney (Anadon *et al.*, 2008b). Rate of elimination is affected by route of administration; chloramphenicol is eliminated more quickly following IV administration compared with oral administration (Anadon *et al.*, 1994a). The limited residue studies of amphenicols performed in laying hens demonstrate that residues are found in both yolk and albumen for several days following oral administration (Table 2). When treatment was repeated for several days, residues persisted longer than a week (Samouris *et al.*, 1993; Akhtar *et al.*, 1996b).

Beta-lactams. Beta-lactams are grouped by a shared structural feature, a beta-lactam ring containing one nitrogen and three carbon atoms (Prescott, 2006). The beta-lactam class encompasses some of the most commonly used antimicrobials, both in human and veterinary medicine, including the penicillins. The broad-spectrum penicillins are effective against many gram-negative and gram-positive bacteria, including anaerobic bacteria (Dorrestein *et al.*, 1984; Vaden & Riviere, 2001). While penicillins are considered less toxic than many other antimicrobials, the potential for allergic reactions in humans makes penicillin residues in food of particular concern (Dewdney *et al.*, 1991). In poultry, penicillins are given orally for preventative and therapeutic purposes (Prescott, 2006). The effectiveness of orally administered penicillins is reduced by their susceptibility to hydrolysis in the GI tract (Prescott, 2006). In domestic mammals, penicillins are widely distributed in extracellular fluids following absorption (Prescott, 2006), have short half-lives and are metabolized primarily by the kidneys (Vaden & Riviere, 2001). In birds, the available data suggest that the hepatic, rather than renal, excretion pathway may predominate (Dorrestein *et al.*, 1984; Frazier *et al.*, 1995).

Ampicillin, the only penicillin for which egg residue data exists, is relatively stable in gastric acid and well absorbed compared with many other penicillins (Botsoglou & Fletouris, 2001). Nonetheless, bioavailability of ampicillin is higher when injected IM than when given orally (Ziv *et al.*, 1979; Frazier *et al.*, 1995). The greater persistence of ampicillin residues in eggs when administered IM compared with the oral route (Roudaut *et al.*, 1987b) (Table 3) could be tied to this difference in bioavailability.

Cephalosporins, like penicillins, are a sub-group of beta-lactams derived from fungi (*Cephalosporium acremonium*) (Vaden & Riviere, 2001). First-generation cephalosporins such as cephalexin are primarily effective against *Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* spp. Following oral administration of cephalexin to chickens, the drug is widely distributed and found in high concentrations in the bile, suggesting hepatic metabolism (Kitagawa *et al.*, 1988). Cephalexin appears to preferentially deposit in egg yolk, and residues can be long lasting (Kitagawa *et al.*, 1988).

Macrolides. The macrolide antibiotics (e.g. erythromycin, tylosin, spiramycin) are a structurally similar group of primarily bacteriostatic compounds. Most drugs in this class were isolated from soil bacteria of the genus *Streptomyces* (Papich & Riviere, 2001). Macrolides are effective against *Mycoplasma* spp. and gram-positive organisms such as *Streptococcus* spp. and *Staphylococcus* spp., but are only slightly effective against gram-negative bacteria (Botsoglou & Fletouris, 2001). In laying hens, the most common route of administration is oral, although one instance of IM dosing is included in Table 4 (Roudaut & Moretain, 1990), and bioavailability appears to be high (Goudah *et al.*, 2004; Abu-Basha *et al.*, 2007b). In birds as in mammals, available data suggest that macrolides are widely distributed and penetrate well into tissues and cells following absorption (Anadon & Reeve-Johnson, 1999; Botsoglou & Fletouris, 2001; Keles *et al.*, 2001; Goudah *et al.*, 2004; Fricke *et al.*, 2008). In mammals, macrolides are metabolized by the liver and excreted in bile. Some of the metabolized drug is re-absorbed in the GI tract, but most is excreted in faeces, and secondarily in urine (Giguere, 2006). In birds, tylosin is excreted primarily in faeces, but a large portion is also excreted in urine (van Leeuwen, 1991; Lewicki *et al.*, 2008). Persistent macrolide residues can be deposited in eggs following oral (via feed or water) or parenteral administration to laying hens. Most macrolides are found in egg yolk for several days after residues become undetectable in the albumen (Table 4), as might be expected owing to macrolides' lipophilicity (Anadon & Reeve-Johnson, 1999) and the longer developmental timeline of yolk compared with albumen. Although spiramycin appears to be an exception, persisting in egg albumen longer than in egg yolk, this pattern is likely attributable to the higher sensitivity of the assay used to detect the drug in albumen (Roudaut & Moretain, 1990).

Nitrofurans. Nitrofurans are synthetic bacteriostatic agents that are identified by their common 5-nitrofuran ring (Botsoglou & Fletouris, 2001; Papich & Riviere, 2001). In most countries, nitrofurans are banned from use in food animals for their carcinogenic and genotoxic properties (Botsoglou & Fletouris, 2001; Dowling, 2006). Before they were banned, nitrofurans were commonly used as feed additives and to treat and prevent bacterial infections in food animals (Botsoglou & Fletouris, 2001; Vass *et al.*, 2008). Nitrofurans are most effective against gram-negative bacteria, but they also exhibit activity against gram-positive bacteria and some protozoa (Papich & Riviere, 2001; Vass *et al.*, 2008). In both birds and mammals, nitrofurans are rapidly metabolized following oral administration and the majority of a dose is quickly eliminated in the urine, but metabolites bind easily to tissues and can persist at low concentrations for weeks following treatment (Craine & Ray, 1972; Bishop, 2001; Botsoglou & Fletouris, 2001; Papich & Riviere, 2001; Vass *et al.*, 2008). The rapid metabolism of nitrofurans has made screening for parent drugs difficult in food products, but the development of assays that can detect nitrofuran metabolites have been used to demonstrate the persistence of residues in egg yolk and albumen (McCracken *et al.*, 2001; Stachel *et al.*, 2006) (Table 5).

Polymyxins. Polymyxins are polypeptide antibiotics that are effective against gram-negative bacteria. Polymyxins are most commonly used topically, as systemic use is associated with

Table 2. Amphenicol residues in chicken eggs following treatment of laying hens

Amphenicols	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Chloramphenicol	EU: prohibited USA: prohibited	None	Colorimetric	0.1 mg/kg	NS*	Water	40 mg/L†	NS	5	Y: >5; A: 4	Sisodia and Dunlop (1972)
			RIA*	1 μg/kg	5 μg/kg		500 mg/L	3	8	WE: >17	Scherk and Agthe (1986)
							1000 mg/L	3	6	WE: >19	
			RIA	0.3 μg/kg	0.5 μg/kg		60 mg/kg bw*	10	10	WE: >72	Schwarzer and Dorn (1987)
			HPLC*	10 μg/kg	NS	Feed	800 mg/kg feed	NS	1	Y: 4; A: 9	Samouris *et al.* (1993)
			HPLC	NS	0.02 mg/kg		400 mg/kg feed‡	7.5	14	WE: 8	Petz (1984)
			HPLC	10 μg/kg	NS		200 mg/kg feed	NS	5	Y: 6; A: 2	Samouris *et al.* (1998)
							500 mg/kg feed	NS	5	Y: 8; A: 3	
							800 mg/kg feed	NS	5	Y: 9; A: 3	
							1000 mg/kg feed	NS	5	Y: 9; A: 4	
			RIA	0.3 μg/kg	0.5 μg/kg		35 mg/kg bw§	3.25	7	WE: 0	Schwarzer and Dorn (1987)
							35 mg/kg bw§	3.75	7	WE: 0	
							35 mg/kg bw§	4.25	7	WE: 0	
							35 mg/kg bw§	4.75	7	WE: 23	
							35 mg/kg bw§	5.25	7	WE: 23	
							35 mg/kg bw§	10	7	WE: 73	
			LSC*	NS	NS	Gavage	0.5 mg¶	NS	5	Y: >7; A: 3	Akhtar *et al.* (1996b)
							5.0 mg¶	NS	5	Y: >7; A: 3	
Thiamphenicol	EU: not approved USA: not approved	None	HPLC	NS	10 μg/kg	Oral (capsule)	40 mg/kg bw**	6	1	Y: 10; A: 2	Giorgi *et al.* (2000)
							40 mg/kg bw**	6	5	Y: 8; A: 1	

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †chloramphenicol given in a commercial formulation, Kamycetin® from K-vet Laboratories, Hespeler, ON, Canada; ‡chloramphenicol was given with an equal concentration (0.04%) furazolidone; §groups of young birds were dosed at the ages of 13, 15, 17, 19, 21 and 40 weeks, respectively; ¶^{14}C-radiolabelled chloramphenicol was used; **thiamphenicol given as thiamphenicol base in the glycinate form.

Table 3. Beta-lactam residues in chicken eggs following treatment of laying hens

Beta-lactams	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Time until residues no longer detected (days from last treatment)	Source
Ampicillin	EU: not approved USA: not approved	None	Bioassay	Y: 0.005, A: 0.008 mg/kg	NS*	Water	100 mg/L†	11	5	WE: 0	Roudaut *et al.* (1987b)
							200 mg/L†	11.5	5	Y: 2; A: 0	
							1500 mg/L†	18	5	Y: 3; A: 0; WE: 3	
						IM*	20 mg/kg† bw*	12	1‡	Y: 5; A: 2	
			Bioassay	Y: 2.1 μg/kg	NS		40 mg/kg bw	12.5	1	Y: 7	Donoghue *et al.* (1997)
							40 mg/kg bw	12.5	2	Y: 8	
							40 mg/kg bw	12.5	3	Y: 9	
Cephalexin	EU: not approved USA: not approved	None	ELISA*	60 μg/kg	NS	Feed	20 mg/hen	NS	7	Y: >21; A: 0§	Kitagawa *et al.* (1988)

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †ampicillin given as ampicillin sodium; ‡two injections of 10 mg/kg were given 6 h apart; §$n = 1$.

nephrotoxicity and respiratory paralysis (Riviere & Spoo, 2001). Colistin (polymyxin E), the only polymyxin for which egg residue data are available, is not well absorbed from the GI tract (Botsoglou & Fletouris, 2001), and residues were not detectable in eggs of hens given colistin in drinking water (Roudaut, 1989a) (Table 6). However, bioavailability is much higher when colistin is given IM or SC (Botsoglou & Fletouris, 2001). When laying hens were given colistin through IM injection, residues were still detectable in eggs after 7 days (the duration of the study) (Roudaut, 1989a). Excretion of metabolized drug is primarily renal in mammals (Botsoglou & Fletouris, 2001). Excretion pathways have not been described in avian species, but following SC injection of colistin (with amoxicillin) in turkeys, residues persisted much longer in kidneys than in other tissues (Tomasi *et al.*, 1996).

Quinolones and fluoroquinolones. Quinolones (e.g. oxolinic acid) and their synthetic flouride-containing derivatives, fluoroquinolones (e.g. enrofloxacin, sarafloxacin), share a common core structure and activity against gram-negative microbes; fluoroquinolones are additionally effective against some gram-positive organisms (Bishop, 2001; Botsoglou & Fletouris, 2001; Martinez *et al.*, 2006). Flouroquinolones are prohibited from extra-label use in food-producing animals in the US.

Oxolinic acid, the only quinolone for which data are available for laying hens, has high oral bioavailability and is quickly absorbed in the GI tract and widely distributed to tissues (EMEA, 1998a; Hamamoto *et al.*, 2001). Excretion is via both urine and faeces in chickens and mammals (EMEA, 1998a). Residues persist in both tissues and eggs for several days (EMEA, 1998a; Roudaut, 1998).

Orally administered fluoroquinolones are quickly absorbed, with bioavailability generally around 50–60% (Ding *et al.*, 2001; Anadon *et al.*, 1992, 2002; Varia *et al.*, 2009). Metabolism and distribution to tissues is extensive (Anadon *et al.*, 1992, 2001, 2002), and elimination half-lives are generally between 3 and 8 h, with some variation (Ding *et al.*, 2001; Anadon *et al.*, 2002; Kalaiselvi *et al.*, 2006; Silva *et al.*, 2006; Varia *et al.*, 2009). Elimination pathways of fluoroquinolones have not been explicitly studied in avian species, but following oral administration to chickens, residues of parent fluoroquinolones and metabolites are found in both liver and kidney (Anadon *et al.*, 2001, 2002, 2008a). In mammals, route of elimination varies with drug. Of the compounds listed in Table 7, enrofloxacin is eliminated via the renal system, perfloxacin through the hepatic system, and danofloxacin, norfloxacin, and ciprofloxacin are excreted through both renal and hepatic pathways (Martinez *et al.*, 2006). When given orally or by IM injection to laying hens, fluoroquinolone residues appear in eggs around 24 h after the first dose and persist in both yolk and albumen for several days after cessation of treatment (Maxwell *et al.*, 1999; Lolo *et al.*, 2005; Herranz *et al.*, 2007).

Sulfonamides. Sulfonamides as a group are synthetic compounds derived from sulfanilamide that share a common mode of action, but vary widely in their chemical characteristics, usual route of

Table 4. Macrolide residues in eggs following treatment of laying hens

Macrolides	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Tylosin	EU: approved USA: approved	200 μg/kg (EU & USA)	LC/MS*	0.5 μg/kg	1 μg/kg	Water	500 mg/L†	5	5	WE: 8	Hamscher *et al.* (2006)
			Bioassay	Y: 0.2, A: 0.15 mg/kg	NS*		500 mg/L†	7–16	5	Y: 0; A: 0	Roudaut and Moretain (1990)
			Bioassay	Y: 0.5, A: 0.45 mg/kg	NS		500 mg/L	NS	7	Y: 6; A: 3	Yoshimura *et al.* (1978)
			LSC*	0.02 mg/kg	NS		529 mg/L†	NS	3	WE: 6	Marth *et al.* (2001)
			Bioassay	Y: 0.2, A: 0.15 mg/kg	NS		1000 mg/L†	7–16	5	Y: 6; A: 1	Roudaut and Moretain (1990)
			Bioassay	NS	NS		530 mg/L	7.5	7	WE: 0	McReynolds *et al.* (2000)
							530 mg/L	7.5	10	WE: 0	
			Bioassay	0.15 mg/kg	NS		500 mg/L†	5	1	WE: 3	Iritani *et al.* (1976)
							500 mg/L†	5	3	WE: 4	
							500 mg/L†	5	5	WE: 5	
			Bioassay	0.4 mg/kg	NS	Feed	20 mg/kg feed‡	10	7	WE: 0	Yoshida et al. (1973a)
			Bioassay	Y: 0.2, A: 0.15 mg/kg	NS		400 mg/kg feed‡	7–16	7	Y: 0; A: 0	Roudaut and Moretain (1990)
			Bioassay	0.4 mg/kg	NS		500 mg/kg feed‡	10	7	WE: 0	Yoshida et al. (1973a)
			LC/MS	0.5 μg/kg	1 μg/kg		1500 mg/kg feed§	5	5	WE: 8	Hamscher *et al.* (2006)
			Bioassay	0.4 mg/kg	NS		8000 mg/kg feed‡	10	7	Y: 6; A: 2	Yoshida *et al.* (1973a)
Spiramycin	EU: not approved USA: not approved	None	Bioassay	Y: 0.33, A: 0.1 mg/kg	NS	Water	400 mg/L¶	7–16	5	Y: 9; A: 10	Roudaut and Moretain (1990)
			Bioassay	Y: 0.5, A: 0.4 mg/kg	NS		500 mg/L	NS	7	Y: 20; A: 14	Yoshimura *et al.* (1978)

Table 4. (Continued)

Macrolides	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
			Bioassay	0.45 mg/kg	NS	Feed	20 mg/kg feed	10	7	Y: 0; A: 1; WE: 1	Yoshida *et al.* (1971)
							50 mg/kg feed	10	7	WE: 2	
							100 mg/kg feed	10	7	WE: 2	
							200 mg/kg feed	10	7	WE: 1	
			Bioassay	Y: 0.33, A: 0.1 mg/kg	NS		400 mg/kg feed**	7–16	7	Y: 7; A: 15	Roudaut and Moretain (1990)
			Bioassay	0.45 mg/kg	NS		500 mg/kg feed	9–10	7	WE: 5	Yoshida *et al.* (1971)
							1000 mg/kg feed	9–10	7	Y: >7; A: >7; WE: $7 < x < 12$	
			Bioassay	Y: 0.33, A: 0.1 mg/kg	NS	IM*	50 000 mg/kg†† bw*	7–16	1	Y: 8; A: 10	Roudaut and Moretain (1990)
Erythromycin	EU: approved USA: approved	EU: 150 μg/kg; USA: 25 μg/kg	Bioassay	Y: 0.04; A: 0.01 mg/kg	NS	Water	220 mg/L	7–16	5	Y: 6; A: 2	Roudaut and Moretain (1990)
							500 mg/L	7–16	5	Y: 7; A: 3	
			Bioassay	Y: 0.1; A: 0.05 mg/kg	NS		500 mg/L	NS	7	Y: 10; A: 6	Yoshimura *et al.* (1978)
			LC/MS	0.2 μg/kg	0.5 μg/kg		1500 mg/L 20% erythromycin	NS	5	WE: >3	Bogialli *et al.* (2009a)
			Bioassay	Y: 0.04; A: 0.01 mg/kg	NS	Feed	400 mg/kg feed	7–16	7	Y: 5; A: 2	Roudaut and Moretain (1990)
Josamycin	EU: not approved USA: not approved	None	Bioassay	A: 0.3; Y: 0.6 IU/g	NS	Water	225 mg/L	7–16	5	Y: 2; A: 0	Roudaut and Moretain (1990)
Kitasamycin	EU: not approved USA: not approved	None	Bioassay	Y: 0.75; A: 0.3 mg/kg	NS	Water	500 mg/L	NS	7	Y: 4; A: 3	Yoshimura *et al.* (1978)
Oleandomycin	EU: not approved USA: not approved	None	Bioassay	Y: 0.75; A: 0.4 mg/kg	NS	Water	500 mg/L	NS	7	Y: 13 A: 10	Yoshimura *et al.* (1978)

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †tylosin given as tylosin tartrate; ‡tylosin given as tylosin phosphate; §a commercial preparation of 25% tylosin (25 g tylosin phosphate/100 g) was mixed in the feed; ¶spiramycin given as spiramycin adipate; **spiramycin given as spiramycin embonate; ††aqueous solution of spiramycin base (50 g/kg).

Table 5. Nitrofuran residues in eggs following treatment of laying hens

Nitrofurans	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Furazolidone	EU: prohibited USA: prohibited	None	Colorimetric	NS*	NS	Water	50 mg/L (20 mg/hen)	12	5†	WE: 3	Krieg (1972)
							100 mg/L (10–20 mg/hen)	12	8	WE: 7	
			LC/MS-MS*	AOZ‡ 0.03 μg/kg	NS	Feed	7.5 mg/kg bw*	NS	5	WE: 5	Stachel *et al.* (2006)
			HPLC*	1 μg/kg	NS		100 mg/kg feed	16	28	WE: 9	Botsoglou *et al.* (1989)
							200 mg/kg feed	16	14	WE: 10	
							400 mg/kg feed	16	14	WE: 11	
			LC/MS*	AOZ§ 1.0 μg/kg	Not given		400 mg/kg feed	NS	11	WE: >21	McCracken *et al.* (2001)
			Colorimetric	NS	NS		400 mg/kg feed	12	7	WE: 6	Krieg (1972)
							400 mg/kg feed	12	14	WE: 6	
			HPLC*	5 μg/kg	Not given		30 mg/hen	NS	1	WE: >5	Beek and Aerts (1985)
				NS	0.01 mg/kg		400 mg/kg§	7.5	14	WE: 5	Petz (1984)
			Colorimetric	NS	NS	Gavage	20 mg/hen	12	8	WE: 5	Krieg (1972)
							50 mg/hen	12	8	WE: 5	
Furaltadone	EU: prohibited USA: prohibited	None	HPLC	1.0 μg/kg	NS	Water	107 mg/L	NS	6	WE: >4	Kumar *et al.* (1994)
			LC/MS-MS	AMOZ¶ 0.05 μg/kg	NS	Feed	7.5 mg/kg bw	NS	>5	WE: >5	Stachel *et al.* (2006)
			HPLC	5 μg/kg	NS		100 mg/kg feed**	9	7	Y: 6; A: 2	Petz (1993)
Nitrofurazone	EU: prohibited USA: prohibited	None	LC/MS	1.7 μg/kg	NS	Feed	300 mg/kg feed	NS	16	WE: >16	Cooper *et al.* (2008)
			HPLC	5 μg/kg	NS		100 mg/kg feed**	9	7	Y: 7; A: 9	Petz (1993)
			Colorimetric	≤ 0.03 mg/kg	NS		80 mg/kg feed	NS	6	WE: 18	Palermo and Gentile (1975)
Nitrofurantoin	EU: prohibited USA: prohibited	None	HPLC	1 μg/kg	NS	Feed	100 mg/kg feed**	9	7	Y: 0; A: 6	Petz (1993)

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †treated water was provided on days 1–3, 5 and 7; ‡AOZ: 3-amino-2-oxazolidinone, marker residue for furazolidone; §furazolidone given with an equal concentration (0.04%) chloramphenicol in the feed; ¶AMOZ: 3-amino-5-methyl-morpholino-2-oxazolidinone, marker residue for furaltadone; **diet in this study contained 100 mg/kg each of furaltadone, nitrofurazone, nitrofuantoin and sulfaquinoxaline.

Table 6. Residues of miscellaneous drugs in eggs following treatment of laying hens

Drug	Approval status (laying hens)*	Tolerance/maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Time until residues no longer detected (days from last treatment)	Source
Colistin	EU: approved; USA: not approved	300 μg/kg (EU)	Bioassay	Y: 3 IU/g (0.1 mg/kg); A: 6 IU/g (0.2 mg/kg)	NS*	Water	1 000 000 IU/L (3 mg/kg bw*)†	14–15	5	Y: 0; A: 0; WE: 0	Roudaut (1989a)
						IM*	1.67 mg/kg bw†	14–15	1	Y: 7; A: 0; WE: >7	

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †colistin sulphate used.

administration, and pharmacokinetics (Bishop, 2001). Sulfonamides' antimicrobial activity arises from their ability to inhibit parts of the microbe's folic acid pathway, which interferes with DNA synthesis (Botsoglou & Fletouris, 2001). Sulphonamides are effective against gram-positive and gram-negative bacteria, protozoa, and coccidia. In many cases, sulfonamides are combined with diaminopyrimidine potentiators such as trimethoprim, and with other coccidiostats and adjuvants to increase effectiveness (Botsoglou & Fletouris, 2001). Side effects of sulfonamides in poultry can include renal damage caused by precipitates forming in the urine, regurgitation after oral administration, and vitamin K deficiency (Frazier *et al.*, 1995; Bishop, 2001; Botsoglou & Fletouris, 2001). In general, sulfonamides are absorbed moderately well from the GI tract, depending on solubility, and absorption occurs more rapidly in birds than mammals (Botsoglou & Fletouris, 2001). Absorbed sulfonamides distribute widely to tissues, and the main excretion pathway in both mammals and birds is via the kidneys, although some excretion also occurs via faeces (Frazier *et al.*, 1995; Botsoglou & Fletouris, 2001).

In poultry, the most common route of administration is oral, in feed or water. Residues generally appear to persist longer in egg yolk that albumen (Table 8), although sulfonamides are initially deposited at higher concentrations in the albumen compared with the yolk following treatment (Romvary & Simon, 1992; Atta & El-zeini, 2001; Roudaut & Garnier, 2002; Tansakul *et al.*, 2007). The concentration of sulfonamides in albumen drops exponentially after about 1 day following treatment, but declines more slowly in yolk, likely attributable to the deposition of residues in yolks in several stages of development (Furusawa *et al.*, 1998).

Sulfonamide synergists. Poultry are often treated with sulfonamides in combination with other anti-protozoal agents to increase efficacy; these 'sulfonamide synergists' are combined with sulfonamides in Table 8. Dihydrofolate reductase/thymidylate synthase inhibitors (e.g. trimethoprim, ormetoprim, pyrimethamine) and diaveridine, a pyrimidine derivative, act synergistically with sulfonamides to treat coccidial infections. The limited data available on the kinetics of these compounds in birds suggest that following oral administration, bioavailability can range from 35–80%, and the drugs are widely distributed throughout the body (Fellig *et al.*, 1971; Cala *et al.*, 1972; Queralt & Castells, 1985; Loscher *et al.*, 1990; Baert *et al.*, 2003). Avian species rapidly eliminate trimethoprim and ormetoprim from the body (Fellig *et al.*, 1971; Romvary & Horvay, 1976), while pyrimethamine appears to persist in the blood and tissues for a prolonged period (Blom, 1975). There is little information on the excretion pathways of the dihydrofolate reductase/thymidylate synthase inhibitors in avian species. In mammals, excretion is primarily renal (Lindsay & Blagburn, 2001). Trimethoprim, ormetoprim and pyrimethamine residues have all been detected in both yolk and albumen of eggs laid more than a week after treatment has ended (Table 8).

Tetracyclines. Tetracyclines are naturally occurring products of fungi in the genus *Streptomyces*, or semi-synthetic derivatives of

Table 7. Fluoroquinolone residues in eggs following treatment of laying hens

Fluoroquinolones	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Enrofloxacin	EU: not approved USA: prohibited	None	Bioassay	NS*	NS	Water	5 mg/kg† bw* (Turkey)	8.5	5	Y: >7; A: 7; WE: >7	Delaporte *et al.* (1994)
							10 mg/kg bw (Turkey)	9	5	Y: 13; A: 11; WE: 13	
			HPLC/MS*	2 μg/kg	NS		12 mg/hen‡	NS	5	Y: 16; A: 16	Lolo *et al.* (2005)
			Bioassay	NS	NS		50 mg/L	7.5	7	Y: 4	McReynolds *et al.* (2000)
							50 mg/L	7.5	9	Y: >7	
			ASTED-LC*	0.6 μg/kg	1 μg/kg	Oral	11 mg/hen	NS	7	WE: >14§	Schneider and Donoghue (2000)
			Bioassay & LC/MS*	NS	1.5 μg/kg	Oral (bolus)	11 mg/hen¶	NS	3	WE: >8	Donoghue and Schneider (2003)
			HPLC	NS	0.019 mg/kg	Oral	5 mg/kg bw**	NS	5	Y: 7; A: 10; WE: 10	Gorla *et al.* (1997)
			Bioassay	0.096 mg/kg	NS		10 mg/kg bw	7.5	3	Y: 5; A: 3	Ahmed *et al.* (1998)
			HPLC	Y: 0.1; A: 0.2 μg/kg	Y: 0.4; A: 0.07 μg/kg		10 mg/kg bw	NS	4	A: >10; WE: >10§	Huang *et al.* (2006)
			PLE, LC-FLD*	41 μg/kg	NS		10 mg/kg bw††	NS	4	WE: >9	Herranz *et al.* (2007)
			LC/MS	0.2 μg/kg	0.4 μg/kg		50 mg/kg bw	NS	3	WE: >16§	Bogialli *et al.* (2009b)
			HPLC/MS	2 μg/kg	NS	IM*	15 mg/hen‡	NS	5	Y: 18; A: 17	Lolo *et al.* (2005)
Sarafloxacin	EU: not approved USA: prohibited	None	ASTED-LC	2 μg/kg	3 μg/kg	Oral (capsule)	5 mg/hen	9	5	WE: >5§	Schneider and Donoghue (2000)
			LSC*	NS	NS	Oral	10.5 mg/hen‡‡	NS	5	Y: 9; A: 5	Shaikh and Chu (2000)
			LSC	10 μg/kg	NS		10.5 mg/hen‡‡	NS	5	Y: 9; A: 6	Chu *et al.* (2000)
			HPLC	0.2 μg/kg	1 μg/kg	IM	25 mg/hen§§	50th week of lay	3	WE: >5§	Maxwell *et al.* (1999)

Table 7. (Continued)

Fluoroquinolones	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Ciprofloxacin	EU: not approved	None	HPLC	NS	0.156 μg/g	Oral	5 mg/kg bw	NS	5	Y: 6; A: 0; WE: 6	Gorla *et al.* (1997)
	USA: prohibited		HPLC	0.01 mg/kg	NS		10 mg/kg bw	NS	5	WE: 9[§]	Xie *et al.* (2005)
							20 mg/kg bw	NS	5	WE: 10[§]	
Danofloxacin	EU: not approved	None	HPLC	NS	5 μg/kg	Water	50 mg/L[¶¶]	7	12	Y: 12; A: 5	Yang *et al.* (2006)
	USA: prohibited										
Pefloxacin	EU: not approved	None	HPLC/MS/MS*	0.2 μg/kg	0.5 μg/kg	Feed	200 mg/kg feed	25th week of lay	5	WE: >29	Shen *et al.* (2008)
	USA: prohibited						400 mg/kg feed	25th week of lay	5	WE: >29	
							800 mg/kg feed	25th week of lay	5	WE: >29	
Flumequine	EU: not approved	None	Bioassay	0.05 mg/kg	NS	Oral	12 mg/kg bw	NS	1	Y: 6; A: 3	Samaha *et al.* (1991)
									5	Y: 5; A: 2	
	USA: prohibited		Bioassay	0.04 mg/kg	NS		12 mg/kg	7.5	3	Y: 6; A: 4	Ahmed *et al.* (1998)
			HPLC	5 mg/kg	NS	Water	200 mg/L (40 mg/hen)	NS	5	Y: 12; A: 10[§]	Riberzani *et al.* (1993)
			Bioassay	0.05 mg/kg	NS	IM	12 mg/kg bw	NS	1	Y: 6; A: 2	Samaha *et al.* (1991)
									5	Y: 5; A: 2	
Norfloxacin	EU: not approved	None	HPLC	2.5 mg/kg	NS	Water	175 mg/L***	NS	5	Y: >6; A: >6	Rolinski *et al.* (1997)
	USA: prohibited										
Oxolinic acid	EU: not approved	None	HPLC	NS	5 μg/kg	Water	0.5 g/L (12 mg/kg bw)[†††]	NS	5	Y: 7; A: 10; WE: 9	Roudaut (1998)
	USA: not approved					Feed	300 mg/kg feed (13 mg/kg bw)[†††]	NS	5	Y: 8; A: 9; WE: 9	

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; [†]treatment was a commercial 10% enrofloxacin solution; [‡]a commercial 5% enrofloxacin preparation was used; [§]$n < 5$ or not specified; [¶]treatment was with a commercial preparation of 23.3 mg/mL enrofloxacin; **hens treated with a solution of 5% active compound; [††]treatment was with a commercial preparation of 100 mg/mL enrofloxacin; [‡‡]^{14}C-labelled sarafloxacin hydrochloride was administered; [§§]a commercial preparation of 88.5% sarafloxacin hydrochloride was used; [¶¶]danofloxacin methanesulphonate was dissolved in drinking water; ***a 7% norfloxacin nicotinate powder was added to drinking water; [†††]treatment was sodium oxolinate dissolved in drinking water.

Table 8. Residues of sulfonamides and dihydrofolate reductase inhibitors in eggs following treatment of laying hens

Sulphonamides	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Sulphadimidine (sulfamethazine)	EU: not approved	None	HPLC*	NS*	0.005 mg/kg	Water	1000 mg/L[a] (81 mg/kg bw*)	NS	5	Y: 15; A: 12; WE: 13	Roudaut and Garnier (2002)
	USA: not approved						2000 mg/L[a] (120 mg/kg bw)	NS	5	Y: 14; A: 20; WE: 18	
			HPLC	0.09 mg/kg	0.3 mg/kg		2000 mg/L	10	6	WE: 10	Ivona *et al.* (2004)
			Colorimetric	Y: 2, A: 1 mg/kg	NS		1000 mg/L	NS	8	Y: 9; A: 7	Blom (1975)
			Colorimetric	NS	NS		1000 mg/L	24	5[b]	WE: 5	Krieg (1966)
							1000 mg/L	24	8	Y: 8; A: 7; WE: 8	
			HPLC	0.02 mg/kg	NS	Oral (bolus)	100 mg/kg bw	NS	5	WE: >7[c]	Nouws *et al.* (1988)
			HPLC	0.02 mg/kg	0.05 mg/kg		1 mg/kg bw	5.5–6.5	1	Y: 0; A: 1	Tansakul *et al.* (2007)
							3 mg/kg bw	5.5–6.5	1	Y: 2; A: 1	
							10 mg/kg bw	5.5–6.5	1	Y: 5; A: 1	
							30 mg/kg bw	5.5–6.5	1	Y: 8; A: 3	
							100 mg/kg bw	5.5–6.5	1	Y: 9; A: 7	
			HPLC	0.05 mg/kg	NS	Oral (capsule)	100 mg/kg bw	12	1	WE: >8	Geertsma *et al.* (1987)
							100 mg/kg bw	12	5	WE: >8[c]	
Sulphadimethoxine	EU: not approved	None	Colorimetric	0.05 mg/kg	NS	Water	400 mg/L[d]	6	4	Y: 10; A: 7[c]	Yamamoto *et al.* (1979)
	USA: not approved		HPLC	NS	0.005 mg/kg		500 mg/L[e] (46 mg/kg bw)	NS	5	Y: 14; A: 15; WE: 15	Roudaut and Garnier (2002)
			Bioassay	NS	NS		500 mg/L	7.5	9	WE: 0	McReynolds *et al.* (2000)
			HPLC	0.01 mg/kg	NS	Feed	10 mg/kg feed	7.5	14	Y: 6; A: 1	Nagata *et al.* (1992b)
			HPLC	0.01 mg/kg	NS		25 mg/kg feed form?	7	21	Y: 6; A: 2[c]	Nagata *et al.* (1989)
			HPLC	0.01 mg/kg	NS			7	21	Y: 6; A: 2[c]	Nagata *et al.* (1992a)
			HPLC	0.01 mg/kg	NS		50 mg/kg feed		21	Y: 6; A: 2[c]	Nagata *et al.* (1989)
			HPLC	0.01 mg/kg	NS			7	21	Y: 6; A: 2[c]	Nagata *et al.* (1992a)
			HPLC	0.01 mg/kg	NS		100 mg/kg feed	7	21	Y: 7; A: 4[c]	Nagata *et al.* (1989)
			HPLC	0.01 mg/kg	NS			7	21	Y: 7; A: 4[c]	Nagata *et al.* (1992a)
			HPLC	0.01 mg/kg	NS		400 mg/kg feed	6	5	Y: 9; A: 7; WE: 8	Furusawa *et al.* (1994)

Table 8. (Continued)

Sulphonamides	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
			Colorimetric	0.1 mg/kg	NS	Feed	2000 mg/kg feed	12	30	Y: >10; A: 5	Onodera *et al.* (1970)
			LSC*	0.01 mg/kg	NS	Feed	0.02% (13.3 mg/kg bw) (Chicken)[f]	8	14	Y: 14; A: 4; WE: 9[c]	Laurencot *et al.* (1972)
							0.01% (13.4 mg/kg bw) (Turkey)[f]	11	14	Y: 15; A: 7; WE: 14[c]	
			HPLC	0.01 mg/kg	NS	Feed	10 mg/kg feed[g]	7.5	14	Y: 7; A: 3	Nagata *et al.* (1992b)
Sulfaguanidine	EU: not approved USA: not approved	None	FAST-LC*	10 μg/kg	NS	Oral (capsule)	90 mg/hen	NS	1	Y: 12; A: >3; WE: 10[c]	Aerts *et al.* (1986)
							180 mg/hen	NS	1	WE: >10[c]	
Sulfamerazine	EU: not approved USA: not approved	None	Colorimetric	0.1 mg/kg	NS	Feed	2000 mg/kg feed	12	30	Y: 4; A: 4	Onodera *et al.* (1970)
Sulfaquinoxaline	EU: not approved	None	LC-MS*	9 μg/kg	11 μg/kg	Water	250 mg/L	NS	4[h]	WE: >9[c]	Cavaliere *et al.* (2003)
	USA: not approved		Colorimetric	Y: 0.161, A: 0.167 mg/kg	NS		400 mg/L (53.6 mg/kg bw)	NS	3	Y: 9; A: 7	Romvary and Simon (1992)
			Colorimetric	Y: 2, A: 1 mg/kg	NS		400 mg/L	NS	8	Y: 14; A: 9	Blom (1975)
			Colorimetric	NS	NS		326 mg/L[i]	10	3	Y: 12; A: 10	Rana *et al.* (1993)
			LSC	NS	NS	Oral	6.2 mg/kg bw	NS	5	Y: 15; A: 11	Shaikh and Chu (2000)
			HPLC	0.01 mg/kg	NS		200 mg/kg feed[j]	7	7	Y: 10; A: 6; WE: 9[c]	Furusawa *et al.* (1998)
			Colorimetric	NS	NS		200 mg/kg bw	NS	1	WE: >5	Schlenker and Simmons (1950)
						Feed	125 mg/kg feed	NS	10	WE: >4	
							500 mg/kg feed	NS	10	WE: >4	
			Colorimetric	0.1 mg/kg	NS		500 mg/kg	18–30	12[k]	Y: >5; A: >5	Righter *et al.* (1970)
							1000 mg/kg feed	18–30	10	WE: >4	
				NS	NS	Feed	100 mg/kg feed[l]	9	7	Y: 10; A: 9	Petz (1993)
				0.01 mg/kg	NS	Feed	60 mg/kg[m]	5.5	14	WE: 12	Nose *et al.* (1982)
				0.03 mg/kg	NS	Water	0.6%[n]	NS	1[o]	Y: 6; A: >5	Sakano *et al.* (1981)

Table 8. (Continued)

Sulphonamides	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Sulphamonomethoxine	EU: not approved	None	HPLC	0.01 mg/kg	NS	Feed	25 mg/kg feed	7	21	Y: 4; A: 2[c]	Nagata *et al.* (1989)
	USA: not approved		HPLC	0.01 mg/kg	NS			7	21	Y: 4; A: 2[c]	Nagata *et al.* (1992a)
			HPLC	0.01 mg/kg	NS		50 mg/kg feed	7	21	Y: 4; A: 2[c]	Nagata *et al.* (1989)
			HPLC	0.01 mg/kg	NS			7	21	Y: 4; A: 2[c]	Nagata *et al.* (1992a)
			HPLC	0.01 mg/kg	NS		100 mg/kg feed	7	21	Y: 7; A: 2[c]	Nagata *et al.* (1989)
			HPLC	0.01 mg/kg	NS			7	21	Y: 7; A: 2[c]	Nagata *et al.* (1992a)
			HPLC	0.01 mg/kg	NS		400 mg/kg feed		5	Y: 8; A: 5; WE: 8	Furusawa and Mukai (1995)
			Colorimetric	0.1 mg/kg	NS		50 mg/kg feed	12	30	Y: 0; A: 0	Onodera *et al.* (1970)
							2000 mg/kg feed		30	Y: 10; A: 6	
Sulphanilamide	EU: not approved	None	Colorimetric	Y: 2; A: 1 mg/kg	NS	Water	1000 mg/L	NS	8	Y: 17; A: 14	Blom (1975)
	USA: not approved			0.04 mg/kg	NS	Oral (capsule)	75 mg/kg bw		1	Y: >7; A: 6[c]	Shaikh *et al.* (1999)
			LSC	NS	NS	Oral	105.6 mg/kg bw	NS	1	Y: 9; A: 6[c]	Shaikh and Chu (2000)
Sulfamethoxazole	EU: not approved	None	Colorimetric	0.16 mg/L	NS	SC*	50 mg/kg bw	NS	1	Y: 10; A: 8	Romvary *et al.* (1988)
	USA: not approved		Flourometric	NS	0.1 mg/kg	Feed	2000 mg/kg feed[p]	7–10	5	Y: >10; A: 5	Oikawa *et al.* (1977)
							4000 mg/kg feed[p]	7–10	5	Y: >10; A: 7	
						IM*	200 mg/kg bw[q]	7–10	5	Y: >10; A: 7	
Sulfadimethoxine & ormetoprim			Bioassay	NS	NS	Feed	250 mg/kg[r]	7.5	9	WE: 0	McReynolds *et al.* (2000)
Diaveridine	EU: not approved	None		0.04 mg/kg	NS	Water	0.6%[n]	NS	1	Y: 7; A: >6	Sakano *et al.* (1981)
	USA: not approved										
Sulphadiazine	EU: not approved	None	HPLC	0.02 mg/kg	NS	Water	0.2 g/L	6.5	5	Y: 4; A: 5	Atta and El-zeini (2001)
	USA: not approved						0.4 g/L	6.5	5	Y: 6; A: 7	
Trimethoprim	EU: not approved	None	HPLC	0.02 μg/g	NS	Water	0.2 g/L[s]	6.5	5	Y: 5; A: 4	Atta and El-zeini (2001)
							0.4 g/L[s]	6.5	5	Y: 7; A: 6	
	USA: not approved		HPLC	0.02 mg/kg	NS	Feed	4 mg/kg feed	11	19	Y: 4; A: 0	Nagata *et al.* (1991)
							16 mg/kg feed	11	19	Y: 10; A: 2	
							56 mg/kg feed	11	19	Y: 11; A: 8	

Table 8. (Continued)

Sulphonamides	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Ormetoprim	EU: not approved USA: not approved	None		0.01 mg/kg	NS	Feed	0.02% (7.8 mg/kg bw) (Chicken)	24	14	Y: 8; A: 4; WE: 8[c]	Laurencot *et al.* (1972)
							0.01% (7 mg/kg bw) (Turkey)	11	14	Y: 14; A: 3; WE: 13[c]	
Sulphaquinoxaline: Sulphadimidine: Sulphamerazine[t]	EU: not approved USA: not approved		Colorimetric	Y: 0.161, A: 0.167 mg/kg	NS	Water	390 mg/L (56.9 mg/kg bw)	NS	3	Y: 5; A: 2[u]	Romvary and Simon (1992)
			Colorimetric	0.16 mg/kg	NS		300 mg/L	NS	3	Y: 6; A: 3	Romvary *et al.* (1988)
Pyrimethamine	EU: not approved	None	HPLC	0.02 mg/kg	NS		1 mg/kg feed[f]	7.5	14	Y: 10; A: 3	Nagata *et al.* (1992b)
				0.02 mg/kg	NS		1 mg/kg feed	7.5	14	Y: 11; A: 2	
	USA: not approved		Colorimetric	Y: 1, A: 0.5 mg/kg	NS	Water	0.01%	NS	8	Y: >20; A: 9	Blom (1975)
			HPLC	0.02 mg/kg	NS	Feed	0.1 mg/kg feed	7	21	Y: 2; A: 0[c]	Nagata *et al.* (1990)
							1 mg/kg feed	7	21	Y: 9; A: 0[c]	
							10 mg/kg feed	7	21	Y: 12; A: 5[c]	

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; [a]treatments prepared using a 33% aqueous solution of sodium sulphadimidine; [b]medication given on days 1, 2, 5, 6 and 10; [c]$n < 5$, or not given; [d]treatment was sulfadimethoxine sodium salt; [e]treatment was with a 25% aqueous solution of sulfadimethoxine; [f]the doses in the feed were made up of sulfadimethoxine and ormetroprim together in a 5:3 ratio; [g]sulphadimethoxine and pyrimethamine given together in this study; [h]medication given on days 1, 2, 6 and 7; [i]treatment was a commercial liquid preparation of 3.44 g sulfaquinoxaline/100 mL; [j]medicated feed was prepared using sulphaquinoxaline sodium salt; [k]medication given on days 1, 2, 6, 7, 11 and 12; [l]sulfaquinoxaline given with nitrofurazone, nitrofurantoin and furaltadone each at 100 mg/kg feed; [m]sulfaquinoxaline, ethopabate and amprolium were given together in the feed at 60, 5 and 100 mg/kg respectively; [n]sulfaquinoxaline and diaveridine given together in a 4:1 ratio in this study; [o]a single day of treatment is implied but not explicitly stated; [p]preparation was 10% sulfamethoxazole-free base mixed with starch powder; [q]an aqueous preparation of sulfamethoxazole monoethanolamine at an equivalent concentration of 100 mg free base/mL was used; [r]proportions of the two drugs were not specified; [s]a preparation of 8% trimethoprim and 40% sulphadiazine was given; [t]sulfaquinoxaline, sulfadimidine and sulfamerazine were given in a 3:5:5 ratio; [u]number of days until no residues were detectable of any of the three drugs administered. Depletion information was not provided for individual drugs.

such products (Chopra & Roberts, 2001). Drugs in this class are widely used in food animals for disease prevention and treatment, as well as growth promotion in countries where such use is legal (Botsoglou & Fletouris, 2001; Chopra & Roberts, 2001). Tetracyclines are effective against a broad spectrum of gram-positive and gram-negative bacteria, *Mycoplasma*, *Chlamydophila*, and *Rickettisa* spp. (Bishop, 2001; Botsoglou & Fletouris, 2001). The most common and practical method of administration of tetracyclines to poultry is via feed or water. In general, tetracyclines are absorbed moderately well by the digestive system in mammals, but absorption may be less complete in birds (Anadon *et al.*, 1994b; Botsoglou & Fletouris, 2001). Absorption depends on the lipophilicity of the compound; oxytetracycline is the least lipophilic and therefore the most poorly absorbed following oral administration, and doxycycline is the most lipophilic of the tetracyclines (Botsoglou & Fletouris, 2001). Tetracyclines have a high affinity for metallic ions such as calcium, iron, magnesium and zinc (Bishop, 2001; Botsoglou & Fletouris, 2001), which will impede absorption if present in feed or the digestive system. Once tetracyclines are absorbed, they are distributed throughout the body and concentrate in the liver and kidney. In both birds and mammals, tetracyclines are excreted through the renal and biliary systems (Frazier *et al.*, 1995).

Tetracyclines are also deposited in the eggs of laying hens. Residues appear more rapidly in egg albumen than yolk following drug administration, but concentrations reach higher levels and persist longer in egg yolk (Yoshida *et al.*, 1973c; Roudaut *et al.*, 1989; Omija *et al.*, 1994; Zurhelle *et al.*, 2000). The residue levels reached, and the rate of their depletion from eggs depends on the method of administration, the dose and the specific drug given. Doxycycline is deposited into eggs at higher levels than tetracycline, and tetracycline reaches higher concentrations than oxytetracycline, when the same dose and route are used (Nogawa *et al.*, 1981; Roudaut *et al.*, 1989; Yoshimura *et al.*, 1991). Variation in the persistence of residues in eggs may reflect differences in absorption among drugs (Table 9). Doxycycline was detected in eggs for almost a month following cessation of the medication (Yoshimura *et al.*, 1991), while following a similar dosage regimen of oxytetracycline, residues were detected for 4–10 days (Nogawa *et al.*, 1981; Yoshimura *et al.*, 1991).

Endoparasiticides

Anthelmintics. As a class, anthelmintics are used to treat helminth parasite infections, but anthelmintic drugs are diverse in their structures and mechanisms of action (Barragry, 1984b; McKellar & Jackson, 2004). Benzimidazoles (flubendazole and albendazole), levamisole and ivermectin are the only anthelmintics for which egg residue data are available (Table 10). Flubendazole is used to treat nematodes in many food animal species, including poultry (Botsoglou & Fletouris, 2001). Following oral administration to chickens, flubendazole and albendazole are absorbed relatively quickly, reaching peak plasma concentrations in 2–4 h (Csiko *et al.*, 1996; EMEA, 1999, 2006). In chickens, tissue concentrations of flubendazole following oral administration are highest in the liver and kidney, suggesting that at least some excretion occurs via the urine (Botsoglou & Fletouris, 2001). Despite a rapid rate of elimination, detectable residues of flubendazole and albendazole can be found in eggs laid up to a week or more after treatment (Table 10) (Csiko *et al.*, 1995; Kan *et al.*, 1998). Residues are more persistent in the egg yolk than albumen (Csiko *et al.*, 1995; Kan *et al.*, 1998; Botsoglou & Fletouris, 2001).

Levamisole is used for treating nematode infections, but is ineffective against cestodes or trematodes (Botsoglou & Fletouris, 2001). In mammals, levamisole is well absorbed when given orally and is excreted relatively rapidly in the urine (Barragry, 1984a). There are no data available on the absorption or primary excretion pathways of levamisole in birds, but the drug concentrates in the liver following oral dosing in chickens (FAO/WHO, 1991), and residues are found in the eggs of laying hens for up to 2 weeks after treatment (El-Kholy & Kemppainen, 2005).

Ivermectin, a mixture of two avermectins, is effective against nematodes and arthropod pests, but not cestodes or trematodes (Botsoglou & Fletouris, 2001). There is very little information on the metabolism of ivermectin in avian species, but it is well studied in mammals. Regardless of route of administration, ivermectin is widely distributed to tissues. Because of its lipophilicity, ivermectin can accumulate in fat, where it can persist for prolonged periods (Canga *et al.*, 2009). Ivermectin is not highly metabolized and excretion is primarily via the faeces (Canga *et al.*, 2009). When ivermectin is administered to laying hens, residues are preferentially deposited in the egg yolk (Keukens *et al.*, 2000) and can be found in eggs laid for several days following cessation of treatment (Table 10).

Coccidiostats

Drugs used as anti-coccidials come from a number of different drug classes and have a corresponding variety of excretion and disposition patterns in poultry. It should be noted that many anti-coccidials, such as nitroimidazoles, ionophores, triazines, and sulfonamides, also have antibacterial properties.

Nitroimidazoles. The nitroimidazoles (dimetridazole, ronidazole, ipronidazole) are active against gram-negative and gram-positive anaerobic bacteria as well as protozoa (Edwards, 1993; Bishop, 2001). However, nitroimidazoles are suspected mutagens and carcinogens, and their use in food animals is limited (Botsoglou & Fletouris, 2001; Dowling, 2006). In avian species, nitroimidazoles are rapidly absorbed from the GI tract and widely distributed to tissues (Rosenblum *et al.*, 1972; Herman *et al.*, 1989; FAO/WHO, 1990; Aerts *et al.*, 1991; Posyniak *et al.*, 1996b). Excretion occurs via the faeces and urine in birds and mammals (Rosenblum *et al.*, 1972; Morton *et al.*, 1973; Aerts *et al.*, 1991; Dowling, 2006). Ronidazole is excreted mostly unchanged, while ipronidazole and dimetridazole are more extensively metabolized (Aerts *et al.*, 1991; Polzer *et al.*, 2004).

When given orally to laying hens, dimetridazole and ronidazole are deposited in eggs at higher concentrations than

Table 9. Tetracycline residues in eggs following treatment of laying hens

Tetracyclines	Approval status (laying hens)*	Tolerance/maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Oxytetracycline	EU: approved USA: not approved	EU: 200 μg/kg	Bioassay	Y: 0.2, A: 0.07 mg/kg	NS*	Water	0.1 g/L (10 mg/kg bw*)	NS	5	Y: 0; A: 0	Roudaut *et al.* (1987a)
							0.25 g/L (25 mg/kg bw)		5	Y: 4; A: 3	
			Bioassay	0.05 mg/kg	NS		0.4 g/L	12	7	Y: 3; A: 0	Omija *et al.* (1994)
			Bioassay	Y: 0.3, A: 0.075 mg/kg	NS		0.5 g/L†	NS	7	WE: 4‡	Nogawa *et al.* (1981)
			Bioassay	Y: 0.2, A: 0.07 mg/kg	NS		0.5 g/L (50 mg/kg bw)	NS	5	Y: 4; A: 3	Roudaut *et al.* (1987a)
			Bioassay	Y: 0.3, A: 0.07 mg/kg	NS		0.5 g/L§	NS	7	Y: 10; A: 6	Yoshimura *et al.* (1991)
			Bioassay	0.05 mg/kg	NS		0.6 g/L	12	7	Y: 5; A: 1	Omija *et al.* (1994)
							0.8 g/L	12	7	Y: 5; A: 2	
			HPLC*	0.05 mg/kg	NS		2 g/L¶	NS	7	Y: 12; A: 9	Nagy *et al.* (1997)
			Bioassay	5 mg/kg	NS		125 mg/hen	9.5	5	WE: 19	Frieser *et al.* (1986)
			Bioassay	0.27 mg/kg	NS	Feed	20 mg/kg feed	8	7	Y: 0; A: 0	Yoshida *et al.* (1973b)
			Bioassay	0.08 mg/kg	0.1 mg/kg		25 mg/kg feed	6	28	WE: 0	Katz *et al.* (1973)
							50 mg/kg feed	6	28	WE: 0	
			Bioassay	Y: 258, A: 117 μg/kg	NS		50 mg/kg feed	14	5	Y: 0; A: 0	Donoghue and Hairston (1999)
			Bioassay	0.08 mg/kg	0.1 mg/kg		100 mg/kg feed	6	28	WE: 0	Katz *et al.* (1973)
			Bioassay	Y: 258, A: 117 μg/kg	NS		200 mg/kg feed	14	5	Y: 0; A: 1	Donoghue and Hairston (1999)
			Bioassay	Y: 0.2, A: 0.07 mg/kg	NS		300 mg/kg feed (18 mg/kg bw)	NS	7	Y: 2; A: 1	Roudaut *et al.* (1987a)
			Bioassay	Y: 0.2, A: 0.07 mg/kg	NS		600 mg/kg feed (36 mg/kg bw)	NS	7	Y: 4; A: 2	Roudaut *et al.* (1987a)
			HPLC	2.2 μg/kg	13 μg/kg		800 mg/kg feed†	16	7	WE: >10	De Ruyck *et al.* (1999)
			Bioassay	0.27 mg/kg	NS		4000 mg/kg feed	8	7	Y: 5; A: 2	Yoshida *et al.* (1973b)
			Bioassay	Y: 0.2, A: 0.07 mg/kg	NS	IM*	15 mg/kg bw	NS	3	Y: 7; A: 5	Roudaut *et al.* (1987a)
							30 mg/kg bw	NS	3	Y: 11; A: 9	
			HPLC	0.05 mg/kg	NS		200 mg/kg bw¶	NS	5	Y: 12; A: 5	Nagy *et al.* (1997)

Table 9. (Continued)

Tetracyclines	Approval status (laying hens)*	Tolerance/maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Chlortetracycline	EU: approved; USA: approved	200 μg/kg (EU); 0.4 mg/kg (USA)	Bioassay	Y: 0.06, A: 0.012 mg/kg	NS	Water	0.5 g/L†	NS	7	WE: 6‡	Nogawa *et al.* (1981)
			Bioassay	2.5 mg/kg	NS		125 mg/hen	9.5	5	WE: 24	Frieser *et al.* (1986)
			LC-APCI-MS*	NS	NS	Feed	300 mg/kg feed (120 g/hen)	9	9	WE: >9	Kennedy *et al.* (1998b)
			Bioassay	Y: 0.06, A: 0.01 mg/kg	NS		600 mg/kg feed (36 mg/kg bw)	NS	7	Y: 9; A: 5; WE: 9	Roudaut *et al.* (1989)
			HPLC & LC/MS-MS*	10 μg/kg	NS		1000 mg/kg feed	NS	17	Y: >5; A: >4	Zurhelle *et al.* (2000)
			Bioassay	0.05 mg/kg	NS		8000 mg/kg	8	7	Y: 5; A: 2	Yoshida *et al.* (1973c)
			Bioassay	0.025 mg/kg	NS		50 mg/kg feed	12	2–3 weeks	WE: 0	Raica *et al.* (1956)
							100 mg/kg feed	12	2–3 weeks	WE: 0	
							200 mg/kg feed	12	2–3 weeks	WE: 0	
							500 mg/kg feed	12	16	WE: 5	
							1000 mg/kg feed	12	16	WE: 6	
							2000 mg/kg feed	12	16	WE: 4‡	
			Bioassay	3 μg/kg	NS		50 mg/kg feed	5	97	WE: 1	Katz *et al.* (1972)
							100 mg/kg feed	5	97	WE: 2	
							150 mg/kg feed	5	97	WE: 3	
							200 mg/kg feed	5	97	WE: 3	
			Bioassay	NS	NS		3 mg/kg feed	NS	21	WE: 0	Durbin *et al.* (1953)
							10 mg/kg feed	NS	21	WE: 0	
							50 mg/kg feed	NS	21	WE: 0	
							100 mg/kg feed	NS	21	WE: 0	
							200 mg/kg feed	NS	21	WE: 0	
							2000 mg/kg feed	NS	21	WE: 14	
							10 000 mg/kg feed	NS	21	WE: 14	
							20 000 mg/kg feed	NS	21	WE: 21	
Tetracycline	EU: approved; USA: not approved	200 μg/kg (EU)	Bioassay	Y: 0.15, A: 0.07 mg/kg	NS	Water	0.25 g/L (25 mg/kg bw)	NS	5	Y: 6; A: 1; WE: 6	Roudaut *et al.* (1989)
							0.5 g/L (50 mg/kg bw)		5	Y: 9; A: 2; WE: 9	
			Bioassay	Y: 0.3, A: 0.075 mg/kg	NS		500 μg/mL†	NS	7	WE: 5‡	Nogawa *et al.* (1981)
			Bioassay	5 μg/kg	NS		125 mg/hen	9.5	5	WE: 23	Frieser *et al.* (1986)
			Bioassay	Y: 0.15, A: 0.07 mg/kg	NS	Feed	300 mg/kg feed (18 mg/kg bw)	NS	7	Y: 8; A: 1; WE: 8	Roudaut *et al.* (1989)
							600 mg/kg feed (36 mg/kg bw)		7	Y: 11; A: 2; WE: 11	
Doxycycline	EU: not approved; USA: not approved	None	Bioassay	Y: 0.15 A: 0.04 mg/kg	NS	Water	0.5 g/L**	NS	7	Y: 27; A: 25	Yoshimura *et al.* (1991)

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †drug provided in the form of its hydrochloride salt; ‡$n < 5$ or not given; §a commercial oxytetracylcine preparation of 100 mg/mL was used; ¶a commercial preparation of 800 mg/g oxytetracycline hydrochloride was used; **a commercial preparation of 800 mg/g doxycycline hydrochloride was used.

Table 10. Residues of anthelmintic drugs in chicken eggs following treatment of laying hens

Anthelmintics	Approval status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Flubendazole	EU: approved; USA: not approved	EU: 400 μg/kg	HPLC*	0.3 mg/kg	0.6 mg/kg	Feed	2.6 mg/kg feed†	6	21	WE: 0	Kan *et al.* (1998)
							9.4 mg/kg feed†	6	21	WE: 6	
							27 mg/kg feed†	6	21	WE: >6	
Levamisole	EU: not approved; USA: not approved	None	HPLC	0.001 mg/kg	0.025 μg/g	Oral	40 mg/kg‡ bw*	8	1	WE: 14	El-Kholy and Kemppainen (2005)
Ivermectin	EU: not approved; USA: not approved	None	HPLC	0.5 μg/kg	NS	Feed	0.1 mg/kg feed	6	21	WE: 0	Keukens *et al.* (2000)
							0.4 mg/kg feed	6	21	Y: 6; A: 0	
							0.8 mg/kg feed	6	21	Y: >6; A: 0	
Albendazole	EU: not approved; USA: not approved	None	HPLC	10 μg/kg	NS	Water	10 mg/kg bw	9	1	Y: 8; A: 4	Csiko *et al.* (1995)

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †prepared using a commercial 5% premix; ‡treatment was with levamisole hydrochloride.

ipronidazole, and residues of all three drugs are distributed uniformly between yolk and albumen (Mortier *et al.*, 2005) (Table 11).

Ionophores. Many polyether ionophores (e.g. lasalocid, monensin, narasin, salinomycin) are widely used anticoccidials in the poultry industry and are commonly given in feed as disease preventatives or growth promoters (Botsoglou & Fletouris, 2001). Ionophore coccidiostats are derived from bacterial fermentation products (Botsoglou & Fletouris, 2001). The anticoccidial activity of ionophores is related to their affinity for cations, which when bound to ionophore medications form lipophilic complexes that affect their transport through biological membranes (Elsasser, 1984; Botsoglou & Fletouris, 2001). Residues of the polyether ionophores in food products are of special concern because of the high degree of toxicity of these drugs to many species (Dowling, 2006).

When administered orally to chickens and quail, the available data show that ionophores are rapidly absorbed and widely distributed to tissues (Catherman *et al.*, 1991; Atef *et al.*, 1993; Akhtar *et al.*, 1996a; Henri *et al.*, 2009). Bioavailability varies among drugs from less than 30% to greater than 75% (Donoho, 1984; Atef *et al.*, 1993; Henri *et al.*, 2009). Metabolism is extensive (Donoho, 1984; Sweeney *et al.*, 1996; FAO/WHO, 2008) and elimination is generally rapid, but lasalocid may persist in tissues for longer periods than other ionophores (EMEA, 2004). Narasin and monensin are known to be excreted via faeces in chickens (Donoho, 1984; FAO/WHO, 2009).

When given to laying hens, ionophores concentrate in the egg yolks to a greater extent than in the albumen (Kan & Petz, 2000; Mortier *et al.*, 2005; Rokka *et al.*, 2005), but residues are also detectable in albumen when drugs are given at high dosages (Akhtar *et al.*, 1996a; Kan & Petz, 2000) (Table 11). Of the commonly used ionophores, lasalocid produces the highest residue concentrations in eggs, salinomycin produces relatively low residue levels, and monensin residues are sometimes not detectable at all in the eggs of treated hens (Kennedy *et al.*, 1998a) (Table 11).

Triazines. Diclazuril, clazuril, and toltrazuril are structurally similar members of the triazine group (Botsoglou & Fletouris, 2001). Diclazuril and toltrazuril are characterized by extensive distribution to tissues, long elimination half-lives and elimination via the faeces in both birds and mammals (EMEA, 1996, 1998b). While toltrazuril is relatively well absorbed from the GI tract and extensively metabolized (EMEA, 1998b), orally administered diclazuril is minimally metabolized, and the majority of the parent drug is excreted in the faeces (EMEA, 1996).

When repeated oral doses of diclazuril or toltrazuril are given to laying hens, both result in persistent residues in tissues and eggs (EMEA, 1996; Mortier *et al.*, 2005; Mulder *et al.*, 2005) (Table 11). While there is very little information on the pharmacokinetics of clazuril, a single study on laying hens shows that clazuril accumulates in eggs in a pattern similar to that of diclazuril (Mortier *et al.*, 2005), persisting for many days in the eggs after treatment has ended (Giorgi & Soldani, 2008).

Table 11. Residues of anticoccidial drugs in eggs following treatment of laying hens

Coccidiostats	Approval Status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Salinomycin	EU: not approved; USA: not approved	None	HPTLC*	10 μg/kg	NS	Feed	5 mg/kg feed	NS	7	WE: 8	Kan *et al.* (1990)
			HPLC*	5 μg/kg	10 μg/kg		30 μg/g feed†	NS	14	Y: >3; A: 0	Akhtar *et al.* (1996a)
							60 μg/g feed†	NS	14	Y: >3; A: 1	
							90 μg/g feed†	NS	14	Y: >3; A: 2	
							150 μg/g feed†	NS	14	Y: >3; A: 2	
			HPTLC	Y: 10, A: 7.5 μg/kg	NS		60 mg/kg feed‡	14	5	Y: >10; A: 2	Šinigoj-Gačnik and Rojs (2008)
Narasin	EU: not approved; USA: not approved	None	LC-MS/MS*	0.9 μg/kg	NS	Feed	2.5 mg/kg feed	17	21	Y: >7; A: 0	Rokka *et al.* (2005)
			HPTLC	10 μg/kg	NS		5 mg/kg feed	NS	7	WE: 8	Kan *et al.* (1990)
				NS	NS		41 mg/kg feed	NS	14	WE: 17	
				NS	NS		2144 μg/kg feed	NS	14	WE: 8	
			LSC*	NS	NS	IC*	0.62 mg (Chicken)	8	1	Y: 9	Catherman *et al.* (1991)
							0.1 mg (Quail)	NS	1	Y: 13	
			LC-MS/MS	NS	1 μg/kg		2 mg/kg feed§	8–10	14	WE: 12	Mortier *et al.* (2005)
			LC-MS/MS	NS	1 μg/kg		40 mg/kg feed§	8–10	14	WE: 11	
Lasalocid	EU: approved; USA: not approved	EU: 150 μg/kg	LC-MS*	0.3 μg/kg	1 μg/kg	Feed	5 mg/kg feed (0.6 g/day)	9	16	WE: 10	Kennedy *et al.* (1996)
Monensin	EU: not approved; USA: not approved	None	HPTLC	10 μg/kg	NS	Feed	5 mg/kg feed	NS	7	WE: 0	Kan *et al.* (1990)
Amprolium	EU: approved; USA: approved	EU: None required; USA: Y: 8, WE: 4 mg/kg	Fluorometric	0.18 mg/kg	NS	Water	120 mg/L¶	7–20	16	Y: 8	Polin *et al.* (1968)
							240 mg/L¶	7–20	16	Y: 10	
			CF-LC*	Y: 5, A: 3 μg/kg	NS	Feed	5 mg/kg feed	NS	10	WE: 10	Kan *et al.* (1990)
							5 mg/kg feed	NS	14	WE: 10	
			HPLC	Y: 0.005, A: 0.003 mg/kg	NS		5 mg/kg feed	NS	14	Y: >16	Kan *et al.* (1989)
							25 mg/kg feed	NS	14	Y: >16	
							125 mg/kg feed	NS	14	Y: >16	
							250 mg/kg feed	NS	14	Y: >16	
							5 mg/kg feed	NS	10	Y: 6	
							250 mg/kg feed	NS	10	Y: >8	
							125 mg/kg feed	5–6	Hatch-1st lay	Y: 19	
			Fluorometric	0.18 mg/kg	NS		125 mg/kg feed	7–20	16	Y: 7	Polin *et al.* (1968)
							250 mg/kg feed	7–20	16	Y: 8	
			GC*	0.01 mg/kg	NS		125 mg/kg feed	NS	11	Y: 7	Petz *et al.* (1980)
							25 mg/kg feed	NS	11	Y: 8	
				NS	NS		100 mg/kg feed**	5.5	14	WE: >14	Nose *et al.* (1982)

Table 11. (Continued)

Coccidiostats	Approval Status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Halofuginone	EU: not approved;	None	LC-ES-MS/MS*	1 μg/kg	NS	Feed	3 μg/kg feed††	5	14	WE: 0	Yakkundi *et al.* (2002)
	USA: not approved		LC-MS/MS & ELISA*	0.5 μg/kg	1 μg/kg		150 μg/kg feed††	8–10	14	WE: 8	Mortier *et al.* (2005)
			LC-ES-MS/MS	1 μg/kg	NS		300 μg/kg feed††	5	14	WE: >14	Yakkundi *et al.* (2002)
			LC-MS/MS & ELISA	0.5 μg/kg	1 μg/kg		1.5 mg/kg feed††	5	14	WE: 19	Mortier *et al.* (2005)
			HPLC & LC-MS/MS	2 μg/kg	NS		3 mg/kg feed††	5.5	14	WE: 12	Mulder *et al.* (2005)
Meticlorpindol	EU: not approved;	None	HPLC	2 μg/kg	NS	Feed	2 mg/kg feed‡‡ (caged)	6.5	29	A: 4	Hafez *et al.* (1988)
	USA: not approved						2 mg/kg feed‡‡ (raised on deep litter)	6.5	29	A: 6	
							100 mg/kg feed‡‡ (caged)	6.5	14	A: 0	
							100 mg/kg feed‡‡ (raised on deep litter)	6.5	14	A: 28	
			CF-LC	Y: 20, A: 10 μg/kg	NS		10 mg/kg feed	NS	10	WE: 6	Kan *et al.* (1990)
			HPLC	Y: 20, WE: 10 μg/kg	NS		10 mg/kg feed‡‡	NS	10	WE: 6	Mattern *et al.* (1990)
							110 mg/kg feed‡‡	NS	10	Y: 8; A: 14; WE: 14	
Decoquinate	EU: not approved; USA: not approved	None		NS	NS	Feed	40 mg/kg feed	5.5	14	WE: 13	Nose *et al.* (1982)
			LSC & TLC*	0.1 mg/kg	NS		2.6 mg/day	9	19	Y: >16; A: 1; WE: 12§§	Kouba *et al.* (1972)
			LSC	NS	NS	Feed, IV*	0.5 g/kg feed, 0.1 mg IV (Chicken)	8	7, 1	Y: >28; A: 0	Seman *et al.* (1989)
			LSC	NS	NS	Feed, IC*	0.5 g/kg feed, 0.05 IV (Quail)	NS	7, 1	Y: >28; A: 0	
Clazuril	EU: not approved; USA: not approved	None	HPLC	0.09 mg/kg	0.2 mg/kg	Oral (capsule)	3 mg/kg bw¶¶	9–10	1	Y: 0; A: 0	Giorgi and Soldani (2008)
							3 mg/kg bw	9–10	5	Y: 10; A: 3	
Diclazuril	EU: not approved; USA: not approved	None	LC-MS/MS	NS	0.5 μg/kg	Feed	50 μg/kg feed***	8–10	14	WE: 11	Mortier *et al.* (2005)
							1 mg/kg feed***	8–10	14	WE: 23	
Robenidine	EU: not approved; USA: not approved	None	LC-MS/MS	NS	1 μg/kg	Feed	1.8 mg/kg feed†††	8–10	14	WE: 13	Mortier *et al.* (2005)
							36 mg/kg feed†††	8–10	14	WE: 29	

Table 11. (Continued)

Coccidiostats	Approval Status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Nicarbazin	EU: not approved;	None	LC-ES-MS*	NS	1 μg/kg	Feed	12 mg/kg feed (1.44 g/day)	5	16	WE: 12	Cannavan *et al.* (2000)
	USA: not approved		GC	NS	NS		200 mg/kg feed	5.5	14	WE: 29	Nose *et al.* (1982)
			HPLC	2 μg/kg	Not given		2 mg/kg feed (caged)	6	29	Y: 16	Friedrich *et al.* (1985)
							2 mg/kg feed (deep litter)	6	29	Y: >60	
			HPLC	2 μg/kg	Not given		125 mg/kg feed (caged)	7.5	7	Y: 28	Friedrich *et al.* (1984)
							125 mg/kg feed (deep litter)	7.5	7	Y: >53	
			HPLC & GC	0.01 mg/kg	NS		0.45–1.1 mg/kg feed	0–6	Hatch-1st lay	WE: 13	Oishi and Oda (1989)
							0.26 mg/kg feed	NS	1	WE: 7	
							1 mg/kg feed	NS	1	WE: 9	
							0.05 mg/kg feed	NS	10	WE: >5	
							0.1 mg/kg feed	NS	10	WE: 7	
							0.5 mg/kg feed	NS	10	WE: 10	
							1 mg/kg feed	NS	10	WE: >10	
			LC-MS/MS & ELISA	NS	1 μg/kg		2 mg/kg feed§	8–10	14	WE: 15	Mortier *et al.* (2005)
			LC-MS/MS & ELISA	NS	1 μg/kg		40 mg/kg feed§	8–10	14	WE: 24	
Toltrazuril	EU: not approved; USA: not approved	None	LC-MS/MS	1 μg/kg	NS	Water	78 mg/L (9.5 mg/kg bw/day)‡‡‡	5.5	4§§§	Y: >19; A: >19; WE: >19	Mulder *et al.* (2005)
Ethopabate	EU: not approved; USA: not approved	None		NS	NS	Feed	5 mg/kg feed**	5.5	14	WE: 0	Nose *et al.* (1982)
Dinitolmide (Zoalene)	EU: not approved; USA: not approved	None		NS	NS		125 mg/kg feed	5.5	14	WE: >14	Nose *et al.* (1982)
Dimetridazole	EU: prohibited;	None	LC-MS/MS & ELISA	0.5 μg/kg	1 μg/kg	Feed	100 mg/kg feed	8–10	14	WE: 13	Mortier *et al.* (2005)
	USA: prohibited		HPLC	2 μg/kg	NS	Oral	50 mg/kg bw	6.5	3	Y: 5; A: 3; WE: 4	Posyniak *et al.* (1996a)
							250 mg/kg bw	6.5	3	Y: 6; A: 5; WE: 6	
			LC-MS	2 μg/kg	5 μg/kg	Oral (capsule)	75 mg/bird	11	1	Y: 5; A: 5; WE: 5	Aerts *et al.* (1991)
			HPLC	2 μg/kg	NS	IM*	50 mg/kg bw	6.5	3	Y: 6; A: 5; WE: 6	Posyniak *et al.* (1996a)

Table 11. (Continued)

Coccidiostats	Approval Status (laying hens)*	Tolerance/ maximum residue limit*	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Ronidazole	EU: prohibited; USA: prohibited	None	LC-MS	2 μg/kg	5 μg/kg		75 mg/bird	11	1	WE: 7[§§]	Aerts *et al.* (1991)
Ipronidazole	EU: not approved; USA: prohibited	None	LC-MS	5 μg/kg	10 μg/kg		75 mg/bird	11	1	WE: 6	Aerts *et al.* (1991)

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; [†]feed prepared using a commercial 6% salinomycin premix; [‡]medicated feed prepared from a commercial liquid preparation of 9.6% amprolium; **amprolium given together with ethopabate (5 mg/kg feed) and sulfaquinoxaline (60 mg/kg feed); [††]commercially available medicated feed additive containing 6 g/kg halofuginone hydrobromide used; [‡‡]commercially available feed additive containing meticlorpindol and methylbenzoquate in a 12:1 ratio; [§§]$n < 5$ or not given; [¶¶]a veterinary formulation of clazuril (Appertex®, Janssen Pharmaceutica, Beerse, Belgium) used with 2.5 mg active compound per tablet; ***commercially available medicated feed additive containing 0.2% diclazuril used; [†††]commercially available medicated feed additive containing 66 g/kg robenidine hydrochloride used; [‡‡‡]a commercial drinking water additive containing 2.5% toltrazuril was used; [§§§]doses given on days 1, 2, 8 and 9.

All three compounds are deposited primarily in the egg yolk (Mortier *et al.*, 2005; Giorgi & Soldani, 2008).

Benzamides. Benzamide anticoccidials include dinitolmide (also called zoalene), aklomide and nitromide. Of these, dinitolmide is most widely used for treating coccidiosis in poultry (Botsoglou & Fletouris, 2001). Dinitolmide is rapidly absorbed following oral administration to chickens, and broadly and rapidly distributed to tissues (Smith *et al.*, 1963). Following absorption, dinitolmide is extensively metabolized by the liver and excreted in faeces (Smith *et al.*, 1963; Smith, 1964; Pan & Fouts, 1978; Botsoglou & Fletouris, 2001). The single study available on the deposition of dinitolmide in eggs did not continue sampling eggs long enough to establish the full time course of drug elimination, but drug residues were still present 2 weeks after the medication was withdrawn (Nose *et al.*, 1982) (Table 11). Concentrations of dinitolmide residues were approximately 10 times higher in the egg yolk than the albumen (Nose *et al.*, 1982).

Carbanilides. The carbanilide nicarbazin is used for prevention of coccidiosis in poultry. Carbanilides are not intended for use in laying hens because they have been shown to decrease egg production (Botsoglou & Fletouris, 2001; Lindsay & Blagburn, 2001). Nicarbazin is well absorbed from the GI tract and distributed broadly to tissues when given orally to chickens. Nicarbazin is broken down into two major metabolites, 2-hydroxy-4,6-dimethylpyrimidine (HDP) and 4,4′-dinitrocarbanilide (DNC), which differ in pharmacokinetic behaviour. DNC, the marker residue used for evaluating food safety (EFSA, 2010), occurs at much higher levels than HDP and concentrates in the liver and kidneys, and is excreted primarily in the faeces, while HDP is excreted in the urine (Wells, 1999; EFSA, 2010). When given orally to laying hens, DNC is found concentrated in the egg yolk, while HDP is found predominantly in albumen (Cannavan *et al.*, 2000; Mortier *et al.*, 2005) (Table 11). The period during which residues are found in eggs is greatly extended if the hens are kept on litter that is not frequently changed, as shown by studies by Friedrich *et al.* (1984, 1985) (Table 11).

Quinolone derivatives. Buquinolate, decoquinate and methylbenzoquate are quinolone derivatives used for the prevention of coccidiosis in poultry (Botsoglou & Fletouris, 2001). Data on drug deposition in chicken eggs exist only for decoquinate (Table 11). Decoquinate is poorly absorbed from the GI tract of chickens, but what absorption occurs is rapid, and the drug is distributed widely to tissues (Filer *et al.*, 1969; Craine *et al.*, 1971). Metabolism is not extensive, and excretion of the parent compound occurs via the faeces (Filer *et al.*, 1969; Craine *et al.*, 1971). In contrast, in mammals excretion occurs via both urine and faeces (Mitchell *et al.*, 1988). Clearance of decoquinate occurs more slowly in chickens compared with cattle, sheep or even quail (Seman *et al.*, 1986; Mitchell *et al.*, 1988). When administered to laying hens, decoquinate is deposited in egg yolk (Kouba *et al.*, 1972; Nose *et al.*, 1982) and persists for very long

periods [over 4 weeks in some studies (Seman *et al.*, 1989)] after the end of treatment.

Other anti-coccidials. A few anticoccidial drugs included in Table 11 (robenidine, amprolium, halofuginone, meticlorpindol (clopidol) and ethopabate) do not fall into any of the above classes. Of these, only ethopabate was not found to produce persistent drug residues in eggs (Table 11).

Robenidine is a synthetic guanidine derivative that is used to control coccidiosis in poultry and rabbits (Botsoglou & Fletouris, 2001). In chickens, it is incompletely absorbed from the GI tract, but the absorbed portion is well distributed to tissues and extensively metabolized (Zulalian *et al.*, 1975). Excretion occurs over several days following oral administration (Zulalian *et al.*, 1975). Residues are detected in the eggs, primarily the yolk, of treated hens for weeks after medication is withdrawn (Mortier *et al.*, 2005) (Table 11).

Amprolium is structurally similar to vitamin B_1 (Botsoglou & Fletouris, 2001). When administered orally to chickens, bioavailability is low, (Hamamoto *et al.*, 2000), but absorbed amprolium is widely distributed to tissues (Alam *et al.*, 1987) and rapidly eliminated in the urine and faeces (Polin *et al.*, 1967). Amprolium administered to laying hens is deposited primarily in the egg yolk, and residues can be detected in eggs for 2 weeks or more after cessation of treatment, depending on the dose and assay sensitivity (Nose *et al.*, 1982; Kan *et al.*, 1989) (Table 11).

Ethopabate is a benzoic acid used in combination with amprolium to treat coccidiosis in poultry (Botsoglou & Fletouris, 2001). Ethopabate is well absorbed following oral administration to chickens and is rapidly metabolized and almost completely excreted in urine (Buhs *et al.*, 1966). Based on the limited data available, it appears that little or no ethopabate administered orally to laying hens is deposited in eggs (Nose *et al.*, 1982) (Table 11).

Halofuginone is a plant-derived alkaloid (Lindsay & Blagburn, 2001) that is a potent anticoccidial (Botsoglou & Fletouris, 2001). Halofuginone appears to be poorly absorbed from the GI tract in mammals, and only a small fraction of the drug is excreted in the urine (Stecklair *et al.*, 2001), but data are lacking for birds. When given to laying hens at low doses in the feed, halofuginone residues are not detectable in eggs, but as dosage increases, residues appear and can persist for days to weeks, depending on the concentration given (Yakkundi *et al.*, 2002; Mortier *et al.*, 2005; Mulder *et al.*, 2005) (Table 11). Residues occur at similar levels in egg yolk and albumen, in contrast to many drugs reviewed here (Yakkundi *et al.*, 2002), although residues are more persistent in yolk (Mortier *et al.*, 2005).

Meticlorpindol, also called clopidol, is a coccidiostatic pyridinol (Botsoglou & Fletouris, 2001). There are few data on the metabolism of meticlorpindol in poultry, but it has been shown that in chickens the compound is absorbed from the GI tract to a significant extent (McQuistion & McDougald, 1979) and distributed widely to tissues (Pang *et al.*, 2001), but is not extensively metabolized (Smith, 1969). In rabbits, orally administered meticlorpindol is rapidly absorbed and excreted almost completely in urine (Cameron *et al.*, 1975). Meticlorpindol fed to laying hens is deposited in egg albumen at concentrations about twice that found in egg yolk (Mattern *et al.*, 1990), and residues can persist for several weeks when the medication is given at high doses (Hafez *et al.*, 1988; Mattern *et al.*, 1990) (Table 11).

Ectoparasiticides

While ectoparasites rarely cause mortality in poultry, the physical stress associated with infestations can result in decreased production and economic losses (Axtell & Arends, 1990). Some ectoparasites can also be vectors of disease (Shah *et al.*, 2004; Moro *et al.*, 2009). Common poultry parasites include the northern fowl mite (*Ornithonyssus sylviarum* and *Ornithonyssus bursa*), the chicken body louse (*Menacanthus stramineus*), the chicken mite (*Dermanyssus gallinae*), the bedbug (*Cimes lectularius*) and various tick species (Axtell & Arends, 1990; Shah *et al.*, 2004). The primary methods of control of poultry ectoparasites are spraying insecticides on the birds themselves, or treating the environment and removing used or contaminated litter. Classes of ectoparasiticides commonly used in the poultry industry include the carbamates, organophosphates, and pyrethrins. Although they are generally applied topically, most ectoparasiticides can be absorbed through the skin and have toxic effects (Al-Saleh, 1994).

Carbamates. Carbamates (e.g. carbaryl, propoxur) are reversible acetylcholinesterase inhibitors derived from a toxic substance found in Calabar beans, the seeds of *Physostigma venenosum* (Blagburn & Lindsay, 2001). Some carbamates are used to treat ticks, mites, and lice in poultry and livestock (Blagburn & Lindsay, 2001).

Orally administered carbamates are well absorbed from the GI tract in chickens and widely distributed to tissues (Hicks *et al.*, 1970). The major pathway of excretion is via the urine, but eggs laid during and after treatment also contain low-level residues (Paulson *et al.*, 1972). Carbamate residues occur in both egg yolk and albumen, but are more persistent in yolk (Paulson & Feil, 1969; Andrawes *et al.*, 1972) (Table 12). Following topical administration, available data suggest that carbamates can be absorbed and metabolized to a significant degree, and long-lasting residues occur in eggs (Table 12) (Ivey *et al.*, 1984).

Pyrethrins and pyrethroids. Pyrethrins are a group of insecticides derived from the pyrethrum flower (*Chrysanthemum cinerariaefolium*); synthetic forms based on the naturally occurring compounds are called pyrethroids (Blagburn & Lindsay, 2001). Pyrethrins and pyrethroids are among the least toxic of the insecticides and are not as well absorbed through skin as other insecticidal compounds (Al-Saleh, 1994). In general, pyrethrins and pyrethroids are effective against mites, fleas, flies, lice and ticks (Blagburn & Lindsay, 2001). In poultry, permethrin is the primary pyrethroid used to treat ectoparasite infections, and especially infestations of the northern fowl mite, which has

Table 12. Residues of ectoparasiticides in eggs following treatment of laying hens

Ectoparasitics	Approval status (laying hens)*	Tolerance/ maximum residue limit†	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Carbaryl	EU: not approved;	None	Colorimetric	0.1 mg/kg	NS*	Feed	200 mg/kg feed	18	7	Y: 0; A: 0	McCay and Arthur (1962)
	USA: N/A‡		LSC* & LC*	NS	5.0 mg/kg	Oral (Capsule)	7 mg/kg feed equivalent	6	31	Y: >6; A: 1; WE: 6	Andrawes *et al.* (1972)
							21 mg/kg feed equivalent	6	31	Y: >6; A: 1; WE: >6	
							70 mg/kg feed equivalent	6	31	Y: >7; A: 2	
							8.7 mg/day (70 mg/kg feed equivalent)	12	4	Y: >7; A: 2; WE: >7	
			LSC*	NS	NS	Oral (Capsule)	10 mg/kg bw*	NS	1	Y: >12; A: >12; WE: >12	Paulson and Feil (1969)
			GC*	0.01 mg/kg	NS	Dip	0.5% solution§	14	1	WE: 55	Ivey *et al.* (1984)
							1.0% solution§	14	1	WE: >56	
			Colorimetric	0.2 mg/kg	NS	Dust	4 g 5% dust/hen	NS	3¶	WE: 0	Johnson *et al.* (1963)
Propoxur	EU: not approved; USA: N/A	EU: 0.05 mg/kg	LC-DAD*	2 μg/kg	5 μg/kg	Henhouse sprayed	10 g/L**	NS	3††	WE: >25	Hamscher *et al.* (2003)
Permethrin	EU: not approved;	EU: 0.05 mg/kg; USA: 0.1 mg/kg	LSC	0.1 μg/kg	NS	Spray	3.77 mg/bird	7	1	Y: 27; A: 2	Hunt *et al.* (1979)
							11.94 mg/bird	7	1	Y: 48; A: 6	
	USA: N/A		GC	2 μg/kg	NS		20 mg/bird	7	1	Y: >21; A: 0	Braun *et al.* (1981)
			TLC*	10 μg/kg	NS	Oral (capsule)	10 mg/kg bw	NS	3	Y: >9; A: 6	Gaughan *et al.* (1978)
Deltamethrin	EU: not approved;	EU: 0.05 mg/kg; USA: 0.02 mg/kg	LSC & GC-MS*	5 μg/kg	NS	Feed	7.5 mg/bird	13	3	Y: >5; A: 5	Akhtar *et al.* (1985)
	USA: N/A		GC	10 μg/kg	NS	Oral (stomach tube)	10 mg/kg bw	NS	1	Y: >10; A: 10	Saleh *et al.* (1986)
Cypermethrin	EU: not approved;	EU: 0.05 mg/kg	GC	10 μg/kg	NS	Oral (stomach tube)	10 mg/kg bw	NS	1	Y: >10; A: 10	Saleh *et al.* (1986)
	USA: N/A		LSC	5 μg/kg	NS	Feed	3.1–6.1 mg/kg bw	12	3	Y: >11	Akhtar *et al.* (1987)
Fenvalerate	EU: not approved;	EU: 0.02 mg/kg	GC	10 μg/kg	NS	Oral (stomach tube)	10 mg/kg	NS	1	Y: >10; A: 10	Saleh *et al.* (1986)
	USA: N/A		LSC, TLC & GC	0.06 μg/g	NS	Oral (gavage)	7.5 mg/kg bw	12	4	Y: >6; A: 6	Akhtar *et al.* (1989)
			LSC & GLC*	0.02 μg/g	NS	Feed	9.2 mg/kg feed	12	49	WE: 8	Boyer *et al.* (1992)
Fluvalinate	EU: not approved;	None	LSC & LC	NS	NS	Oral (capsule)	0.1 mg/kg	NS	1	Y: 9‡‡	Staiger *et al.* (1982)
	USA: N/A						1 mg/kg bw	NS	1	Y: 12; A: 3‡‡	
							10 mg/kg bw	NS	1	Y: 13‡‡	
							100 mg/kg bw	NS	1	Y: 13‡‡	

Table 12. (Continued)

Ectoparasitics	Approval status (laying hens)*	Tolerance/ maximum residue limit†	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Phoxim	EU: approved; USA: N/A	EU: 60 μg/kg	HPLC*	2 μg/kg	5 μg/kg	Henhouse sprayed	0.2% solution§§	NS	1	WE: >25	Hamscher *et al.* (2007)
						Henhouse sprayed	0.2% solution§§	NS	2††	WE: >25	
Tetrachlorvinphos	EU: not approved; US: N/A	US: 0.2 mg/kg	GC	0.001 mg/kg	NS	Feed	50 mg/kg feed¶¶	NS	14	Y: 0	Wasti and Shaw (1971)
							100 mg/kg feed¶¶	NS	14	Y: 0	
							200 mg/kg feed¶¶	NS	14	Y: 0	
							400 mg/kg feed¶¶	NS	14	Y: 0	
							800 mg/kg feed¶¶	NS	14	Y: 1	
			GLC	0.02 mg/kg	NS		400 mg/kg feed	9	364	Y: 0; A: 0	Sherman and Herrick (1971)
							800 mg/kg feed	9	364	Y: 0; A: 0	
			LSC & GC-MS	0.01 mg/kg	NS		50 mg/kg feed & 450 μg P.O. (capsule)	18	7	WE: >7	Akhtar and Foster (1981)
			GC	0.008 mg/kg	NS	P.O. (Gavage)	25 mg/kg*** bw	NS	7	Y: 1	Yadava and Shaw (1970)
							50 mg/kg*** bw	NS	7	Y: 2	
							100 mg/kg*** bw	NS	7	Y: 3	
							200 mg/kg*** bw	NS	7	Y: >7	
			GC	0.004 mg/kg	NS	Dip	0.5% suspension†††	14	1	WE: 20	Ivey *et al.* (1982)
							1.0% suspension†††	14	1	WE: 14	
			GC	Y: 0.02; A: 0.01 mg/kg	NS	Henhouse sprayed	0.5 g/m^{2}***	NS	1	WE: 1	Pitois *et al.* (1973a)
							1 g/m^{2}***		1	WE: 7	
			GC	0.002 mg/kg	NS	Dust bath boxes or litter treated	450 g 3% dust for 20 birds	NS	28	Y: 0; A: 20	Ivey *et al.* (1969)
							45 g 75% powder for 20 birds	NS	28	Y: 13; A: 34	
Chlorpyrifos	EU: not approved; USA: N/A	0.01 mg/kg (EU & USA)	Potentiometric	0.2 mg/kg	NS	Oral	32 mg/kg bw	9	1	WE: >21	Abbassy *et al.* (1981)
Pirimiphosmethyl	EU: not approved; USA: N/A	EU: 0.05 mg/kg	Potentiometric	0.2 mg/kg	NS	Oral	35 mg/kg bw	9	1	WE: >21	Abbassy *et al.* (1981)
Dichlofenthion	EU: not approved; USA: N/A	None	GLC	Y: 19 μg/kg; A: 86 μg/kg	NS	Feed	50 mg/kg feed	7	55 weeks	Y: 0	Sherman *et al.* (1972)
							100 mg/kg feed	7	55 weeks	Y: 5	
							200 mg/kg feed	7	55 weeks	Y: 10	
							800 mg/kg feed	7	55 weeks	Y: 10	
Malathion	EU: not approved;	USA: 0.1 mg/kg	Radioassay	0.01 mg/kg	NS	Feed	100 mg/kg	8–9	15	Y: >9; A: >9; WE: >9	March *et al.* (1956)
	USA: N/A					Birds sprayed	38 mL of 0.5% solution‡‡‡ (190 mg/bird)	8–9	1	Y: >30	

Table 12. (Continued)

Ectoparasitics	Approval status (laying hens)*	Tolerance/ maximum residue limit†	Analytical method	Limit of detection	Limit of quantification	Route	Dose	Hen age (months)	Treatment duration (days)	Days from last treatment until residues no longer detected	Source
Coumaphos	EU: not approved; USA: N/A	None	Radioassay	0.02 mg/kg	NS	Birds dusted	50 mg/kg bw	18	1	Y: 10; A: 10	Dorough *et al.* (1961)
							50 mg/kg bw	18	2	Y: >12; A: 10	
			Fluorometric	0.02 mg/kg	NS	Henhouse dusted	5% dust, 2 oz/30 ft^2 floor space	NS	1	Y: 0	Shaw *et al.* (1964)
						Henhouse fogged	25% suspension, 2 oz/30 ft^2 floor space	NS	1	Y: 14§§§	
						Oral (capsule)	0.5 mg/kg bw¶¶¶	NS	7–10	Y: 0	
							1 mg/kg bw¶¶¶	NS	7–10	Y: 0	
							5 mg/kg bw¶¶¶	NS	7–10	Y: > 16‡‡	

Y, yolk; A, albumen; WE, whole egg; *see Appendix for list of definitions and abbreviations; †tolerance levels for pesticides in foods are set in the USA by the Environmental Protection Agency. EU maximum residue limits for pesticides in eggs are taken from the Council of the European Economic Community's directives 76/895/EEC, 86/362/EEC, 86/363/EEC and 90/642/EEC; ‡N/A: The US FDA does not issue approvals for pesticides; §prepared from a commercial 80% carbaryl wettable powder; ¶treatments were 4 days apart; **a commercially available propoxur solution (0.5–1%) was used; ††treatments were 7 days apart; ‡‡$n < 5$; §§a commercially available 50% phoxim solution was used to prepare treatments; ¶¶three formulations of encapsulated tetrachlorvinphos were used: a 93% formulation (100, 400 and 800 mg/kg feed); a 60% formulation (50, 100, 200, 400 and 800 mg/kg feed); and a 52% formulation (50 and 100 mg/kg feed). Residues were only detected in eggs of hens fed the 93% formulation at 800 mg/kg feed; ***a 75% powder was used to prepare treatments; †††prepared from a commercial 50% powder; ‡‡‡the 0.5% P^{32}-malathion solution was prepared from a concentrated solution of 57% P^{32}-malathion, 32% xylene and 11% Triton X-100; §§§no data available between days 7 and 14; ¶¶¶a commercial 50% oral drench powder was used.

developed resistance to many other insecticides (Axtell & Arends, 1990). Other pyrethroids commonly used include deltamethrin, cypermethrin and fenvalerate.

Pyrethroids are most often administered to poultry topically, as a spray or dust (Bishop, 2001). When topically applied, pyrethroids are absorbed and widely distributed to tissues, but concentrate particularly in fat and skin (Hunt *et al.*, 1979; Braun *et al.*, 1981; Heitzman, 1997, 2000). Residues in skin and fat are very persistent, as are residues in the egg yolk (Hunt *et al.*, 1979; Braun *et al.*, 1981) (Table 12).

In chickens, orally administered pyrethroids are widely distributed to tissues and extensively metabolized, with the highest residue concentrations occurring in the kidney, liver and fat (Gaughan *et al.*, 1978; Akhtar *et al.*, 1985, 1987, 1989; Hutson & Stoydin, 1987). Residues are found in egg albumen at low levels, and in egg yolks at similar concentrations to those found in kidney and liver for several days following oral dosing (Gaughan *et al.*, 1978; Akhtar *et al.*, 1985, 1989).

Organophosphates. Organophosphate insecticides (e.g. phoxim, coumaphos, tetrachlorvinphos, malathion) are potent acetylcholinesterase inhibitors that are applied to poultry houses or individual birds to treat infestations of lice, mites and ticks (Axtell & Arends, 1990; Blagburn & Lindsay, 2001). In chickens and other animals, organphosphates can be absorbed through the skin as well as through the mucous membranes of the eyes, respiratory tract and digestive system (Gupta & Paul, 1977; Abou-Donia *et al.*, 1982; Al-Saleh, 1994). Following absorption, organophosphates are extensively metabolized and distributed widely to tissues, and residues can be found in muscle, fat, internal organs and skin as well as eggs (March *et al.*, 1956; Ivey *et al.*, 1969; Yadava & Shaw, 1970; Sherman & Herrick, 1971; Pitois *et al.*, 1973b; Gupta & Paul, 1977; Akhtar & Foster, 1981). While in chickens the majority of an organophosphate dose is generally eliminated in a few days, detectable residues can persist in tissues and eggs for several weeks (March *et al.*, 1956; Dorough *et al.*, 1961) (Table 12). The limited available data suggest that in chickens elimination occurs primarily via the urine (Gupta & Paul, 1977). Tetrachlorvinphos residues appear to be more persistent in egg albumen than in yolk (Ivey *et al.*, 1969; Pitois *et al.*, 1973a), while the opposite may be true for coumaphos (Dorough *et al.*, 1961).

CONCLUSIONS

There are a large number of studies describing drug deposition and depletion from chicken eggs, but these are scattered throughout the primary literature. In this review, these data are compiled for easy reference to aid understanding and draw attention to the often overlooked issue of veterinary drug residues in eggs. It is important to note that laying hens deposit veterinary drugs from a wide variety of drug classes into their eggs, and residues can persist for some time after treatment has ended.

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APPENDIX

Definitions and abbreviations

Approval status	Approval by the Food and Drug Administration (USA) or the European Commission (EU).
Tolerance/maximum residue limit	'Tolerance' refers to the maximum drug residue level established by the U.S. Food and Drug Administration that is allowed for a particular drug in a given food product. 'Maximum residue limit' is the equivalent term for maximum allowable drug residue levels established by the European Commission (EC regulation 37/2010).
ASTED-LC	Automated sequential trace enrichment dialysis liquid chromatography
bw	Body weight
CF-LC	Continuous flow liquid chromatography
ELISA	Enzyme-linked immunosorbent assay
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
GLC	Gas-liquid chromatography
HPLC	High-performance liquid chromatography
HPLC-MS (-MS/MS)	High-performance liquid chromatography-mass spectrometry (or tandem mass spectrometry)
HPTLC	High-performance thin-layer chromatography
IC	Intra-cardiac
IM	Intramuscular
LC	Liquid chromatography
LC-APCI-MS	Liquid chromatography-atmospheric pressure chemical ionization mass spectrometry
LC-DAD	Liquid chromatography-diode array detection
LC-ES-MS/MS	Liquid chromatography-electrospray-tandem mass spectrometry.
LC-MS (-MS/MS)	Liquid chromatography-mass spectrometry (or tandem mass spectrometry)
LSC	Liquid scintillation counter (used to quantify radio-labelled drug)
NS	Not specified
PLE, LC-FLD	Pressurized liquid extraction and liquid chromatography with fluorescence detection.
RIA	Radioimmunoassay
SC	Subcutaneous
TLC	Thin-layer chromatography