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Kinetic Modelling and Residue Depletion of Drugs in Eggs

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Abstract 1. For the purpose of describing the relationship between plasma concentration of
 drugs and their deposition into eggs, a physiologically-based pharmacokinetic model was
 developed.

4 2. By incorporating the physiology of egg formation into the model, the transfer of drugs into
5 the egg albumin(albumen) and yolk could be described using rate constants.

6 3. Using datasets from the literature, the model was used to describe concentrations in
7 albumin and yolk of sulphanilamide, sulphaquinoxaline and pyrimethamine as a function of
8 time.

9 4. The model could be used as a tool to obtain an insight into those properties of a drug which
10 are responsible for the amount of residue in eggs, and could help in the design of critical
11 studies for determining withdrawal periods for eggs.

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INTRODUCTION

Veterinary drugs are therapeutically used in laying hens. The residues of these drugs and their metabolites are to some extent deposited in the eggs laid by the birds. Withdrawal periods are set to ensure consumer safety; only eggs laid after the withdrawal period may be designated for human consumption. In order to set safe withdrawal periods for eggs, residue depletion studies are performed. The disposition and depletion of a wide range of veterinary drugs in the egg albumin and yolk have been studied and described by many authors. Kan and Petz (2000) studied the factors that determine the distribution of residues between egg albumin and yolk of a wide range of drugs. They found that pKa values, lipid solubility or binding to albumen macromolecules could not be used to predict the distribution between the albumin and the yolk. The processes governing drug disposition in albumin and yolk are still not well understood. Some authors have proposed kinetic models to describe the residue concentration profiles in eggs laid after drug treatment. Donoghue et al. (1996, 1997) showed that the residue uptake by developing yolks showed a particular pattern following single drug administration which depended on the stage of development in the follicles. Based on their findings, they proposed a model to predict the residue concentration in yolks of laid eggs after multiple drug administration.

Although the authors recognised that plasma profiles will have an important influence on drug disposition in eggs, they did not include plasma profiles in their models. It is often reported that the residue profiles are different between albumin and yolk (Laurencot et al., 1972; Blom, 1975; Oikawa et al., 1977; Rodaut, 1989; Rodaut and Moretain, 1990; Rodaut et al., 1987; Nagata et al., 1989,1990; Chu et al., 2000; Giorgi et al., 2000). Typically, the residue concentrations in the yolk peak later than in the albumin. This is due to the fact that yolk and albumin develop at different stages of egg production, where the formation of yolk takes 8-11 d and the formation of albumin approximately 10 h. The drug disposition in the

yolk depends on the development stage of the oocyte, the plasma drug concentration and the physico-chemical properties of the drug (Geertsma et al., 1987). Therefore, the relationship between these three variables must be studied in order to understand the processes governing the drug residue profiles in eggs. However, the current models of residues in eggs do not include plasma drug concentration profiles. In this paper, we present a physiologically-based pharmacokinetic (PBPK) model that can be used to describe or predict the drug residue profiles of certain veterinary drugs in eggs based on their plasma kinetics. Published data were used to illustrate the applicability of the model, it was however noted that very few authors presented residue concentration data in plasma along with residue data in eggs.

Insights into the relationship between plasma concentration of a drug and its excretion *via* the egg could help in the design of critical residue studies. Furthermore, such a mathematical model could contribute to the study of the processes governing the deposition of chemicals in eggs, for example by relating the fitted model parameters to the physicochemical properties of the substance.

MATERIALS AND METHODS

53 Experimental method

All data for the calibration and testing of the model were obtained from the literature (Blom, 1975; Geertsema et al., 1987; Kan and Petz, 2000). The simulations were made using Multisim, a visual basic programme developed at the Medicines Evaluation Board, Veterinary Medicinal Products Unit, Den Haag, and based on the algorithms of Yamaoka, K. and Nakagawa, T. (1983). The programme is capable of solving sets of predefined differential equations in which time acts as an independent variable.

Description of the mathematical model

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1 2	62	The PBPK-model used to describe the relationship between the plasma conce	entration of a	
3 4	62	drug and its deposition in the agg is depicted in Figure 1		
5	05			
0 7	64	I ne formation of yolk and albumin are two distinct physiological process there		
8 9	65	Therefore, the disposition of a drug into one compartment is described independent	ently from the	
10 11	66	other. It is assumed that the nature of the process that governs the disposition	of drugs into	
12 13	67	egg yolk and egg albumin is that of a filtration-process rather than that of a c	oncentration-	
14 15	68	gradient driven process. This concept is introduced into the present PBPK- mo	odel. In this	
16 17	69	model ky and kw represent constants determining the amount of the administer	ed drug from	
18 10	70	the central compartment into the yolk and the albumin respectively. The concen	tration of the	
20 21	71	drug in the central compartment (plasma) is a function of time itself, and should	l be provided	
22	72	as an input to the model.		
23 24	73	Using the concepts described above, the general equations describing the transport rate		
25 26	74	of drug into the egg yolk and egg albumin are therefore:		
27 28	75	dQy/dt = C1(t). Ky.dWy/dt	[1]	
29 30	76	dQw/dt = C1(t). Kw.dWw/dt	[2]	
31 32	77	where:		
33 34	78	dQy/dt and dQw/dt = the rates of drug deposition into yolk and albumin (mg/day),		
35 36	79	dWy/dt and $dWw/dt =$ the formation rates of yolk and albumin (g/day),	Ky and Kw	
37 38	80	= transport constants into yolk and albumin,		
39 40	81	C1 = plasma concentration (mg/L).		
41 42	82			
43 44	83	Time dependent concentration in egg yolk		
45 46	84	A number of papers describe the rate of yolk formation (Geertsema et al., 1987; I	Kan and Petz,	
47 48	85	2000). It can be deduced from these papers that the formation rate of the eg	g yolk is not	
49 50	86	linear. Geertsema et al. (1987) characterised the rapid growth phase as an expon	ential growth	
51 52				
53				
04				

during the final 8-10 d before ovulation. The time dependent course of the egg yolk weight was shown to be sigmoidal when data obtained from the literature are plotted against time. Figure 2 shows the data obtained from literature (Geertsema et al., 1987) fitted according to the sigmoid-function described in equation [3] below. Using this sigmoid function to describe the time dependent weight of the follicle, the weight at time of ovulation (t = 0) can be estimated. As the weight of the follicle after ovulation does not increase, the sigmoid function is cut off at that time point. For an egg laid at time t = tlay, the equation describing the time-dependent weight development of that particular follicle before ovulation was: $Wy(t) = Ay/(1 + e^{-s.(t-(tlay-tsig-tlag))})$ [3] In which: tlay = time of egg lay (d),tlag = time interval between ovulation and egg lay (approximately 1 d), Wy = weight of the follicle at a given time before ovulation (g), Ay = apparent maximum follicle weight (g),s = maximum daily follicle growth rate constant, tsig = pre-ovulation time of maximum follicle growth rate (d). The average follicle develops over an 8-11 d period before the egg is laid (Geertsma et al., 1987). The maximum growth rate is achieved at a time point (tsig), which is approximately 1-3 d before ovulation. From the fitted data, it could be estimated that Ay is approximately 25 g, tsig = 2 d and s = 1 per d. It is clear that these variables may change with the breed and the production phase of the birds used in a particular experiment. The rate of yolk formation can therefore be described as the first derivative of the sigmoid-function [3]: $dWy/dt = Ay.s.e^{-s.(t-(tlay-tsig-tlag))}/(1+e^{-s.(t-(tlay-tsig-tlag))})^2$ [4]

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1 2	112	The overall equation, describing the rate of disposition of drug into the egg-yolk is:		
3 4	113	$dOv(t)/dt = kv.C1(t).Av.s.e^{-s.(t-(tlay-tsig-tlag))}/(1+e^{-s.(t-(tlay-tsig-tlag))})^2$ [5]		
5 6	114	So the time dependent course of the amount of drug in yolk at various egg laying times can be		
7 8		the time dependent course of the amount of drug in york at various egg raying times can be		
9	115	described by the following equation:		
10 11	116	tlay-tlag		
12 13	117	$Qy(tlay) = ky.Ay.s \int C1(t) e^{-s(t-(tlay-tsig-tlag))} / (1 + e^{-s(t-(tlay-tsig-tlag))})^2) dt $ [6]		
14 15	118	t = 0		
16 17	119	Since the weight of a follicle at time of egg lay is equal to its weight at ovulation, in this		
18 19	120	model this weight can be calculated to be:		
20 21	121	$Wy(tlay) = Ay/(1 + e^{-s.(tsig + tlag)})$ [7]		
22 23	122	Therefore, the overall equation describing the time dependent course of the concentration of a		
24 25	123	drug at various laying times Qy(tlay)/Wy(tlay) will be:		
26 27	124	tlay-tlag		
28 29 30 31	125	$Cy(tlay) = ky.(1 + e^{-s.(tsig+tlag)}).s. \int C1(t).e^{-s.(t-(tlay-tsig-tlag))} / (1 + e^{-s.(t-(tlay-tsig-tlag))})^2 dt [8]$		
	126	t = 0		
32 33	127			
34 35	128	Time dependent concentration in egg albumin		
36 37	129	Considering the relatively rapid formation of the albumin in the first 8-10 h (talbumin) after		
38 39	130	ovulation (tlay-tlag), it is assumed, as a first approximation, that formation of this component		
40 41	131	takes place at a constant rate:		
42 43	132	dWw/dt = Aw [9]		
44 45	133	So the equation, describing the disposition rate of a drug in egg albumin is:		
46 47	134	dQw(t)/dt = kw.Aw.C1(t) [10]		
48 49	135	in which:		
50 51 52 53 54 55 56 57 58 59	136	Aw = rate constant of egg albumin formation (g/d)		
60				

1		
2 3	137	The amount of drug in the albumin of an egg laid at $t = tlay$ would then be
4 5	138	tlay –tlag + talbumin
6	139	$Qw(tlay) = kw.Aw \int C1(t) dt $ [11]
8	140	t = tlay-tlag
10	141	Since the weight of egg albumin of a particular egg at $t = tlay$ can be calculated to be
12	142	the integral of equation [11] between $t = tlay-tlag$ and $t = tlay-tlag+talbumin$, being: Ww(tlay)
13	143	= Aw, talbumin, the overall equation describing the time-dependent course of the
15	144	concentration of a drug at various laying times will be:
17 18	145	tlay – tlag + talbumin
19 20	146	$Cw(tlay) = Qw(tlay)/Ww(tlay) = kw/talbumin. \int C1(t) dt $ [12]
21 22	147	t = tlay-tlag
23 24	148	In the simulations the average weight of the albumin, Ww(tlay), was assumed to be 34 g, and
25 26	149	the period of formation, talbumin, was assumed to be 10 h.
27 28	150	
29 30	151	RESULTS AND DISCUSSION
31 32	152	In order to test the mathematical model described above, a number of simulations was
33 34	153	performed using data obtained from the literature (Blom, 1975). In his paper on the residues
35 36	154	of drugs in eggs after medication of laying hens, Blom described the results of an experiment
37 38	155	in which groups of laying hens $(n = 12)$ were given medicated drinking water <i>ad libitum</i> over
39 40	156	8 consecutive d. A number of drugs were administered in that way (three sulphonamides and
41 42	157	pyrimethamine). Throughout the treatment and after its cessation, blood samples and eggs
43 44	158	were collected at various times and subsequently analysed for residues. The results were
45 46	159	reported in tabulated format.
47 48	160	
49 50	161	Simulations of the time dependent concentrations in eggs
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52 53		
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1 2	162	Using the model as described above, attempts were made to fit the time-dependent courses of			
3 4	163	the concentrations of sulphanilamide, pyrimethamine and sulphaninoxaline in egg yolk and			
5	105	the concentrations of surphamaniae, pyrinethannine and surphaquinoxanie in egg york and			
6 7	164	egg albumin as measured by Blom (1975). In order to calculate the time dependent courses of			
8 9	165	the plasma concentrations of the drugs, which are necessary input functions, the t1/2 values of			
10	166	the three compounds were estimated from the graphs. Next, the plasma curves were calculated			
11 12 13	167	assuming a relatively constant concentration during treatment (0-8 d), and a mono-			
14	168	exponential decay after cessation of the treatment.			
15 16 17	169	The following values could be derived from the tabulated data in the article of Blom			
17	170	(1975):			
19 20	171	Sulphanilamide $t1/2 = 1.2 d$ Csteady-state (d 8) = 58 mg/l			
21 22 23 24 25 26 27	172	Pyrimethamine $t1/2 = 2.1 d$ Csteady-state (d 8) = 1.6 mg/l			
	173	Sulphaquinoxaline $t1/2 = 1.3 d$ Csteady-state (d 8) = 96 mg/l			
	174	As a result, Figures 3 and 4 show the obtained data points and the simulations according to			
27 28	175	the model. Table and Figures 3 & 4 near here			
29 30	176	The only parameters used as variables in the 'fitting' of the data points according to the			
31 32 33 34 35 36	177	model were ky (for the egg yolk data) and kw (for the egg albumin data). These variables			
	178	obviously depend, among other things, on plasma protein binding, pKa-value and/or the			
	179	lipophilic affinity of a drug. The Table shows the values of ky and kw calculated from the fits.			
37 38	180	These results show that where the value of kw (rate constant for deposition in egg-			
39 40 41 42 43 44	181	albumin) is relatively constant, the values for ky (rate constant for deposition in egg-yolk) are			
	182	strongly drug related.			
	183	Limitations to the model			
45 46	184	Egg production is not uniform with regard to development time, the number of oocytes in the			
47 48	185	fast-growing stage, egg weight and the proportional weights of the yolk and albumin			
40 49 50 51 52	186	(Laurencot et al., 1972). Therefore, in some cases the fixed values in the model (for example,			

the time point of maximum oocyte growth) may need to be regarded as variables and altered. However, in studying a number of drugs using the same experimental conditions these values could be considered constant. Also the data used did not allow the establishment of the exact times of egg lay after dosing, and only rough estimates of the actual time-dependent course of the plasma concentrations could be calculated, because the experimental data sets did not focus specifically on all these aspects. Therefore, further experimental studiesfocusing on these aspects, would help to further validate the model. In conclusion, the model offers a generally-applicable tool that can be used to further investigate the properties of a drug that determine its residues in eggs which is independent of the physiological circumstances such as breed and egg production. REFERENCES BLOM, L. (1975) Plasma half-lives and the excretion into egg-white- and -yolk of three sulphonamides and pyrimethamine after medication to laying hens. Acta Pharmacologica et Toxicologica 37: 79-93 CHU, P-S., DONOGHUE, D.J. & SAIKH, B. (2000) Determination of total ¹⁴C residues of sarafloxacin in eggs of laying hens. Journal of Agricultural and Food Chemistry 48: 6409-DONOGHUE, D.J., HAIRSTON, H., GAINES, S.A., BARTHOLOMEW, M.J. & DONOGHUE, A.M. (1996) Modelling residue uptake by eggs. 1. Similar drug residue patterns in developing yolks following injection with ampicillin or oxytetracyclin. Poultry Science 75: 321-328 DONOGHUE, D.J., HAIRSTON, H., HENDERSON, H. MCDONALD, M., GAINES, S. & DONOGHUE, A.M. (1997) Modelling drug residue uptake by eggs: yolks contain ampicillin

1 2	211	residues even after drug withdrawal and nondetectability in the plasma. <i>Poultry Science</i> 76 :
3 4	212	458-462
5 6	213	GEERTSMA, M.F., NOUWS, J.F.M., GRONDEL, J.L., AERTS, M.M.L, VREE, T.B. &
7 8	214	KAN, C.A. (1987) Residues of sulphadimidine and its metabolites in eggs following oral
9 10	215	sulphadimidine medication of hens. The Veterinary Quarterly 9: 67-75
11 12	216	GIORGI, M., ROMANI, M., BAGLIACCA, M. & MENGOZZI, G. (2000) Determination of
13 14	217	thiamphenicol residues in albumin and yolk of hen eggs. Journal of Veterinary Pharmacology
15 16	218	and Therapeutics 23: 397-399
17	219	KAN, C.A. & PETZ, M. (2000) Residues of veterinary drugs in eggs and their distribution
19 20	220	between yolk and albumin. Journal of Agricultural and Food Chemistry 48: 6397-6403
21 22	221	LAURENCOT, H.J., SCHLOSSER, A. & HEMPSTEAD, J.L. (1972) The deposition and
23 24	222	clearance of Rofenaid® in chicken and turkey eggs. Poultry Science 51: 1181-1187
25 26	223	NAGATA, T., SAEKI, M., IIDA, T., KATAOKA, M. & INO, R. (1989) Transfer of dietary
27 28	224	sulfadimethoxine and sulfamonomethoxine into eggs and their disappearance from eggs.
29 30	225	Journal of the Food Hygienic Society of Japan 30 : 375-383
31 32	226	NAGATA, T., SAEKI, M., IIDA, T., KATAOKA, M. & INO, R. (1990) Residue studies in
33 34	227	egg on pyrimethamine given with feed. Journal of the Food Hygienic Society of Japan 31:
35 36	228	297-302
37 38	229	OIKAWA, H., NAKAMOTO, K., HIROTA, K. & KATAGIRI, K. (1977) Clearance of
39 40	230	sulfamethoxazole in eggs and tissues of chickens. Poultry Science 56: 813-821
41 42	231	RODAUT, B. (1989) Residues of aminoglicoside antibiotics in eggs after medication of
43 44	232	laying hens. British Poultry Science 30: 265-271
45 46	233	RODAUT, B. & MORETAIN, J.P. (1990) Residues of macrolide antibiotics in eggs
47 48	234	following medication of laying hens. British Poultry Science 31: 661-675
49 50		
51 52		
53 54		
55 56		
57		

2	235	RODAUT, B., MORETAIN, J.P. & BOISSEAU, J. (1987) Excretion of oxytetracycline in
4 5	236	eggs after medication of laying hens. Food Additives and Contaminants 4: 297-304.
5 6 7	237	
8 9	238	YAMAOKA, K. & NAKAGAWA, T. (1983). A nonlinear least squares program based on
10 11	239	differential equations, MULTI (RUNGE), for Microcomputers. Journal of
12 13	240	Pharmacobio-dynamics, 6: 595-606.
14	241	
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21 22		
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Figure 2. Development of egg yolk according to the sigmoid-function described in equation

[3] using data from Geertsema et al. (1987).



Figure 3. Simulation according to the model of the time dependent course of sulphanilamide

residues in egg albumin and yolk using data points from Blom (1975).

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Figure 4. Simulation according to the model of the time dependent course of pyrimethamine

residues in egg albumin and yolk using data points from Blom (1975).

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200	Compound	kv	kw
	Pyrimethamine	32	0.6
	Sulphanilamide	1	0.7
	Sulphaquinoxaline	0.3	0.3
259			
260			







Figure 3. Simulation of the time dependent course of sulphanilamide residues in egg white and yolk, using data from Blom (1975) 164x116mm (100 x 100 DPI)





Figure 4. Simulation of the time dependent course of pyrimethamine residues in egg white and yolk using data from Blom (1975) 164x116mm (100 x 100 DPI)