A generic avian physiologically-based kinetic (PBK) model

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INTRODUCTION

Physiologically-based kinetic (PBK) models are effective tools for designing toxicological studies and conducting extrapolations to inform hazard characterization in risk assessment by filling data gaps and defining safe levels of chemicals. Testing in birds is performed as a requirement for pesticide registration by regulatory authorities (Regulation (EC) No 1107/2009).

PBK models represent the body as a network of interconnected compartments linked via blood flow, as depicted in Figure 1. After an oral, dermal, or inhalation exposure to a compound, its absorption, distribution, metabolism, and excretion (ADME) processes are simulated by means of ordinary differential equations (ODE), allowing to simulate time-concentration curves in target organs.

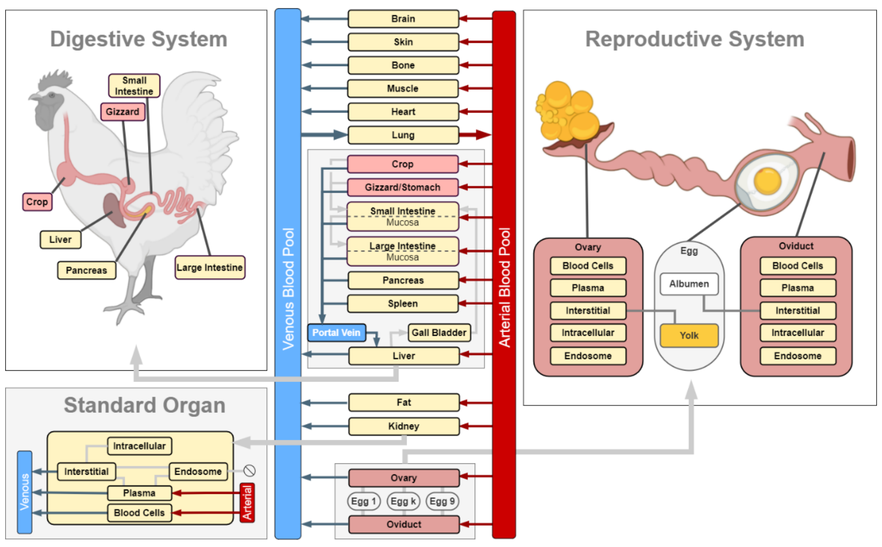

Figure 1. Schematic representation of the avian PBK model, with detail into the hen reproductive system. In the schematic PBK model structure, in the middle of the figure, the boxes in red (Crop, Gizzard/Stomach, and Ovary/Oviduct) are specific to the bird anatomy-physiology and were introduced as new compartments; with a schematic description of the reproductive system and of a standard organ are also displayed. This model is based on the chicken (Gallus gallus) *and extended to the mallard duck* (Anas platyrhynchos) *and bobwhite quail* (Colinus virginianus). *Egg 1, Egg k, and Egg 9, represent the egg cycle. Eggs grow over a nine days period, and thereafter one egg will be laid daily.*

OBJECTIVES

The aim of the project was to develop a generic avian PBK model for male and female birds, for three bird species, with a minimal set of model compartments (i.e., organs) blood, liver, kidneys, brain, muscle, gonads, fat, skin, heart, lung, and the gastrointestinal tract. To predict concentrations in egg white/albumen and yolk the reproductive system included ovary and oviduct. For the model development several partitioning coefficient (PC) calculation methods were explored. The developed PBK models were then qualified (validated) against in vivo (available) data. Finally, models were documented and scored following international guidance documents from WHO (2010) and OECD (2021).

METHODOLOGIES

The generic avian PBK model was developed following a “best practice” workflow describing how to build a PBK model for novel species, coded using PK-Sim and MoBi from the Open Systems Pharmacology Suite (OSPS), codes are available on GitHub..
The PBK analyses were performed using qualified installations of the PBK software PK-Sim (version 8.0). R (distribution 3.6) and RStudio (Version 1.2.5) were used.
The PBK model includes an ovulation model (egg development) to predict concentrations of chemicals in egg from dietary exposure.
The model was parametrized for chicken (*Gallus gallus*), bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynchos*) see Scanes et al., 2022a,b and was calibrated using nine chemicals for which *in vivo* studies were available for validation (see table 1).

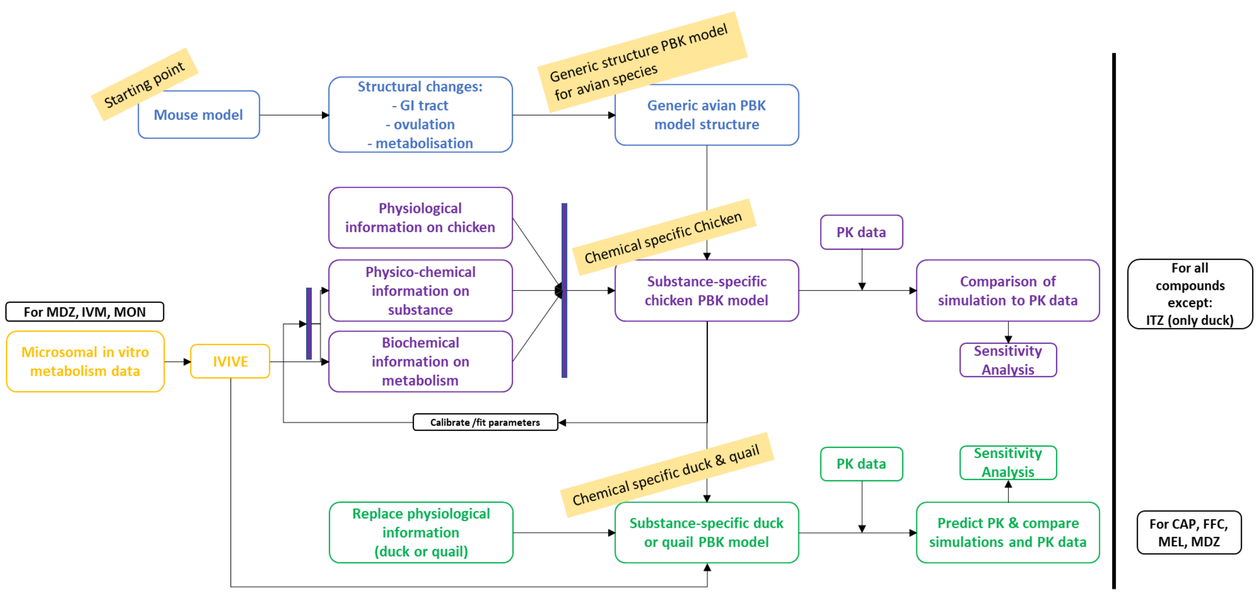

Figure 2. Detailed workflow of the steps taken to develop a generic sex specific avian PBK model, then applied to three bird species. Nine chemicals were used to calibrate the PBK models.

Table 1. List of compounds for which data were available to develop and validate for the three avian PBK model species.

Compound	CAS number	Qualification / Validation*
Chloramphenicol (CAP)	56-75-7	Chicken, duck
Deltamethrin (DTM)	52918-63-5	Chicken
Florfenicol (FFC)	73231-34-2	Chicken, quail
Ivermectin (IVM)	70288-86-7	Chicken
Melamine (MEL)	108-78-1	Chicken, duck, quail
Midazolam (MDZ)	59467-70-8	Chicken, quail
Monensin (MON)	22373-78-0	Chicken
Itraconazole (ITZ)	84625-61-6	Duck
Salinomycin (SAL)	53003-10-4	Chicken

CONCLUSIONS

The overall accuracy of the model predictions across the chemicals analyzed was found to be species- and compound-specific. To this end it was concluded that PBK models were often best informed for only one bird species (mainly chicken based on available literature data). Thus, when extrapolating to the other species (quail and duck) the system-specific compound data, (e.g., fraction unbound), were from the reference bird (chicken). In some cases, there are also marked PK differences between the three avian species. Overall, when developing the avian PBK model, a high variability in input data was observed, hinting at a great need for improved experimental and analytical consistency.

RESULTS

Simulations of tissue time-concentration (PK profile) curves were run for the nine-chemicals listed in table 1. However, in vivo egg data were available in chicken only for six chemicals (figure 3) and only for one chemical (MEL) in duck and quail (figure 4).
In order to assess the overall performance of the models, an analysis of the overall data points against the model predictions as a “goodness of fit” (GoF) criterium (as described in Lautz et al. (2020)) was made. The models were evaluated within a range of -three and -ten fold to account for variability from the in vivo studies. The performance analysis was conducted for each chemical by comparing all observed in vivo data by species, in figure 5 GoF plots for MEL in the three bird species are reported.

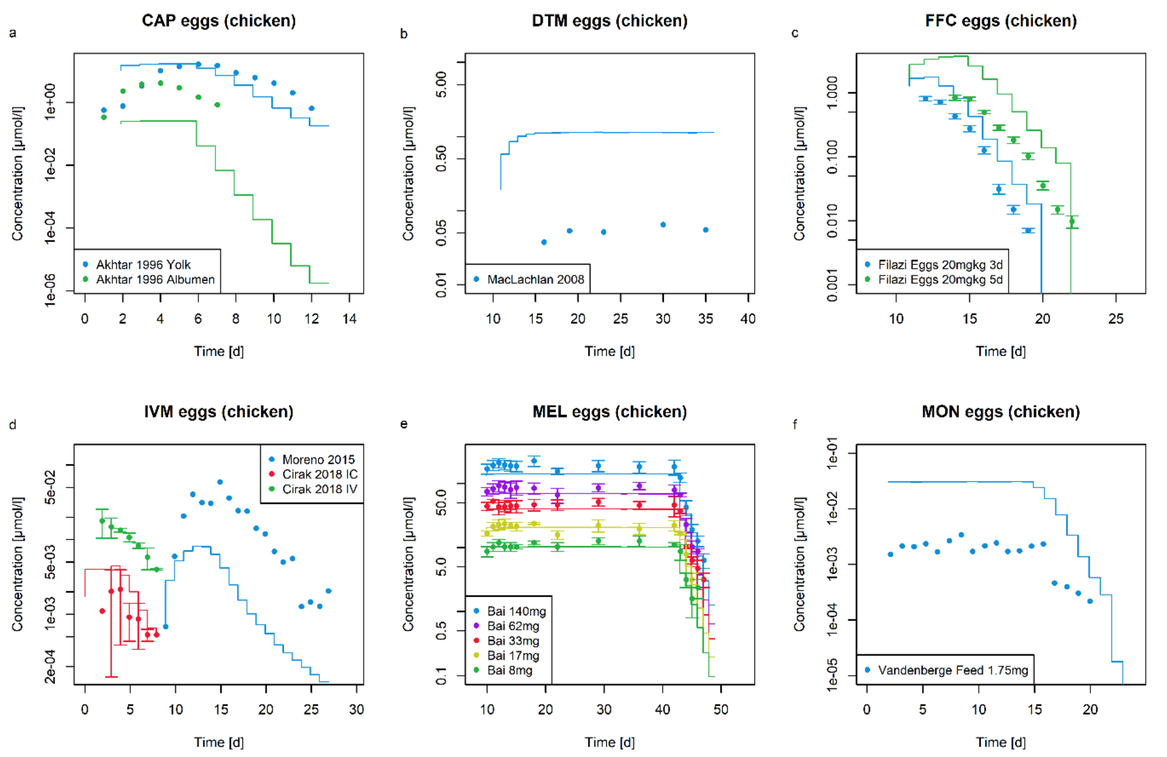

Figure 3 Chicken PBK model egg time (d, days) – concentration (umol/L) profile for six chemicals simulated by the general avian PBK model (continuous line) as compared to in vivo data (dots). Panel a) Simulation of Chloramphenicol (CAP) concentration in egg yolk and albumen evaluated with in vivo data, where laying hens were dosed multiple IC doses of 0.5 and 5 mg of CAP over a time period of 5 days; b) Deltamethrin (DTM) PBK model simulations, where laying hen were fed 20 mg/kg for 28 days (feed consumption of 104g/d); c). The antibiotic drug Florfenicol (FFC) simulations using the PBK model and measured from an in vivo study; d) Ivermectin (IVM) in vivo studies in laying hens, as compared to PBK model time concentration simulations in egg yolk; e) Melamine (MEL) PBK Model Egg concentration in time profile simulated as compared to the in vivo available data; f) PBK model simulation of Monensin (MON) egg concentrations in laying hen compared to in vivo data.

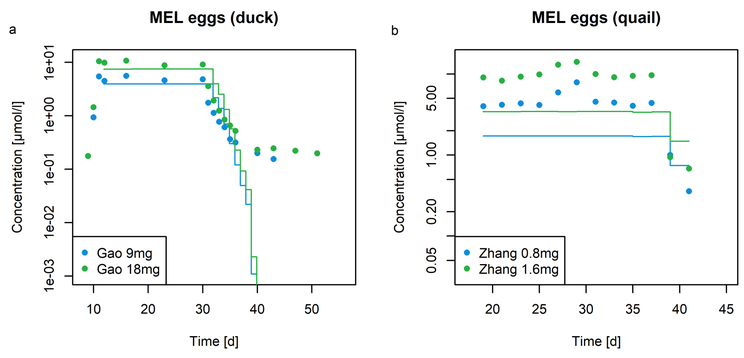

Figure 4 Duck and quail PBK model egg time (in days, d) - concentration (umol/L) profile for Melamine (MEL) chemicals simulated by the general avian PBK model (continuous line) set as laying hen as compared to in vivo data (dots).

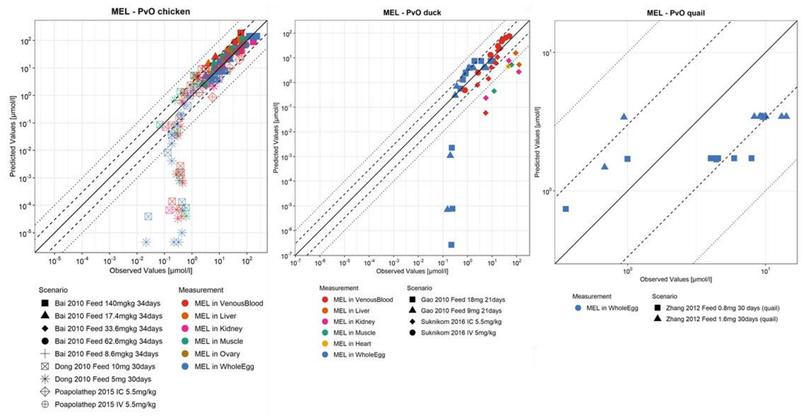

Figure 5 Comparison between quantities measured in avian in vivo studies and PBK model predictions for Melamine (MEL) in various organs for three species (chicken, duck, quail - as specified on the plots). Dotted lines represent 3-fold (dashed) and 10-fold (dotted) changes. Organs and experimental dataset references are indicated in legends: colours and shapes represent organs and studies, respectively.

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