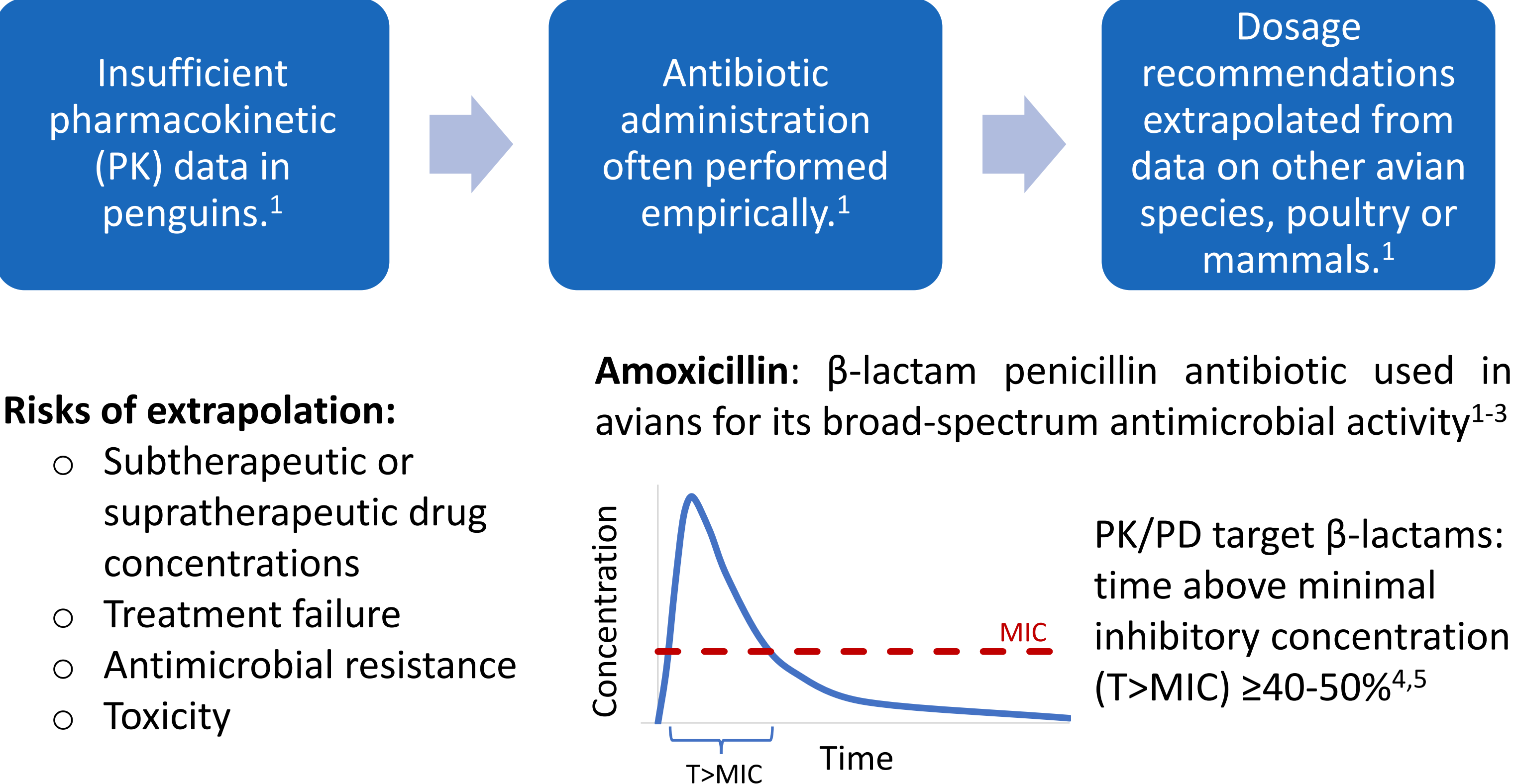


Population Pharmacokinetic Modeling of Amoxicillin in Penguins

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Introduction



PK data on amoxicillin in penguins are scarce, leading to **uncertainty about the optimal dose required to reach target concentrations.**

Objective: To characterize the pharmacokinetic parameters of amoxicillin in penguins.

Methods

- 1- Prospective study** at Marineland Parks, France
- Single intramuscular **amoxicillin** dose of 600 mg per penguin
 - Blood samples collected between 15 min to 96h post-dose (1-3 per penguin)
 - Quantification of amoxicillin plasma levels by **LC-MS/MS** (Liquid chromatography-tandem mass spectrometry)
- 2- Pharmacokinetic Analyses**
- **Non-compartmental analysis (NCA)** using the *Sparse NCA* function in Pkanalix v2024R1 → initial PK parameter estimates
 - **PopPK analysis** performed using nonlinear mixed-effects modeling in NONMEM v7.6 via Pirana v23.10.1
 - One- and two-compartment models tested with proportional, additive and combined error models
 - Covariate effects of body weight (BW) and sex evaluated based on changes in objective function value (OFV), interindividual variability (IIV) and relative standard error (RSE%)
 - Bootstrap analysis (n=1000) performed using the final model
 - **Data visualization and statistics** performed in R v4.4.2 with RStudio v2024.09.1
 - Observed vs. predicted concentrations (individual and population)
 - Weighted residuals vs. time / predicted concentrations
 - PK parameters vs. covariates (BW, sex)

Key findings

- This is the first popPK model to describe the PK profile of amoxicillin in penguins.
- Administered doses, standardized by BW, are generally higher than those reported in the literature for other avian species.^{2,3,6}
- The rapid absorption observed in penguins aligns with findings in birds.
- PK parameter differences, likely due to penguin-specific anatomical and physiological traits, highlight the need for popPK studies to allow tailored treatment.^{2,3,7}
- Simulations based on the final amoxicillin model will be performed to identify an optimal dosing regimen in penguins.

Results

Table 1. Characteristics of the population

Characteristics (units)	Median [range]
Number of penguins (M/F)	18 (7/11)
Age (years)	3 [1-21]
Body weight (kg)	4.00 [3.65-4.84]
Number of occasions	23
Number of blood samples	45

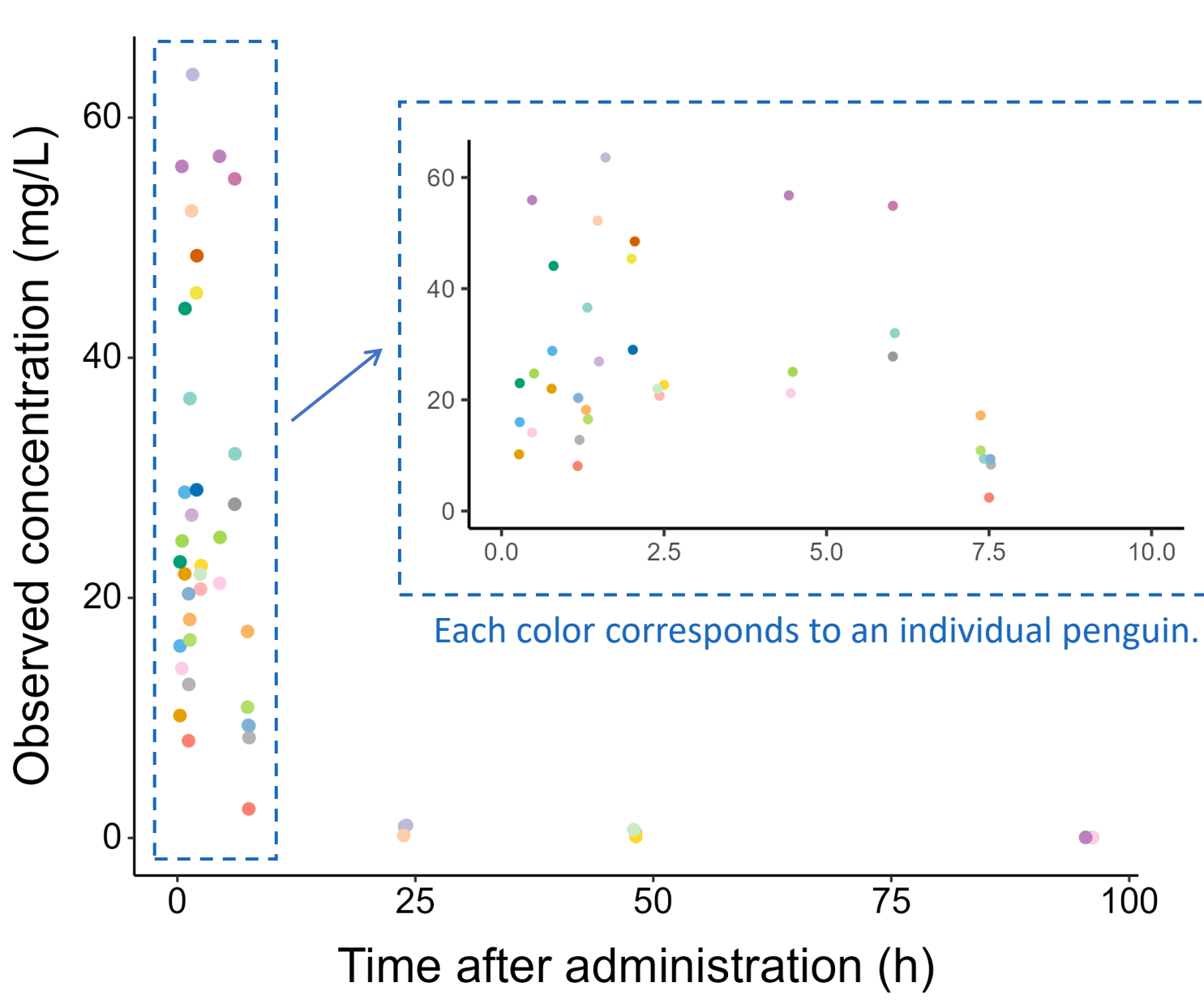


Figure 1. Observed amoxicillin concentrations over time

- High absorption observed and sparse data: NONMEM subroutine ADVAN1 TRANS2
- A one-compartment model with proportional error best described the data
- Body weight: significant covariate for apparent volume of distribution (V/F)
- Sex: significant covariate for apparent clearance (CL/F)

Table 2: Amoxicillin PK parameter and bootstrap estimates from the final model

Parameters		Estimates	RSE%	Bootstrap Mean (95% CI)
CL/F (L/h) ^a	θ ₁	2.49	10.1	2.51 (2.01-3.24)
	θ ₂	0.522	18.9	0.588 (0.431-0.776)
V/F (L) ^b	θ ₃	17.6	13.9	18.0 (13.9-23.6)
	θ ₄	0.760	43.0	0.577 (-0.298-1.27)
IIV (CV%)	CL/F	23.3	23.7	18.5 (3.20-28.1)
	V/F	47.6	36.3	46.6 (21.1-63.2)
RUV (mg/L)		0.389	13.5	0.377 (0.287-0.499)

^aCL/F = ($\theta_1 \times \theta_2 \times \text{SEX}$)
^bV/F = $\theta_3 \times \exp(\theta_4 \times (\text{BW} - \text{BW}_{\text{med}}))$ where BW_{med} is the penguins' median BW.
RSE relative standard error, CI confidence interval, IIV interindividual variability, CV coefficient of variation, RUV residual unexplained variability

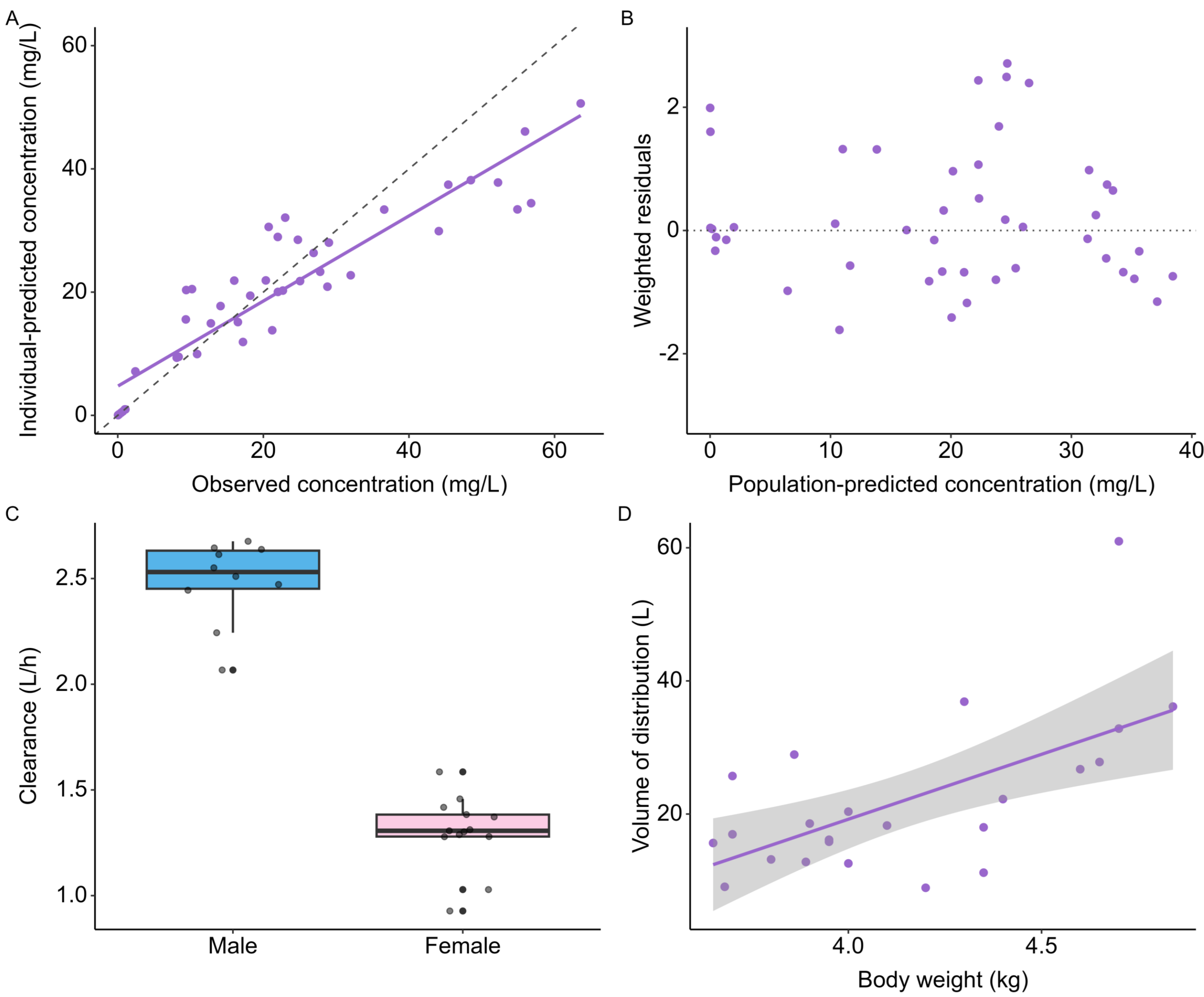


Figure 2: Diagnostic plots and covariate relationships from the final popPK model (A) Individual-predicted vs. observed concentrations, (B) Weighted residuals vs. population-predicted concentrations, (C) CL/F stratified by sex, (D) BW - V/F relationship

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