

Building and evaluation of a PBPK model for amikacin in adults

Version	1.2-OSP10.0
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	https://github.com/Open-Systems-Pharmacology/Amikacin-Model/releases/tag/v1.2
OSP Version	10.0
Qualification Framework Version	2.3

This evaluation report and the corresponding PK-Sim project file are filed at:

<https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/>

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1 Introduction

The presented model building and evaluation report evaluates the performance of a PBPK model for amikacin in adults.

Amikacin is a semi-synthetic aminoglycoside antibiotic used for a number of bacterial infections. Amikacin is administered in several forms, including intravenous or intramuscular injection. The PBPK model for amikacin was previously developed in PK-sim for adults ([Wendl 2011](#)) and preterm neonates ([Claassen 2015](#)). As the latter model was built more recently, this PBPK model was evaluated in evaluated its predictive performance of glomerular filtration rate (GFR) mediated clearance in adults without further changes. In this chapter we show that amikacin adequately described the pharmacokinetics of amikacin in adults, based on the PBPK model build and reported in preterm-neonates.

The amikacin model is a whole-body PBPK model, allowing for dynamic translation between individuals with GFR based renal elimination. The amikacin report demonstrates the level of confidence in the amikacin PBPK model build with the OSP suite with regard to reliable predictions of amikacin PK in adults during model-informed drug development.

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016). Relevant information on anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in adults was gathered from the literature and has been previously published (PK-Sim Ontogeny Database Version 7.3). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available PK-Sim® Ontogeny Database Version 7.3 (Schlender 2016) or otherwise referenced for the specific process.

The Amikacin model was evaluated in its performance in adults using data of the following publication:

- Walker JM, Wise R, Mitchard M. The pharmacokinetics of amikacin and gentamicin in volunteers: a comparison of individual differences. J Antimicrob Chemother. 1979 Jan;5(1):95-9.
(<https://academic.oup.com/jac/article/5/1/95/747852>)

As the PBPK of Amikacin has been previously developed, this model was rebuilt, without any further parameter identification using the Parameter Identification module provided in PK-Sim®.

Simulations using this PBPK model were compared to the reported data to evaluate model appropriateness and to assess model qualification, by means of diagnostics plots and predicted versus observed concentration-time profiles, of which the results support an adequate prediction of the PK in adults.

During model building, uncertainties in data quality, as well as study differences may cause not being able to adequately describe the PK of all reported clinical studies.

2.2 Data

2.2.1 In vitro / physico-chemical data

A literature search was performed to collect available information on physicochemical properties of amikacin. The obtained information from literature is summarized in the table below, and is used for model building.

Parameter	Unit	Amikacin literature	Description
MW	g/mol	588.6 (Claassen 2015)	Molecular weight
pKa		9.7, 8.92, 8.13 (Claassen 2015)	Acid dissociation constants
Solubility (pH)	mg/L	50 (Drugbank.ca)	Solubility
logMA		-0.48 (Claassen 2015)	Partition coefficient between octanol and water
fu		1 (Claassen 2015)	Fraction unbound
GFR		1 (Claassen 2015)	Glomerular Filtration Rate fraction

2.2.2 Clinical data

A literature search was performed to collect available clinical data on amikacin in adults.

The following publication was found in adults for the evaluation of the reported amikacin PBPK model:

Publication	Study description
Walker 1979	The pharmacokinetics of amikacin and gentamicin in healthy volunteers

2.3 Model Parameters and Assumptions

2.3.1 Absorption

As amikacin was administered only intravenously, absorption did not play a role in the PK of amikacin.

2.3.2 Distribution

Amikacin is a renally cleared antibiotic with relatively low distribution volume (approximately 0.25–0.50 L/kg in adults) Lanao et al. ([Lanao 1982](#)).

As the FDA ([FDA Label](#)) and the US national library of medicine (DailyMed) ([DailyMed](#)) report a serum protein binding $\leq 10\%$, and reports of serum protein binding range from 0 to 11% Claassen et al. ([Claassen 2015](#)) has applied a fraction unbound of 1 in the reported amikacin PBPK model.

As the FDA ([FDA Label](#)) and the US national library of medicine (DailyMed) ([DailyMed](#)) report a serum protein binding $\leq 10\%$ and range from 0 to 11% respectively, Claassen et al. ([Claassen 2015](#)) has applied a fraction unbound of 1 in the reported amikacin PBPK model.

The PK-Sim standard organ-plasma partition coefficient and cell permeability calculation methods that are built in PK-Sim were applied to evaluate the observed clinical data. Specific organ permeability normalized to surface area was automatically calculated by PK-Sim.

2.3.3 Metabolism and Elimination

Amikacin is eliminated by the kidneys without metabolism. In adults with normal renal function, 94–98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration in the kidney within 24 hours. ([DailyMed](#))

3 Results and Discussion

The previously developed PBPK model **amikacin** was evaluated with available clinical pharmacokinetic data in healthy adults after intravenous amikacin administration.

The fit resulted in an adequate description of the available data.

3.1 Final input parameters

The compound parameter values of the final amikacin PBPK model are illustrated below.

Compound: Amikacin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	50 mg/l	Publication-In Vitro-Drugbank.de	Measurement	True
Reference pH	7	Publication-In Vitro-Drugbank.de	Measurement	True
Lipophilicity	-0.48 Log Units	Publication-Other-Claassen et al 2015	Measurement	True
Fraction unbound (plasma, reference value)	1	Publication-Other-Claassen et al 2015	Measurement	True
Is small molecule	Yes			
Molecular weight	588.6 g/mol	Publication-Claassen et al 2015		
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Processes

Systemic Process: Glomerular Filtration-Claassen et al 2015

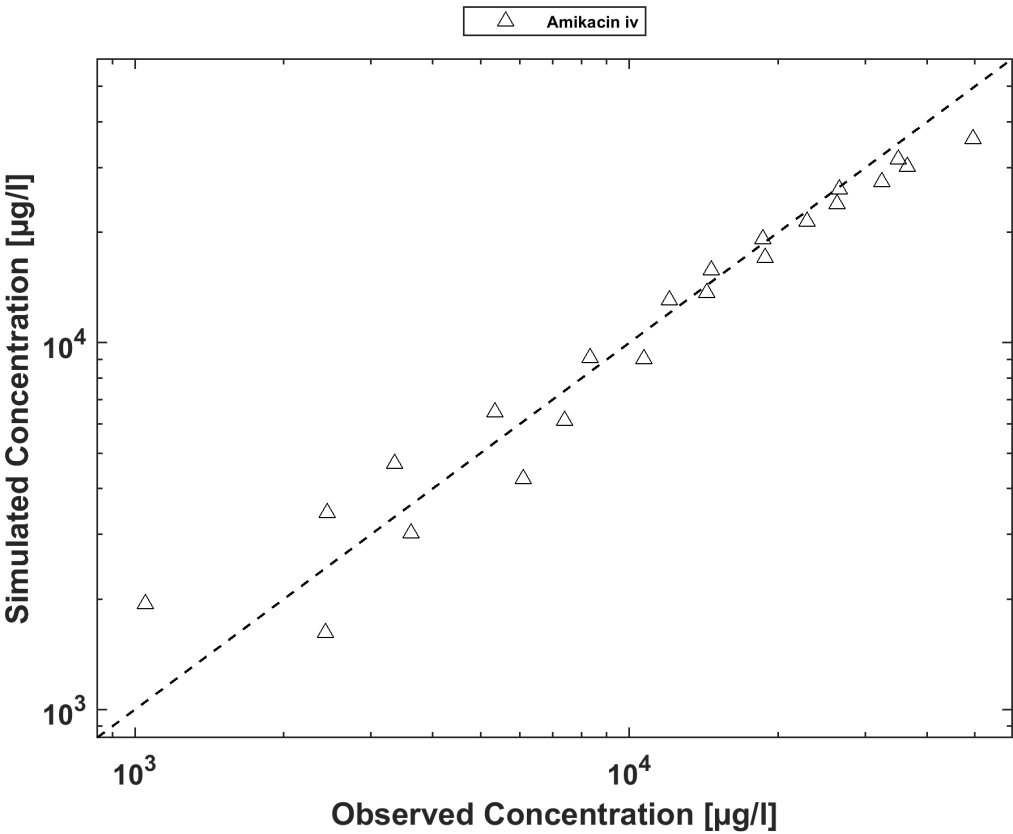
Species: Human

Parameters

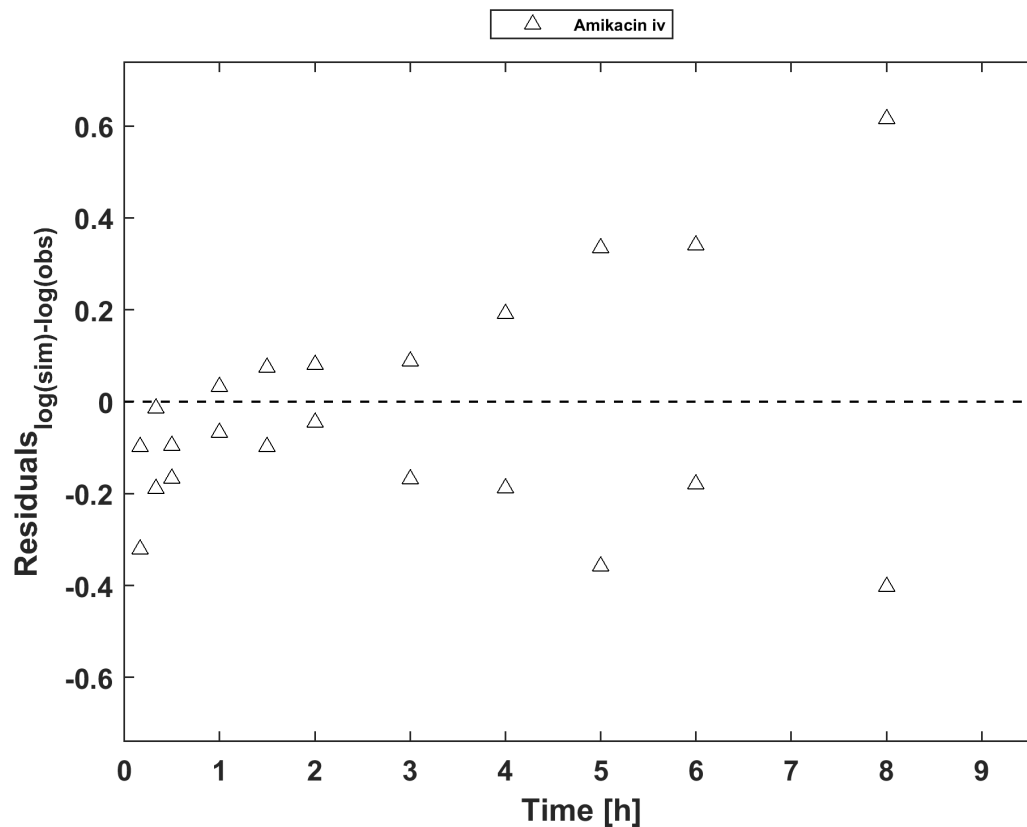
Name	Value	Value Origin
GFR fraction	1	Publication-Claassen et al 2015

3.2 Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for amikacin PBPK model performance (observed versus individually simulated plasma concentration and weighted residuals versus time of all data used for model building.



Goodness of fit plot for concentration in plasma.

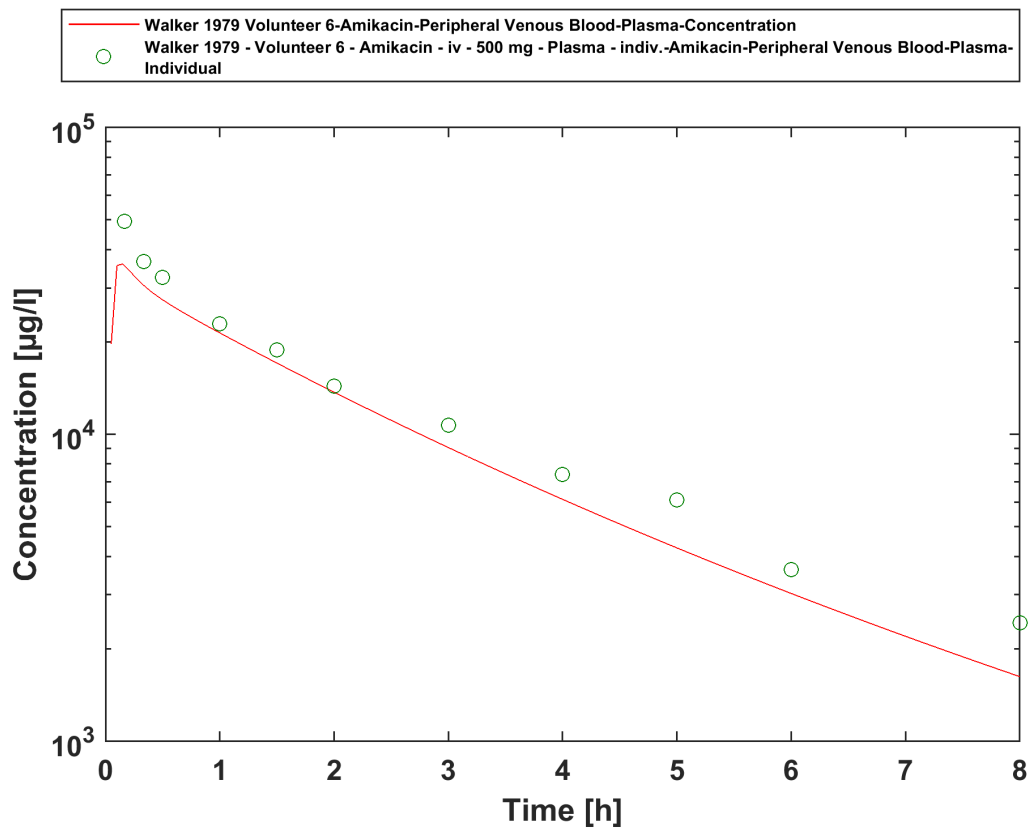


Goodness of fit plot for concentration in plasma.

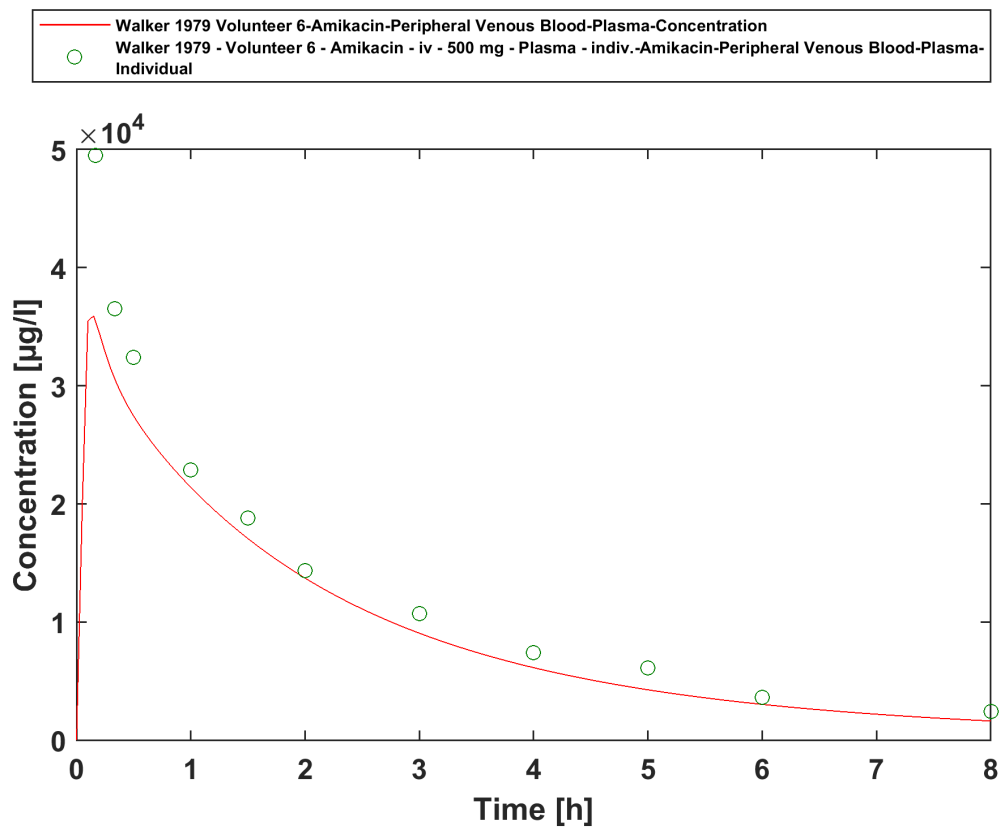
GMFE = 1.207636

3.3 Concentration-Time Profiles

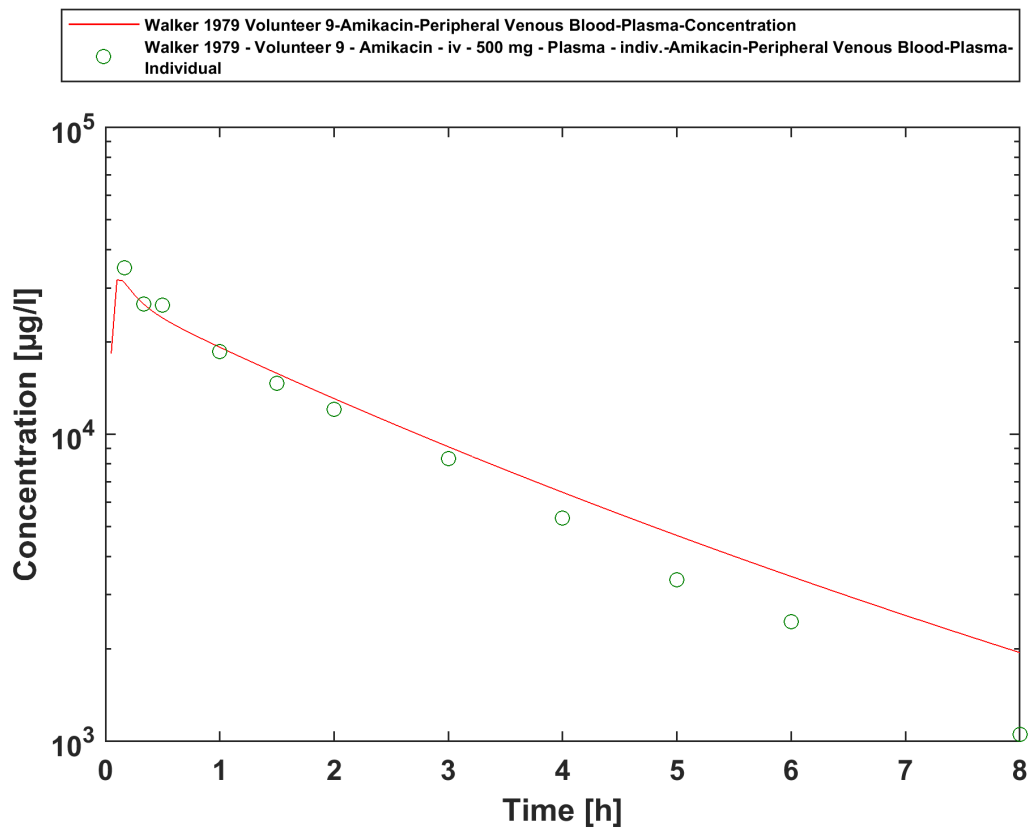
Simulated versus observed plasma concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.



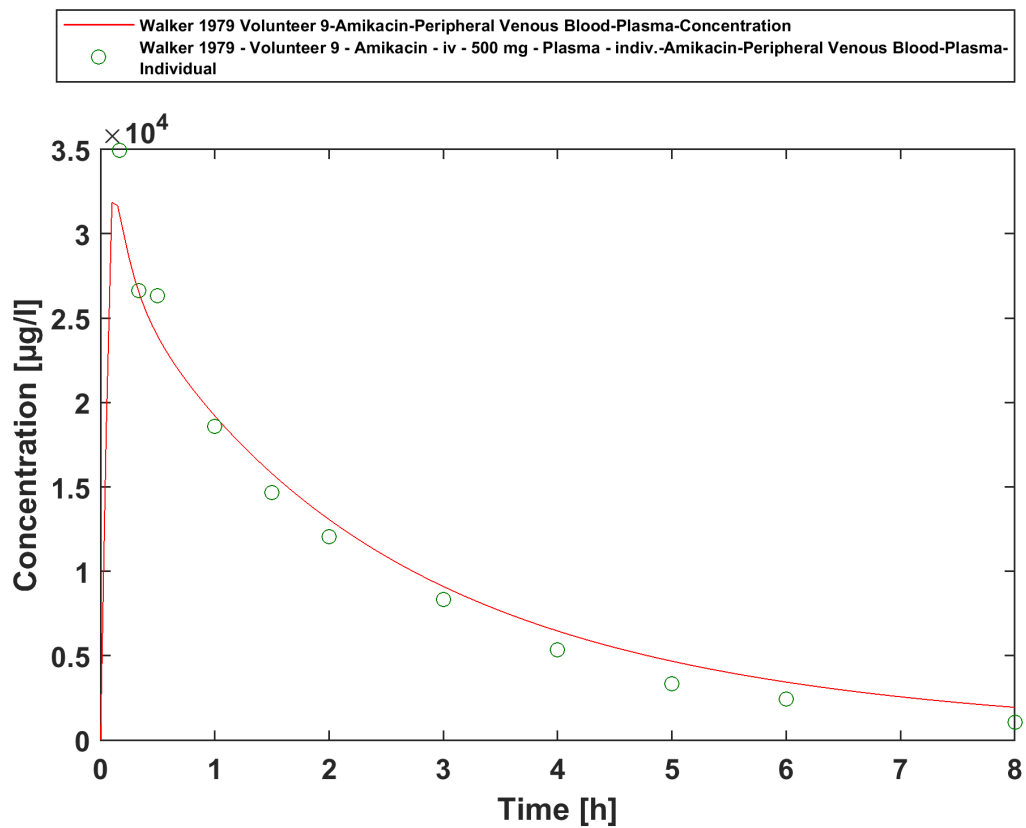
Time Profile Analysis



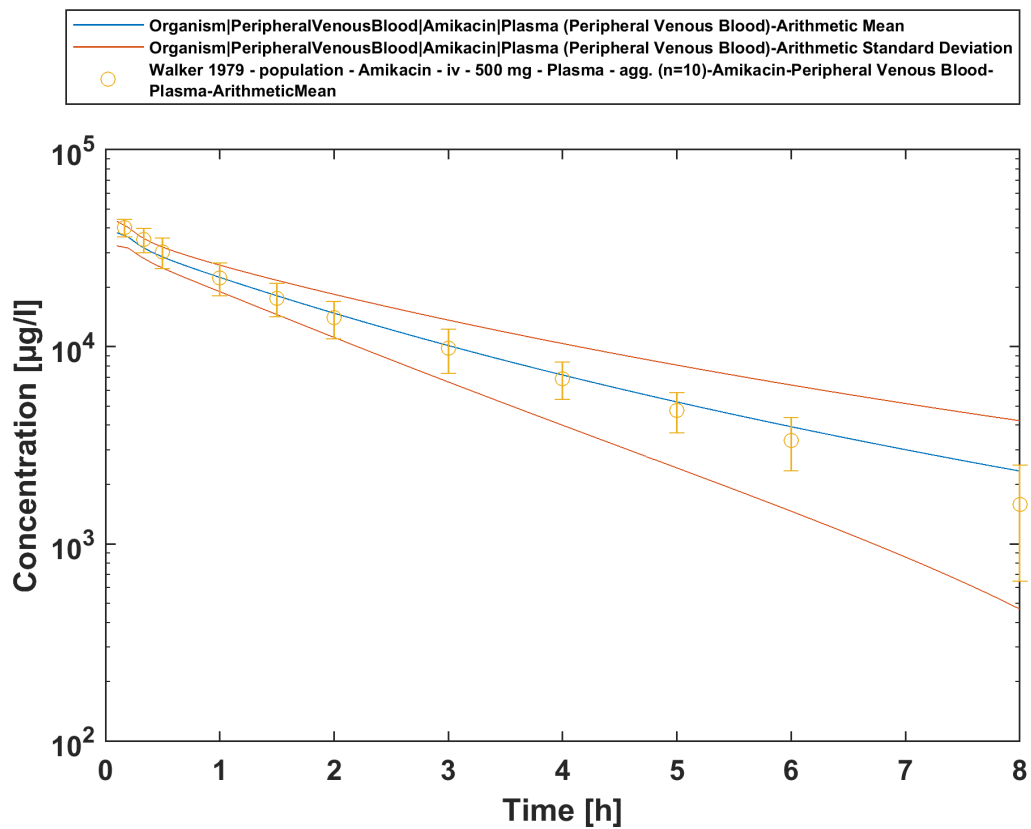
Time Profile Analysis 1



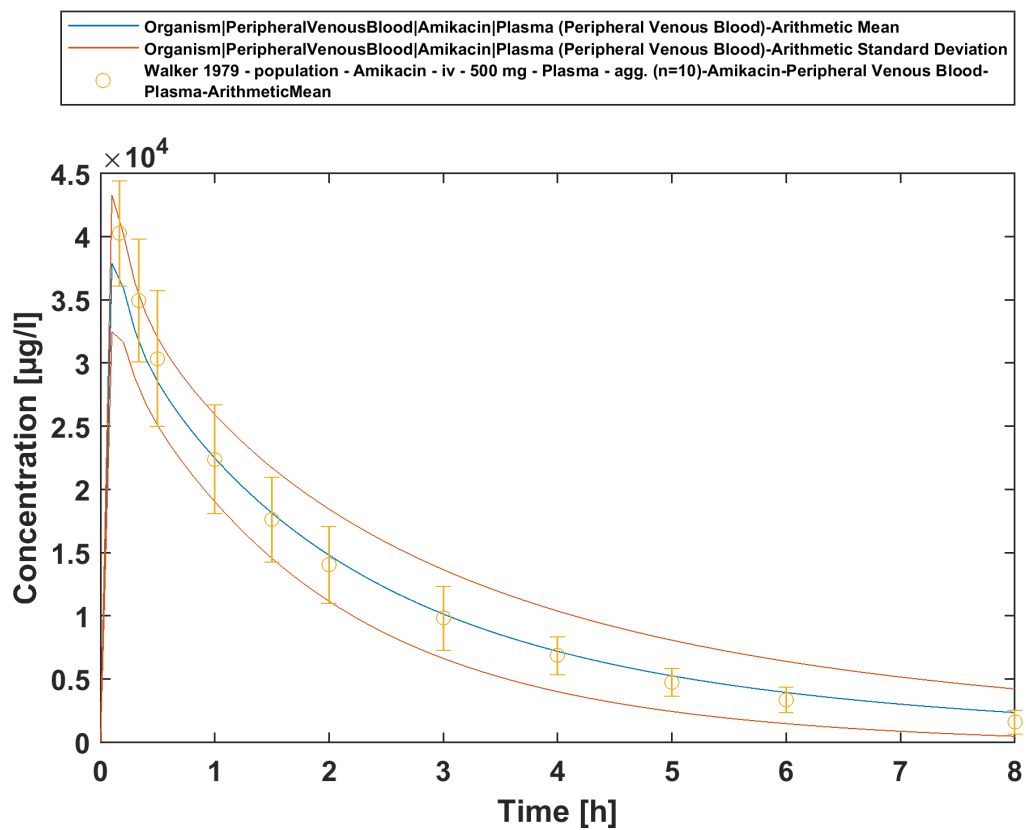
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1

4 Conclusion

The amikacin PBPK model applies glomerular filtration and adequately describes the pharmacokinetics of amikacin in adults receiving intravenous administration of amikacin.

This model could be applied for the investigation translation to special populations such as pediatrics with regard to renal elimination via glomerular filtrations.

5 References

Claassen 2015 Claassen K, Thelen K, Coboeken K, Gaub T, Lippert J, Allegaert K, Willmann S1. Development of a Physiologically-Based Pharmacokinetic Model for Preterm Neonates: Evaluation with In Vivo Data. *Curr Pharm Des.* 2015;21(39):5688-98.

DailyMed <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6ec3129b-c53b-4bdb-913d-a2d0060fa140&type=display>

Drugbank.ca (<https://go.drugbank.com/drugs/DB00479>)

FDA Label https://s3-us-west-2.amazonaws.com/drugbank/fda_labels/DB00479.pdf?1540245531

Kuepfer 2016 Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D. Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model. *CPT Pharmacometrics Syst Pharmacol.* 2016 Oct;5(10):516-531. doi: 10.1002/psp4.12134. Epub 2016 Oct 19.

Lanao 1982 Lanao JM, Dominguez-Gil A, Dominguez-Gil AA, et al. Modification in the pharmacokinetics of amikacin during development. *Eur J Clin Pharmacol* 1982; 23(2): 155-60.

PK-Sim Ontogeny Database Version 7.3 (<https://github.com/Open-Systems-Pharmacology/OSP Suite.Documentation/blob/38cf71b384cfc25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf>)

Walker 1979 Walker JM, Wise R, Mitchard M. The pharmacokinetics of amikacin and gentamicin in volunteers: a comparison of individual differences. *J Antimicrob Chemother.* 1979 Jan;5(1):95-9.

Wendl 2011 Wendl T, Niederalt C, Becker C, et al. Modeling of renal failure, dialysis, inhalation and mechanical ventilation: Development of a whole-body physiologically-based pharmacokinetic (PBPK) model for ICU patients with and without renal failure receiving inhalatively administered Amikacin via a tracheal tube. Presented at: *The Annual Meeting of the Population Approach Group in Europe* Athen. 2011; Abstr. 2194.