

Building and evaluation of a PBPK model for digoxin in adults

Version	2.0-OSP12.3
based on <i>Model Snapshot and Evaluation Plan</i>	https://github.com/Open-Systems-Pharmacology/Digoxin-Model/releases/tag/v2.0
OSP Version	12.3
Qualification Framework Version	3.7

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 digoxin in adults.

Digoxin is a cardiac glycoside used to treat atrial fibrillation, atrial flutter and heart failure. Digoxin is transported by P-glycoprotein 1 (P-gp), also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1) or cluster of differentiation 243 (CD243) poly-glycoprotein. P-gp and mainly excreted unchanged via the kidneys with a small fraction eliminated via biliary excretion and only a very low degree of hepatic metabolism ([Greiner 1999](#), [Ochs 1978](#)). Many other substrates of P-gp are metabolized by CYP3A4, setting digoxin apart as an exception and thereby turning it into a model victim drug of P-gp-mediated DDIs.

Digoxin is reported to have a large volume of distribution due to extensive tissue binding and to be mainly excreted unchanged to urine (50 - 70%) while the remainder of a dose is eliminated by hepatic metabolism and biliary excretion ([Ochs 1978](#), [Bauer 2008](#)). The final digoxin model applies target-binding, transport by P-gp in various organs including gut, liver and kidney, an unspecific hepatic metabolic clearance and glomerular filtration, and adequately described the pharmacokinetics of digoxin in adults.

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

2 Methods

The PBPK model for digoxin in this report is based on the developed and published digoxin PBPK model by Hanke *et al.* 2018. ([Hanke 2018](#))

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 ([Schlender 2016](#)). 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 ([PK-Sim Ontogeny Database Version 7.3](#)) or otherwise referenced for the specific process.

First, a base mean model was built using data from the single dose escalation study to find an appropriate structure describing the PK of digoxin. The mean PK model was developed using a typical European individual. Unknown parameters were identified using the Parameter Identification module provided in PK-Sim®. Structural model selection was mainly guided by visual inspection of the resulting description of data and biological plausibility.

Once the appropriate structural model was identified, additional parameters for different formulations were identified, if available.

A final PBPK model was established and simulations were compared to the reported data to evaluate model appropriateness and to assess model, 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 digoxin. The obtained information from the literature is summarized in the table below, and is used for model building.

Parameter	Unit	Digoxin literature	Description
MW	g/mol	780.93 (Drugbank)	Molecular weight
pKa		none	Acid dissociation constant
Solubility (pH)	mg/L	64.8 (7) (Drugbank)	Solubility
logP		1.22, 1.62, 1.67 (Alsenz 2007 , Hinderling 1984 , Atkinson 1988)	Partition coefficient between octanol and water
fu		70.0, 71.0, 77.7 (Hinderling 1984 , Obach 2008 , Neuhoff 2013)	Fraction unbound
ATP1A2 KD	μmol/L	0.0256 (Katz 2010)	Dissociation constant
ATP1A2 koff	1/min	n.a.	Dissociation rate constant
P-gp KM	μmol/L	73.0, 177.0 (Collett 2004 , Troutman 2003)	Michaelis-Menten constant
P-gp kcat	1/min	n.a.	P-gp catalytic rate constant
CLhep	mL/min	n.a.	Hepatic plasma clearance
GFR fraction	1/min	1	Fraction of filtered drug reaching the urine
Formulation		solution	Formulation used in predictions
Cell permeabilities		PK-Sim	Permeation across cell membranes
Partition coefficients		Rodgers & Rowland	Organ-plasma partition coefficients
Specific intest. perm.	dm/min	n.a.	Normalized to surface area
Specific organ perm.	dm/min	n.a.	Normalized to surface area

- ATP1A2: ATPase Na⁺/K⁺ transporting subunit alpha 2, CL: clearance, GFR: glomerular filtration rate, intest.: intestinal, n.a.: not available, perm.: permeability, P-gp: Pglycoprotein, PK-Sim: PK-Sim Standard calculation method, R + R: Rodgers and Rowland calculation method

2.2.2 Clinical data

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

The following publications were found in adults for model building and evaluation:

Publication	Study description
Becquemont 2001	Becquemont, L. et al. Effect of grapefruit juice on digoxin pharmacokinetics in humans. Clin. Pharmacol. Ther. 70, 311–6 (2001).
Ding 2004	Ding, R. et al. Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. Clin. Pharmacol. Ther. 76, 73–84 (2004).
Eckermann 2012	Eckermann, G., Lahu, G., Nassr, N. & Bethke, T.D. Absence of pharmacokinetic interaction between roflumilast and digoxin in healthy adults. J. Clin. Pharmacol. 52, 251–7 (2012).
Friedrich 2011	Friedrich, C. et al. Evaluation of the pharmacokinetic interaction after multiple oral doses of linagliptin and digoxin in healthy volunteers. Eur. J. Drug Metab. Pharmacokinet. 36, 17–24 (2011).
Greiner 1999	Greiner, B. et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J. Clin. Invest. 104, 147–53 (1999).
Gurley 2008b	Gurley, B.J., Swain, A., Williams, D.K., Barone, G. & Battu, S.K. Gauging the clinical significance of P-glycoprotein-mediated herb-drug interactions: comparative effects of St. John's wort, Echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. Mol. Nutr. food Res. 52, 772–9 (2008).
Hayward 1978	Hayward, R.P., Greenwood, H. & Hamer, J. Comparison of digoxin and medigoxin in normal subjects. Br. J. Clin. Pharmacol. 6, 81–6 (1978).
Jalava 1997	Jalava, K.M., Partanen, J. & Neuvonen, P.J. Itraconazole decreases renal clearance of digoxin. Ther. Drug Monit. 19, 609–13 (1997).
Johne 1999	Johne, A. et al. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). Clin. Pharmacol. Ther. 66, 338–45 (1999).
Kirby 2012	Kirby B.J., Collier A.C., Kharasch E.D., Whittington D., Thummel K.E., Unadkat J.D. Complex drug interactions of the HIV protease inhibitors 3: effect of simultaneous or staggered dosing of digoxin and ritonavir, nelfinavir, rifampin, or bupropion. Drug Metab Dispos. 2012 Mar;40(3):610-6.
Kirch 1986	Kirch, W., Hutt, H.J., Dylewicz, P., Gräf, K.J. & Ohnhaus, E.E. Dose-dependence of the nifedipine-digoxin interaction? Clin. Pharmacol. Ther. 39, 35–9 (1986).
Koup 1975	Koup, J.R., Greenblatt, D.J., Jusko, W.J., Smith, T.W. & Koch-Weser, J. Pharmacokinetics of digoxin in normal subjects after intravenous bolus and infusion doses. J. Pharmacokinet. Biopharm. 3, 181–92 (1975).
Kramer 1979	Kramer, W.G. et al. Pharmacokinetics of digoxin: relationship between response intensity and predicted compartmental drug levels in man. J. Pharmacokinet. Biopharm. 7, 47–61 (1979).
Lalonde 1985	Lalonde, R.L., Deshpande, R., Hamilton, P.P., McLean, W.M. & Greenway, D.C. Acceleration of digoxin clearance by activated charcoal. Clin. Pharmacol. Ther. 37, 367–71 (1985).
Larsen 2007	Larsen, U.L. et al. Human intestinal P-glycoprotein activity estimated by the model substrate digoxin. Scand. J. Clin. Lab. Invest. 67, 123–34 (2007).
Martin 1997	Martin, D.E. et al. Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers. Br. J. Clin. Pharmacol. 43, 661–4 (1997).

Publication	Study description
Ochs 1975	Ochs, H., Bodem, G., Schäfer, P.K., Kodrat, G., Dengler, H.J. Absorption of digoxin from the distal parts of the intestine in man. <i>Eur J Clin Pharmacol.</i> 1975 Dec 19;9(2-3):95-7.
Ochs 1978	Ochs, H., Greenblatt, D.J., Bodem, G. & Harmatz, J.S. Dose-independent pharmacokinetics of digoxin in humans. <i>Am. Heart J.</i> 96, 507–11 (1978).
Oosterhuis 1991	Oosterhuis, B., Jonkman, J.H., Andersson, T., Zuiderwijk, P.B. & Jedema, J.N. Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. <i>Br. J. Clin. Pharmacol.</i> 32, 569–72 (1991).
Qiu 2010	Qiu, R. et al. Lack of a pharmacokinetic interaction between dimebon (latrepirdine) and digoxin in healthy subjects. <i>Am. Soc. Clin. Pharmacol. Ther. Meet. Atlanta, GA, USA</i> (2010).
Ragueneau 1999	Ragueneau, I. et al. Pharmacokinetic and pharmacodynamic drug interactions between digoxin and macrogol 4000, a laxative polymer, in healthy volunteers. <i>Br. J. Clin. Pharmacol.</i> 48, 453–6 (1999).
Rengelshausen 2003	Rengelshausen, J. et al. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. <i>Br. J. Clin. Pharmacol.</i> 56, 32–8 (2003).
Rodin 1988	Rodin, S.M., Johnson, B.F., Wilson, J., Ritchie, P. & Johnson, J. Comparative effects of verapamil and isradipine on steady-state digoxin kinetics. <i>Clin. Pharmacol. Ther.</i> 43, 668–72 (1988).
Steiness 1982	Steiness, E., Waldorff, S. & Hansen, P.B. Renal digoxin clearance: dependence on plasma digoxin and diuresis. <i>Eur. J. Clin. Pharmacol.</i> 23, 151–4 (1982).
Tayrouz 2003	Tayrouz, Y. et al. Pharmacokinetic and pharmaceutic interaction between digoxin and Cremophor RH40. <i>Clin. Pharmacol. Ther.</i> 73, 397–405 (2003).
Tsutsumi 2002	Tsutsumi, K. et al. The effect of erythromycin and clarithromycin on the pharmacokinetics of intravenous digoxin in healthy volunteers. <i>J. Clin. Pharmacol.</i> 42, 1159–64 (2002).
Vaidyanathan 2008	Vaidyanathan, S. et al. Pharmacokinetics of the oral direct renin inhibitor aliskiren in combination with digoxin, atorvastatin, and ketoconazole in healthy subjects: the role of P-glycoprotein in the disposition of aliskiren. <i>J. Clin. Pharmacol.</i> 48, 1323–38 (2008).
Verstuyft 2003	Verstuyft, C. et al. Dipyridamole enhances digoxin bioavailability via P-glycoprotein inhibition. <i>Clin. Pharmacol. Ther.</i> 73, 51–60 (2003).
Wagner 1981	Wagner, J.G., Popat, K.D., Das, S.K., Sakmar, E. & Movahhed, H. Evidence of nonlinearity in digoxin pharmacokinetics. <i>J. Pharmacokinet. Biopharm.</i> 9, 147–66 (1981).
Westphal 2000	Westphal, K. et al. Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. <i>Clin. Pharmacol. Ther.</i> 68, 6–12 (2000).

2.3 Model parameters and assumptions

2.3.1 Absorption

For oral administration of digoxin, the following parameters, amongst others, play a role with regards to the absorption kinetics of a compound, which can be estimated with PBPK: solubility, lipophilicity and intestinal permeability. To accurately predict the digoxin plasma concentrations following intravenous and oral administration, the relative expression of P-gp in the intestinal mucosa was increased (3.57-fold) compared to the PK-Sim database RT-PCR expression profile (see table below). This factor has been identified in an optimization that included digoxin plasma concentrations and fraction excreted to urine data following intravenous and oral administration plus digoxin excreted to duodenum measurements after intravenous administration [Caldwell 1976](#). The optimized P-gp expression profile shows highest expression in small intestinal mucosa (1.41 $\mu\text{mol/L}$), followed by kidney (1.00 $\mu\text{mol/L}$), large intestinal mucosa (0.56 $\mu\text{mol/L}$), liver (0.27 $\mu\text{mol/L}$) and tissues of lower expression. Implementation of transport by OATP (4C1) did not improve the model performance and was not used in the final model.

Protein	Mean reference concentration [μmol protein/L in the tissue of highest expression]	Geometric standard deviation of reference concentration	Relative expression in the different organs (PK-Sim expression database profile)	Half-life liver [h]	Half-life intestine [h]
P-gp (efflux)	1.41 optimized	1.60 (Prasad 2014)	RT-PCR, with the relative expression in intestinal mucosa increased by a factor of 3.57 (optimized)(Nishimura 2005)	36	23

2.3.2 Distribution

Digoxin is reported to have a large volume of distribution due to extensive tissue binding and to be mainly excreted unchanged to urine (50 - 70%) while the remainder of a dose is eliminated by hepatic metabolism and biliary excretion ([Ochs 1978](#), [Bauer 2008](#)). Implementation of target-binding to the ATPase Na^+/K^+ transporting subunit alpha 2 (ATP1A2) was crucial, to mechanistically describe the large volume of distribution and the long plasma half-life of digoxin.

It has reported that the fraction unbound of digoxin ranges from 70 to 77.9% ([Hinderling 1984](#), [Obach 2008](#), [Neuhoff 2013](#)).

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation method by Rodgers and Rowland, and PK-Sim standard cell permeability calculation method. Specific organ permeability normalized to surface area was automatically calculated by PK-Sim.

2.3.3 Metabolism and Elimination

The final digoxin model applies target-binding to the ATP1A2, transport by P-gp in various organs including gut, liver and kidney, an unspecific hepatic metabolic clearance and glomerular filtration.

3 Results and Discussion

The PBPK model for digoxin was developed with clinical pharmacokinetic data covering intravenous as well as oral administration with a dose range of 0.125 to 1.5 mg including single dose and multiple dose clinical data, for different types of tablet formulations.

During the model-fitting, the following parameters were estimated (all other parameters were fixed to reported values):

- Lipophilicity
- ATP1A2 Dissociation constant (K_d)
- P-gp catalytic rate constant (K_{cat})
- Hepatic Clearance (CL_{hep})
- Specific intestinal permeability (transcellular)
- Specific organ permeability

The fit resulted in an adequate description of the clinical data. Additional implementation of transport by OATP (4C1) did not improve the model performance and was not used in the final model.

3.1 Digoxin final input parameters

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

Compound: Digoxin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	64.8 mg/l	Internet-In Vitro-Drugbank	Aqueous Solubility	True
Reference pH	7	Internet-In Vitro-Drugbank	Aqueous Solubility	True
Lipophilicity	1.40017663 Log Units	Parameter Identification-Parameter Identification	fitted	True
Fraction unbound (plasma, reference value)	0.71	Publication-In Vitro-Neuhoff 2013	Neuhoff (2013)	True
Permeability	1.0115E-05 dm/min		fitted	True
Specific intestinal permeability (transcellular)	2.7627E-07 dm/min		fitted	True
Is small molecule	Yes			
Molecular weight	780.93 g/mol	Internet-In Vitro-Drugbank		
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard

Processes

Specific Binding: ATP1A2-Katz (2010)

Molecule: ATP1A2

Parameters

Name	Value	Value Origin
koff	0.00098888 1/min	Publication-In Vitro-Katz 2010
Kd	25.6 nmol/l	Parameter Identification

Systemic Process: Total Hepatic Clearance-Fitted

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.71	
Lipophilicity (experiment)	1.40017663 Log Units	
Plasma clearance	0 ml/min/kg	
Specific clearance	0.03758077 1/min	Parameter Identification

Transport Protein: P-gp-Stephens (2001)

Molecule: P-gp

Parameters

Name	Value	Value Origin
Transporter concentration	1 $\mu\text{mol/l}$	
Vmax	8.67 $\mu\text{mol/l/min}$	
Km	177 $\mu\text{mol/l}$	
kcat	71.163 1/min	Parameter Identification

Systemic Process: Glomerular Filtration-Steiness (1982)

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Steiness (1982)

3.2 Digoxin Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for digoxin PBPK model performance (observed versus individually simulated plasma concentration and weighted residuals versus time, including the geometric mean fold error (GMFE)) of all data used for model building.

Table 3-1: GMFE for Goodness of fit plot for concentration in plasma.

Group	GMFE
Digoxin colonic admin.	2.13
Digoxin iv	1.45
Digoxin po SD	1.30
Digoxin po, MD	1.64
All	1.46

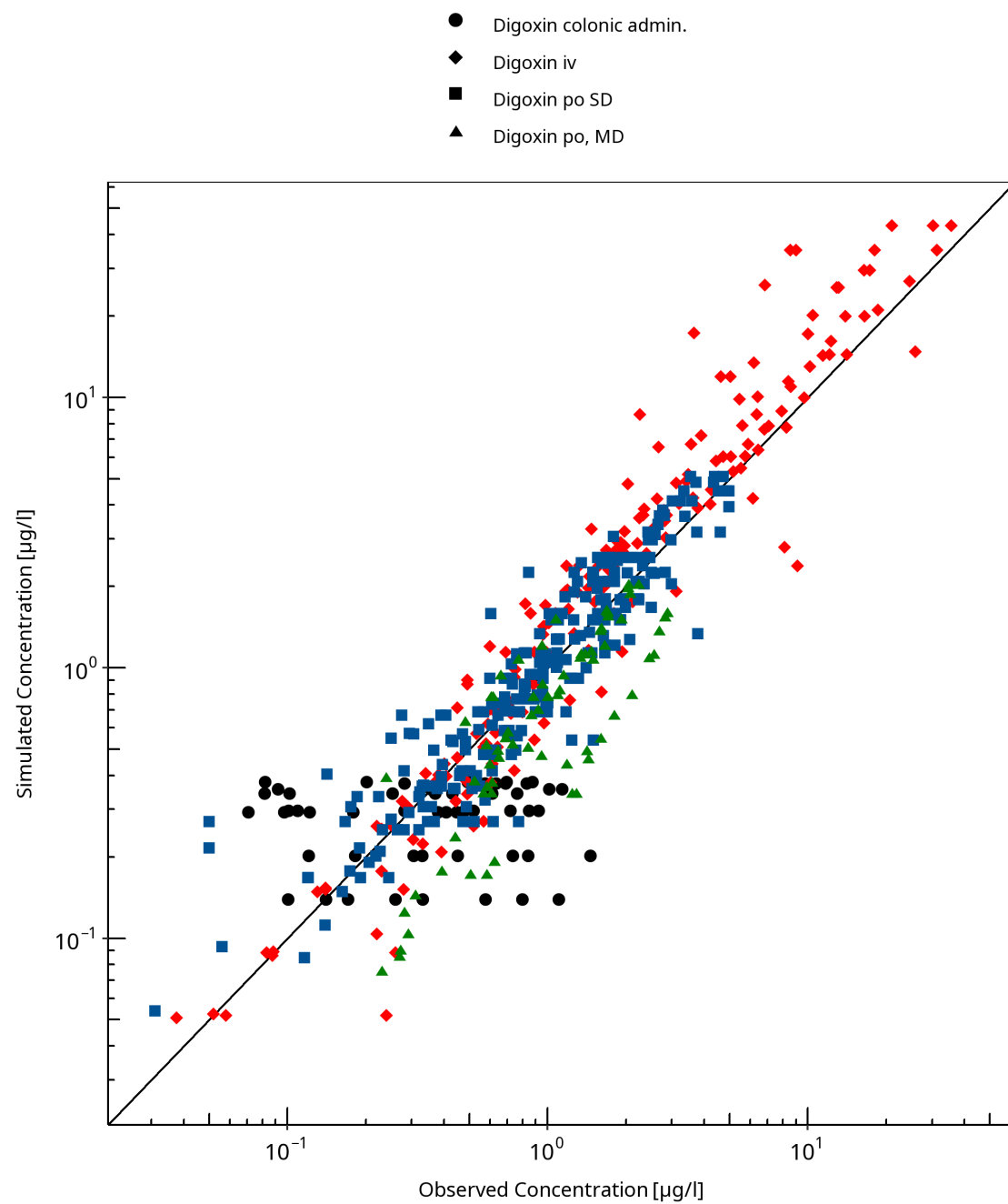


Figure 3-1: Goodness of fit plot for concentration in plasma.

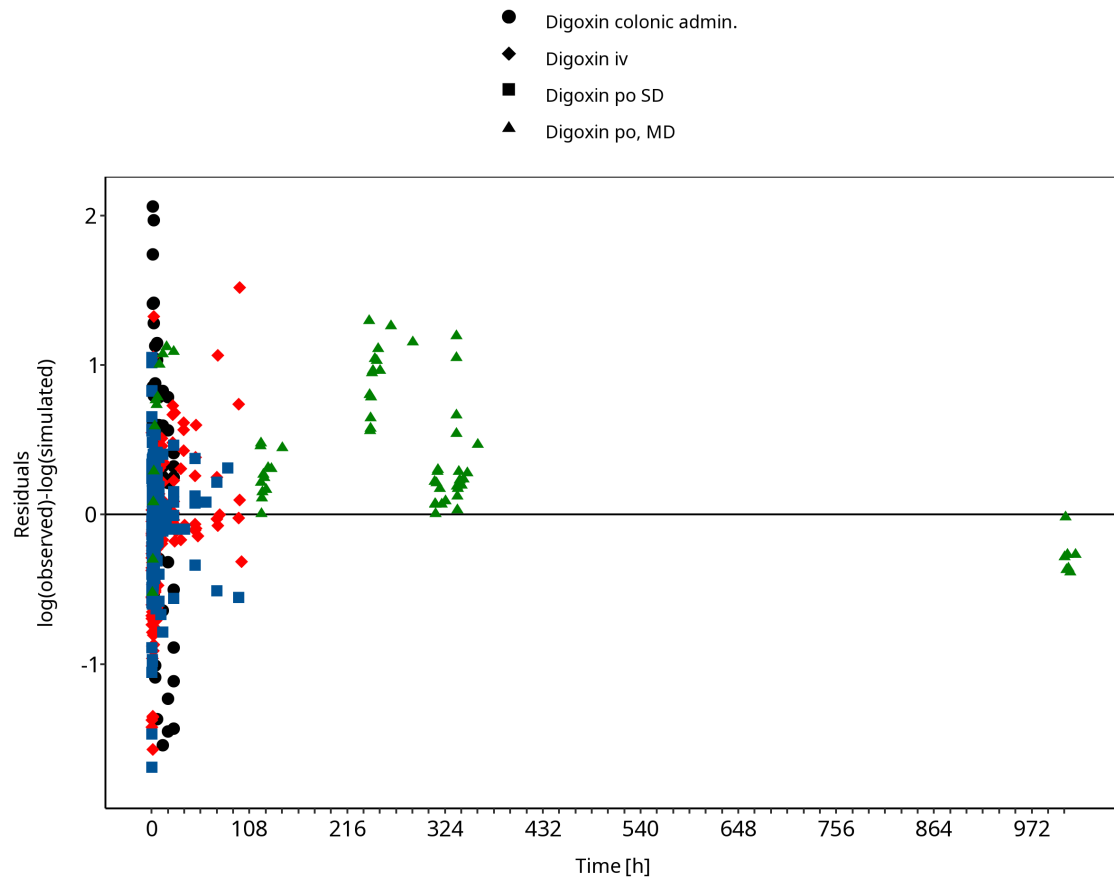


Figure 3-2: Goodness of fit plot for concentration in plasma.

3.3 Digoxin Concentration-Time profiles

Simulated versus observed plasma concentration-time profiles of all data are listed below.

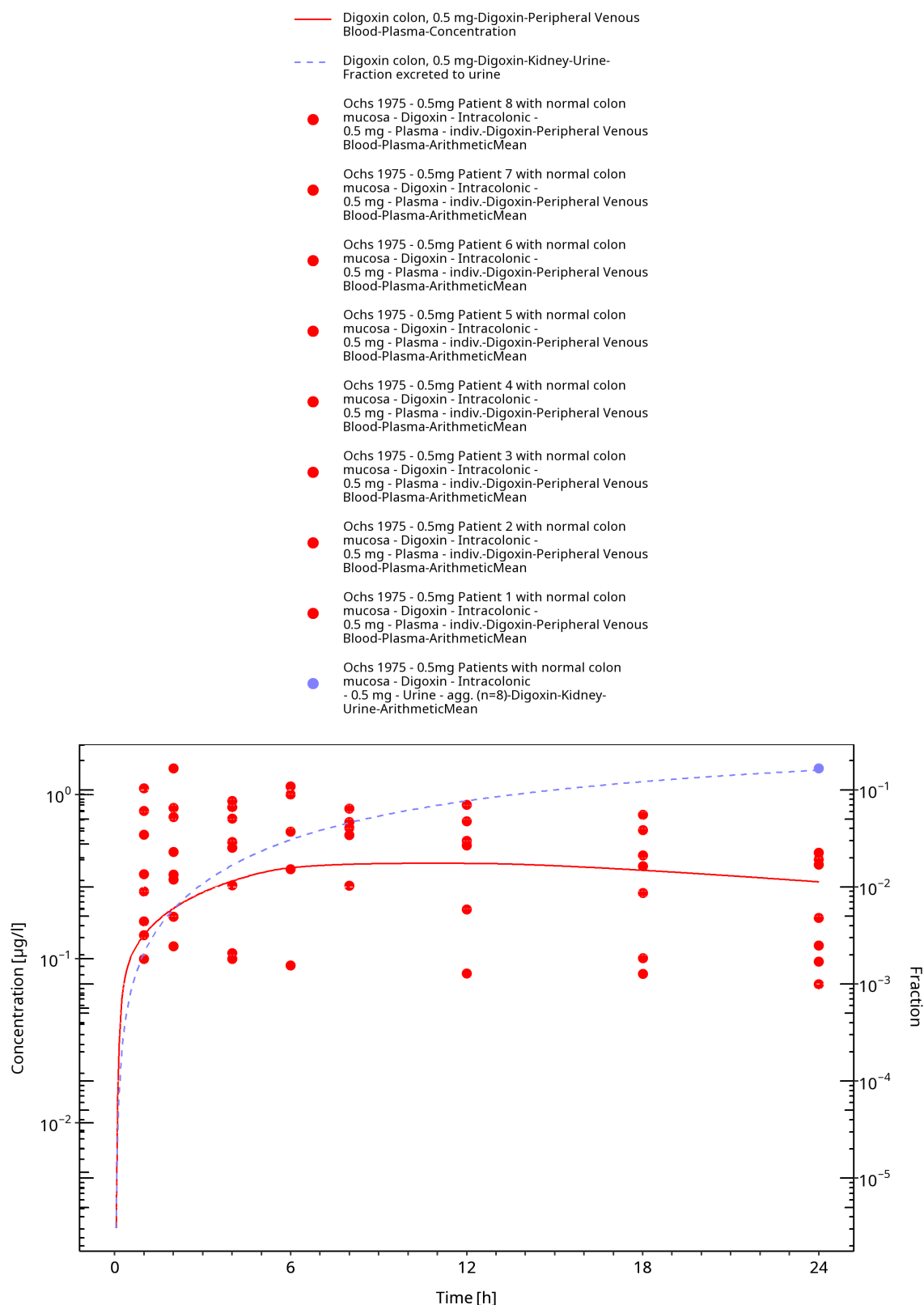


Figure 3-3: Time Profile Analysis 1

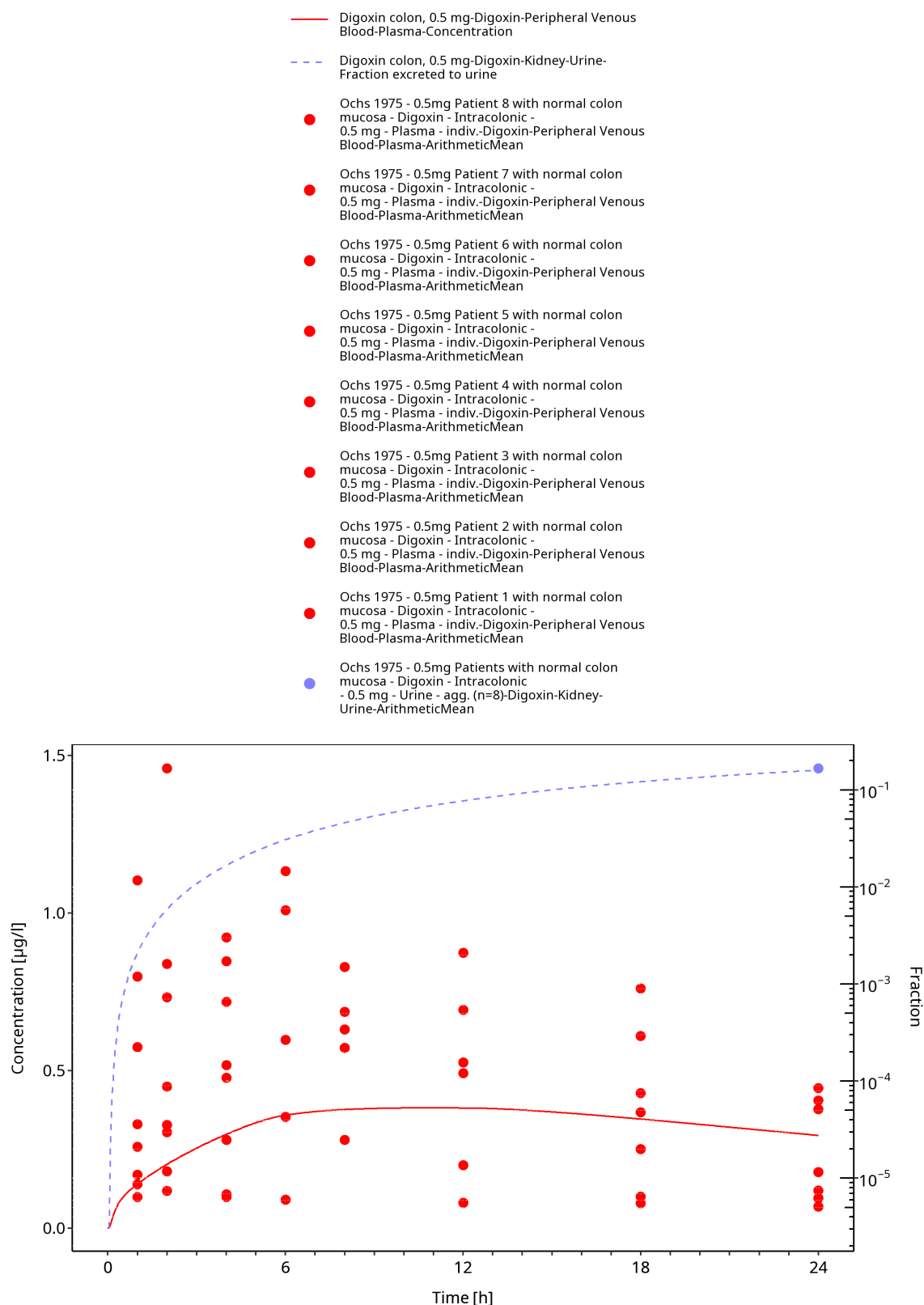


Figure 3-4: Time Profile Analysis

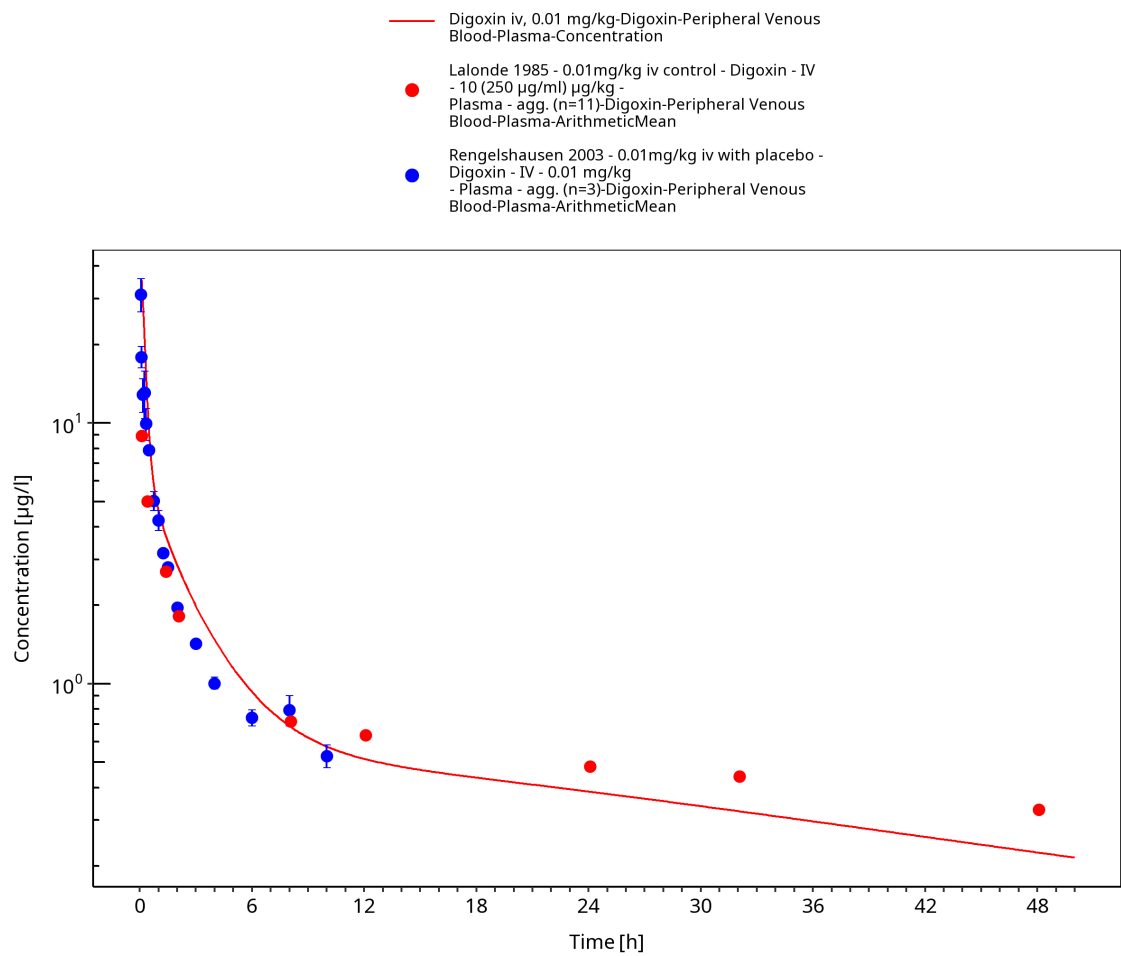


Figure 3-5: Time Profile Analysis

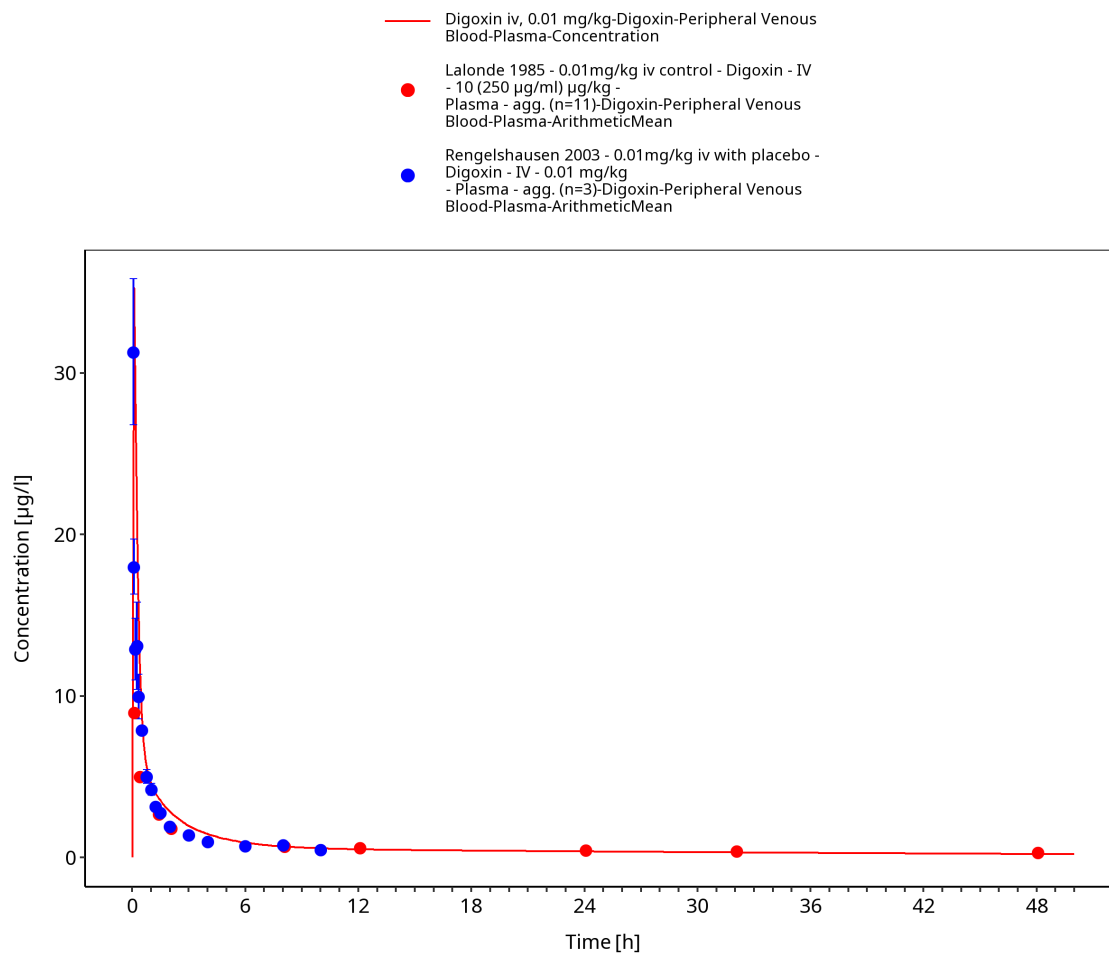


Figure 3-6: Time Profile Analysis 1

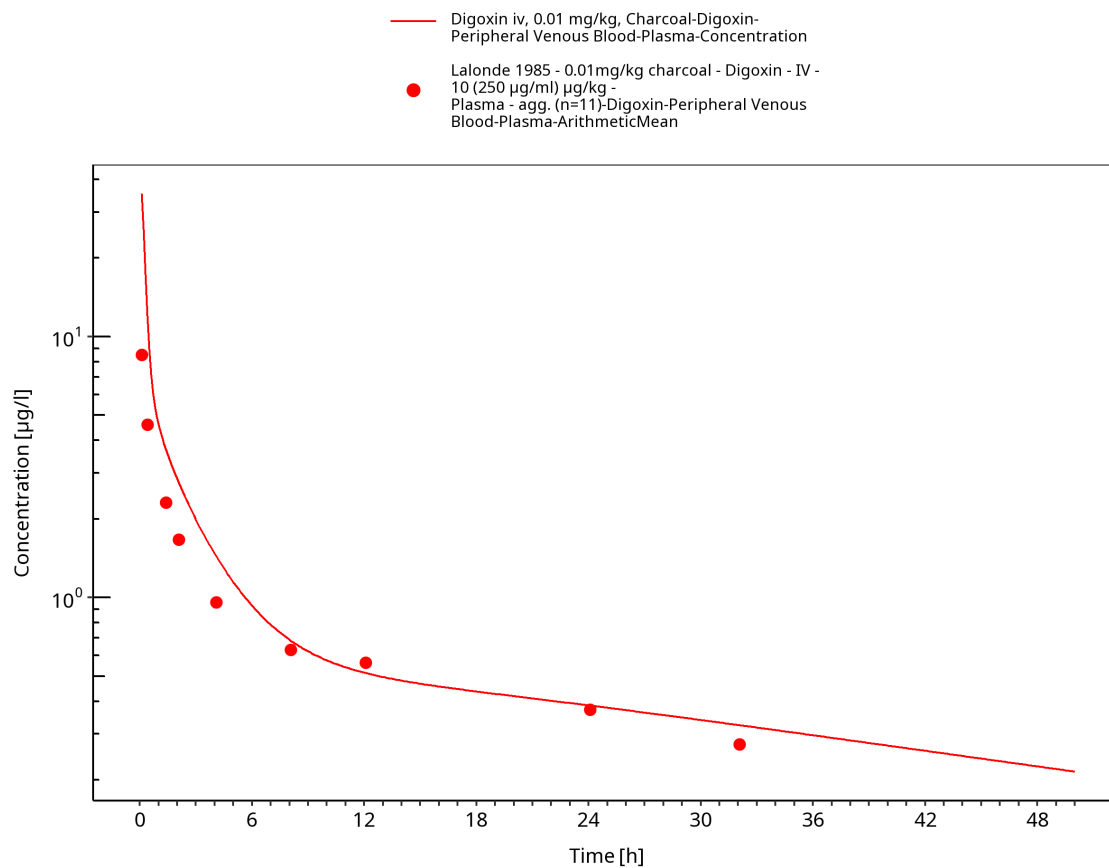


Figure 3-7: Time Profile Analysis

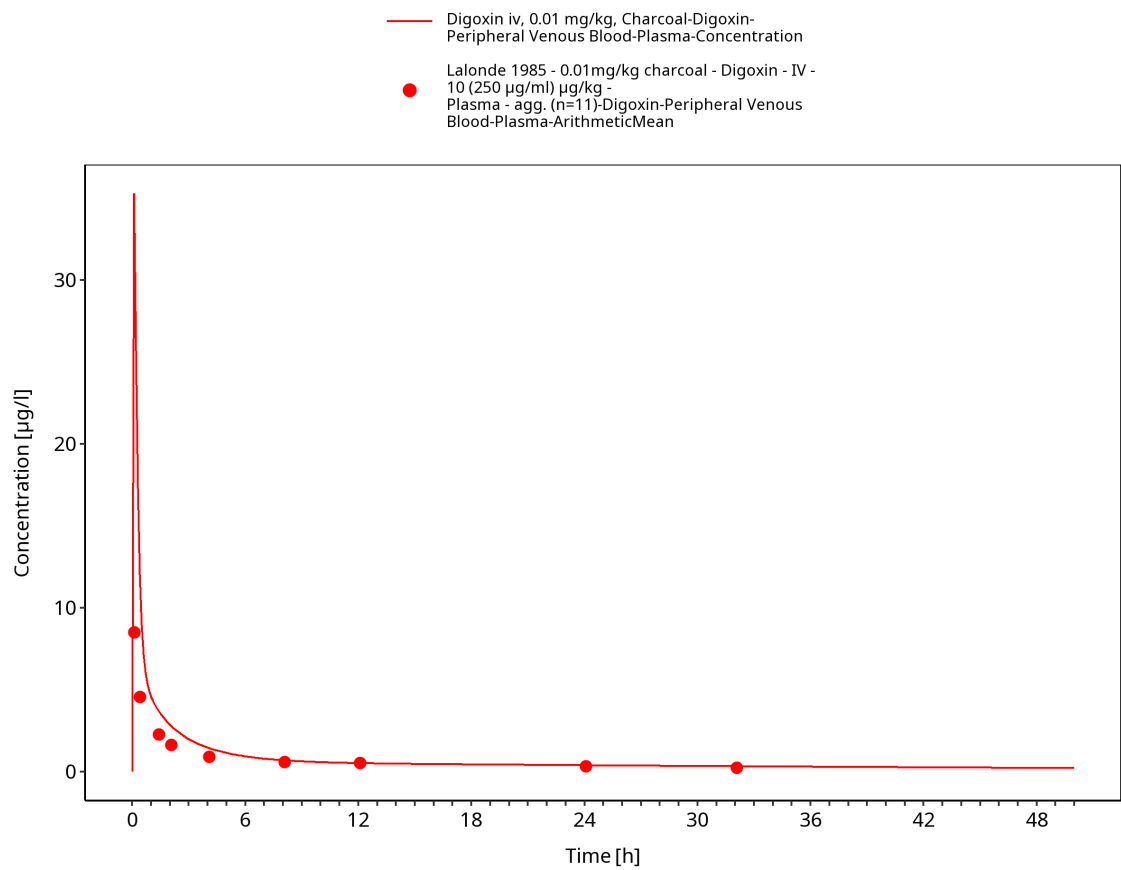
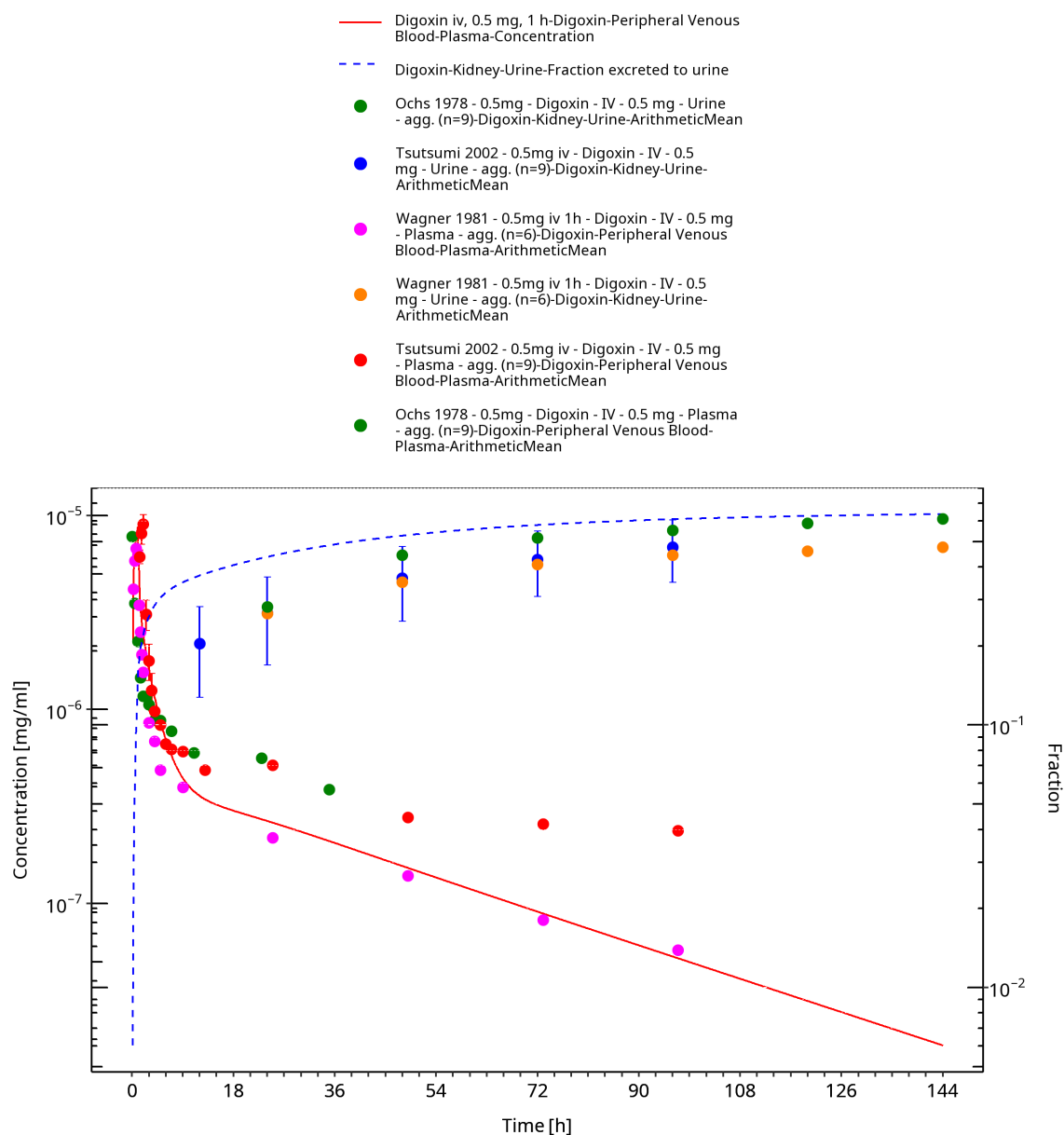


Figure 3-8: Time Profile Analysis 1



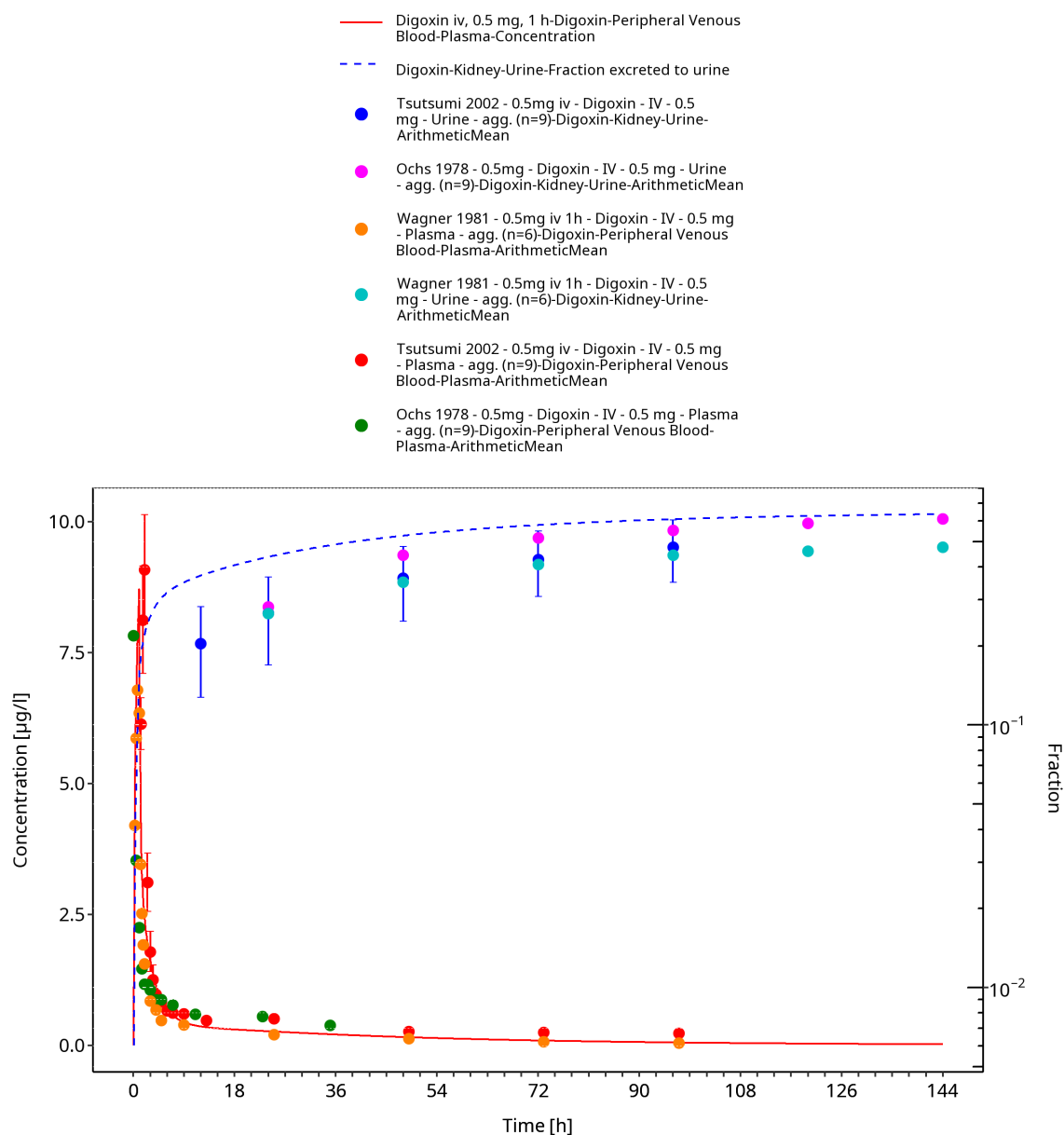


Figure 3-10: Time Profile Analysis 1

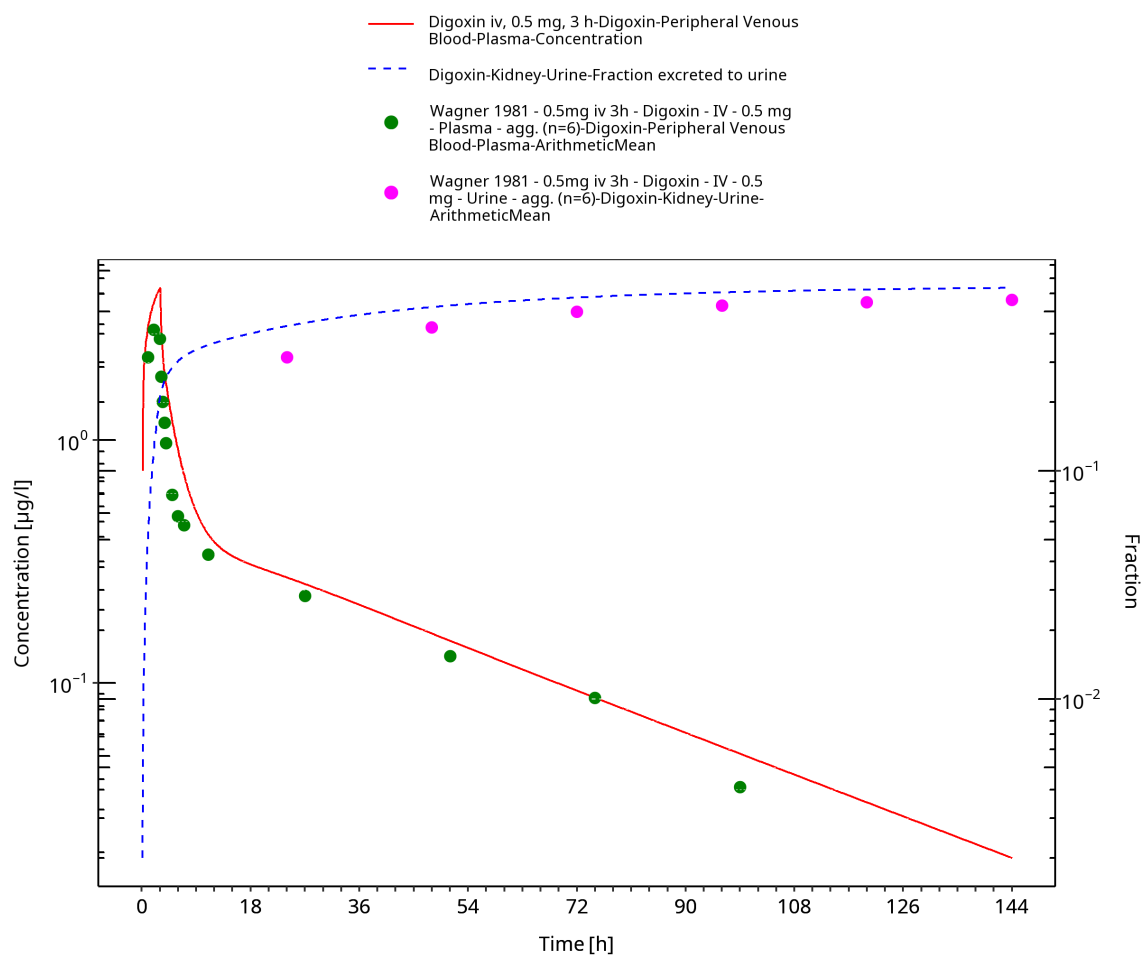


Figure 3-11: Time Profile Analysis

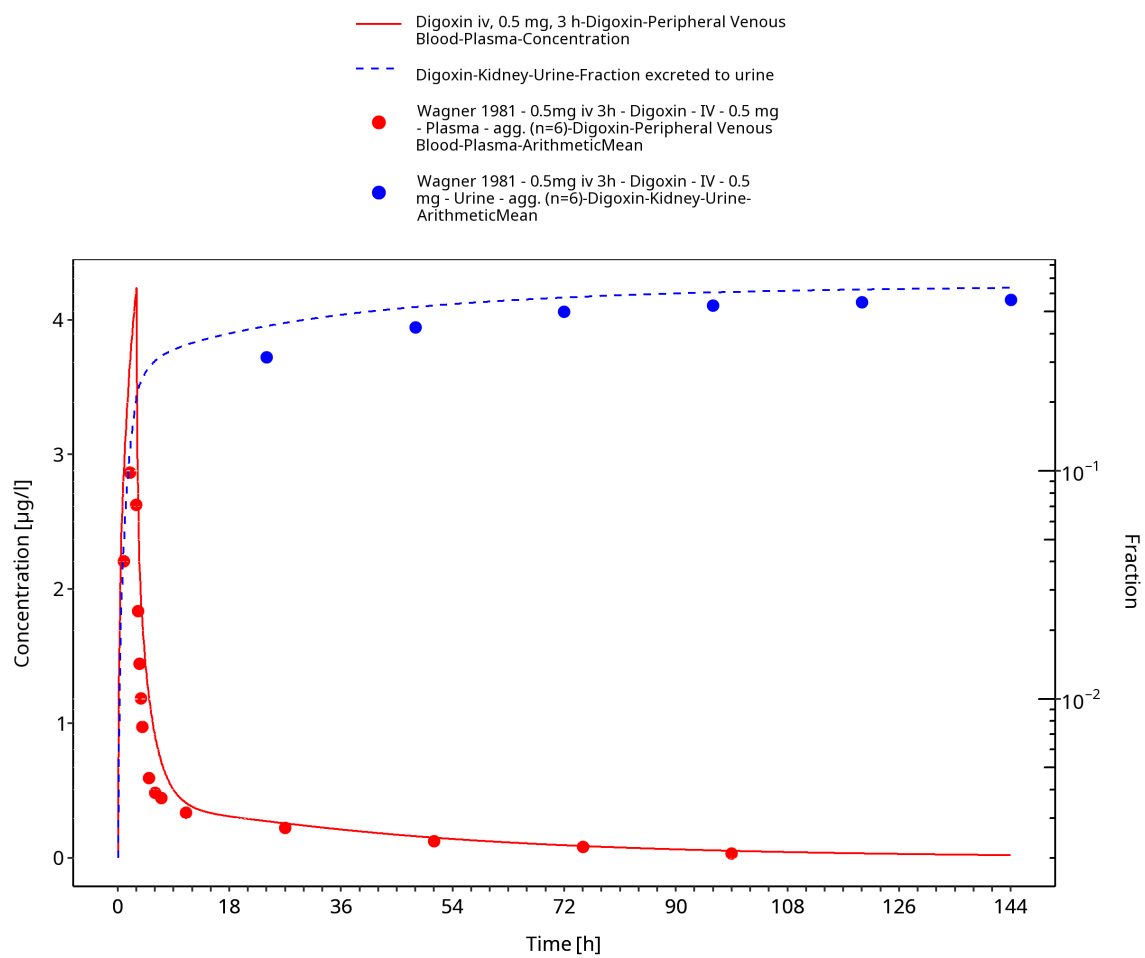


Figure 3-12: Time Profile Analysis 1

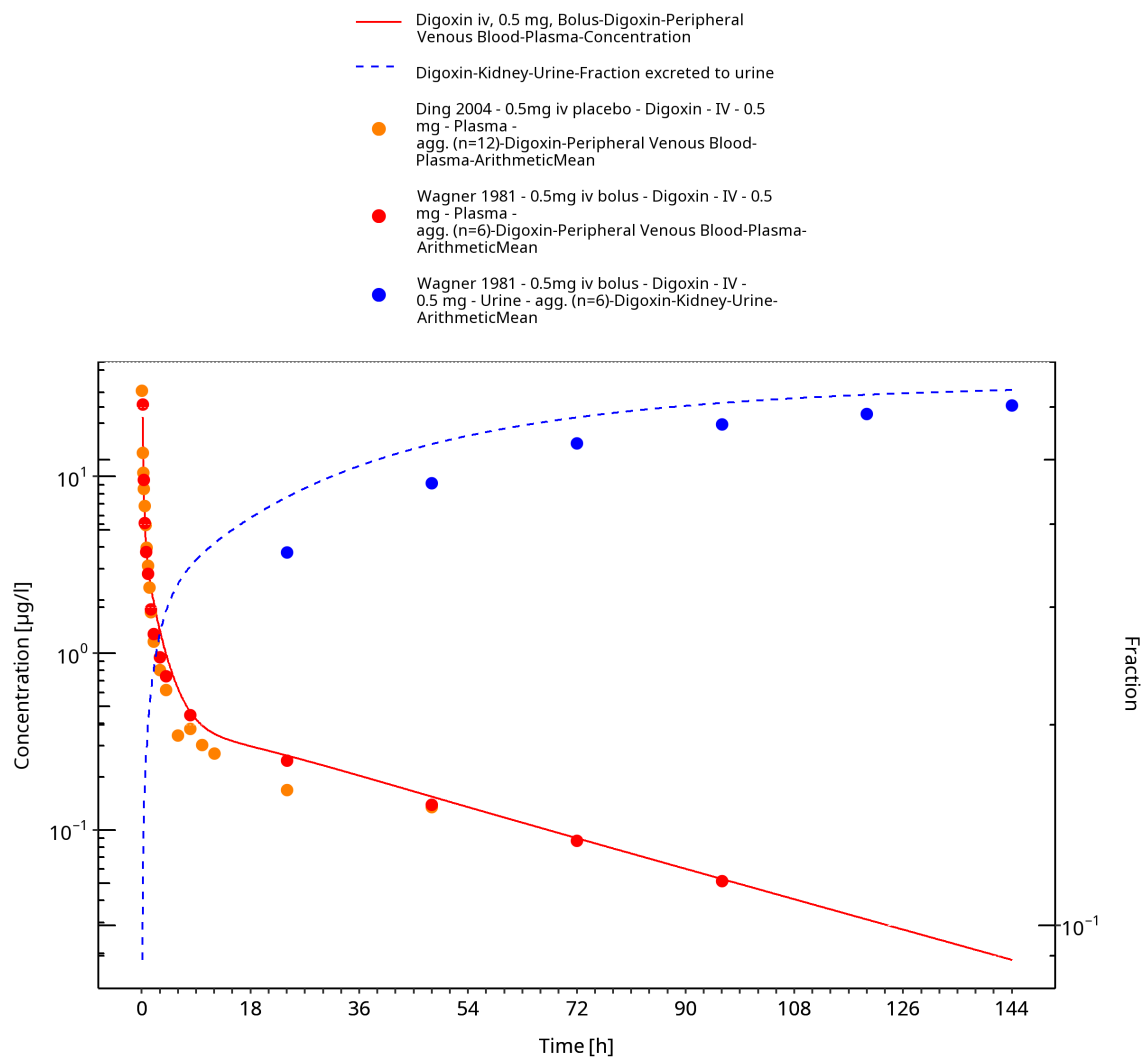


Figure 3-13: Time Profile Analysis

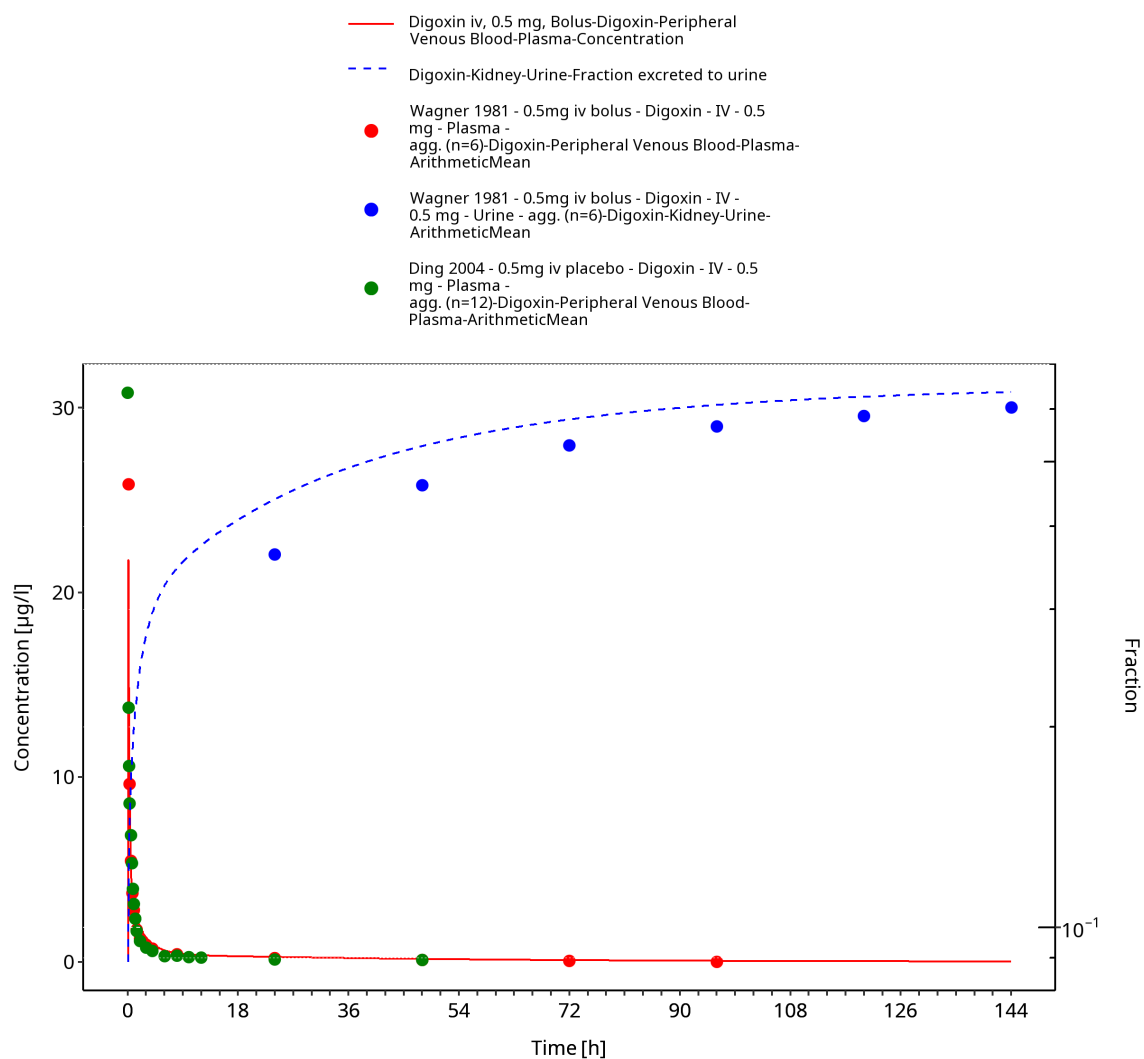


Figure 3-14: Time Profile Analysis 1

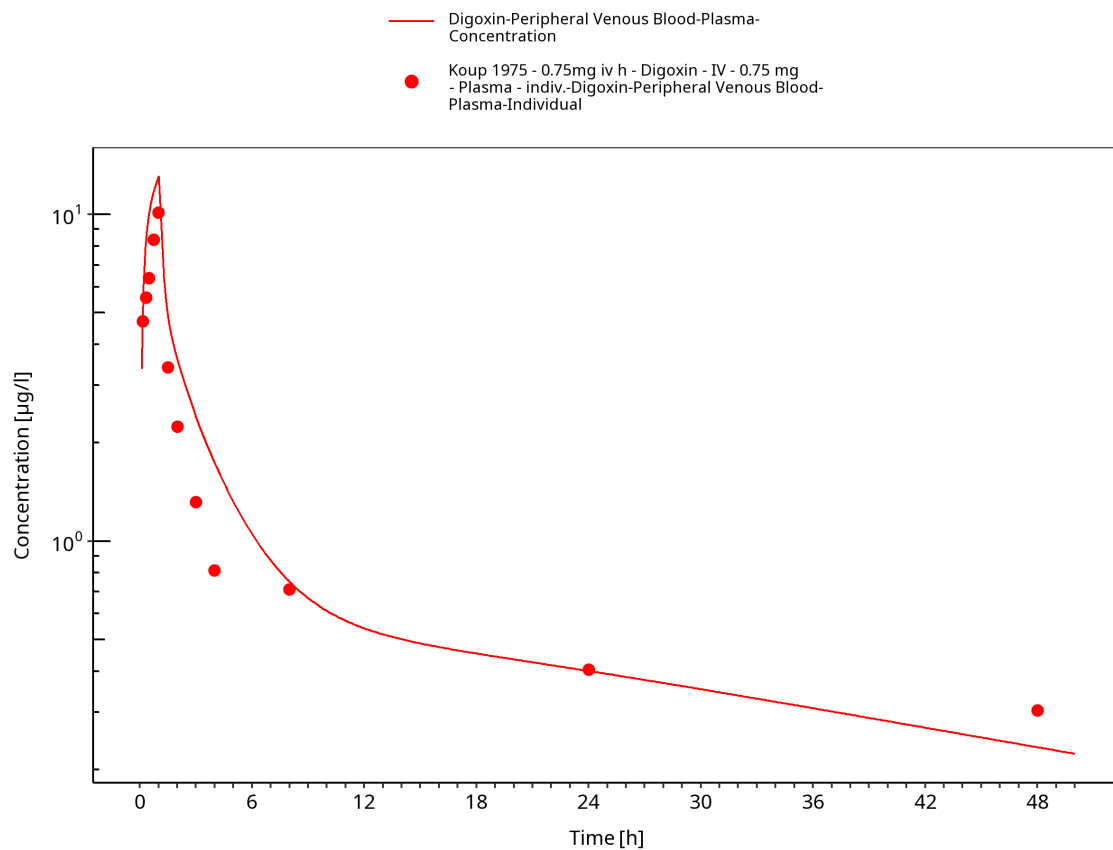


Figure 3-15: Time Profile Analysis

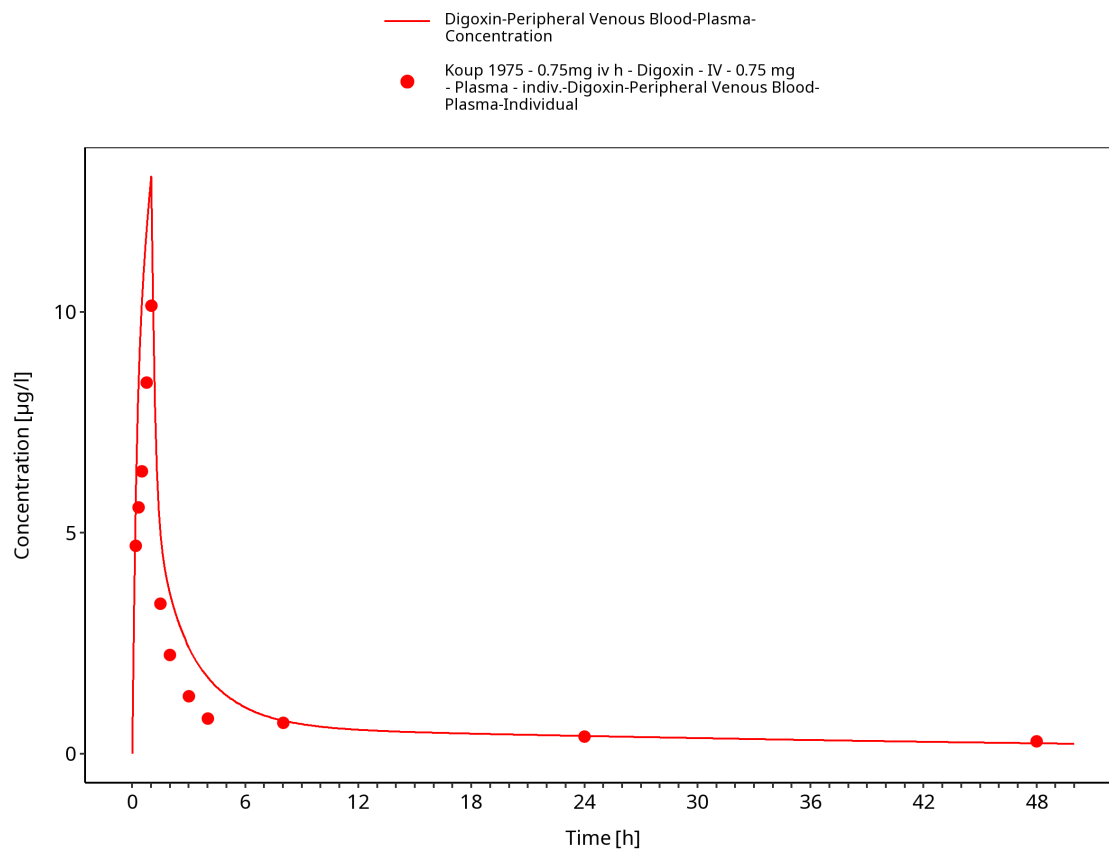


Figure 3-16: Time Profile Analysis 1

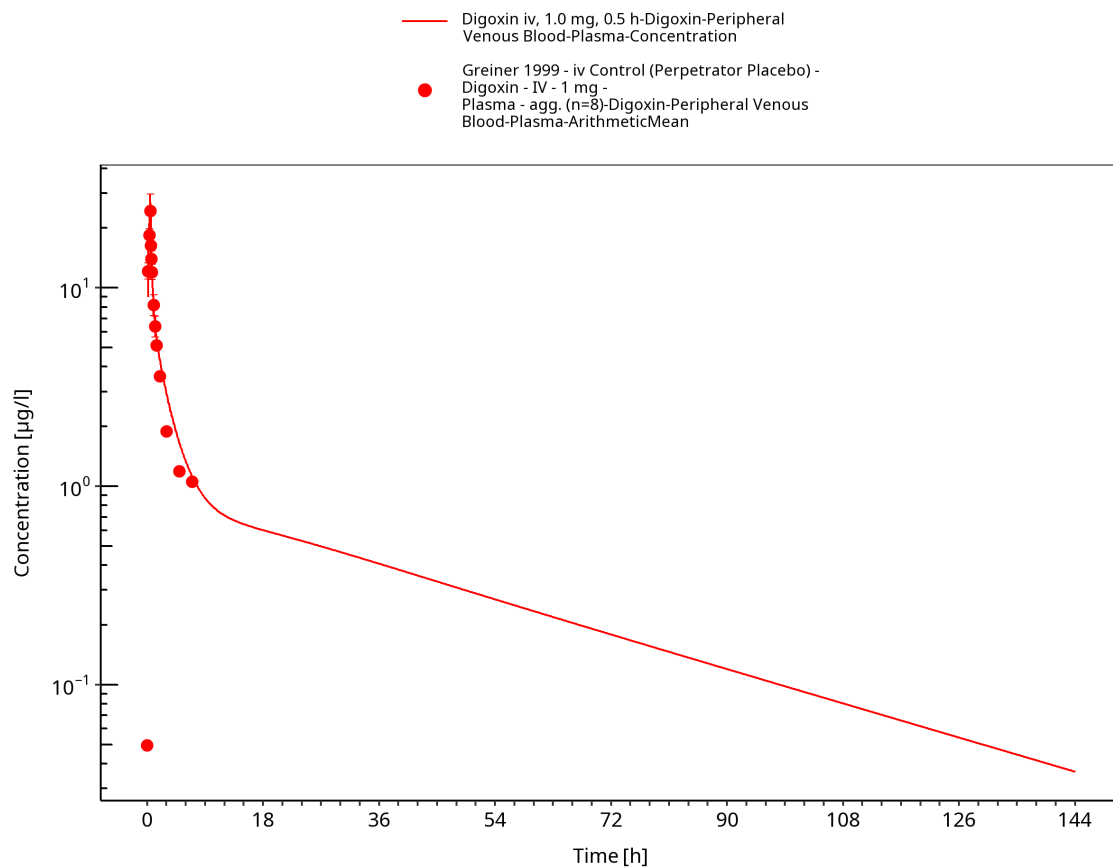


Figure 3-17: Time Profile Analysis

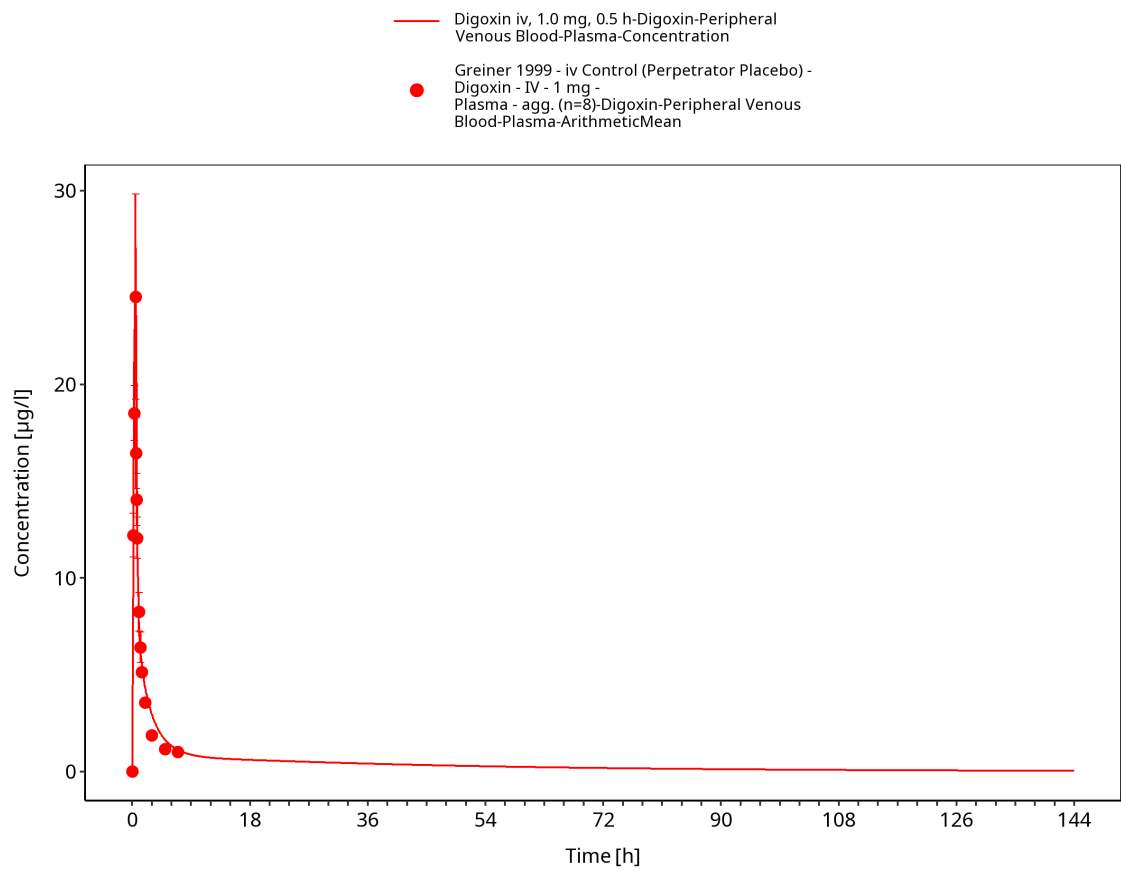


Figure 3-18: Time Profile Analysis 1

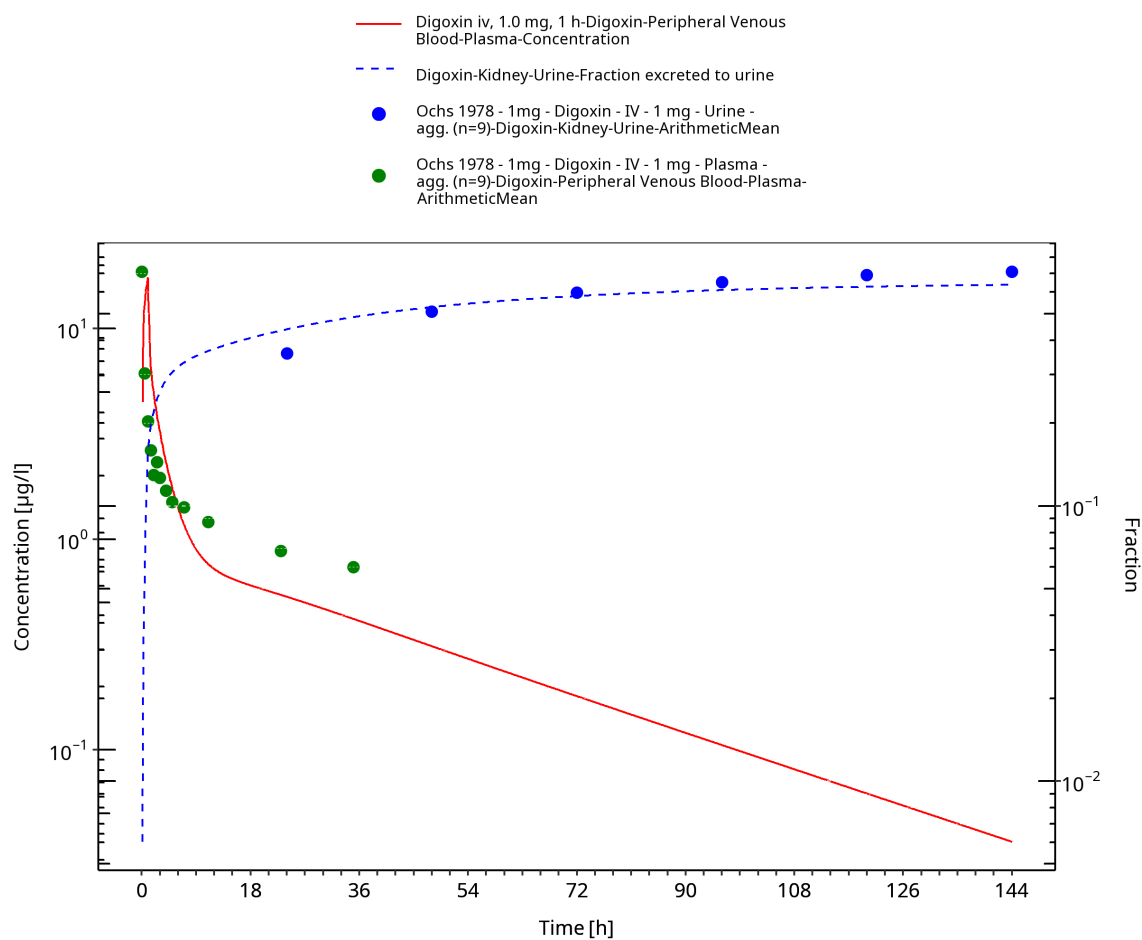


Figure 3-19: Time Profile Analysis

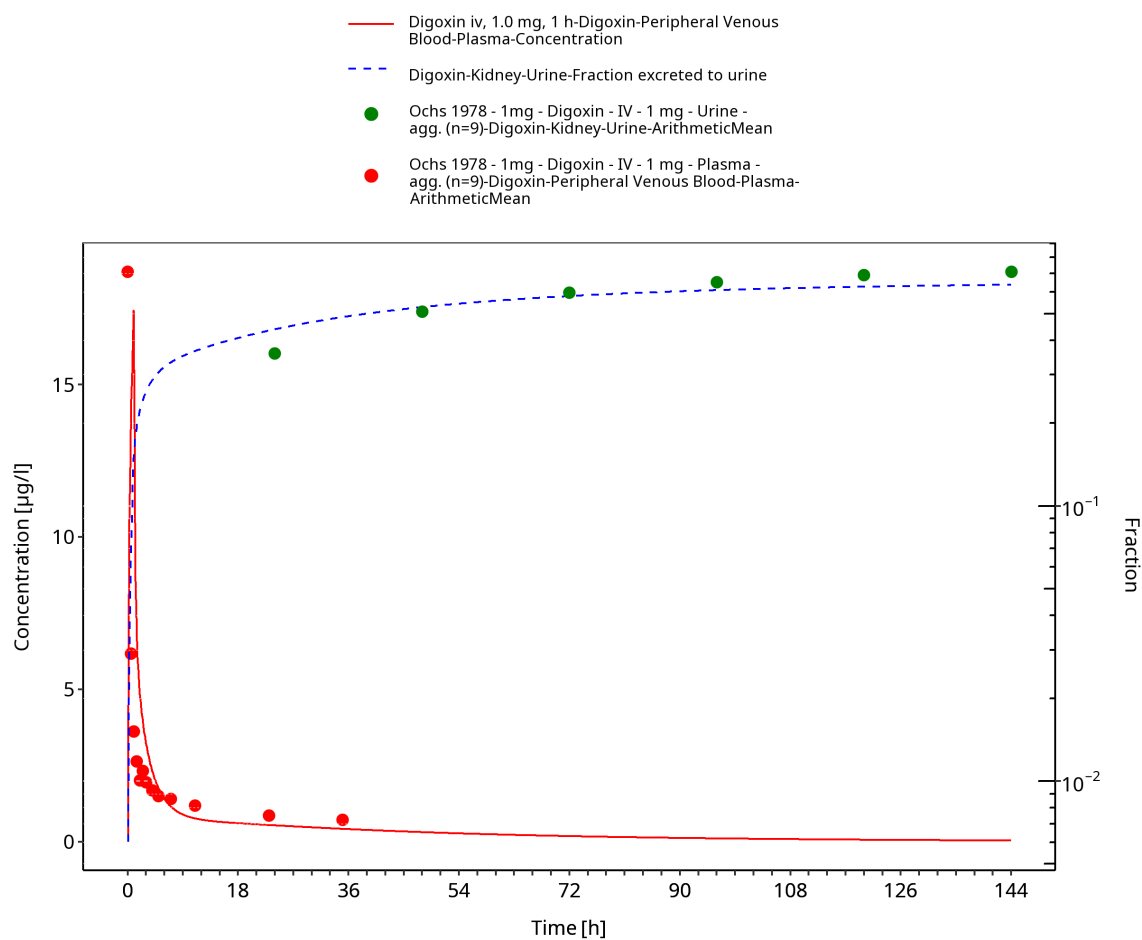


Figure 3-20: Time Profile Analysis 1

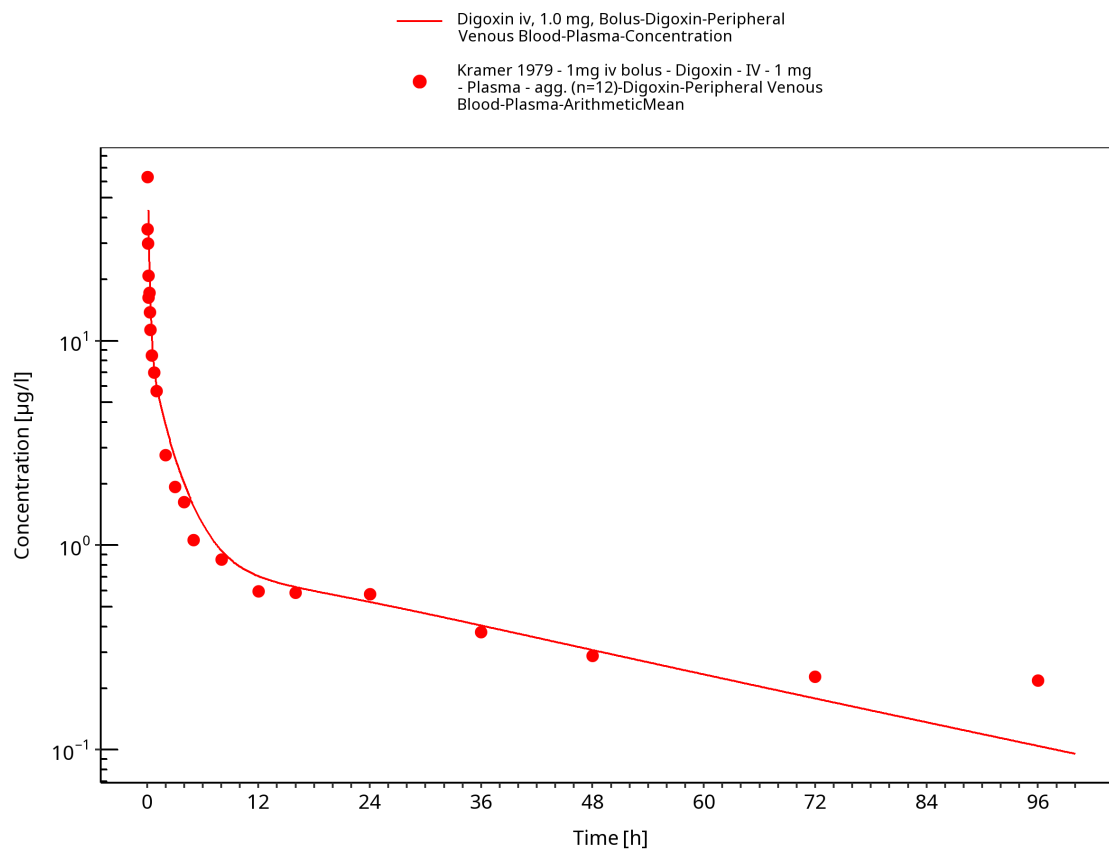


Figure 3-21: Time Profile Analysis

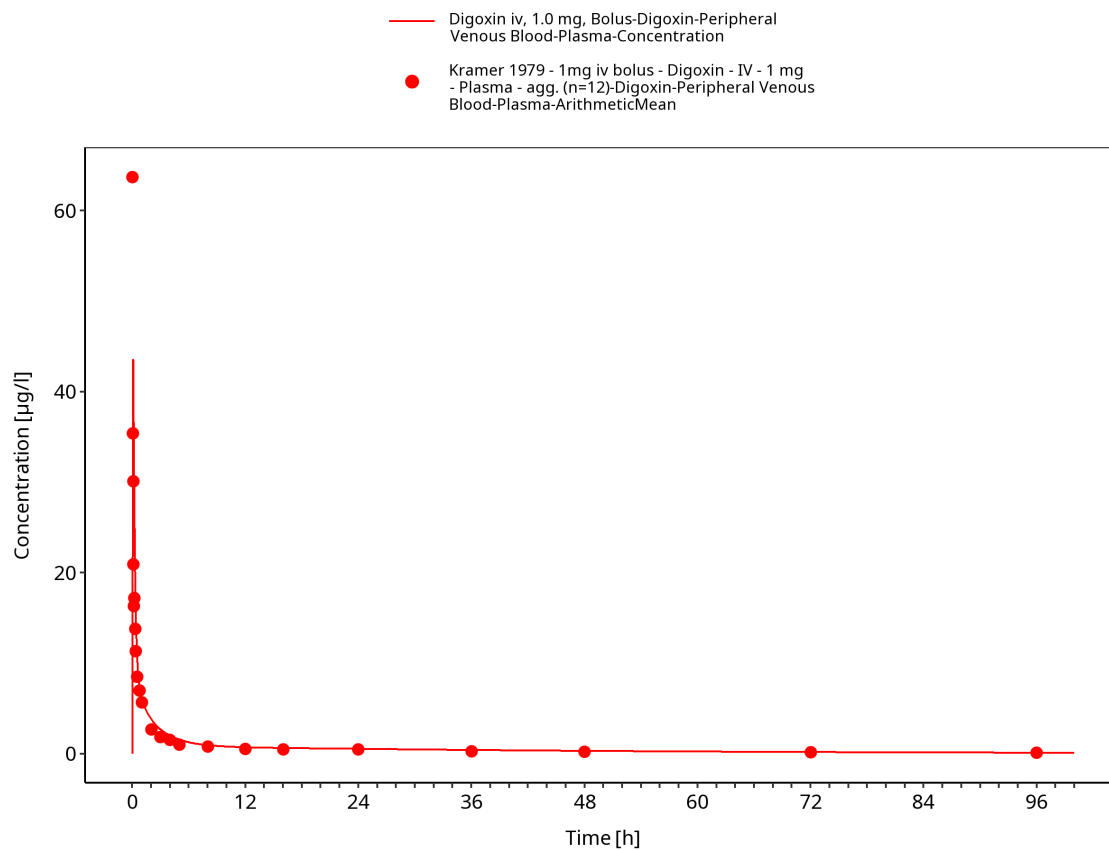


Figure 3-22: Time Profile Analysis 1

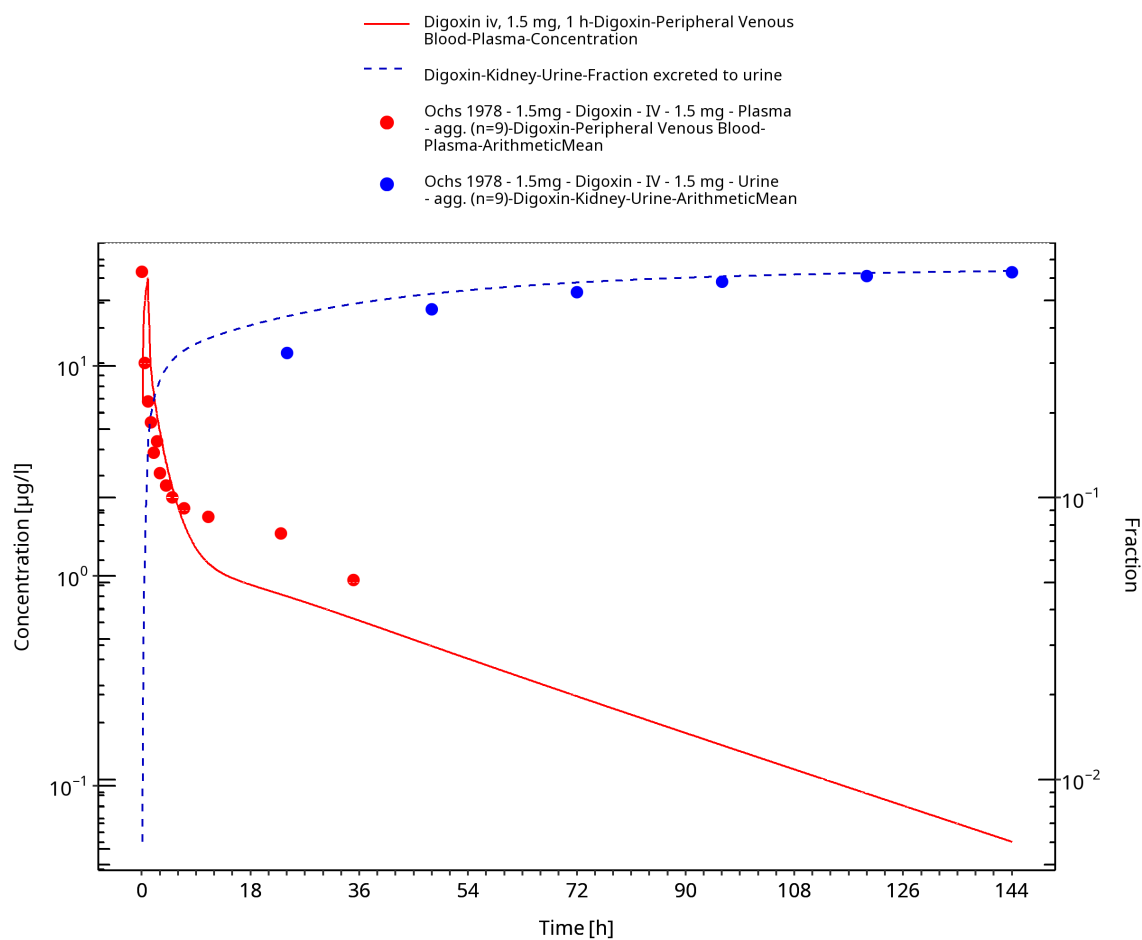


Figure 3-23: Time Profile Analysis

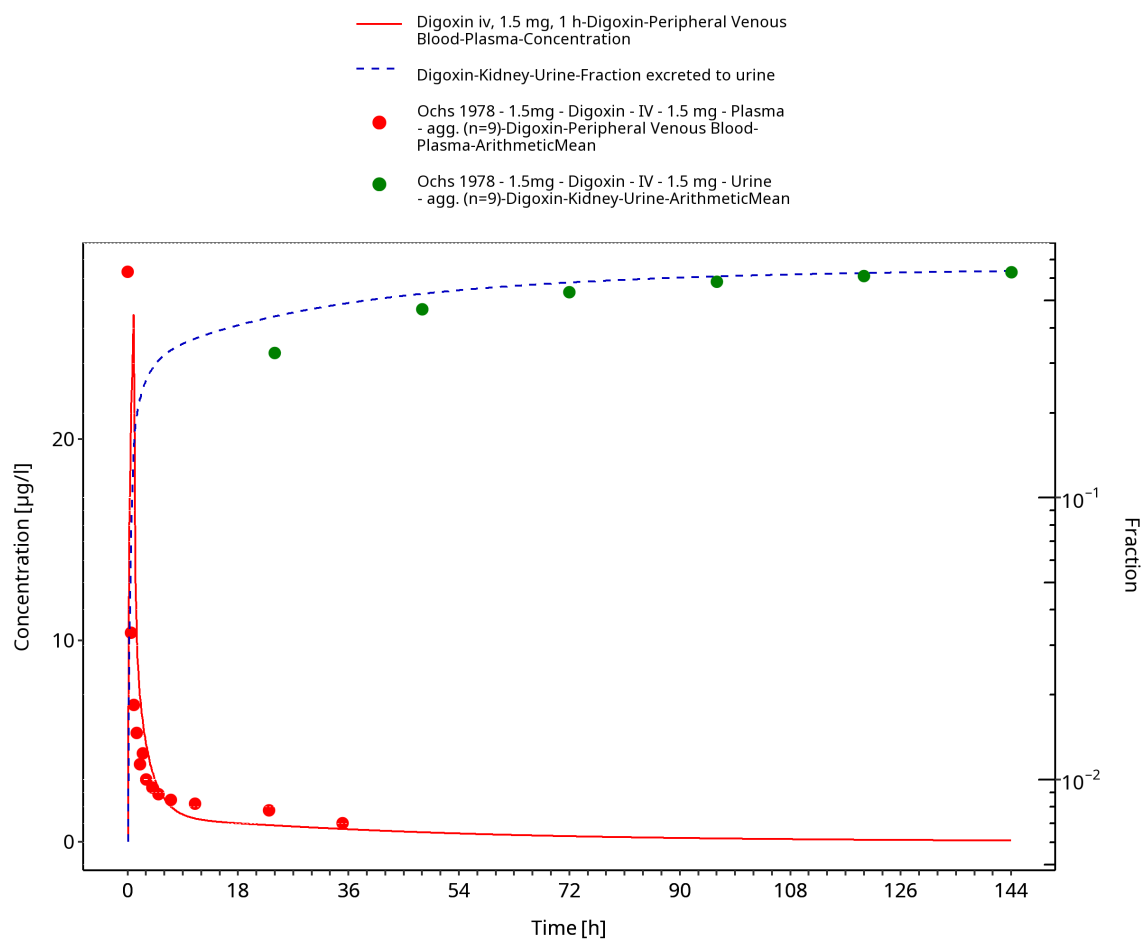


Figure 3-24: Time Profile Analysis 1

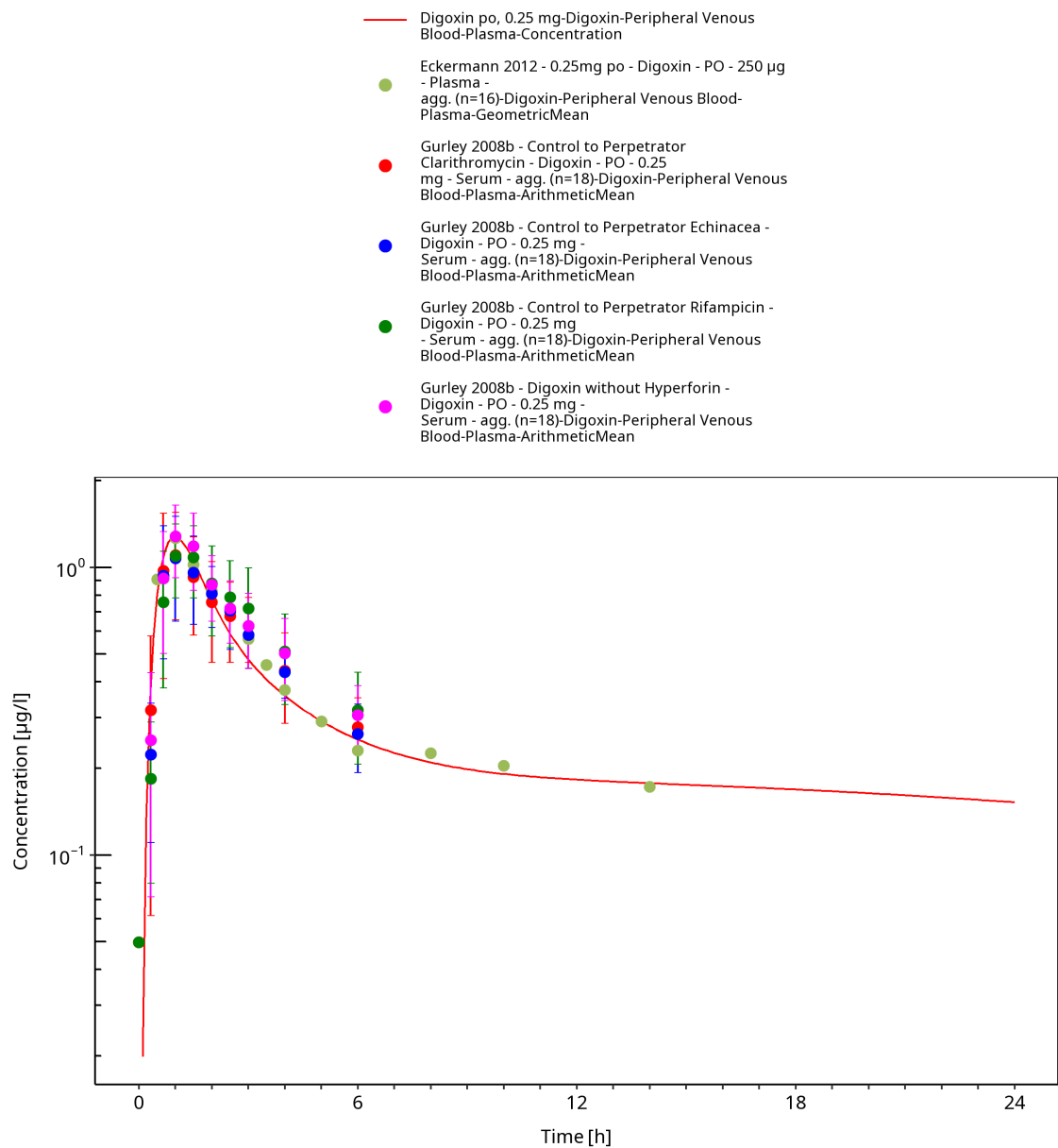


Figure 3-25: Time Profile Analysis

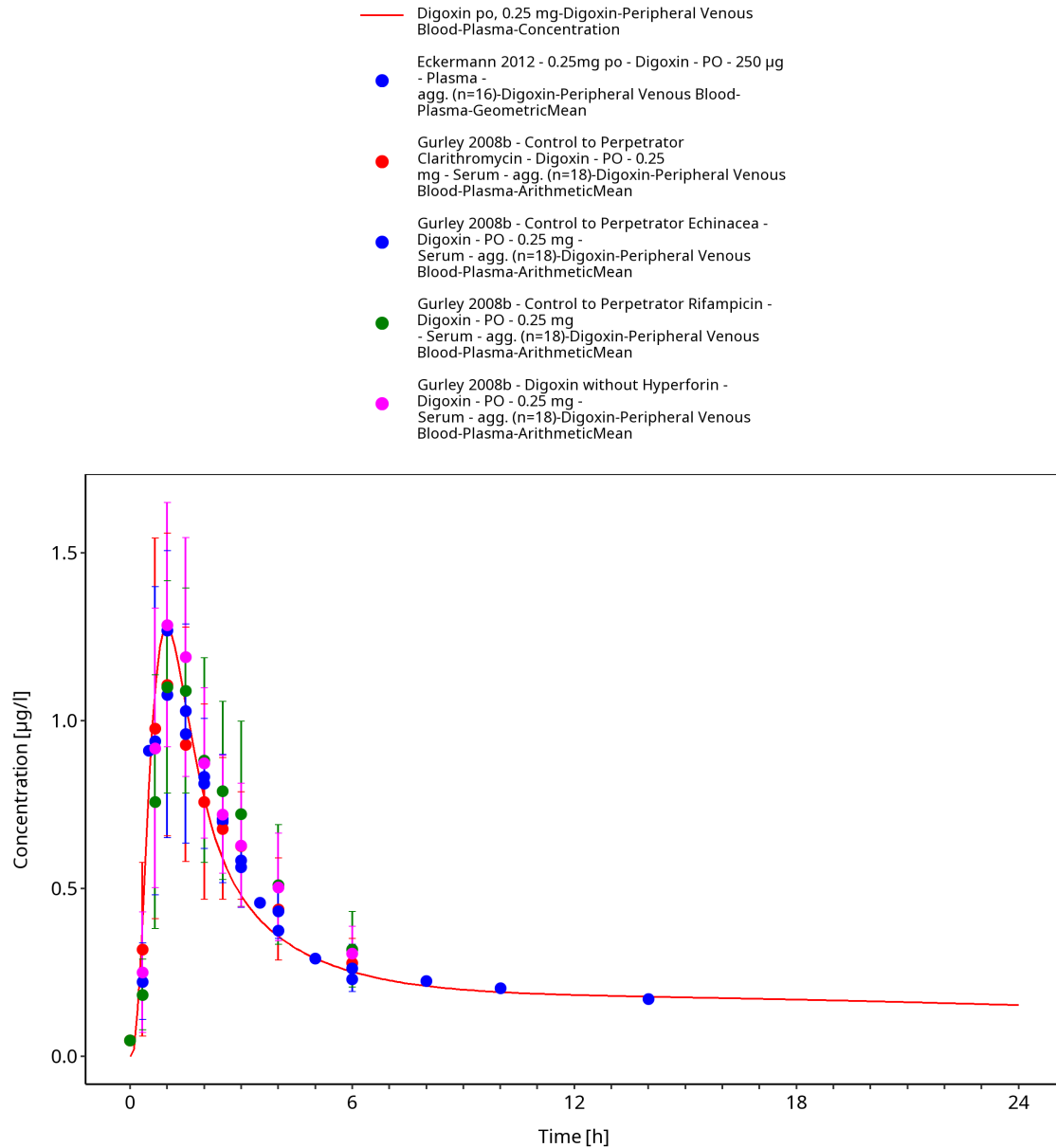


Figure 3-26: Time Profile Analysis 1

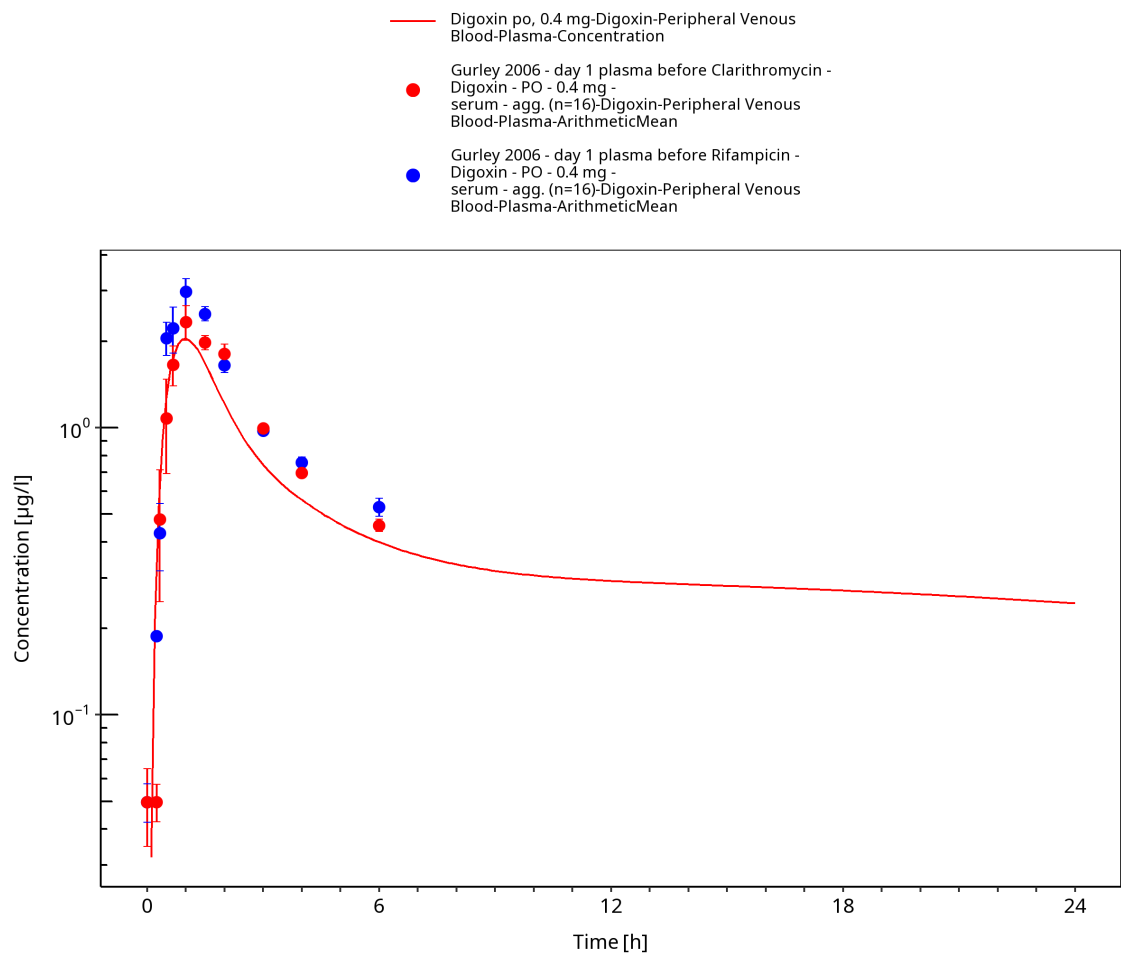


Figure 3-27: Time Profile Analysis

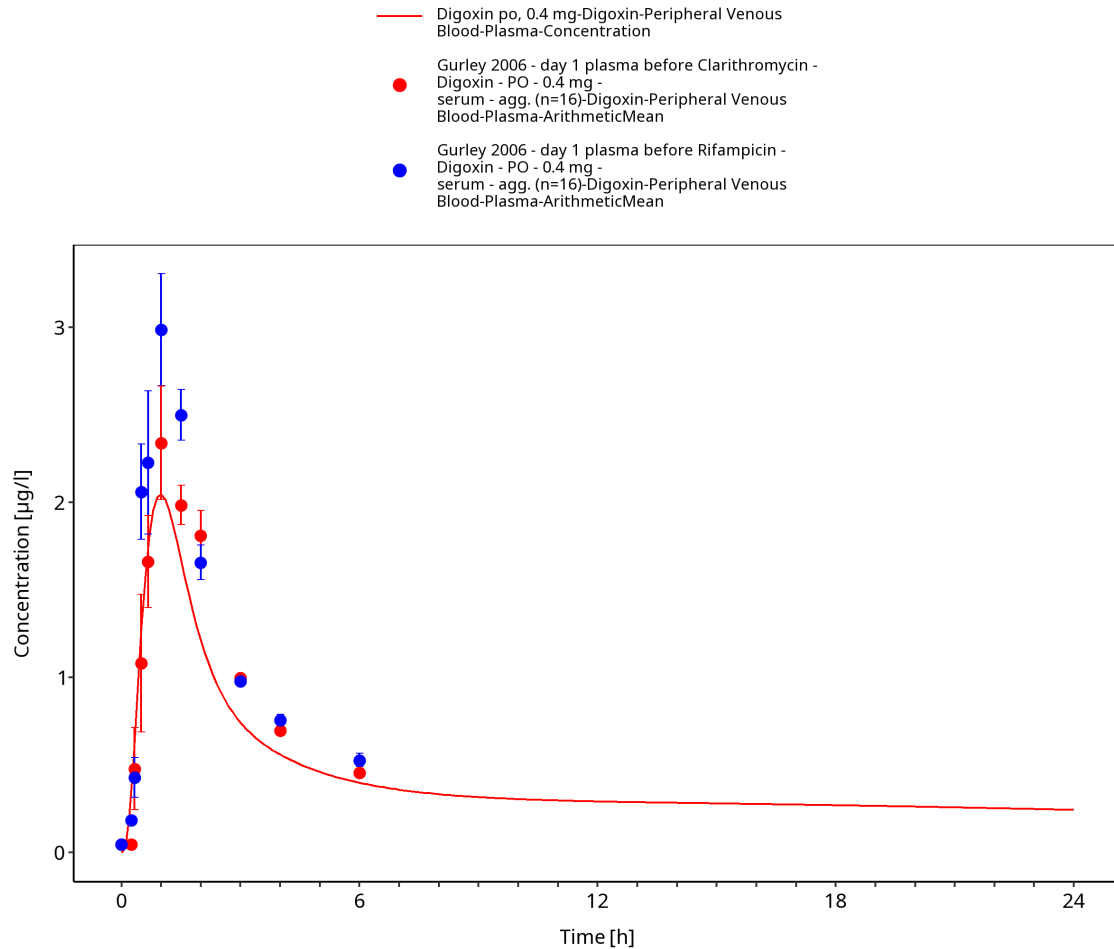
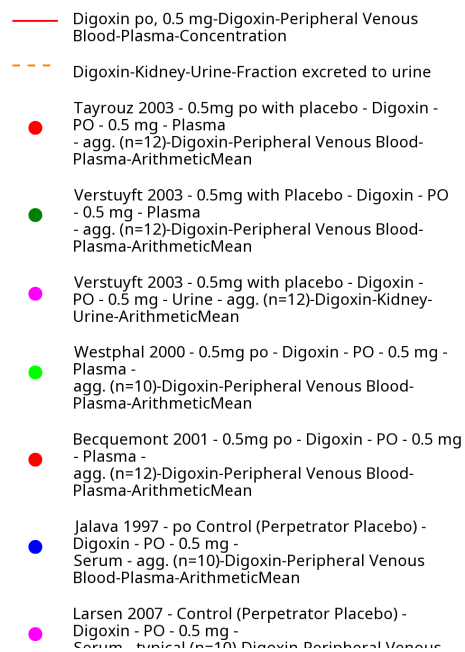


Figure 3-28: Time Profile Analysis 1



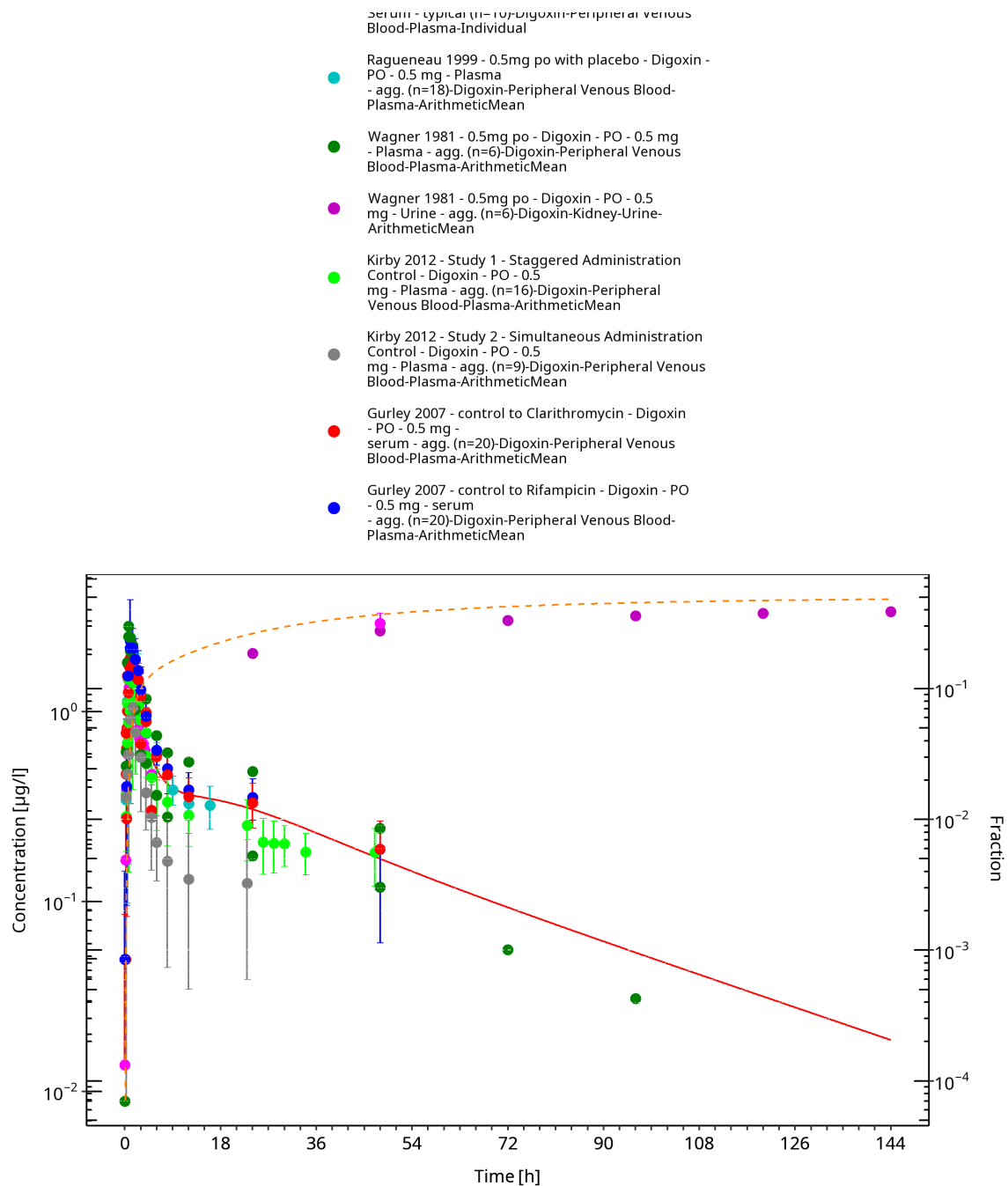
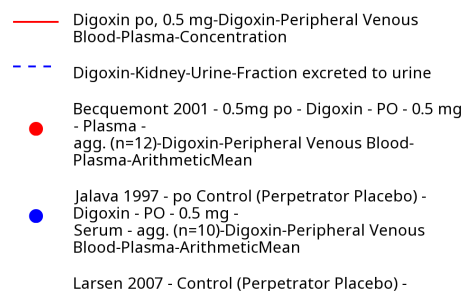


Figure 3-29: Time Profile Analysis



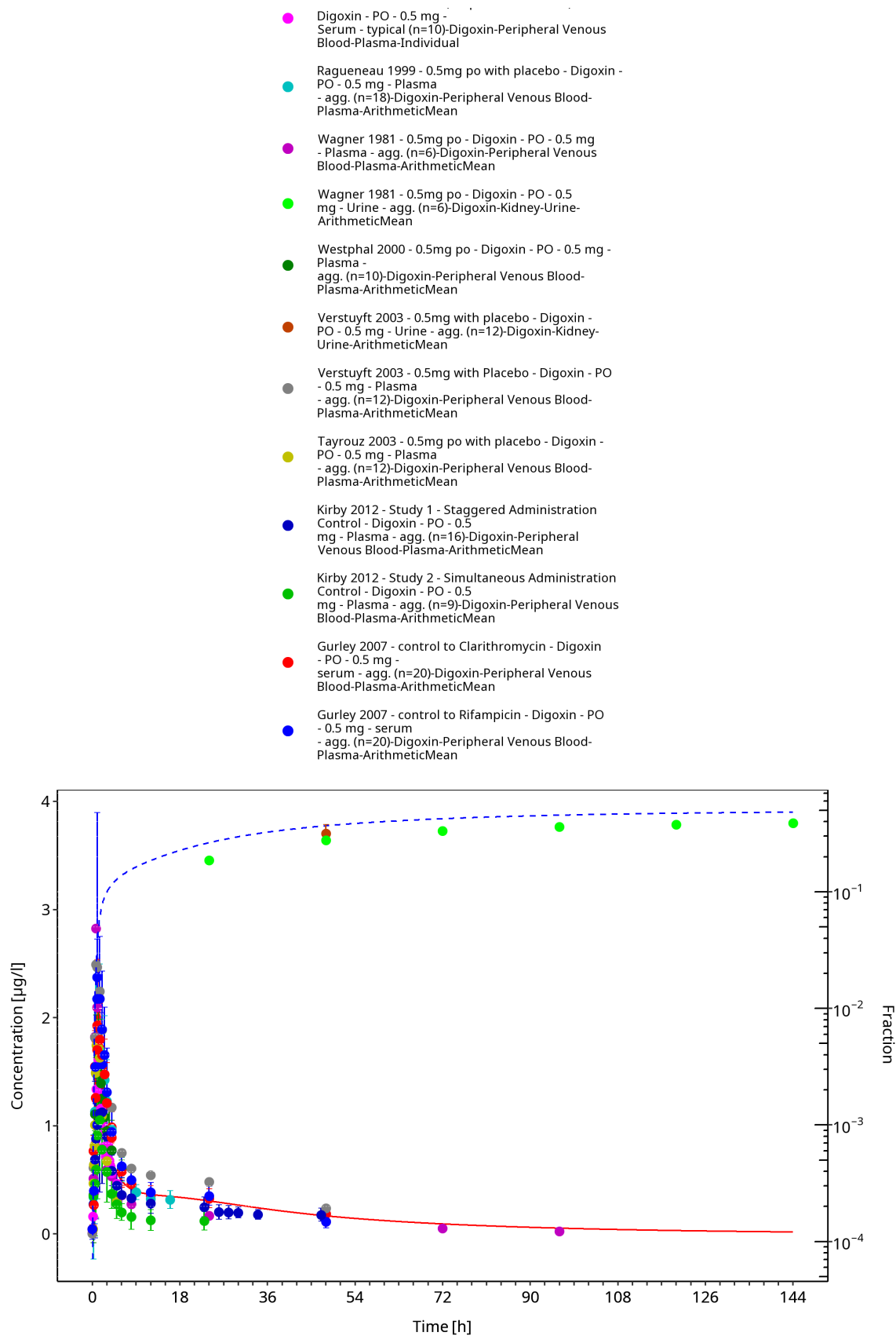


Figure 3-30: Time Profile Analysis 1

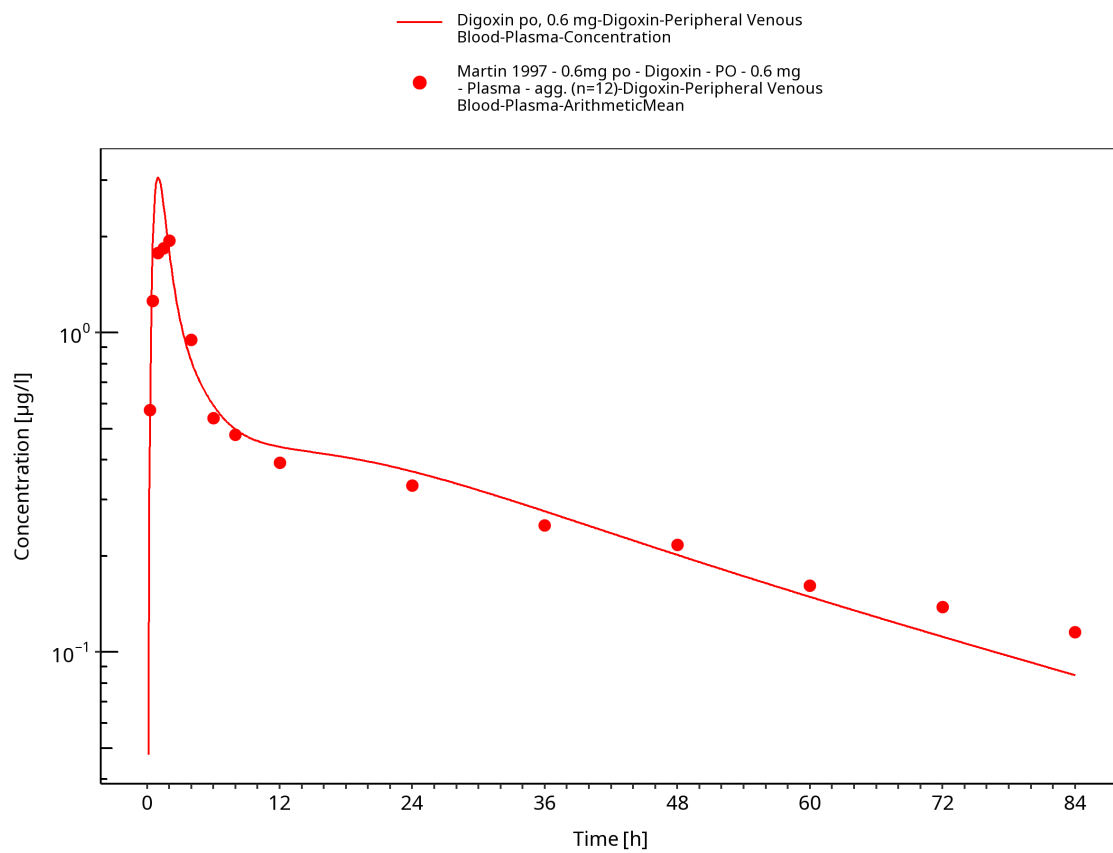


Figure 3-31: Time Profile Analysis

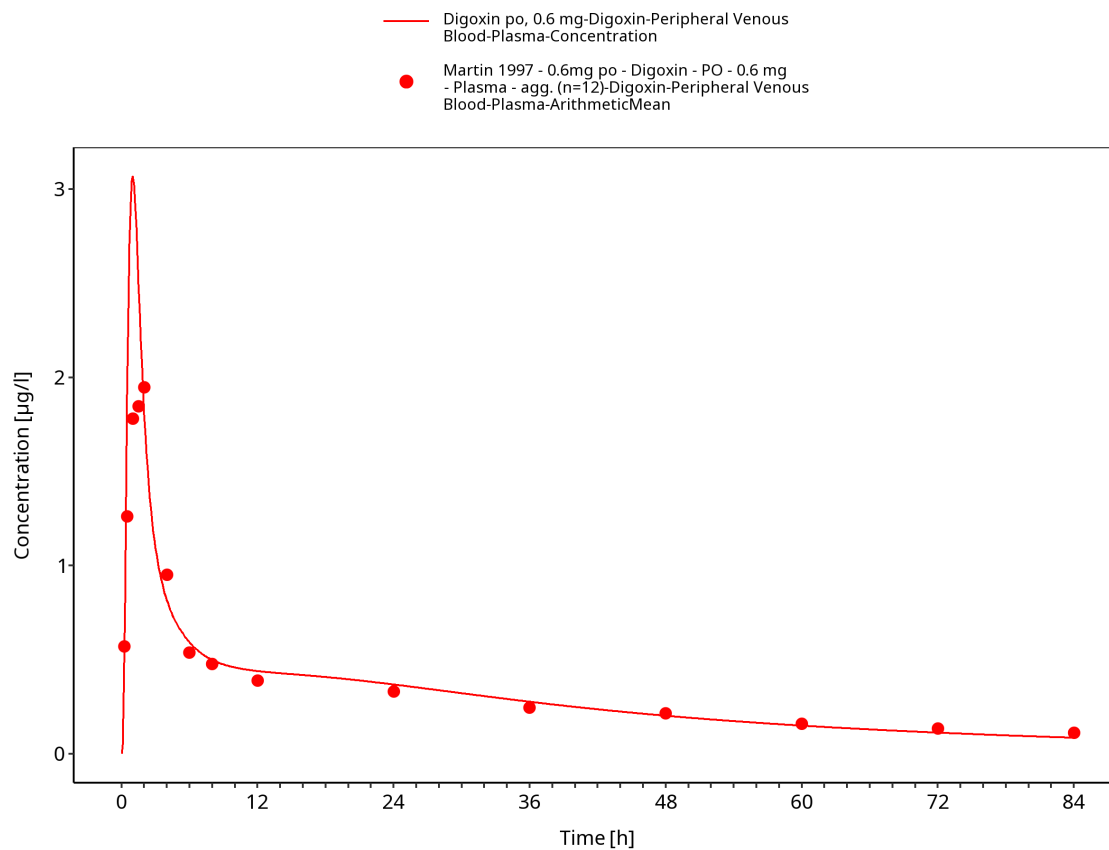


Figure 3-32: Time Profile Analysis 1

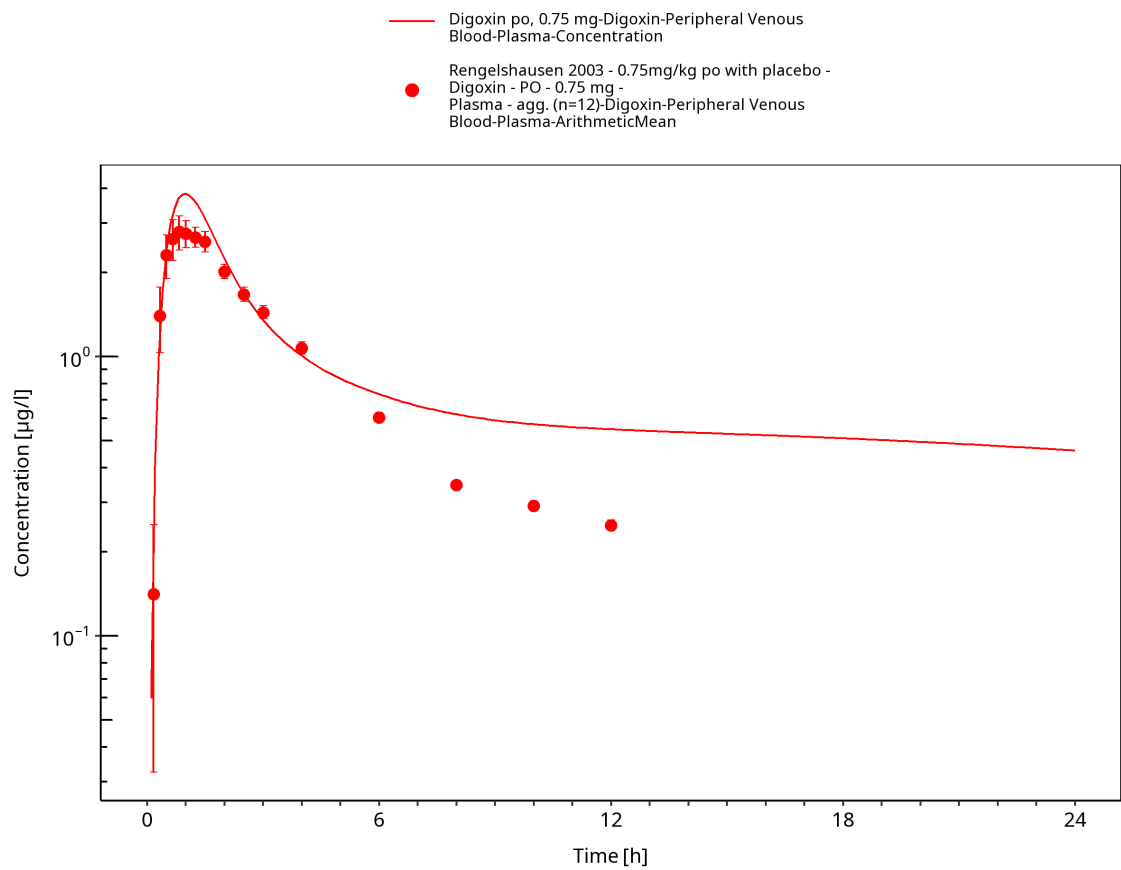


Figure 3-33: Time Profile Analysis

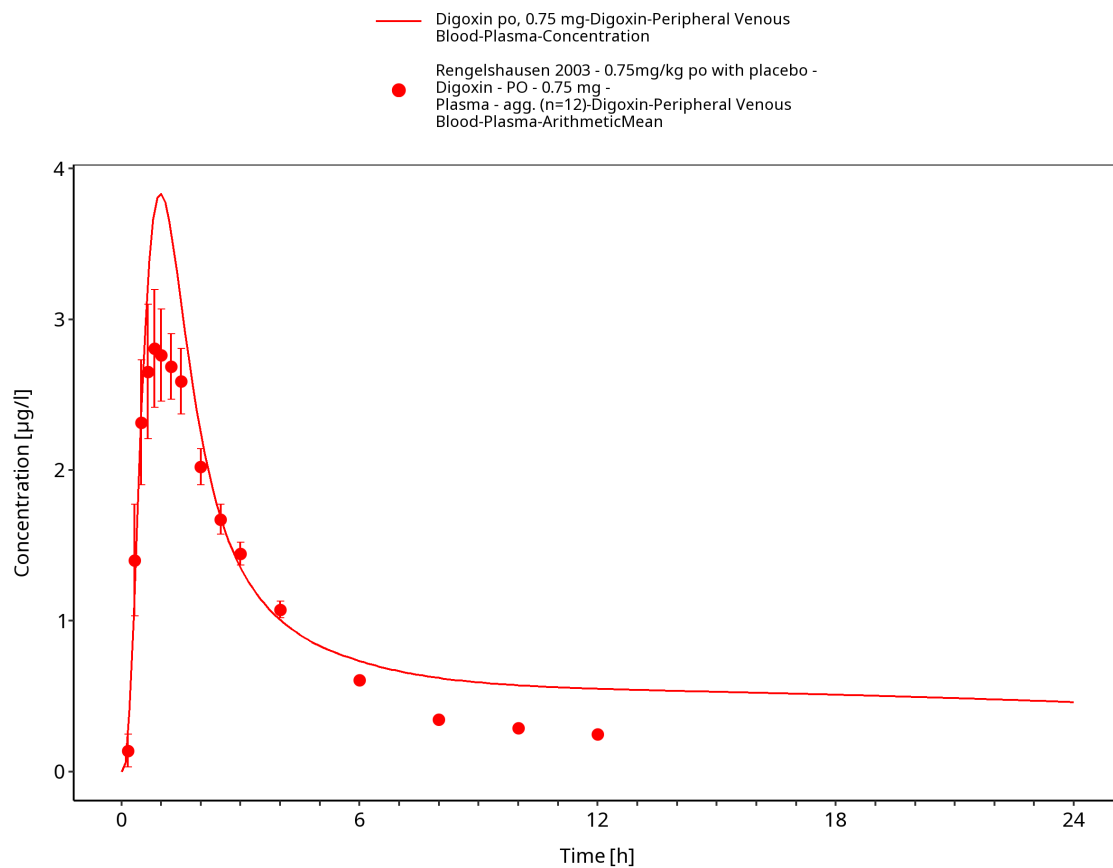


Figure 3-34: Time Profile Analysis 1

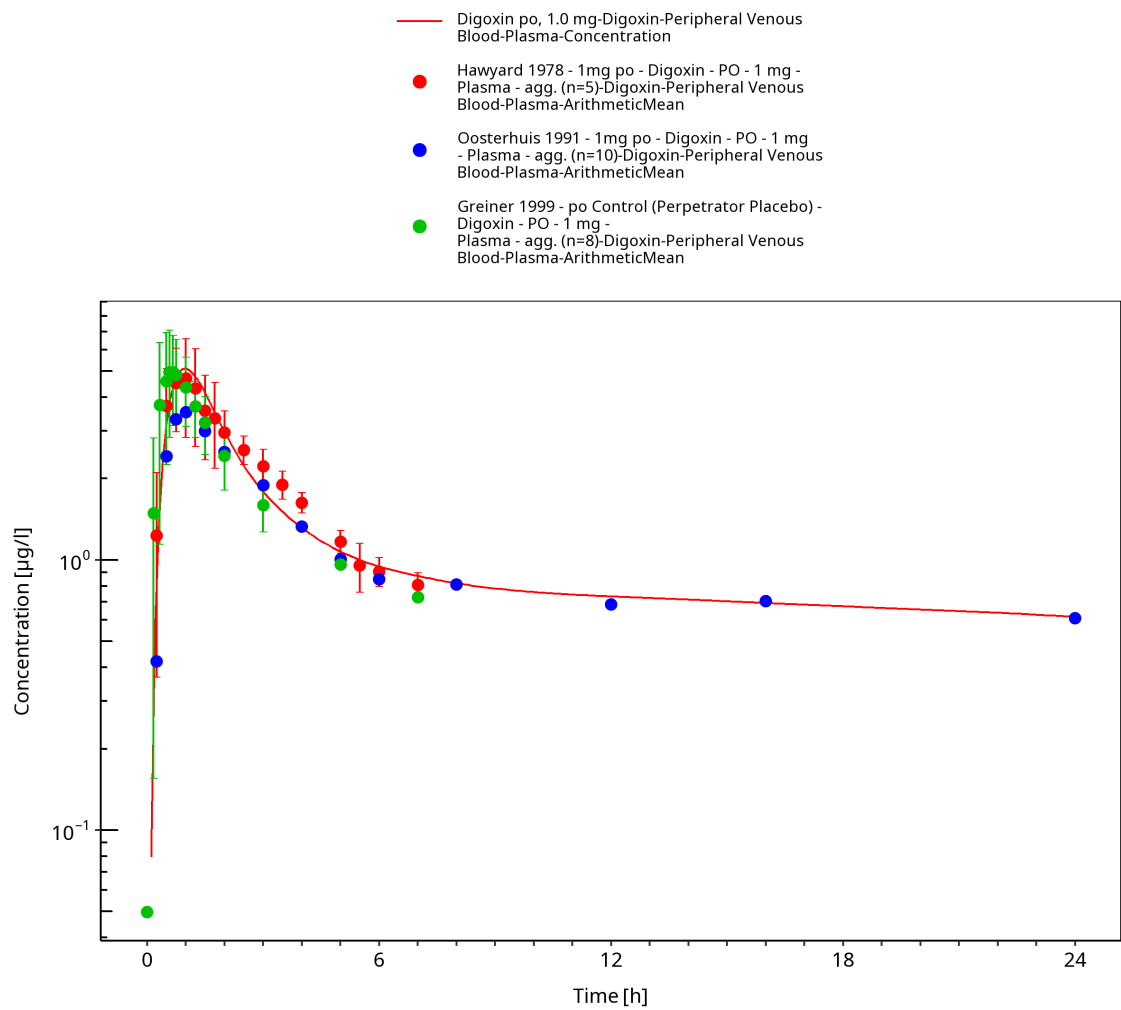


Figure 3-35: Time Profile Analysis

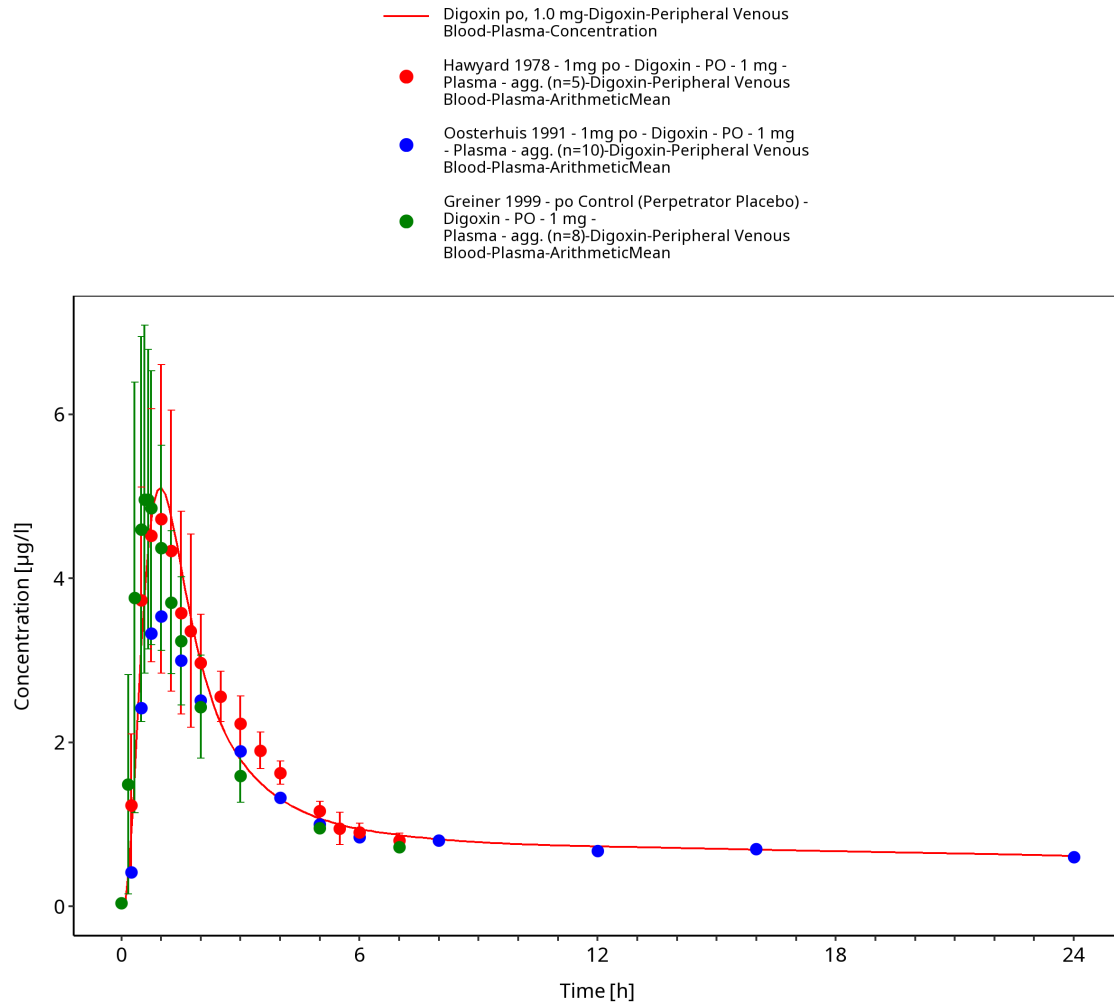


Figure 3-36: Time Profile Analysis 1

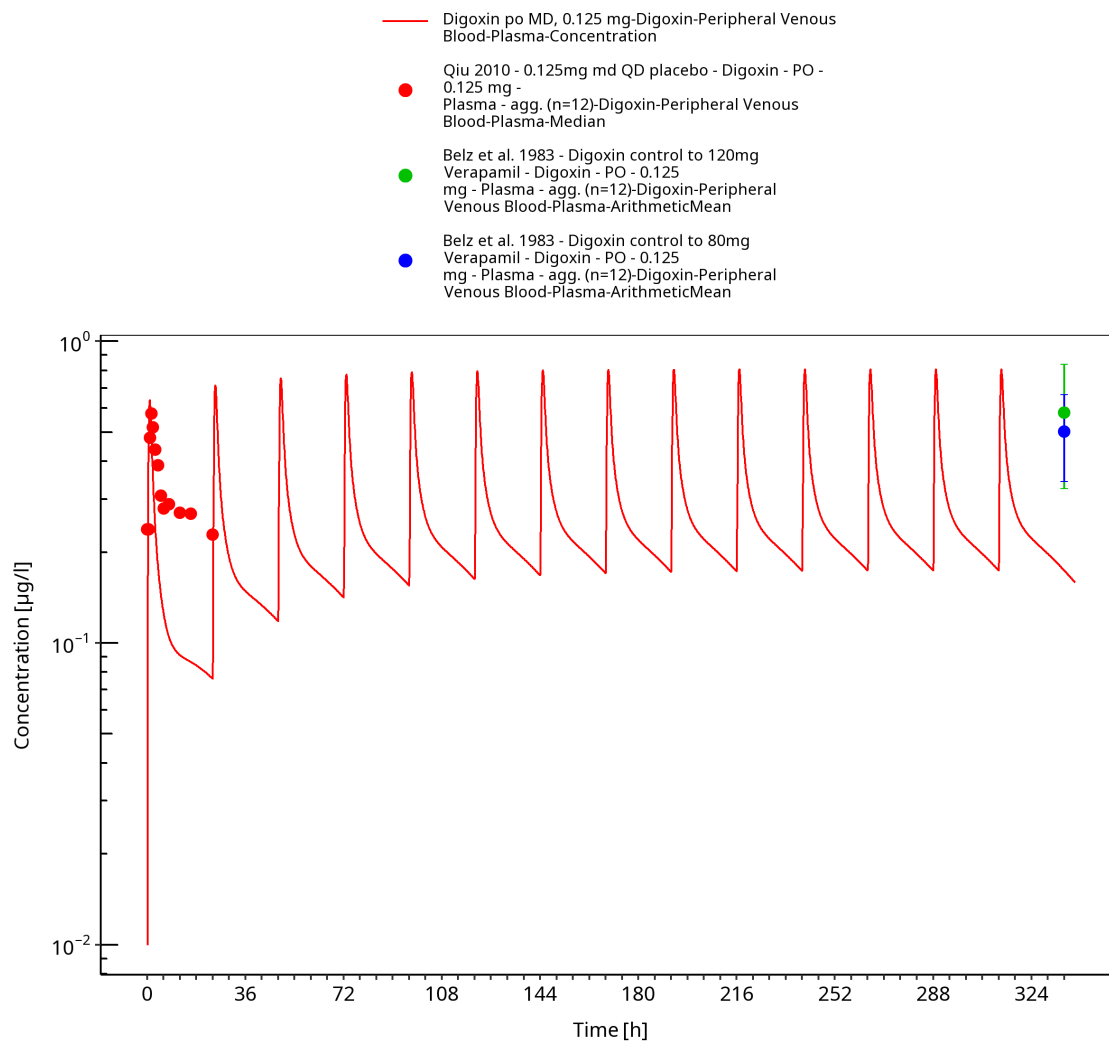


Figure 3-37: Time Profile Analysis

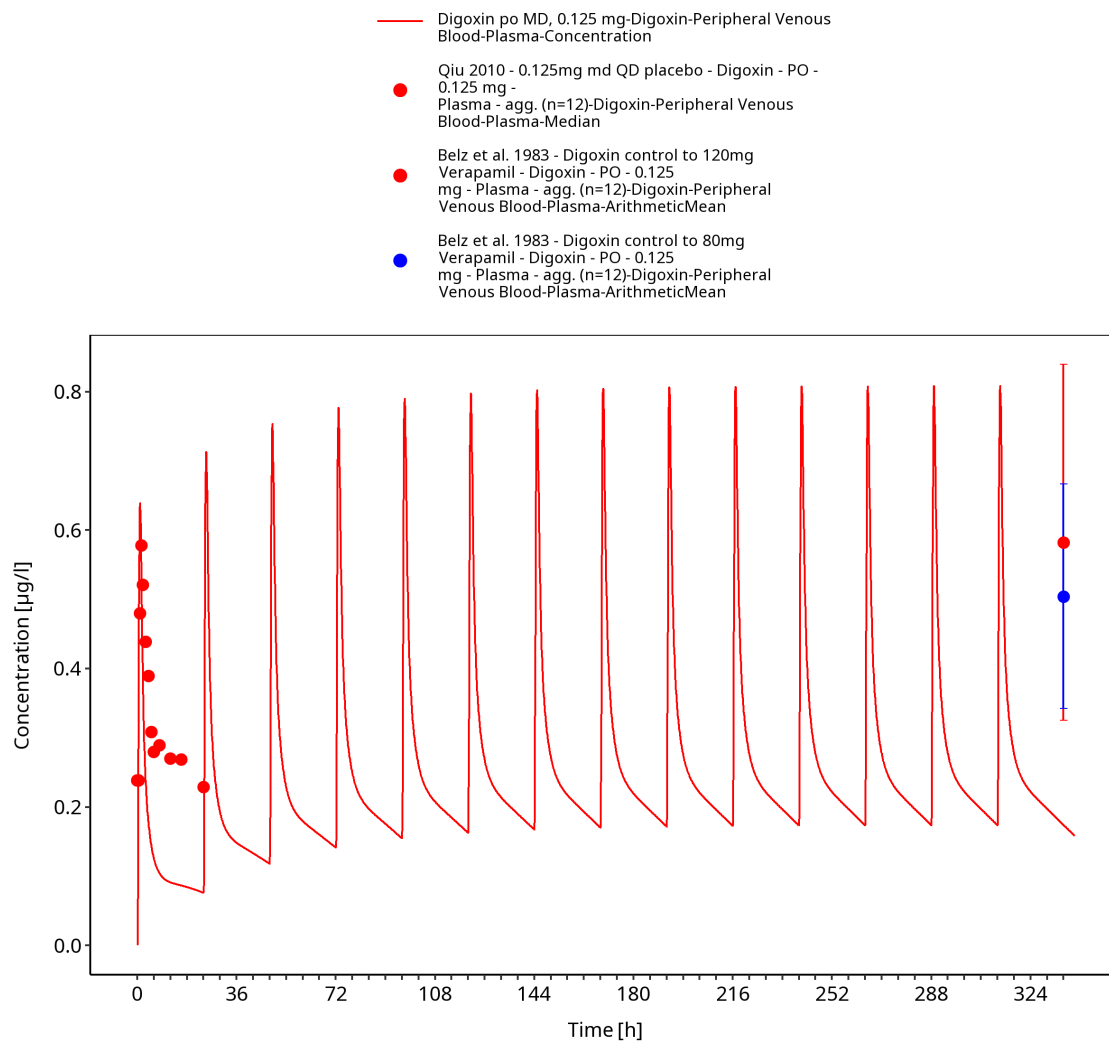


Figure 3-38: Time Profile Analysis 1

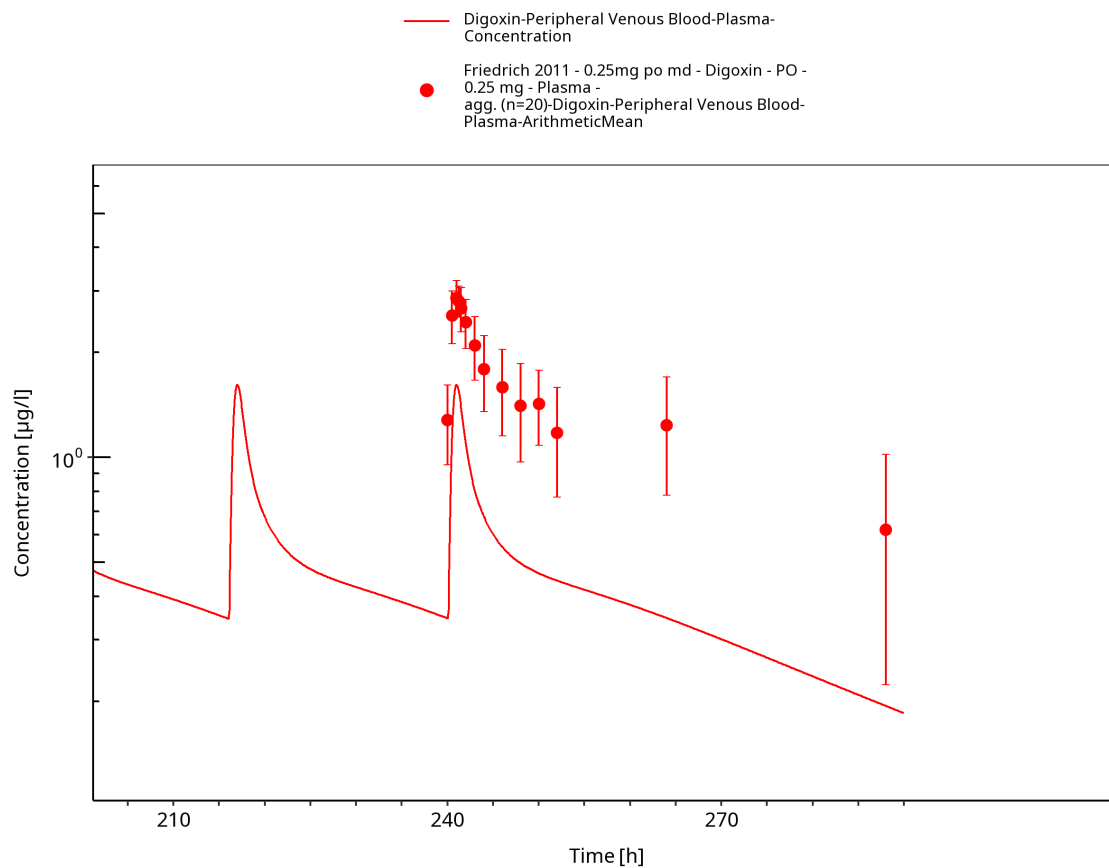


Figure 3-39: Time Profile Analysis

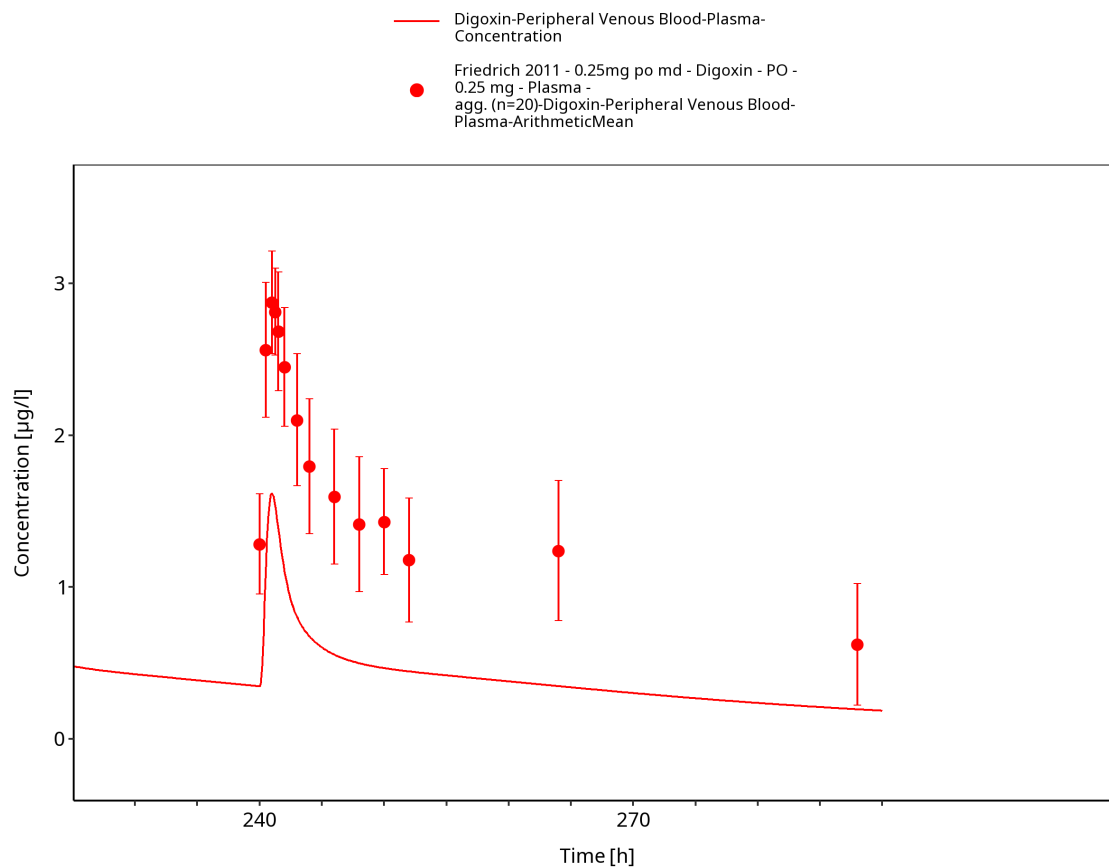


Figure 3-40: Time Profile Analysis 1

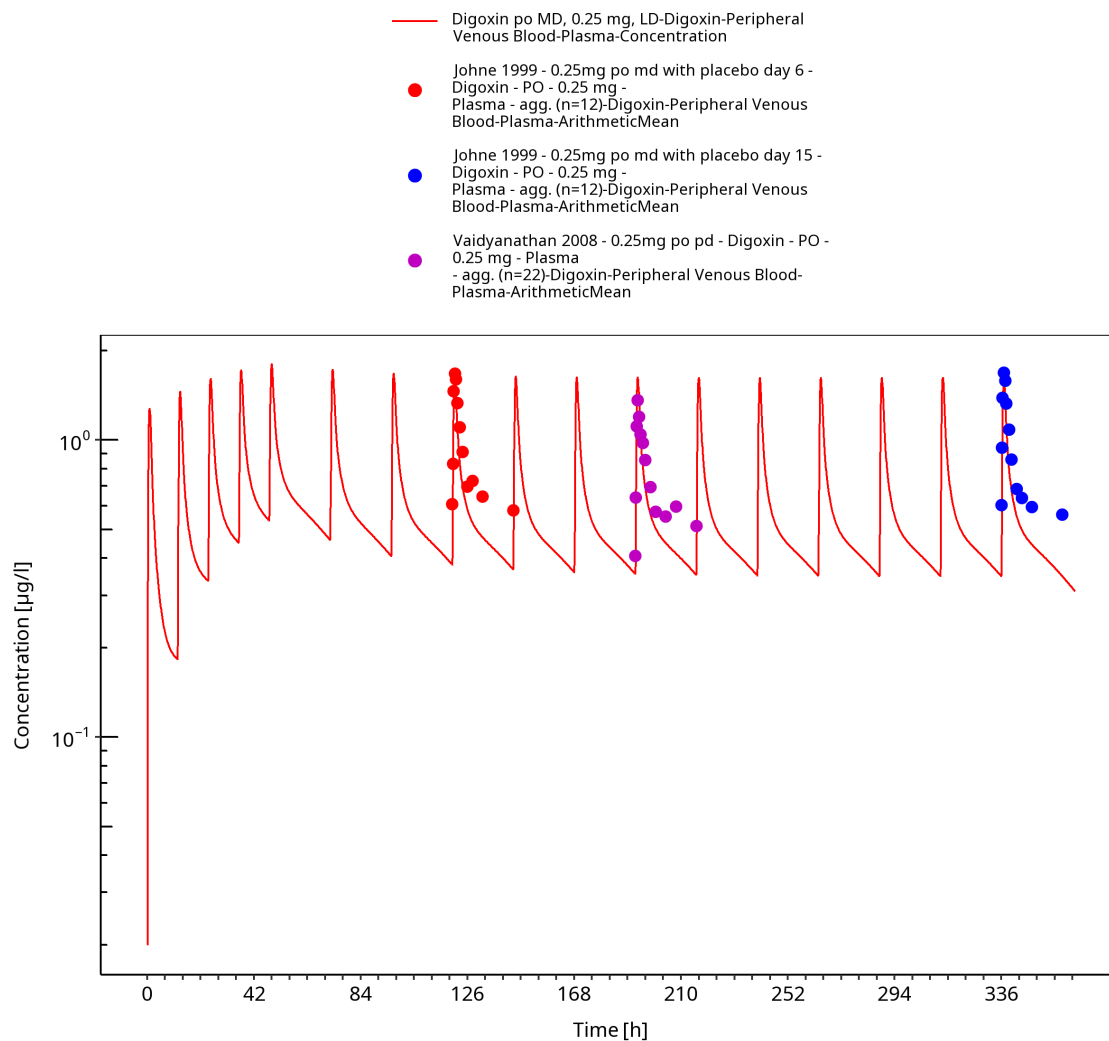


Figure 3-41: Time Profile Analysis

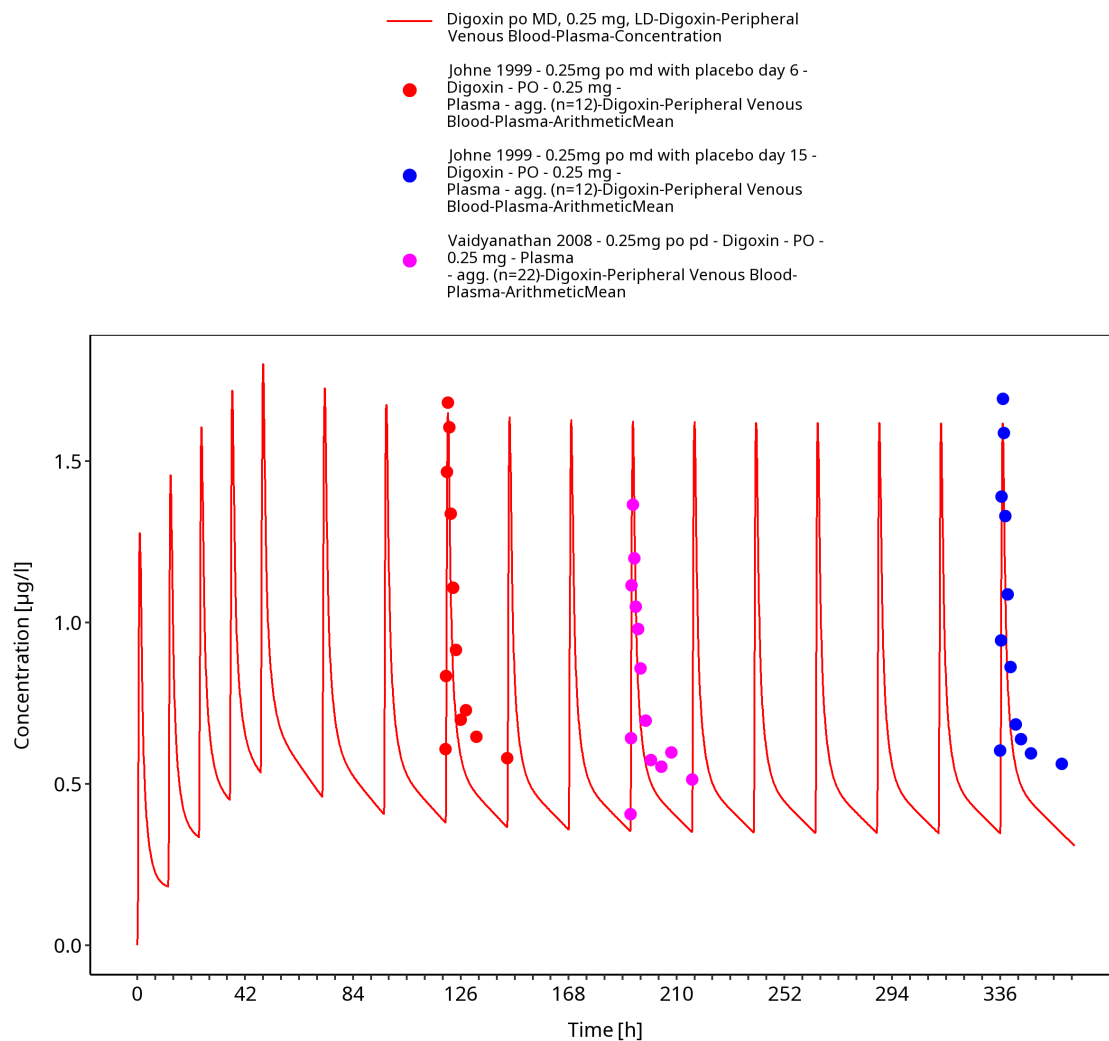


Figure 3-42: Time Profile Analysis 1

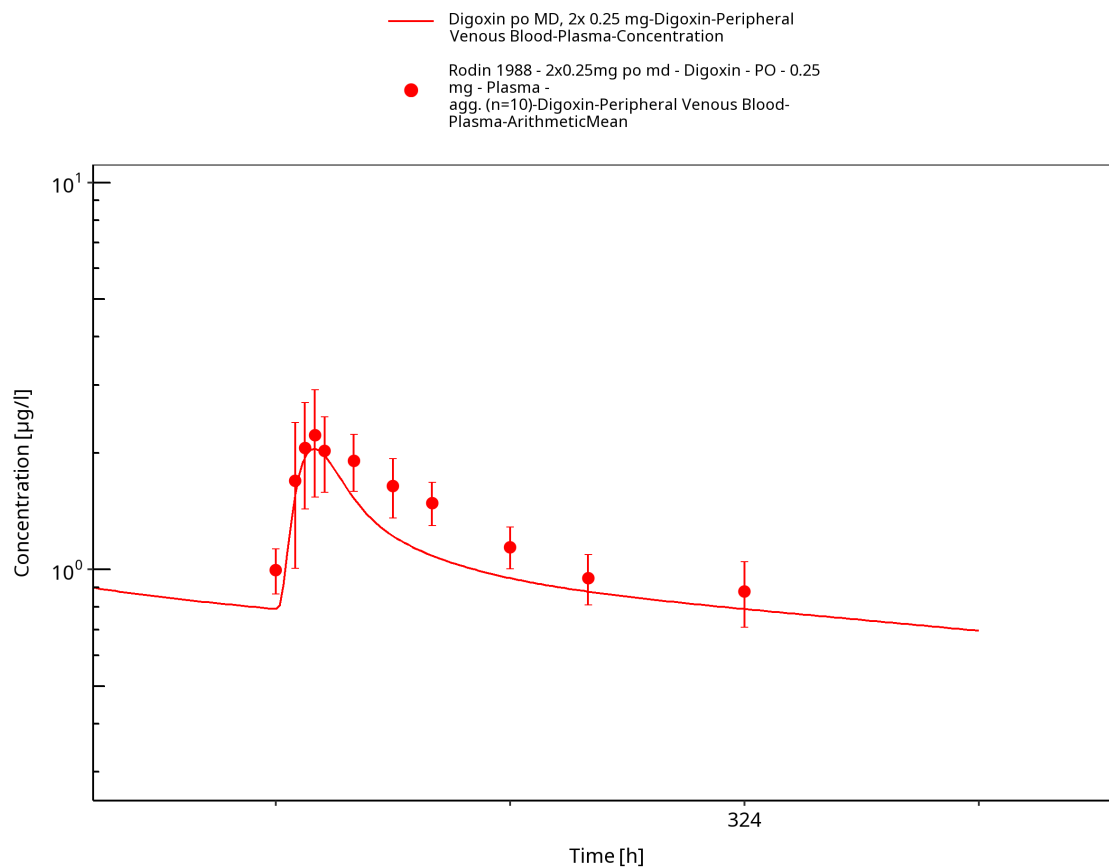


Figure 3-43: Time Profile Analysis

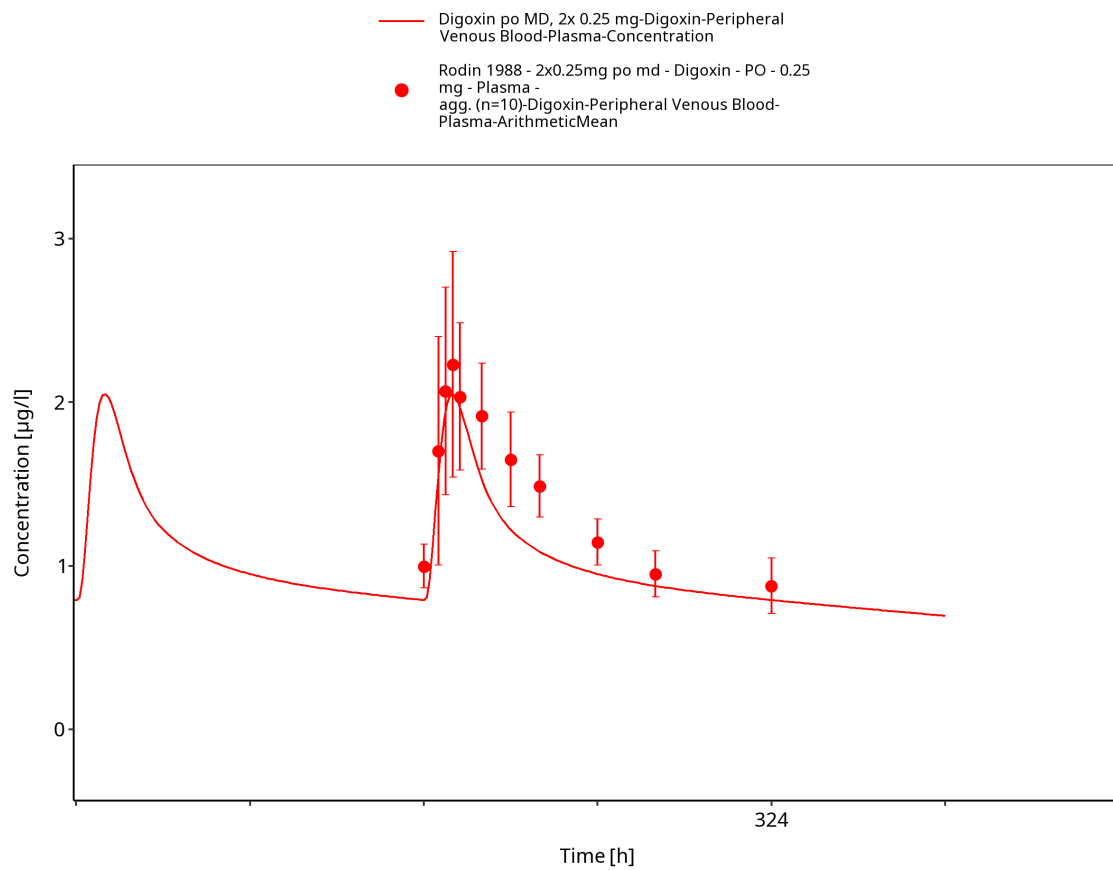


Figure 3-44: Time Profile Analysis 1

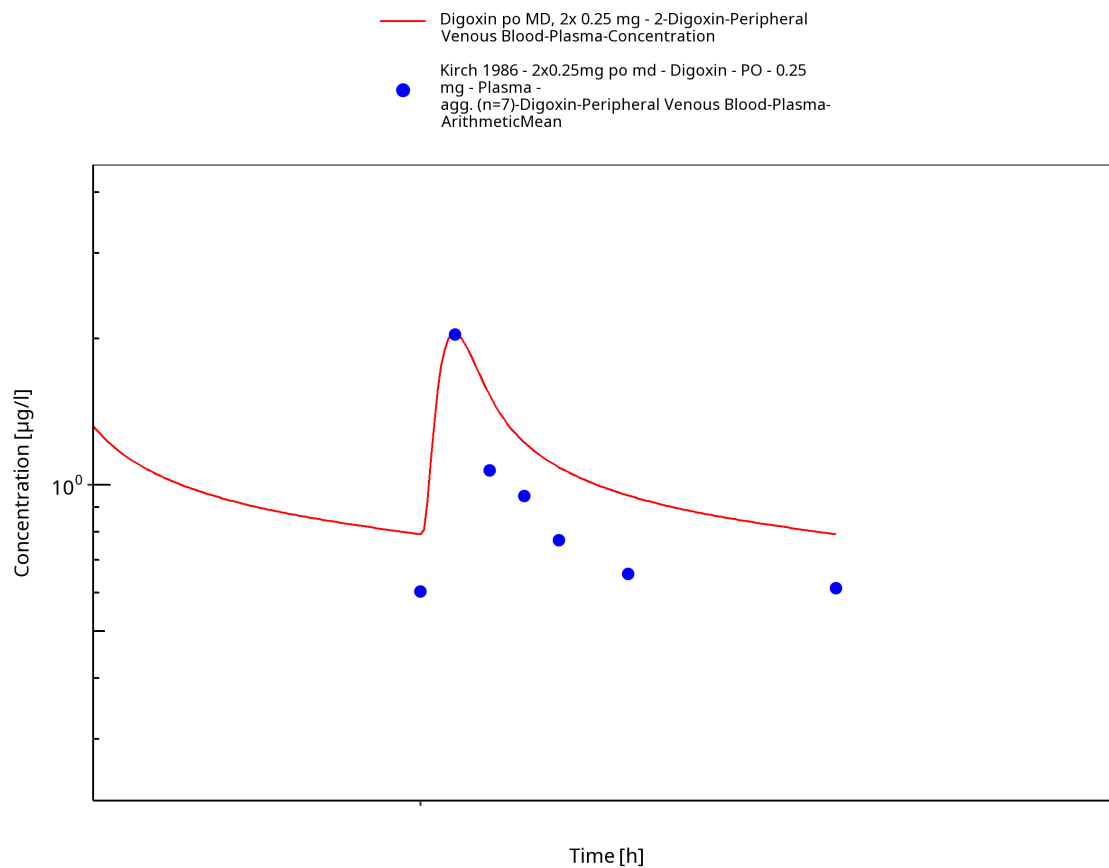


Figure 3-45: Time Profile Analysis

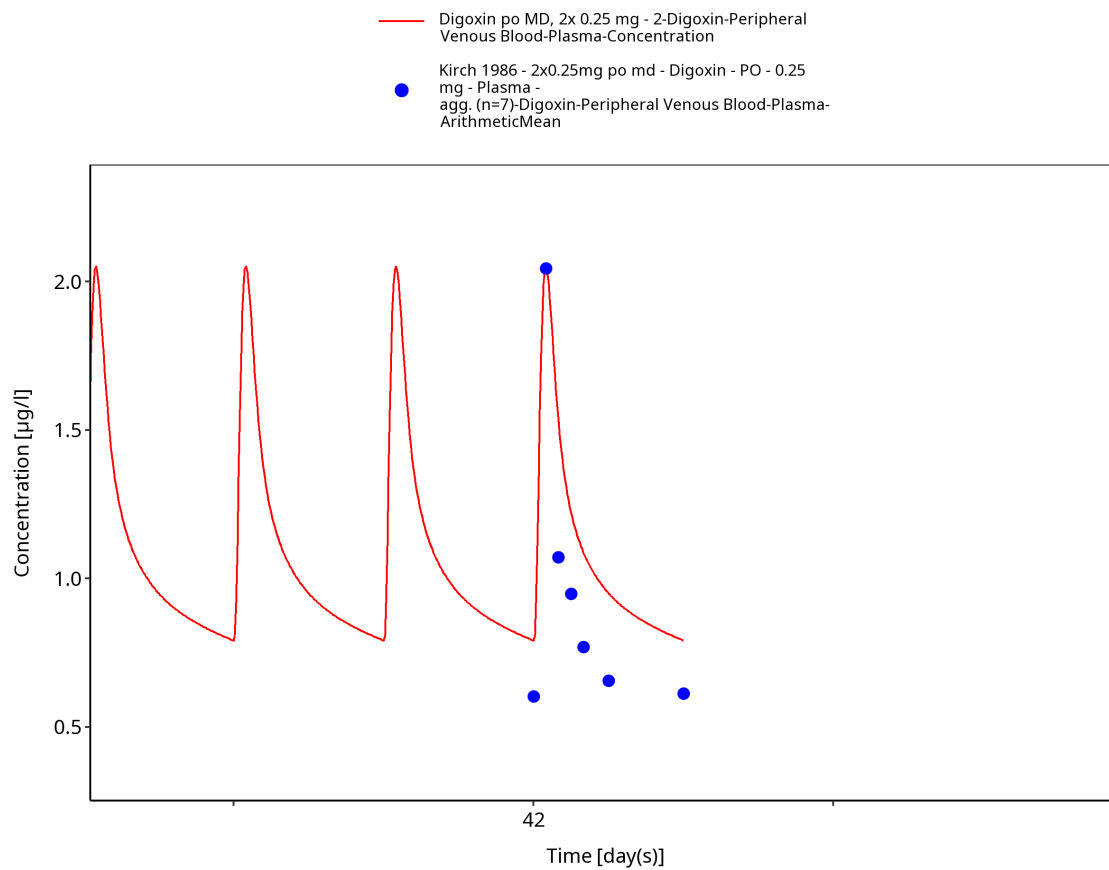


Figure 3-46: Time Profile Analysis 1

4 Conclusion

The final digoxin PBPK model applies elimination mainly via GFR and P-gp and adequately describes the pharmacokinetics of digoxin in adults receiving intravenous, and oral SD and MD of digoxin ranging from 0.125 to 1.5 mg, for different types of tablet formulations that were described using a single formulation.

This model could be applied for the investigation of drug-drug interactions (DDI), and translation to special populations such as pediatrics with regard to P-gp based elimination.

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