

Building and evaluation of a PBPK model for propofol in adults

Version	1.0-OSP12.3
based on <i>Model Snapshot and Evaluation Plan</i>	https://github.com/Open-Systems-Pharmacology/Propofol-Model/releases/tag/v1.0
OSP Version	12.3
Qualification Framework Version	3.6

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

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

Table of Contents

- 1 Introduction
- 2 Methods
 - 2.1 Modeling strategy
 - 2.2 Data used
 - 2.3 Model parameters and assumptions
- 3 Results and Discussion
 - 3.1 Propofol final input parameters
 - 3.2 Propofol Diagnostics Plots
 - 3.3 Propofol Concentration-Time profiles
- 4 Conclusion
- 5 References

1 Introduction

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

Propofol is an anaesthetic agent used for induction and maintenance of general anaesthesia. Propofol is only given intravenously and is mainly metabolized by Uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9) (53-70%) ([Al-Jahdari 2006](#), [Restrepo 2009](#)). The final propofol model features metabolism by UGT1A9 and to a minor extent by Cytochrome P450 2B6 (CYP2B6) ([Al-Jahdari 2006](#), [Oda 2009](#)). Additionally, there is excretion via glomerular filtration. The model adequately describes the pharmacokinetics of propofol in adults.

The propofol model is a whole-body PBPK model, allowing for dynamic translation between individuals with organs expressing UGT1A9. The propofol report demonstrates the level of confidence in the propofol PBPK model build with the OSP suite with regard to reliable predictions of propofol PK 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 ([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 propofol. 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.

A final PBPK model was established and simulations 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 used

2.2.1 In vitro / physicochemical data

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

Parameter	Unit	Literature value (reference)	Description
MW	g/mol	178.2707 (Drugbank.ca)	Molecular weight
pKa		10.1 (Drugbank.ca)	Acid dissociation constant
Solubility (pH)	mg/L	124 (7) (Drugbank.ca)	Solubility
logP (pH 7)		0.58 (Moss 2012)	Partition coefficient between octanol and water
fu		0.024 (Takizawa 2005)	Fraction unbound
K _{m,u} UGT1A9	mM	0.12 (Al-Jahdari 2006)	Unbound Michaelis-Menten constant
V _{max} UGT1A9	nmol/min/mg	2.40 (Al-Jahdari 2006)	Maximum rate of reaction
K _{m,u} CYP2B7	mM	0.03 (Al-Jahdari 2006)	Unbound Michaelis-Menten constant
V _{max} CYP2B7	nmol/min/mg	1.08 (Al-Jahdari 2006)	Maximum rate of reaction

2.2.2 Clinical data

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

The following publications were used in adults for model building and evaluation, of which individual patient data was available for download under <http://opentci.org/data/propofol>:

Publication	Study description
Gepts 1987	Disposition of propofol administered as constant rate intravenous infusion in humans
Schneider 1998	Influence of administration rate on propofol plasma-effect site equilibrium
Struys 2007	The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers

2.3 Model parameters and assumptions

2.3.1 Absorption

Propofol is only administered intravenously.

2.3.2 Distribution

Takizawa et al. ([Takizawa 2005](#)) published a fu in humans to be 0.024. Mazoit et al. ([Mazoit 1999](#)) reported that propofol binds to almost exclusively to serum albumin as plasma protein, which is built-in

as such in the PBPK model.

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 and cell permeability calculation by PK-Sim standard. Specific organ permeability normalized to surface area was automatically calculated by PK-Sim.

2.3.3 Metabolism and Elimination

Propofol undergoes fast biotransformation to different metabolites. (Restrepo 2009) *In vitro* studies show that particularly the UGT1A9 (Court 2005) is involved, followed by CYP2B6 (Oda 2001).

Al-Jahdari et al. (Al-Jahdari 2006) investigated the contribution of the liver and kidneys to propofol metabolism in humans using an *in vitro*–*in vivo* scale up approach. Human kidney and liver microsomal incubations confirmed the dominant role of UGT metabolism for propofol. Propofol was in particular metabolized by UGT1A9 and CYP2B6. The apparent arithmetic mean unbound K_m ($K_{m,u}$) values in the liver for the glucuronidation and hydroxylation of propofol by UGT1A9 and CYP2B6 were 0.12 (standard deviation (SD): 0.072) and 0.0072 (SD: 0.0) mM, respectively. (Al-Jahdari 2006) The corresponding V_{max} values (nmol/min/mg protein) were 2.40 (SD: 0.2) for UGT1A9, and 1.08 (SD: 0.1) for CYP2B6. In the kidney the $K_{m,u}$ and V_{max} values for glucuronidation by UGT1A9 were 0.38 (SD: 0.19) mM, and 7.97 (4.5) (nmol/min/mg protein), respectively. The $K_{m,u}$ and V_{max} for hydroxylation were reported to be negligible. (Al-Jahdari 2006)

The abundance of proteins in different organs in PK-Sim is calculated from relative expression values. For each organ, the relative expression defines the concentration of the protein in whole organ as a fraction of a defined reference concentration value. The relative gene expressions for both UGT1A9 and CYP2B6 are derived from reported Reverse Transcription-Polymerase Chain Reaction (RT-PCR) values by Nishimura et al. (Nishimura 2006)

The reported 25.9 pmol/mg UGT1A9 protein expression level in human liver microsomes (HLM) by Ohtsuki et al. (Ohtsuki 2012) was used to calculate the reference concentration imputed in PK-Sim. The relationship between age and human microsomal protein (MPPGL) observed by Barter et al. (Barter 2007) is estimated 40 mg/g for a 30 year old individual. As the expression of UGT1A9 is highest in the kidney and relatively 10% in the liver (Nishimura 2006), this resulted in a reference concentration of 10.36 $\mu\text{mol/L}$ liver tissue for UGT1A9 which is imputed in PK-Sim. For CYP2B6, which is mainly expressed in the liver, the reported CYP2B6 protein expression level of 1.56 $\mu\text{mol/L}$ liver tissue by Rodriguez et al. (Rodrigues 1999) is imputed as reference concentration in PK-Sim. The reported expression level in HLM for CYP2B6 is 39 pmol/mg microsomal protein. (Rodrigues 1999)

For the estimation of propofol clearance in PK-Sim, K_{cat} is estimated, which is $V_{max}/\text{protein}$ expression level in HLM.

Although UGT1A9 expression is highest in the kidney (Nishimura 2006), as no measurement results were available for CYP2B6 mediated hydroxylation in the kidney, the reported liver *in vitro* $K_{m,u}$ and V_{max} values for UGT1A9 and CYP2B6 were included in the model. Reported V_{max} values were in units nmol/min/mg protein and thus not directly transferable into the PBPK model. Therefore, a joint scaling factor $f_{activity}$ on the *in vitro* K_{cat} values was estimated to match observed *in vivo* data, and keeping the relative relationship between those *in vitro* values (0.89 and 0.53 nmol/min/mg) for UGT1A1 and CYP2B6 fixed according to:

$$K_{\text{cat, UGT1A9}} = f_{\text{activity}} * K_{\text{cat, in-vitro, UGT1A9}}$$

$$K_{\text{cat, CYP2B6}} = f_{\text{activity}} * K_{\text{cat, in-vitro, CYP2B6}}$$

It is especially important to fix the relative contribution of both enzymes as a ratio to ensure that, when translating to other populations (e.g. children where both enzymes may undergo a different ontogeny pattern, or patients who have differently reduced amounts of UGT1A1 vs CYP2B6) the relative contributions can be adequately scaled. Note that the estimated scaling factor f_{activity} will be directly implemented into the final *in vivo* V_{max} values (only $K_{\text{cat, UGT1A9}}$ and $K_{\text{cat, CYP2B6}}$ will be reported in [section 3](#)).

Finally, as ~0.3% of the dose is excreted in human urine as unchanged parent compound, GFR is introduced in the propofol PBPK model.

3 Results and Discussion

The PBPK model propofol was developed with clinical pharmacokinetic data after intravenous administration covering a dose range of 1-36mg/kg, including bolus infusion as well as continuous infusion clinical data.

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

- K_{cat} (as unique scaling factor $f_{activity}$, as described in [section 2.3.3](#))
- Lipophilicity

The mean model fit resulted in an adequate description of all data, that showed to be highly variable. The reported 2.5 mg/kg bolus infusion data by Struys et al. ([Struys 2007](#)) only contained concentration time profiles over 5 minutes. Nevertheless this data was included in the analysis, and showed overprediction in the first 2 minutes by the model, compared to available 1 mg/kg and 2 mg/kg data reported by Schnider et al. ([Schnider 1998](#)) that was well described by the propofol PBPK model. This discrepancy in propofol distribution was assumed to be inter-study variability related.

Overall, the model results show that the PBPK model of propofol adequately described the data for all available doses.

3.1 Propofol final input parameters

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

Compound: Propofol

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	124 mg/l	Internet- https://www.drugbank.ca/drugs/DB00818 , in water @ 25°C	Measurement	True
Reference pH	7	Internet- https://www.drugbank.ca/drugs/DB00818 , in water @ 25°C	Measurement	True
Lipophilicity	3.5486243812 Log Units	Parameter Identification-Parameter Identification	Fit	True
Fraction unbound (plasma, reference value)	0.024	Publication-Drugbank.ca	Measurement	True
Is small molecule	Yes			
Molecular weight	178.2707 g/mol	Internet-Drugbank.ca		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Al-Jahdari 2005

Metabolizing Enzyme: UGT1A9-Al-Jahdari 2006 Liver

Molecule: UGT1A9

Metabolite: Propofol glucuronide

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	2.4 nmol/min/mg mic. protein	Publication-In Vitro-Al-Jahdari 2006 HLM
Content of CYP proteins in liver microsomes	25.9 pmol/mg mic. protein	Publication-Assumption-Ohtsuki 2012 (UGT1A9)
Km	0.12 mM	Publication-In Vitro-Al-Jahdari 2006 HLM (corrected for fu, mic)
kcat	471.8406263631 1/min	Parameter Identification

Metabolizing Enzyme: CYP2B6-Cumulative CYP Action

Molecule: CYP2B6

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	1.08 nmol/min/mg mic. protein	Publication-In Vitro-Al-Jahdari 2006 HLM
Content of CYP proteins in liver microsomes	39 pmol/mg mic. protein	Publication-Assumption-Rodriguez 1999 (CYP2B6)
Km	0.0072 mM	Publication-Al-Jahdari 2005 HLM (corrected for fu,mic)
kcat	141.007756417 1/min	Parameter Identification

3.2 Propofol Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for propofol PBPK model performance (individually simulated versus observed 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
Propofol bolus + continuous IV infusion	1.68
Propofol bolus IV infusion	2.33
Propofol continuous IV infusion	1.29
All	1.57

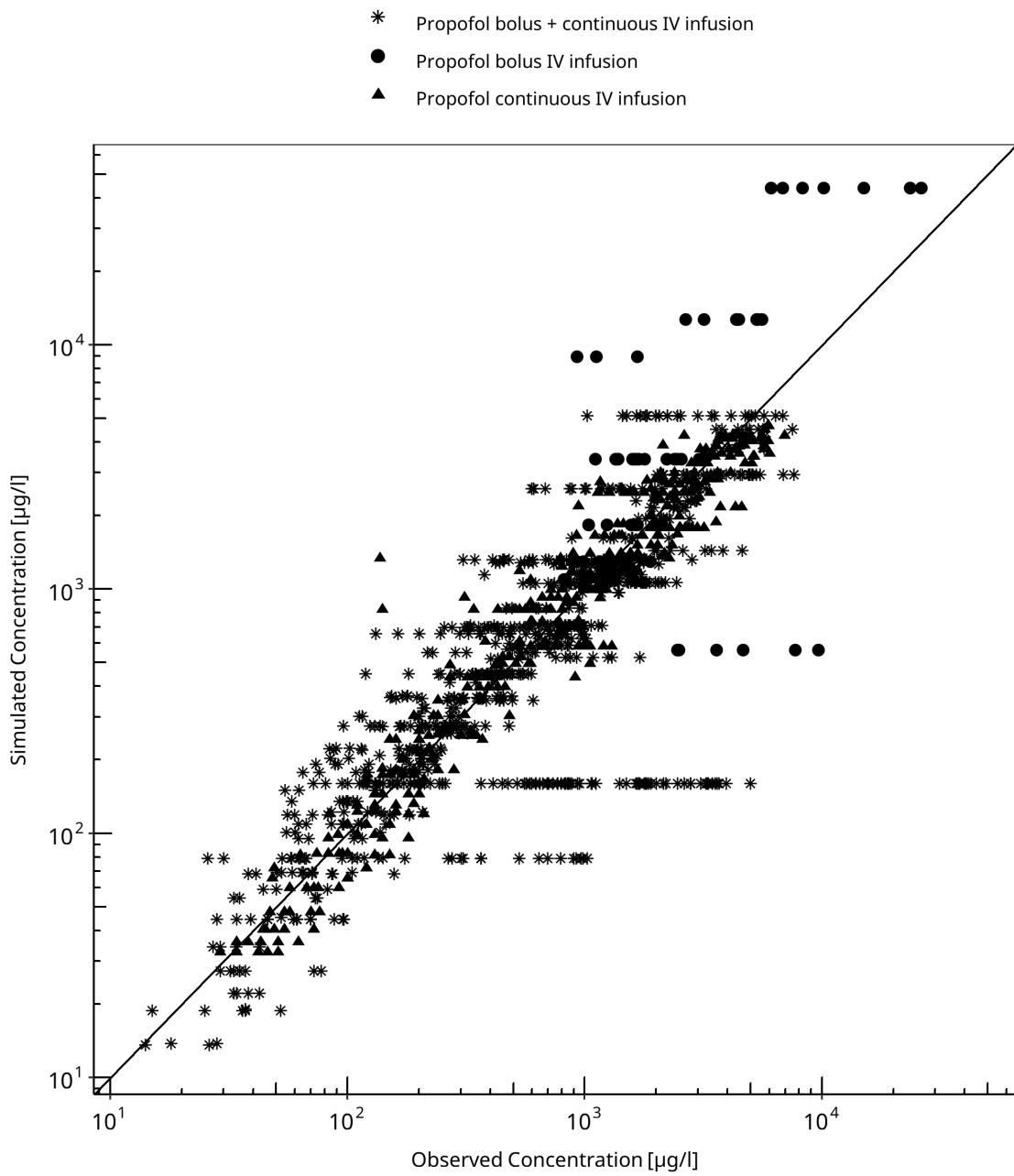


Figure 3-1: Goodness of fit plot for concentration in plasma.

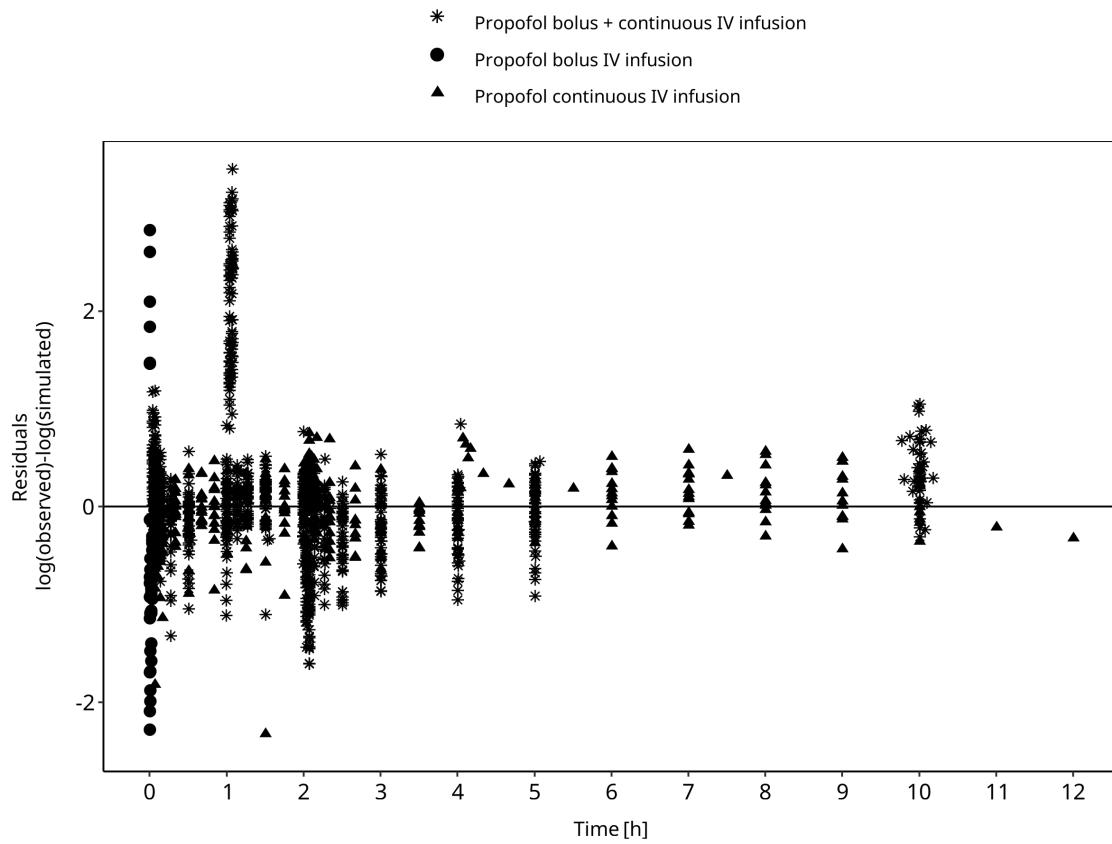


Figure 3-2: Goodness of fit plot for concentration in plasma.

3.3 Propofol Concentration-Time profiles

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

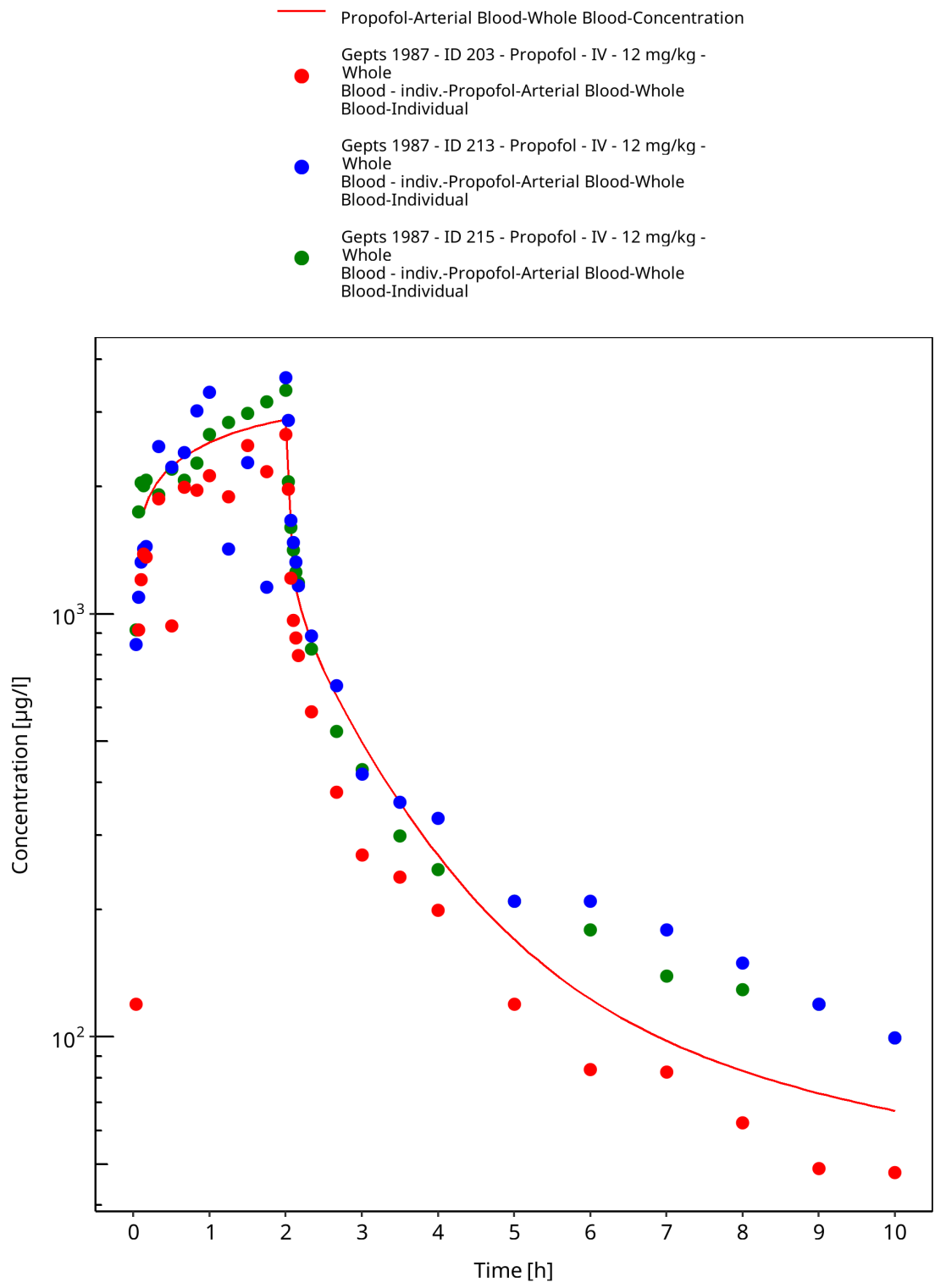


Figure 3-3: Time Profile Analysis

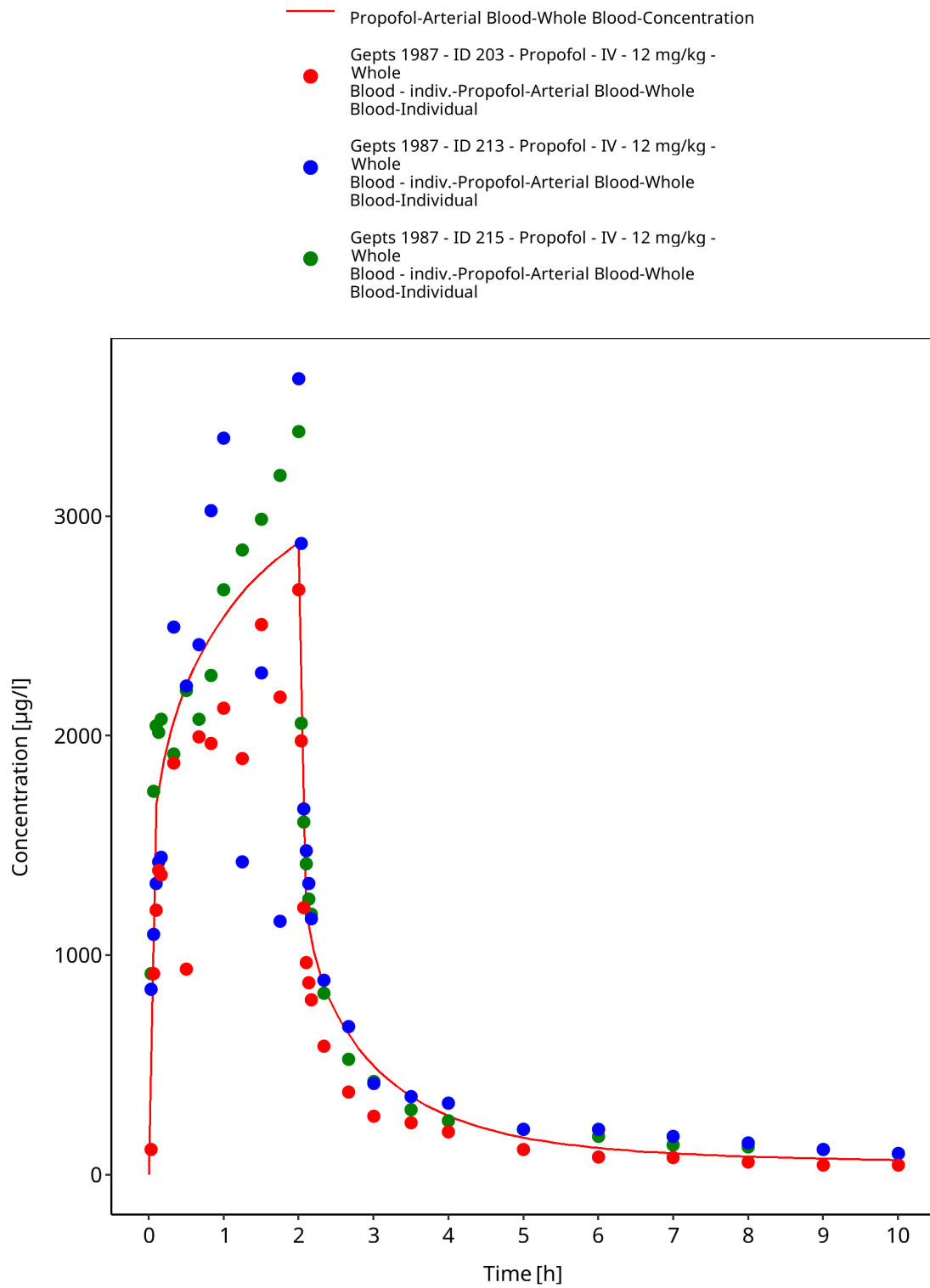


Figure 3-4: Time Profile Analysis 1

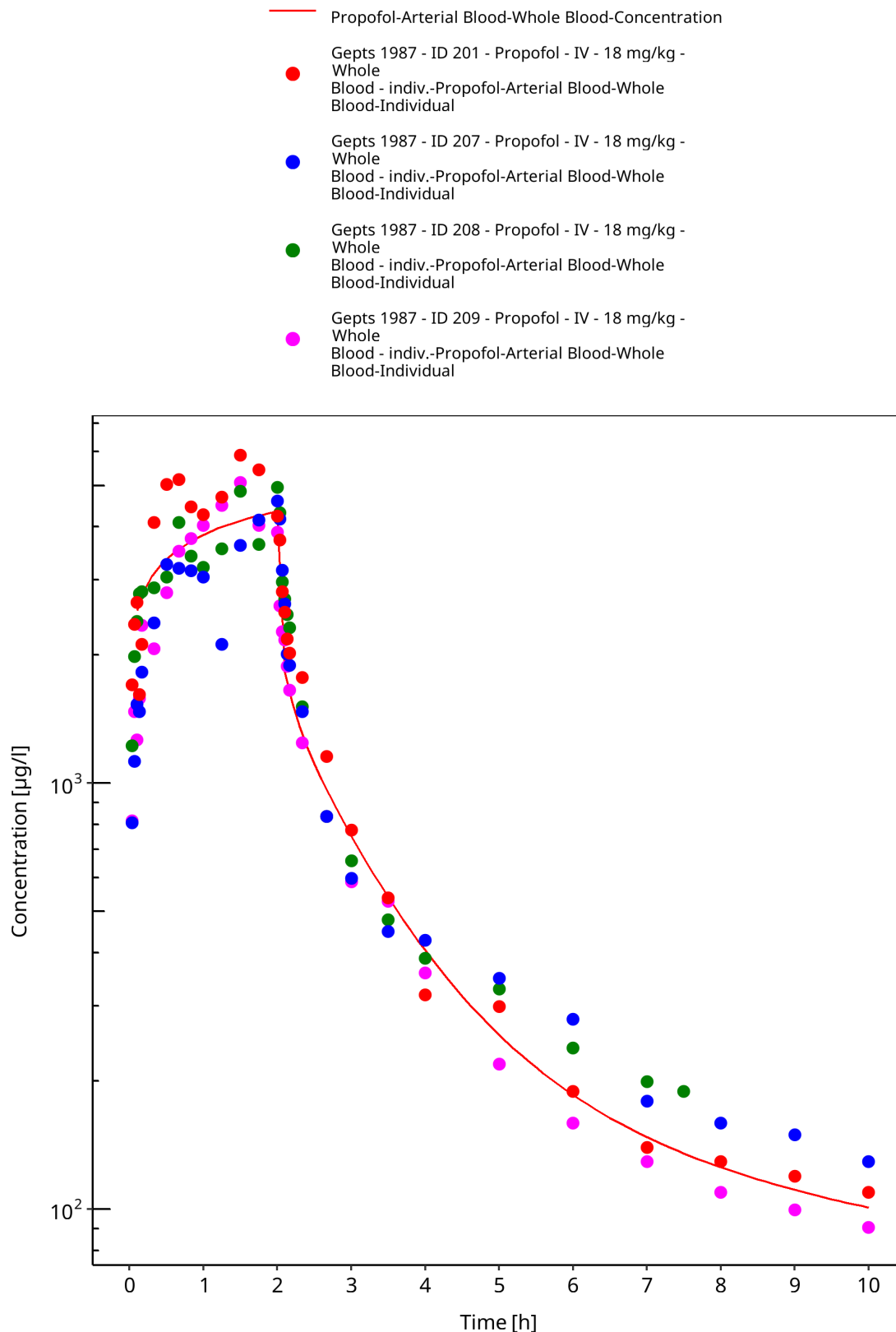


Figure 3-5: Time Profile Analysis

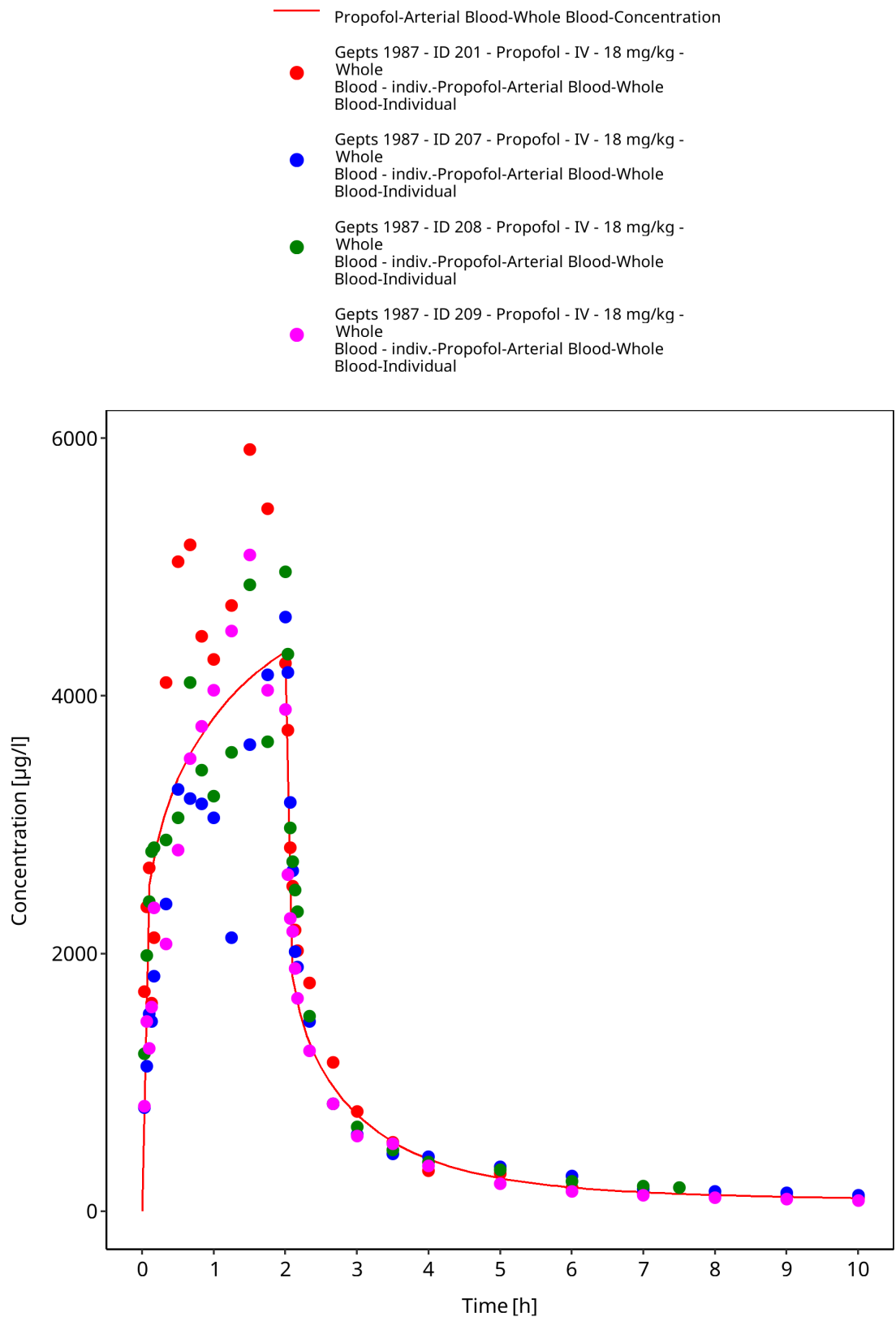


Figure 3-6: Time Profile Analysis 1

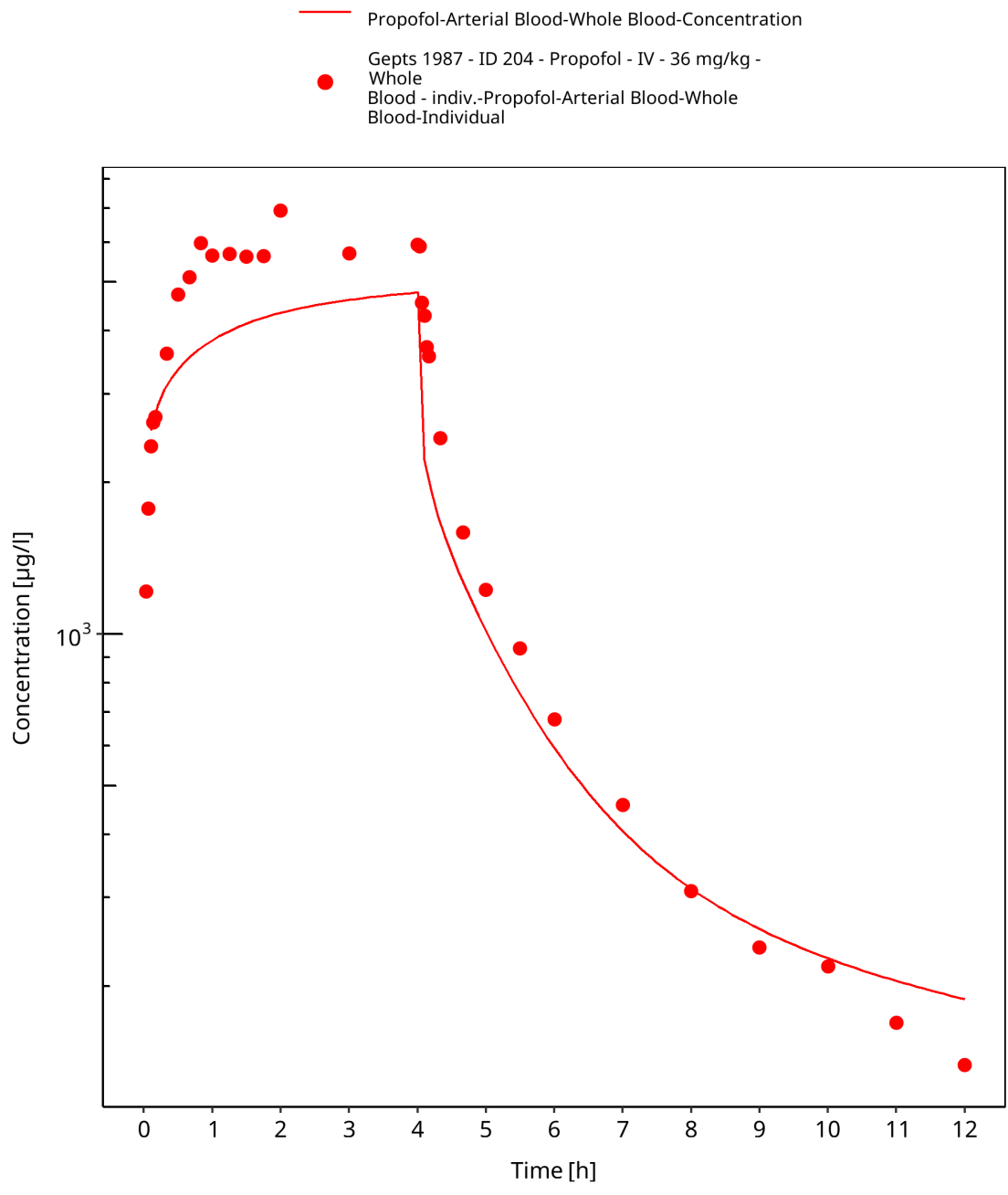


Figure 3-7: Time Profile Analysis

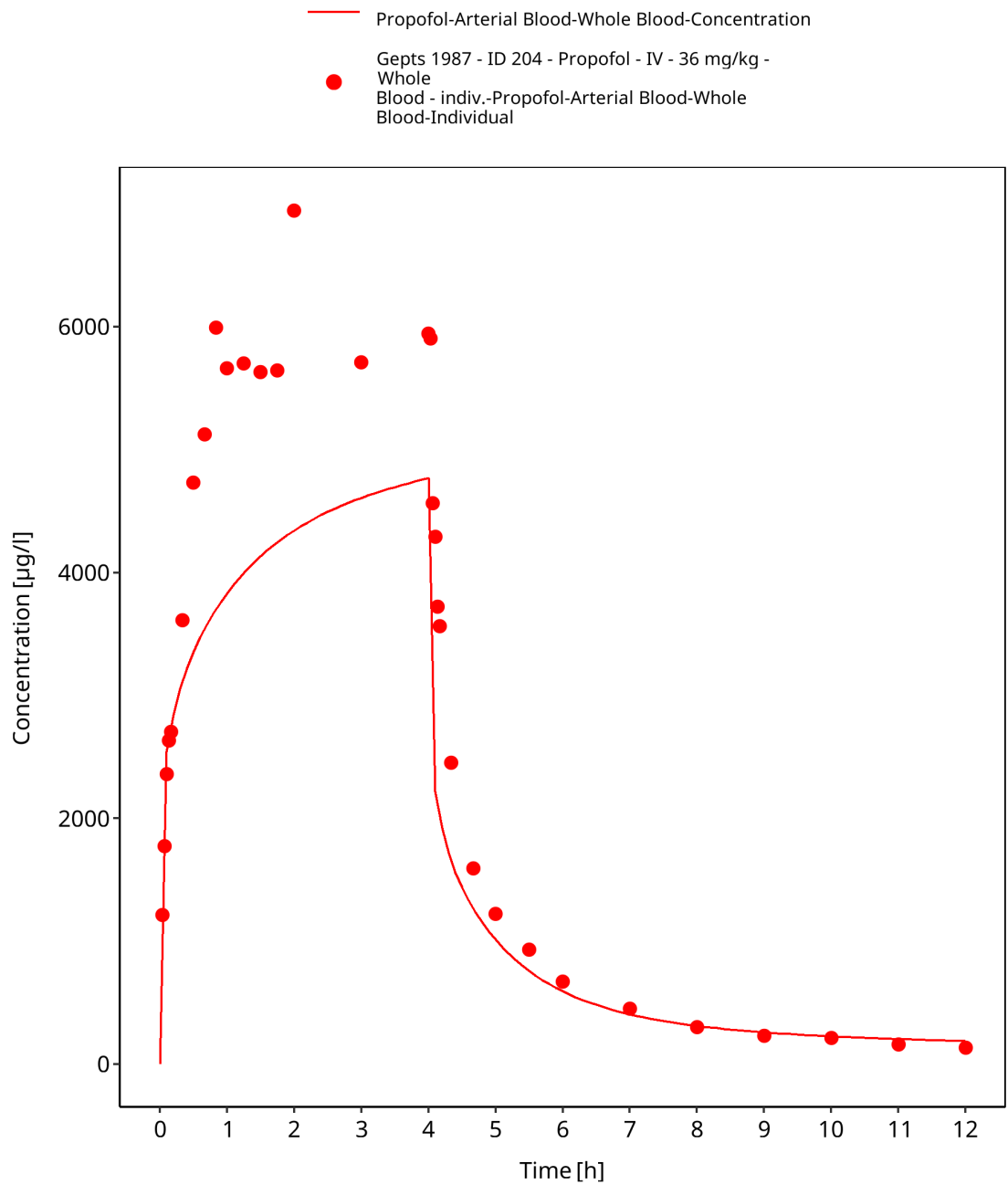


Figure 3-8: Time Profile Analysis 1

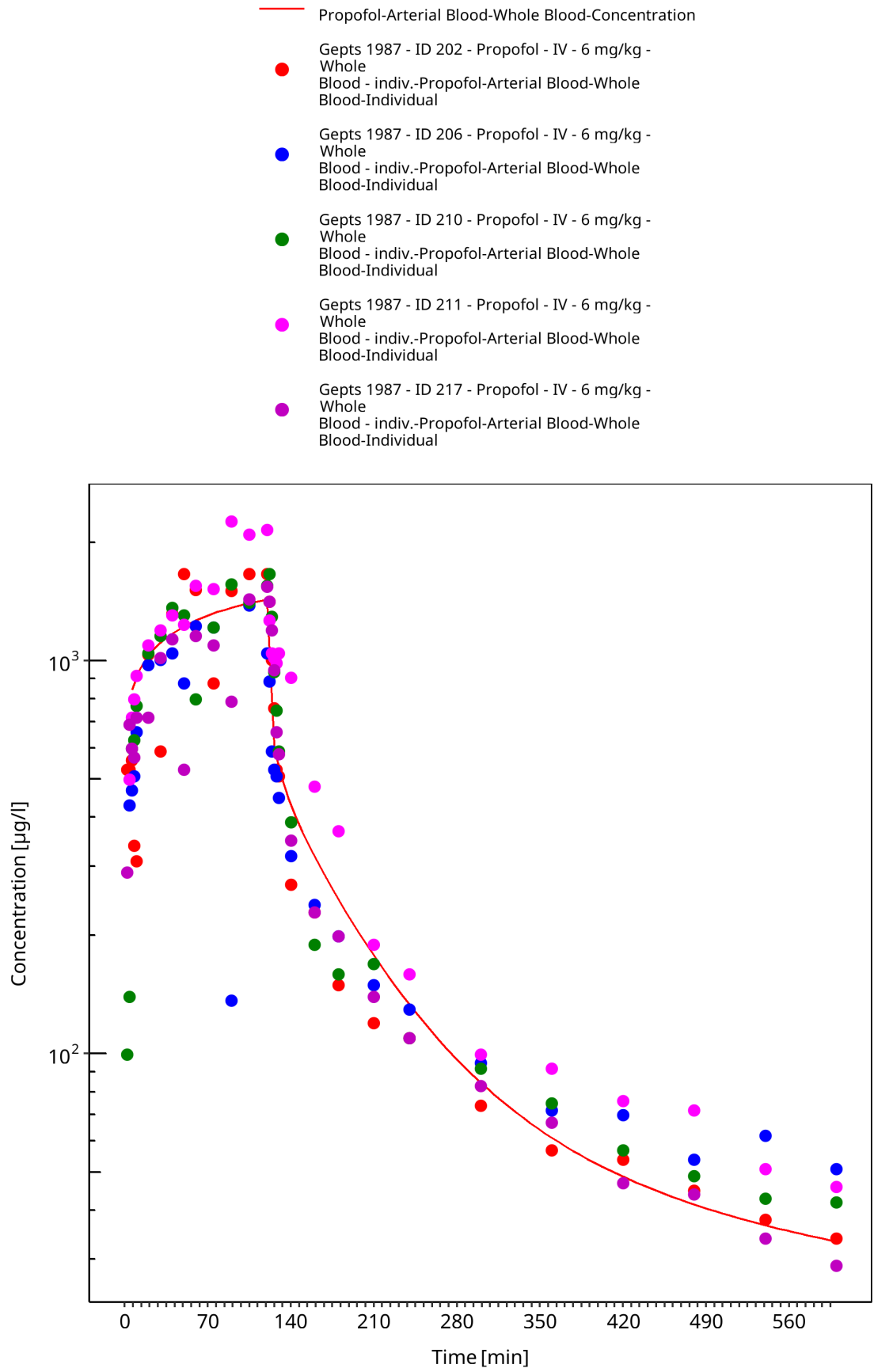


Figure 3-9: Time Profile Analysis

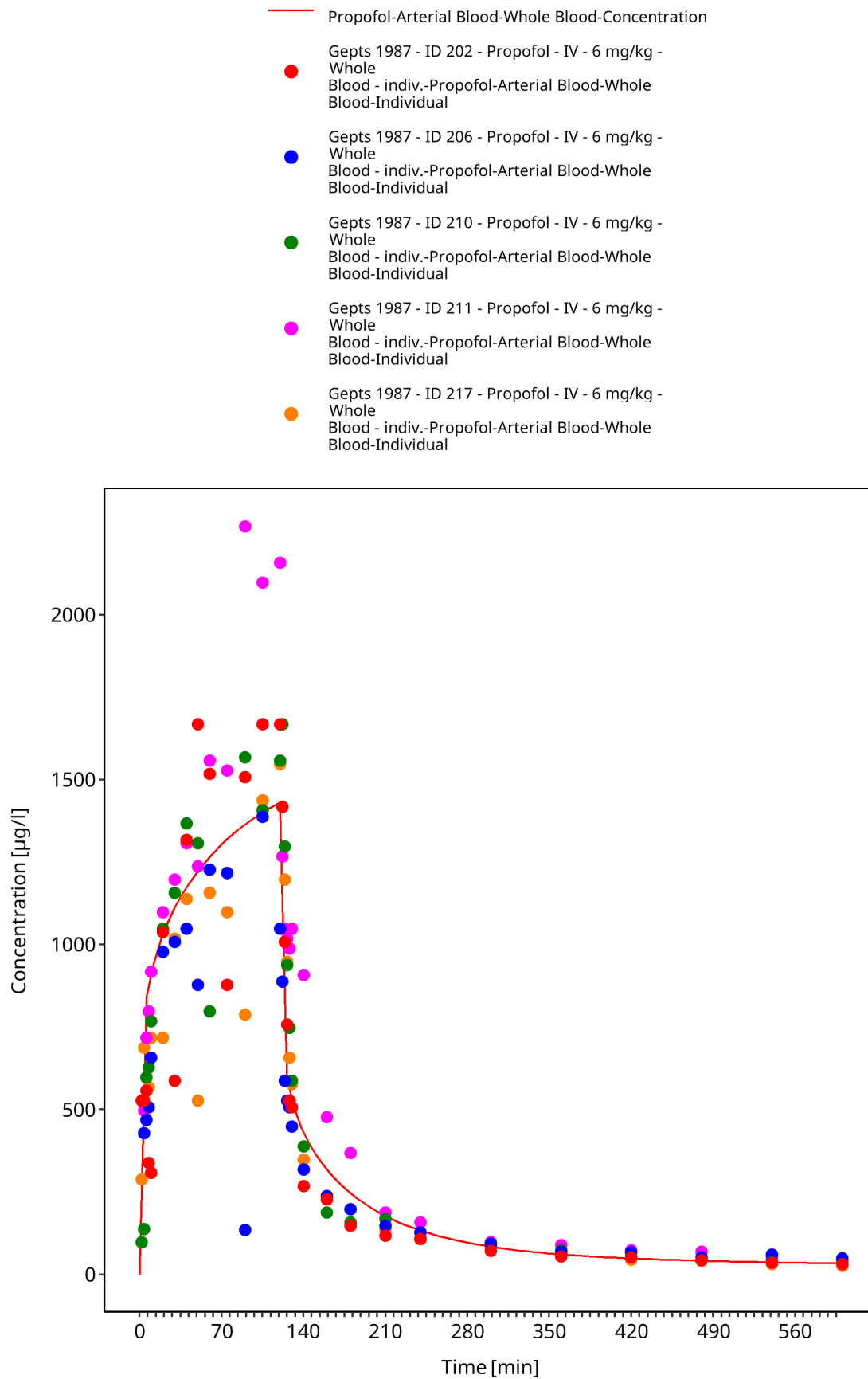


Figure 3-10: Time Profile Analysis 1

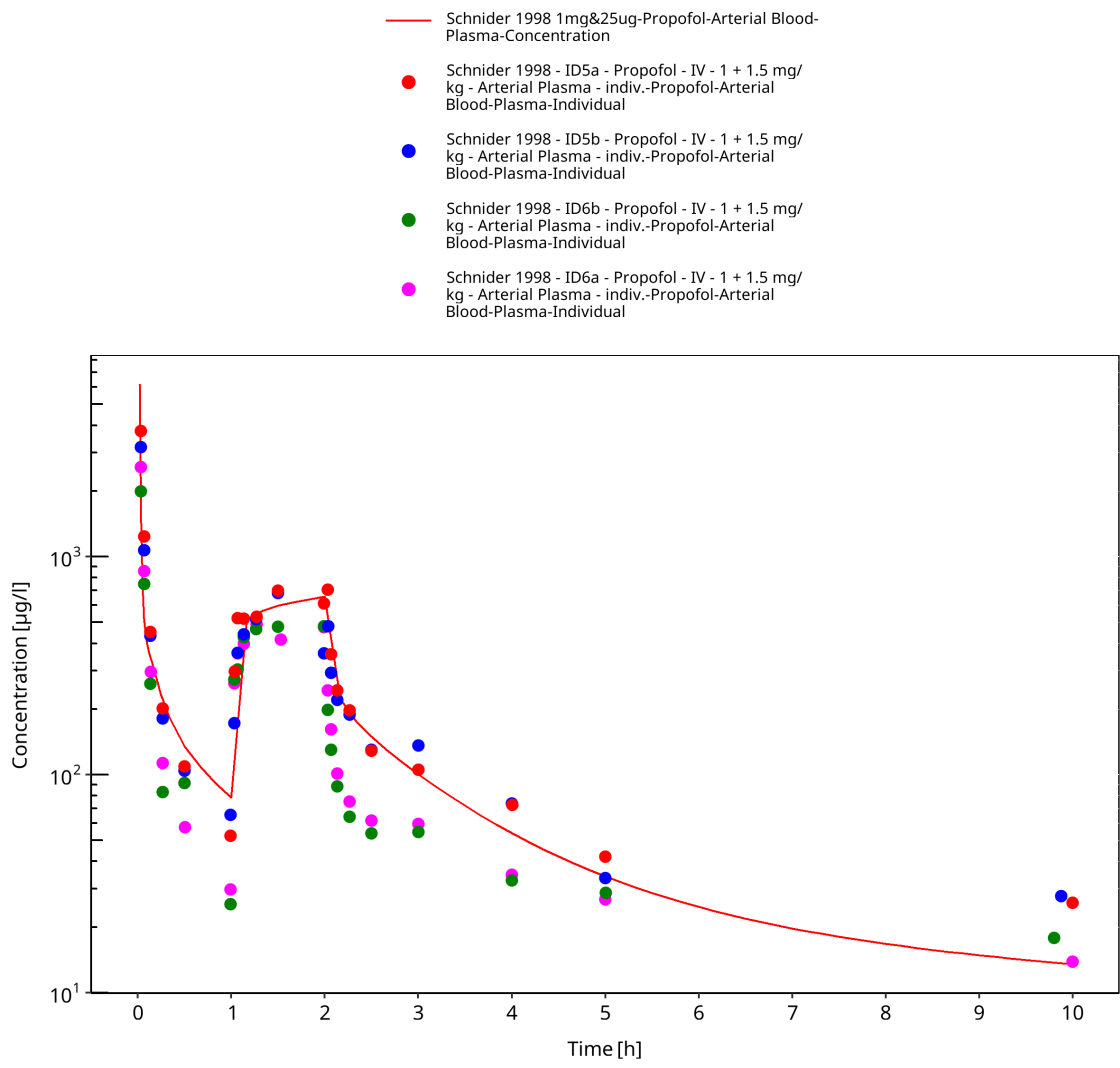


Figure 3-11: Time Profile Analysis

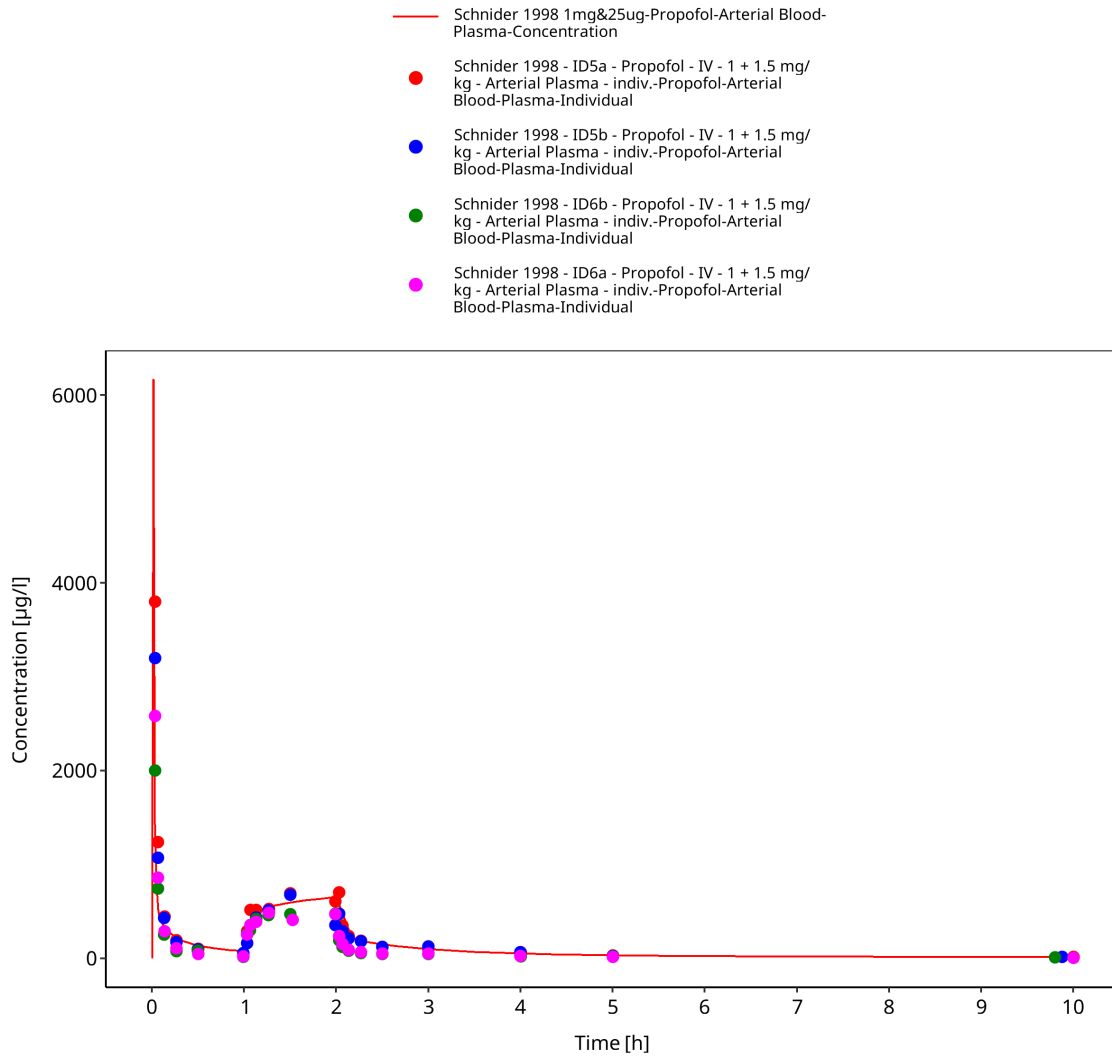


Figure 3-12: Time Profile Analysis 1

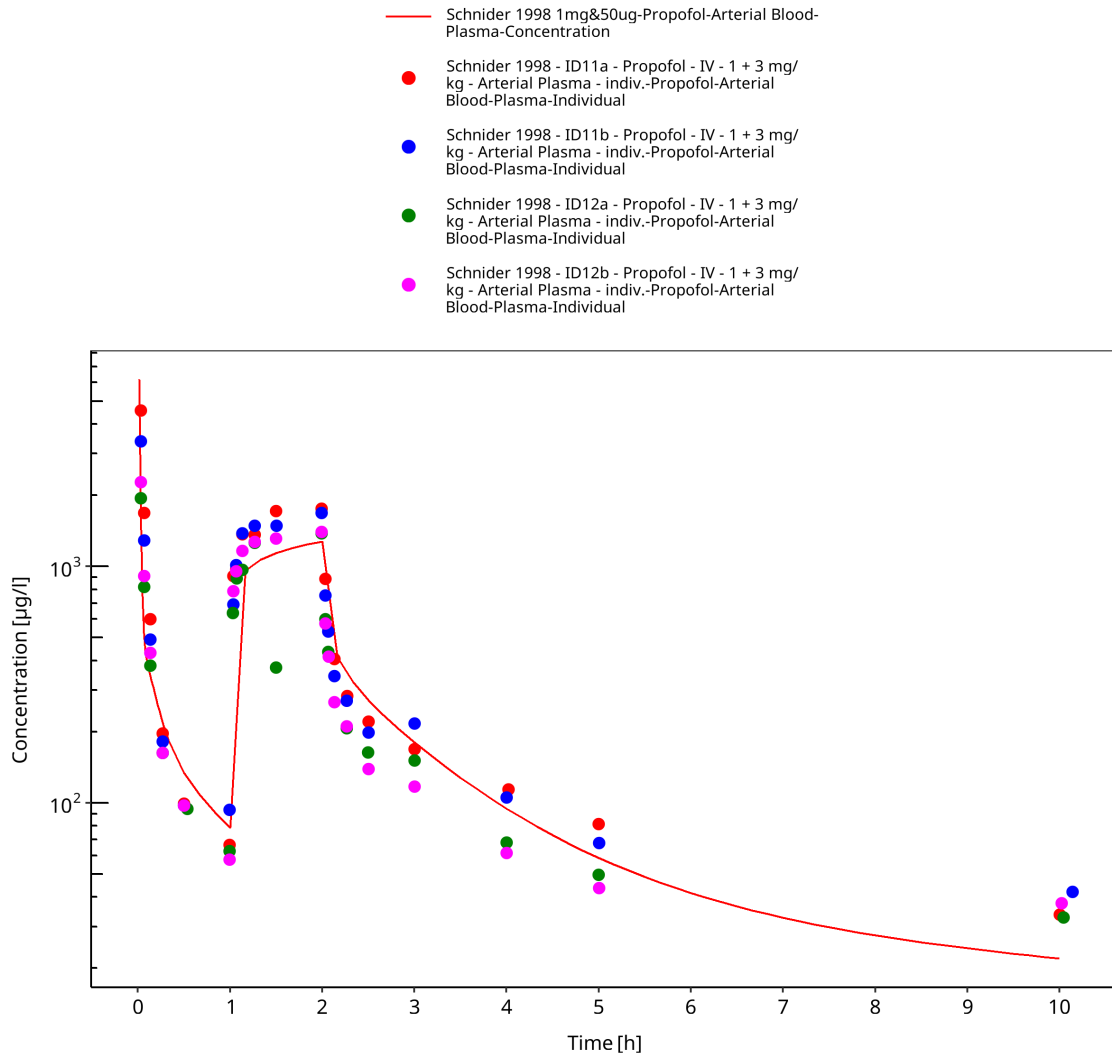


Figure 3-13: Time Profile Analysis

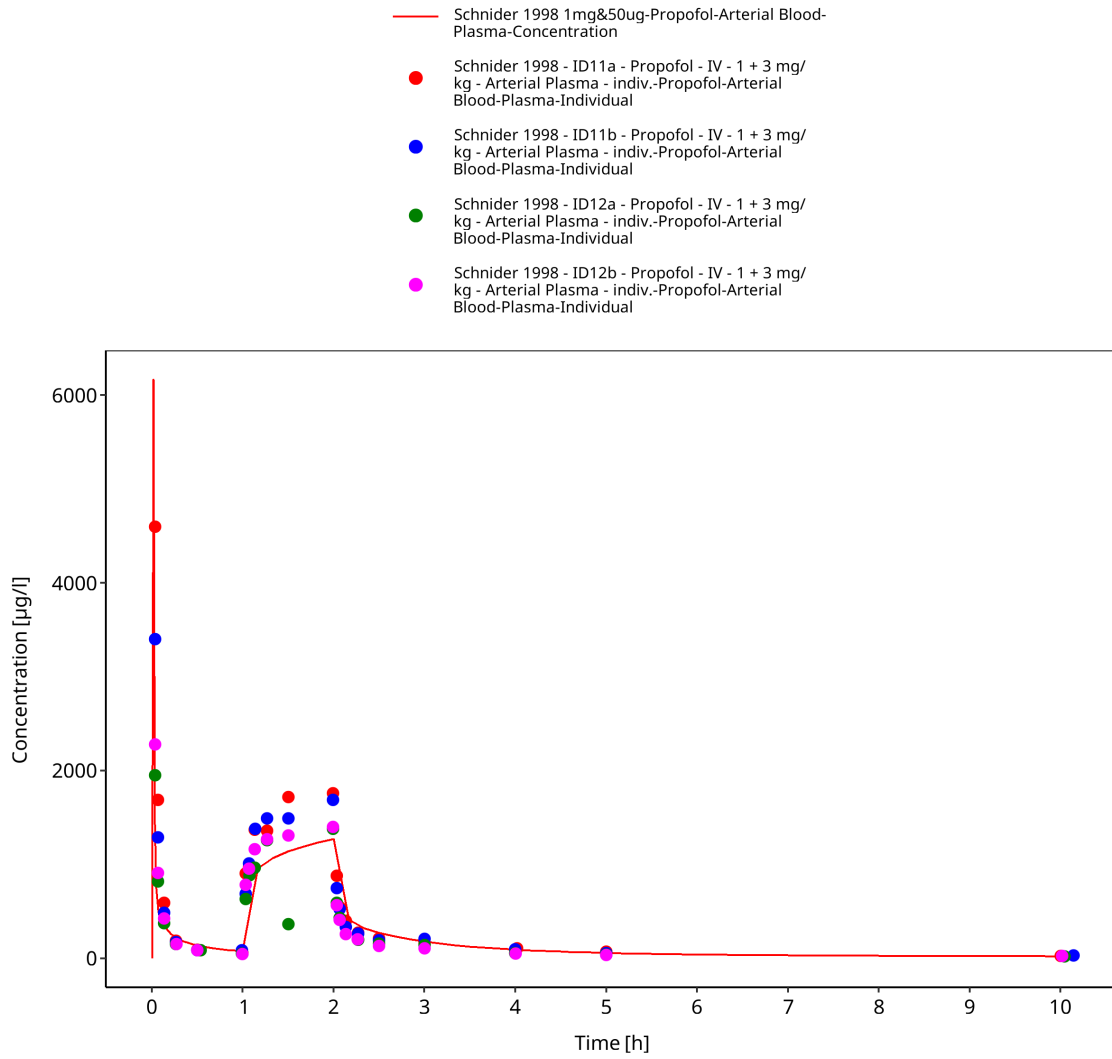


Figure 3-14: Time Profile Analysis 1

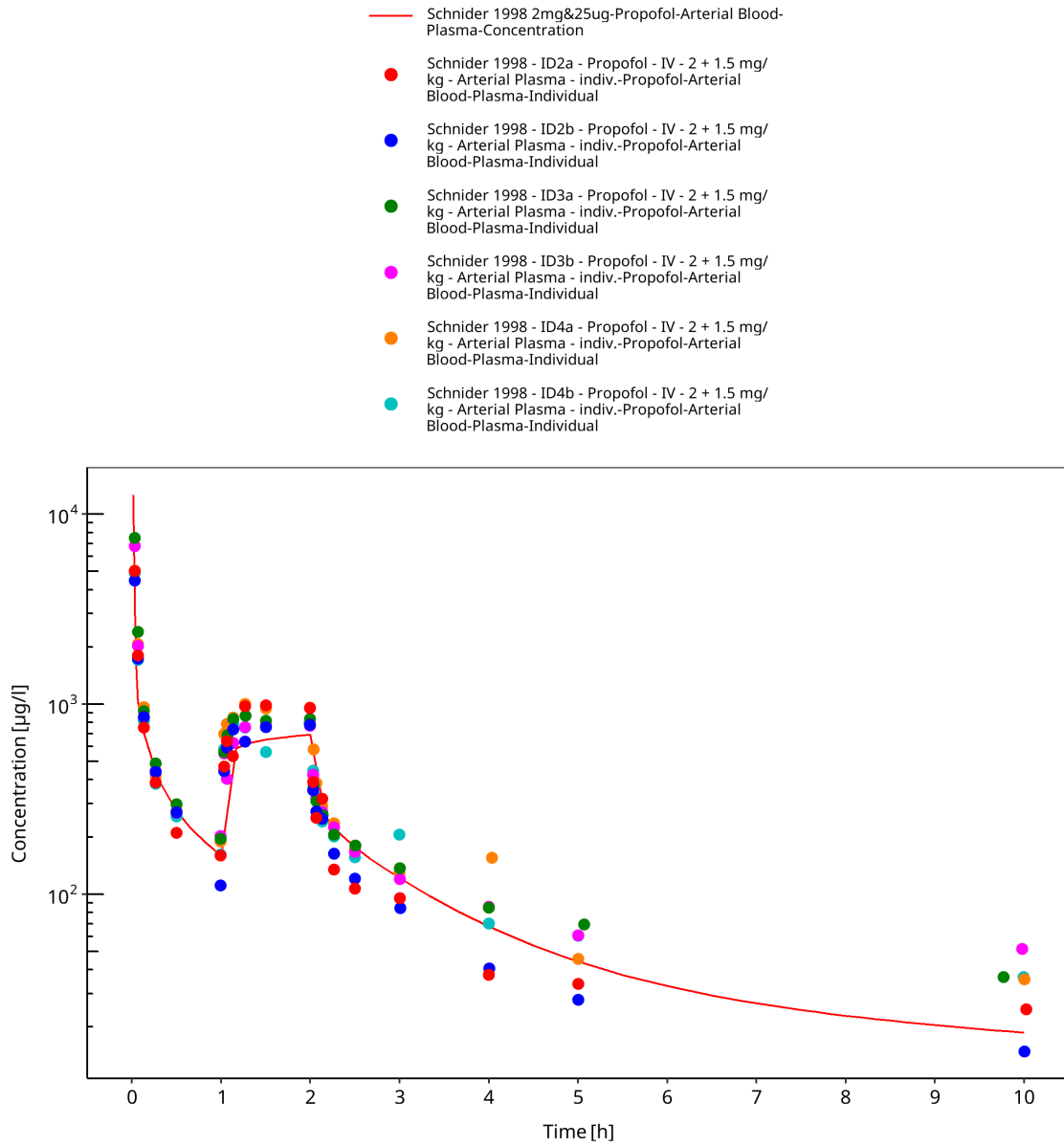


Figure 3-15: Time Profile Analysis

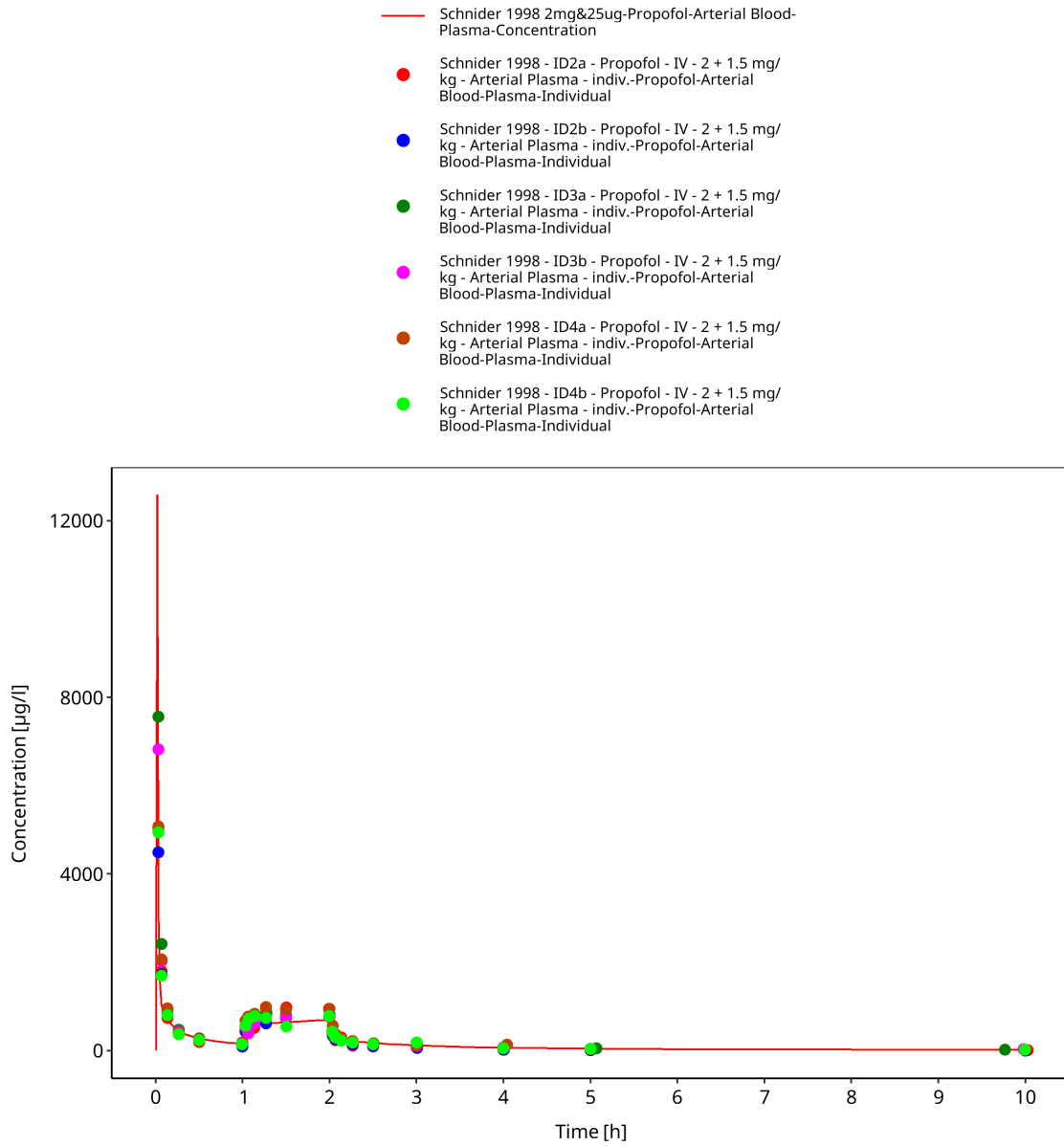


Figure 3-16: Time Profile Analysis 1

- Schnider 1998 2mg&50ug-Propofol-Arterial Blood-Plasma-Concentration
- Schnider 1998 - ID7a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID7b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID8a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID8b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID9a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID9b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID10a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID10b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

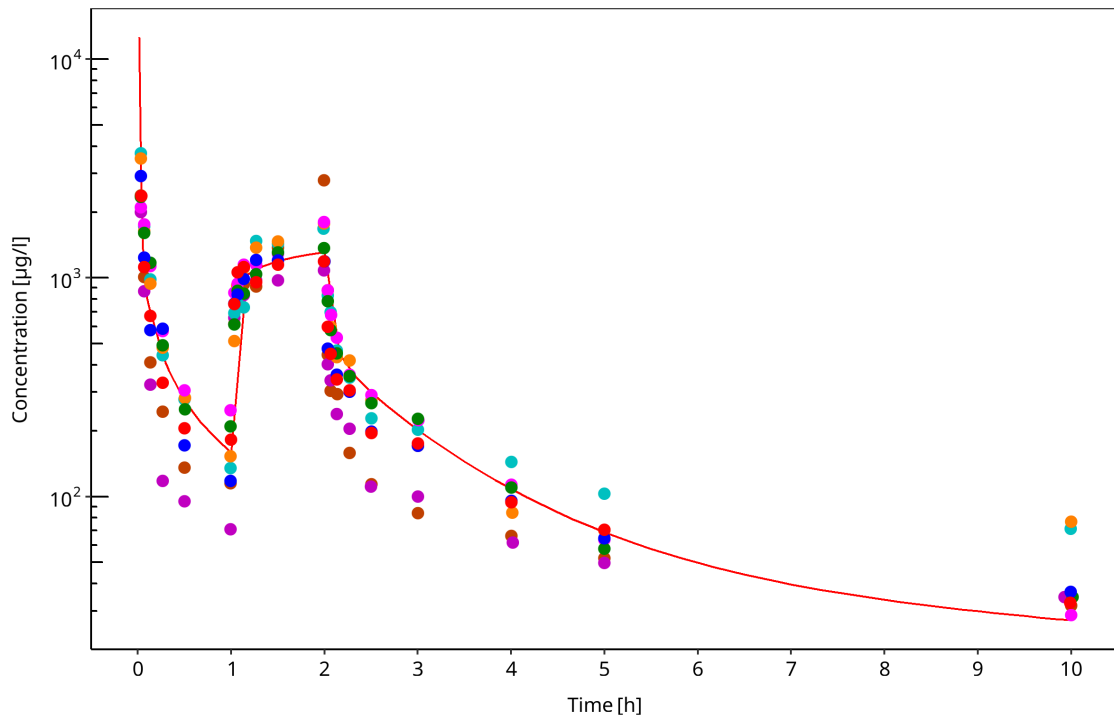


Figure 3-17: Time Profile Analysis

- Schnider 1998 2mg&50ug-Propofol-Arterial Blood-Plasma-Concentration
- Schnider 1998 - ID7a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID7b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID8a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID8b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID9a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID9b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID10a - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID10b - Propofol - IV - 2 + 3 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

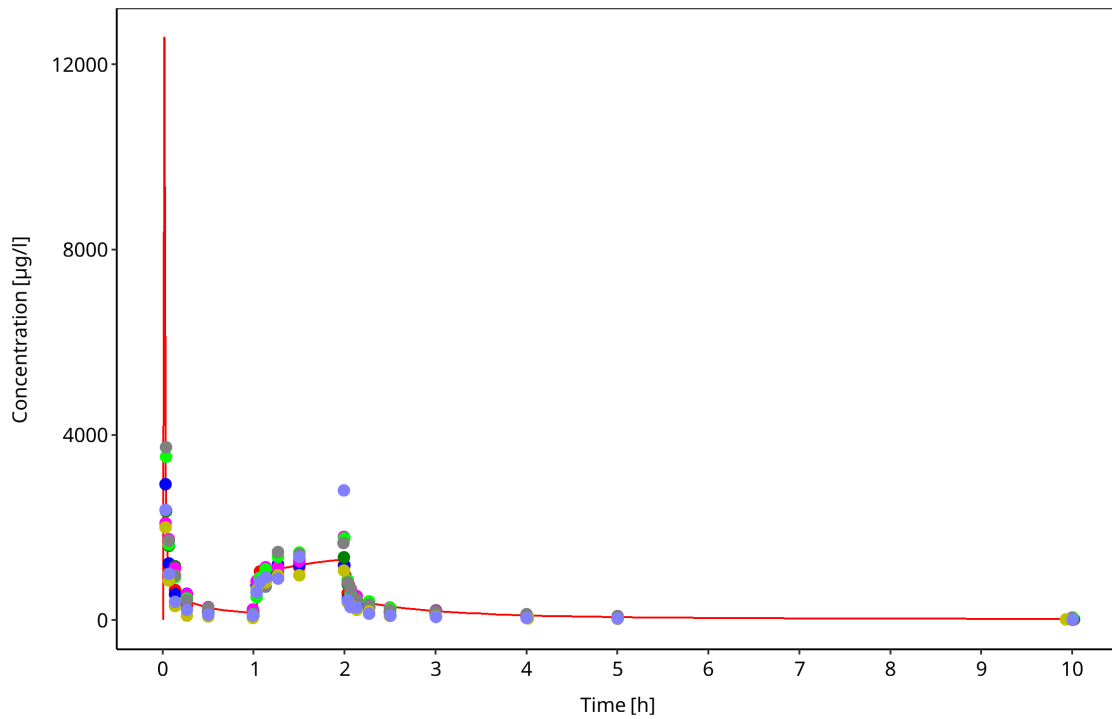


Figure 3-18: Time Profile Analysis 1

- Schnider 1998 2mg&100ug-Propofol-Arterial Blood-Plasma-Concentration
- Schnider 1998 - ID13a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID13b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID14a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID14b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID15a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID15b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID16a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID16b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

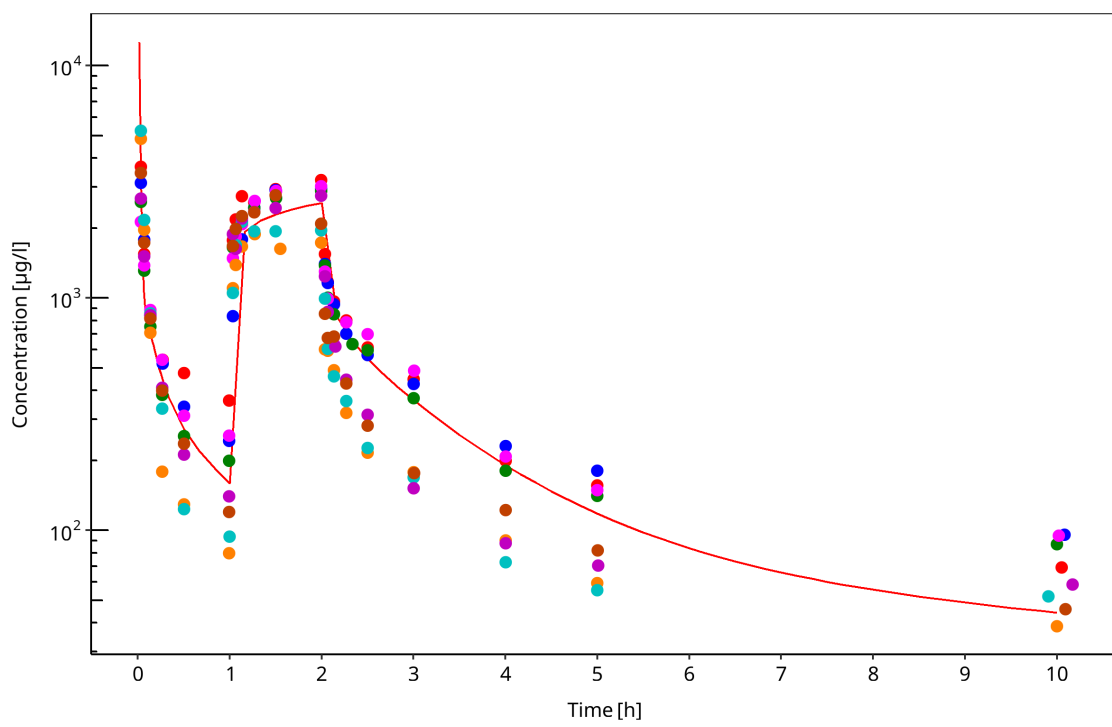


Figure 3-19: Time Profile Analysis

- Schnider 1998 2mg&100ug-Propofol-Arterial Blood-Plasma-Concentration
- Schnider 1998 - ID13a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID13b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID14a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID14b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID15a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID15b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID16a - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID16b - Propofol - IV - 2 + 6 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

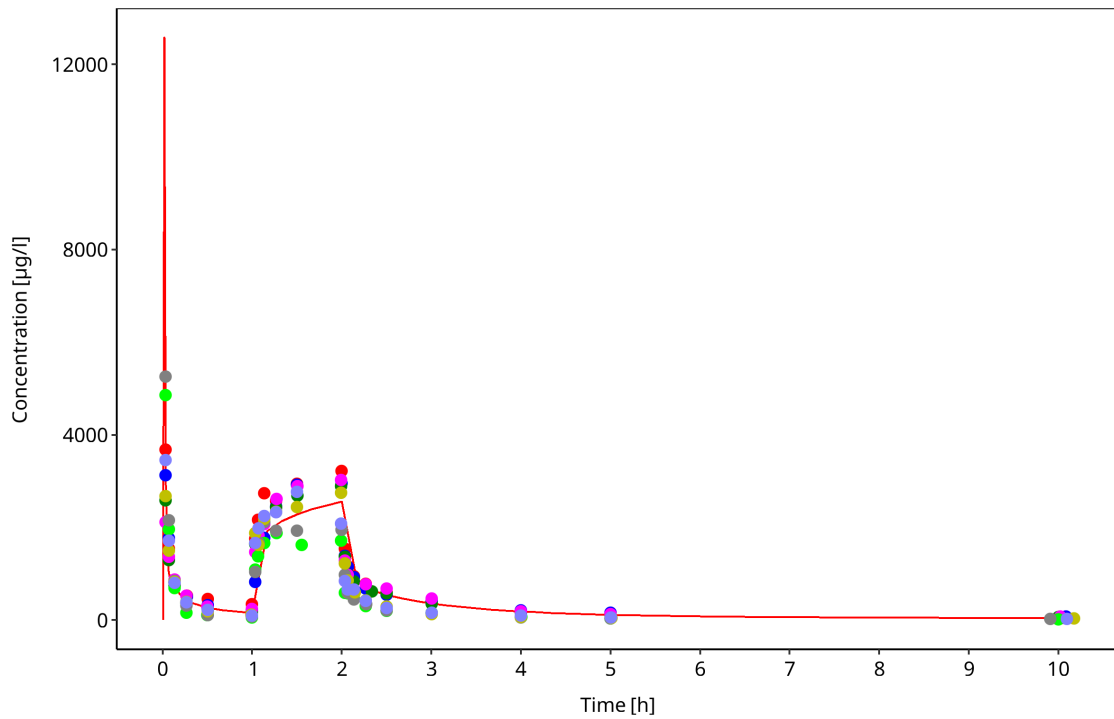


Figure 3-20: Time Profile Analysis 1

- Schnider 1998 2mg&200ug-Propofol-Arterial Blood-Plasma-Concentration
- Schnider 1998 - ID19a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID19b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID20a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID20b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID21a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID21b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID22a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID22b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

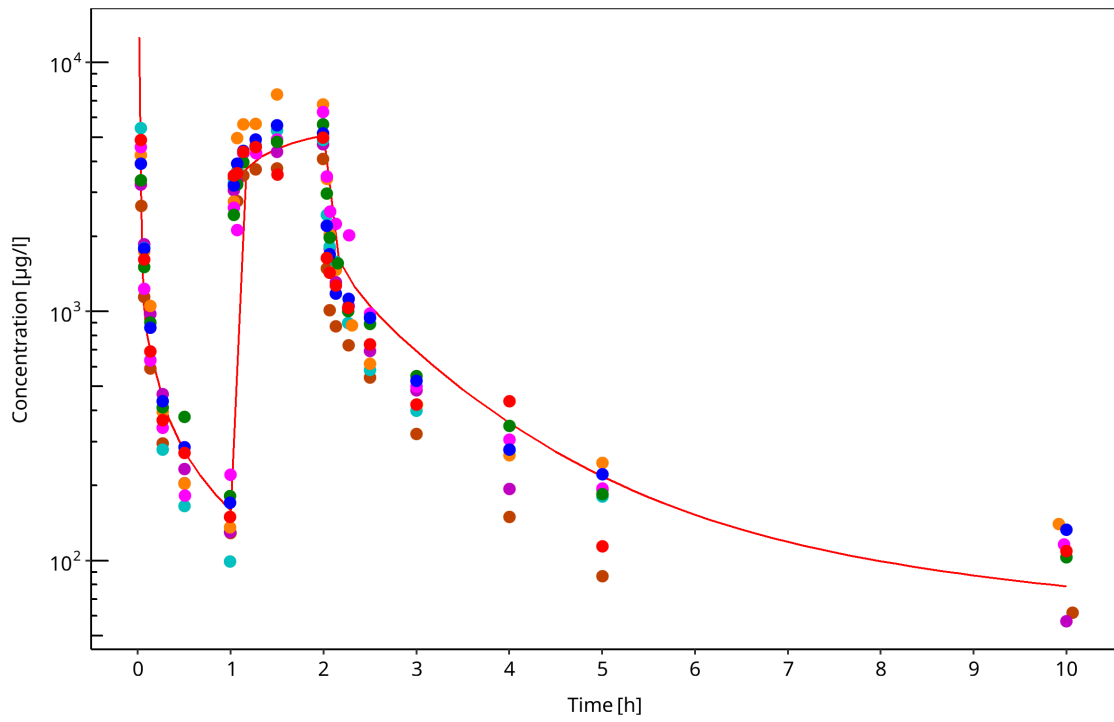


Figure 3-21: Time Profile Analysis

- Schnider 1998 2mg&200ug-Propofol-Arterial Blood-Plasma-Concentration
- Schnider 1998 - ID19a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID19b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID20a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID20b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID21a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID21b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID22a - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Schnider 1998 - ID22b - Propofol - IV - 2 + 12 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

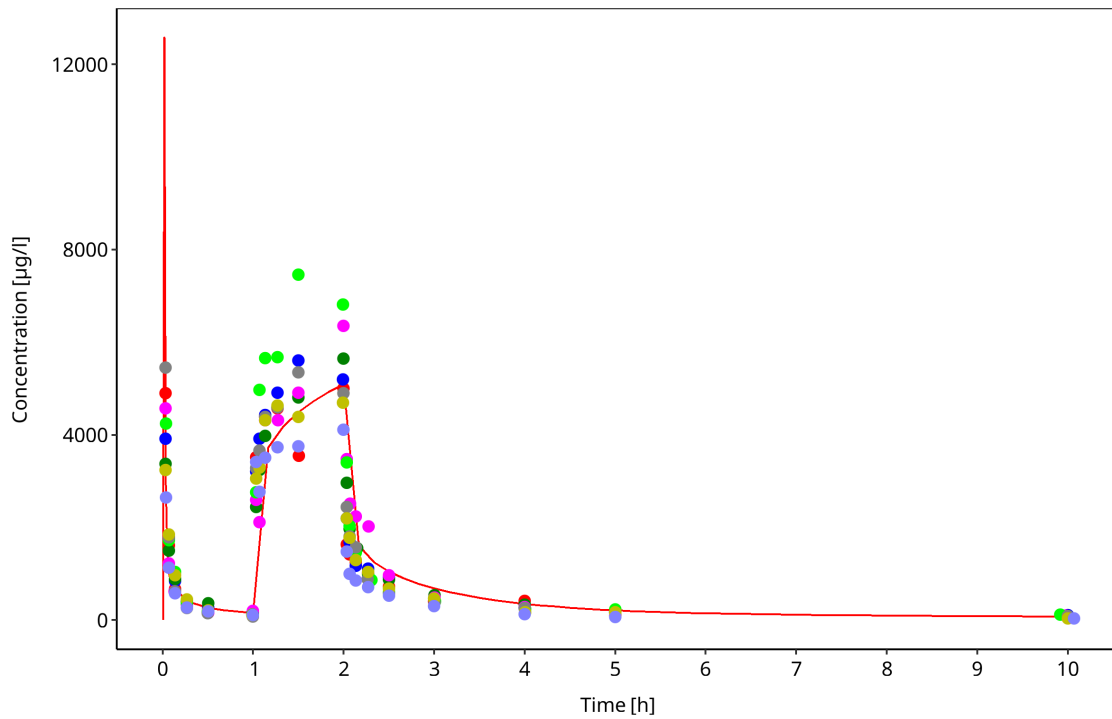


Figure 3-22: Time Profile Analysis 1

- Struys 2007 Bolus Study-Propofol-Arterial Blood-Plasma-Concentration
- Struys 2007 - ID1 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID10 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID2 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID3 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID4 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID5 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID6 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID7 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID8 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID9 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

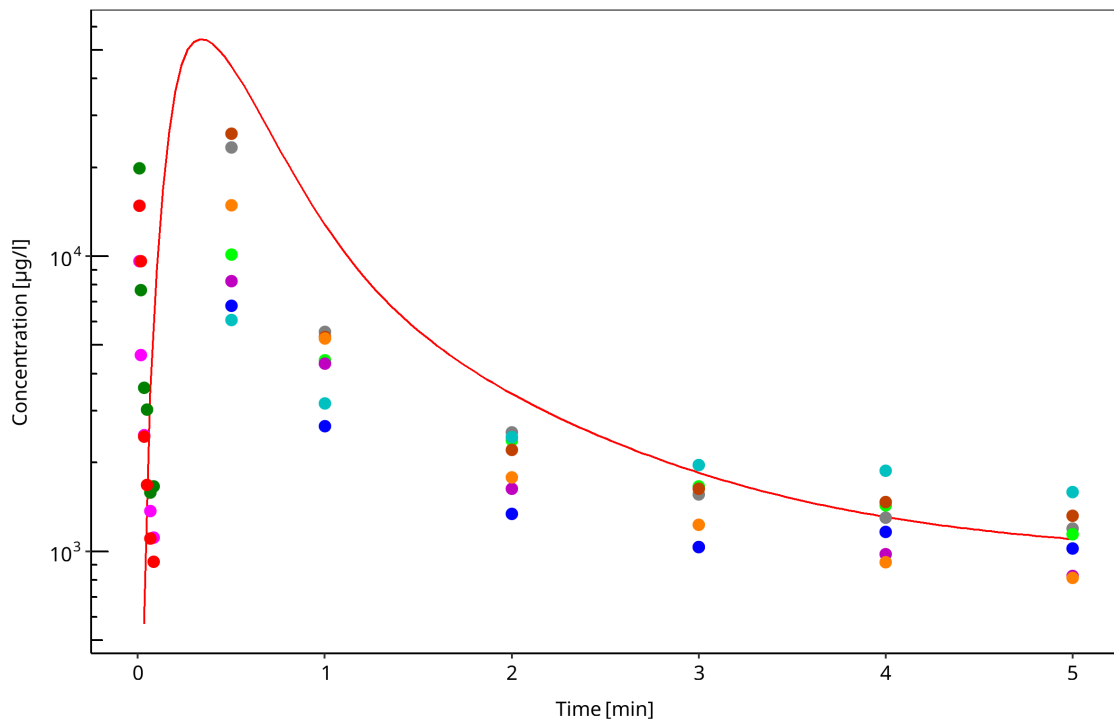


Figure 3-23: Time Profile Analysis

- Struys 2007 Bolus Study-Propofol-Arterial Blood-Plasma-Concentration
- Struys 2007 - ID1 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID10 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID2 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID3 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID4 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID5 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID6 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID7 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID8 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual
- Struys 2007 - ID9 - Propofol - IV - 2.5 mg/kg - Arterial Plasma - indiv.-Propofol-Arterial Blood-Plasma-Individual

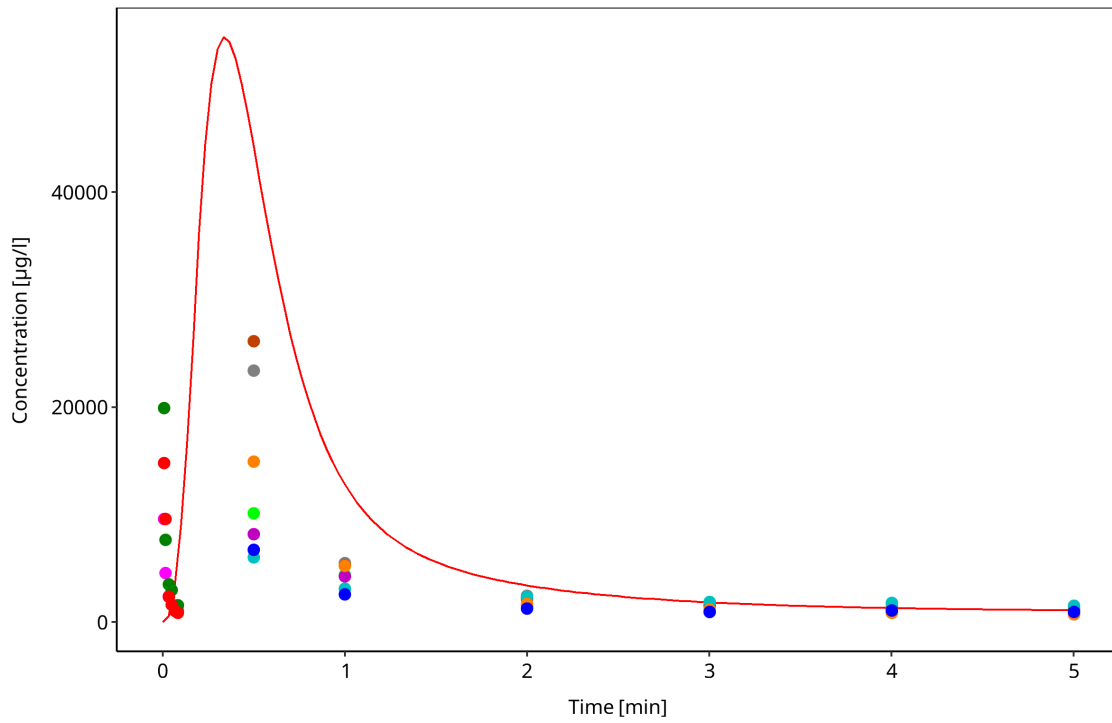


Figure 3-24: Time Profile Analysis 1

4 Conclusion

The final propofol PBPK model applies metabolism by UGT1A9, CYP2B6 and glomerular filtration and adequately describes the pharmacokinetics of propofol in adults receiving intravenous bolus and continuous infusion of propofol ranging from 1 mg/kg to 36 mg/kg.

This model could be applied for the investigation of drug-drug interactions (DDI), and translation to special populations such as pediatrics with regard to UGT1A1 and CYP2B6 metabolism.

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