Building and evaluation of a PBPK model for Warfarin in healthy adults

Version	**main-OSP12.1**
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Warfarin-Model/releases/tag/vmain
OSP Version	12.1
Qualification Framework Version	3.4

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

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

Warfarin is a widely used oral anticoagulant that exerts its therapeutic effect by inhibiting the hepatic synthesis of vitamin K–dependent clotting factors. Warfarin therapy requires careful monitoring because of its narrow therapeutic index and the risk of bleeding Uygungül 2014.

Warfarin is classified as a BCS Class I drug, which means it has high solubility and high permeability. This classification indicates that warfarin is expected to dissolve rapidly and be well absorbed in the gastrointestinal tract Kim 2019.

Warfarin is administered as a racemic mixture of two enantiomers, S-warfarin and R-warfarin, which differ in both potency and metabolism. The S-enantiomer is approximately two- to five-fold more potent as an anticoagulant compared to the R-enantiomer, but it is cleared more rapidly Maddison 2013, Geng 2024. The two enantiomers are metabolized by different cytochrome P450 isoforms. S-warfarin is primarily cleared by CYP2C9 with additional contribution from CYP3A4 and reduction to alcohols, while R-warfarin is metabolized mainly by CYP1A2, CYP2C19, and CYP3A4, as well as reduction to alcohol. Renal elimination of the unchanged parent drug is small for both enantiomers Wittkowsky 2003.

The herein presented model building and evaluation report evaluates the performance of the PBPK model for S-Warfarin and R-Warfarin in healthy adults. Both enantiomers are modeled separately. These models integrate physicochemical properties, binding characteristics, distribution, and the known stereospecific clearance pathways of each enantiomer. The performance of the models is evaluated against published clinical data for different dosing regimens under fasted and fed conditions.

The presented Warfarin PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/Open-Systems-Pharmacology/Warfarin-model).

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016) The relevant 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.

First, a base mean model was built using clinical Phase I data including selected single dose studies with intravenous and oral applications of Warfarin to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK 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 tablet formulations were identified.

The model was then verified by simulating:

- Oral administration of Warfarin in fasted state
- Oral administration of Warfarin in fed state
- Intravenous administration of Warfarin

Details about input data (physicochemical, *in vitro* and clinical) can be found in Section 2.2.

Details about the structural model and its parameters can be found in Section 2.3.

2.2 Data

2.2.1 In vitro / physico-chemical Data

A literature search was performed to collect available information on physicochemical properties of Warfarin . The obtained information from literature is summarized in the table below.

Physicochemical and binding properties

Parameter	Unit	Value	Source	Description
MW	g/mol	308.33	Drugbank	Molecular weight
pK_a	–	5.03 (acid)	Drugbank	Acid dissociation constant
Solubility	mg/L	17 (at pH 7)	Drugbank	Aqueous solubility
fu_{plasma}		0.009	Takahashi 2003	Fraction unbound in plasma (albumin binding)
LogP	–	3.46	Avdeef 1998	Liposomal membrane-water partition coefficient
B/P	–	0.55	—	Blood-to-plasma ratio (used in reduction pathway)

S-warfarin - Metabolic and clearance parameters

Pathway / Enzyme	Parameter	Unit	Value	Source / Note
CYP2C9	Km	µM	4.4	Experimental Km within range 3.5 to 5.54 µM Shaik 2016,Rettie 1992, Rettie 1992, Yong 2009, Crewe 2011
CYP3A4	Km	µM	14.9	Experimental Km within range 14 to 27 Shaik 2016, Jones 2010
Reduction to alcohols	Plasma CL Specific CL	ml/min/kg 1/min	0.14 0.02	Metabolism reduction mediated by aldo-keto reductases (i.e., fraction metabolized ~ 10%) Wittkowsky 2003
Renal clearance	Plasma CL Specific CL	l/h/kg 1/min	0.07 0.02	Consistent with fraction excreted in urine ~ 1% FDA 2010

R-warfarin - Metabolic and clearance parameters

Pathway / Enzyme	Parameter	Unit	Value	Source / Note
CYP1A2	Km	µM	648	Adopted from previous PK-Sim model
CYP2C19	Km	µM	391	Adopted from previous PK-Sim model
CYP3A4	Km	µM	586	Adopted from previous PK-Sim model
Reduction to alcohols	Plasma CL Specific CL	ml/h/kg 1/min	0.27 0.02	
Renal clearance	Plasma CL Specific CL	ml/h/kg 1/min	0.07 0.02	

2.2.2 Clinical Data

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

2.2.2.1 Model Building S-Warfarin

The following studies were used for model building (training data):

Dose [mg]	Dosing	PK data	Dataset	Reference
15	po, sd	plasma	training	Soon 2006
25	po, sd	plasma	training	Schwartz 2008

iv = intravenous; po = oral administration; tab = tablet administration; sd = single dose; qd = once daily

2.2.2.2 Model Verification S- Warfarin

The following studies were used for model verification:

Dose [mg]	Dosing	PK data	Dataset	Reference
0.375	iv, tab, fasted, sd	plasma	verification	O'Sullivan 1993
7.5	po, tab, fasted with meal administration 3h post-dose, sd	plasma	verification	Frymoyer 2010
10	po, tab, fasted, sd	plasma	verification	Kim 2001
10	po, tab, fasted, sd	plasma	verification	Lilja 2007
10	po, tab, fasted, sd	plasma	verification	Ngo 2010
10	po, tab, fasted, sd	plasma	verification	Turpeinen 2013
13	po, tab, fed, sd	plasma	verification	Weber 1999
15	po, tab, fasted, sd	plasma	verification	Schwartz 2009
20	po, tab, fasted, sd	plasma	verification	Ouellet 2006
25	po, tab, fasted, sd	plasma	verification	Almeida 2008
25	po, tab, fasted, sd	plasma	verification	Dingemanse 2013
25	po, tab, fasted, sd	plasma	verification	He 2007
25	po, tab, fasted, sd	plasma	verification	Macha 2013
25	po, tab, fasted, sd	plasma	verification	Malhotra 2011
25	po, tab, fasted, sd	plasma	verification	Rahimy 2002
25	po, tab, fasted, sd	plasma	verification	Sanwald Ducray 2014
25	po, tab, fasted, sd	plasma	verification	Stockis 2013
25	po, tab, fasted, sd	plasma	verification	Toon 1987
25	po, tab, fasted, sd	plasma	verification	Toon 1990
25	po, tab, fed, sd	plasma	verification	Mallikaarjun 1999
25	po, tab, fed, sd	plasma	verification	Sidharta 2014
25	po, tab, fed, sd	plasma	verification	Soon 2006
25	po, tab, fed, sd	plasma	verification	Yin 2011
30	po, tab, fasted with meal administration 4h post-dose, sd	plasma	verification	Liao 1996

iv = intravenous; po = oral administration; tab = tablet administration; sd = single dose; qd = once daily

2.2.2.3 Model Verification R- Warfarin

The following studies were used for model verification:

Dose [mg]	Dosing	PK data	Dataset	Reference

<<<<<<< HEAD | 25| po, tab, fasted, sd |plasma|verification|Almeida 2008| | 25| po, tab, fasted, sd |plasma|verification|Dingemande 2013| | 25| po, tab, fasted, sd |plasma|verification|He 2007| | 25| po, tab, fasted, sd |plasma|verification|Malhotra 2011| | 25| po, tab, fasted, sd |plasma|verification|Rahimy 2002| | 25| po, tab, fasted, sd |plasma|verification|Stockis 2013| | 25| po, tab, fasted, sd |plasma|verification|Toon 2087| | 25| po, tab, fasted, sd |plasma|verification|Toon 1990| | 25| po, tab, fed, sd |plasma|verification|Mallikaarjun 1999| | 25| po, tab, fed, sd |plasma|verification|Sidharta 2014| | 25| po, tab, fed, sd |plasma|verification|Soon 2006| | 25| po, tab, fed, sd |plasma|verification|Yin 2011|

| 25| po, tab, fasted, sd |plasma|verification|Almeida 2008| | 25| po, tab, fasted, sd |plasma|verification|Dingemanse 2013| | 25| po, tab, fasted, sd |plasma|verification|He 2007| | 25| po, tab, fasted, sd |plasma|verification|Malhotra 2011| | 25| po, tab, fasted, sd |plasma|verification|Rahimy 2002| | 25| po, tab, fasted, sd |plasma|verification|Stockis 2013| | 25| po, tab, fasted, sd |plasma|verification|Toon 1987| | 25| po, tab, fasted, sd |plasma|verification|Toon 1990| | 25| po, tab, fed, sd |plasma|verification|Mallikaarjun 1999| | 25| po, tab, fed, sd |plasma|verification|Sidharta 2014| | 25| po, tab, fed, sd |plasma|verification|Soon 2006| | 25| po, tab, fed, sd |plasma|verification|Yin 2011|

c4bac1efd21d652db42ed9b81ab341fed3579aca

iv = intravenous; po = oral administration; tab = tablet administration; sd = single dose; qd = once daily

2.3 Model Parameters and Assumptions

2.3.1 Absorption

The measured solubility of Warfarin was taken from Product information from Drugbank (see Section 2.2.1).

Tablet dissolution was modeled using an empirical Weibull dissolution approach. Both enantiomer share the same absorption processes.

2.3.2 Distribution

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 by `Rodgers and Rowland` and cellular permeability calculation by `Charged dependent Schmitt`.

2.3.3 Metabolism and Elimination

Clearance of warfarin was described through enzymatic and reductive pathways, with only a negligible contribution from renal excretion of unchanged parent drug. The stereospecific nature of warfarin metabolism was explicitly represented by modeling the two enantiomers separately, with different sets of enzymes responsible for their elimination.

For **S-warfarin**, metabolism is dominated by CYP2C9, which is the principal enzyme responsible for oxidative clearance. A smaller contribution from CYP3A4 was also included, together accounting for the observed in-vivo clearance. In addition, a reductive pathway leading to alcohol metabolites was implemented, using literature-based plasma clearance values and a blood-to-plasma ratio of 0.55 Wittkowsky 2003, leading to a hepatic `Specific Clearance` of 0.02 1/min. The renal elimination of unchanged S-warfarin was parameterized but remains negligible, consistent with clinical evidence of ~ 1% fraction excreted in urine FDA 2010. Kinetic constants for CYP2C9 and CYP3A4 were taken from in-vitro studies and the associated `Kcat` were optimized within the current model to achieve agreement with observed plasma concentrations. These optimized values reflect the dominant role of CYP2C9 and the minor but non-negligible contribution of CYP3A4 to the overall clearance of the S-enantiomer.

The clearance of **R-warfarin** was represented by three oxidative enzymes—CYP1A2, CYP2C19, and CYP3A4—together with the same reductive alcohol pathway and minor renal clearance. Experimental information on kinetic constants for R-warfarin is less abundant, and therefore the Km and Vmax values were adopted from a previously developed PBPK model in PK-Sim. The values for the Michaelis–Menten constants are relatively high (Km values of 648 µM for CYP1A2, 391 µM for CYP2C19, and 586 µM for CYP3A4), which indicates a low affinity of these enzymes for R-warfarin. The reduction to alcohols and renal clearance contribute only marginally to the overall disposition of the R-enantiomer.

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
`Intestinal permeability (transcellular)`	0.0015	cm/min
`S-Warfarin CYP2C9 kcat`	0.2	1/min
`S-warfarin CYP3A4 kcat`	0.09	1/min

3 Results and Discussion

The PBPK model for Warfarin, was developed and verified with clinical pharmacokinetic data.

The model was evaluated covering data from studies including in particular

- Intravenous Bolus
- Oral administration over fasted and fed states.

The next sections show:

1. the final model parameters for the building blocks: Section 3.1.
2. the overall goodness of fit: Section 3.2.
3. simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: Section 3.3.

3.1 Final input parameters

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

Compound: S-Warfarin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	17 mg/l	Internet-DrugBank (Tomlin 1997)	Measurement	True
Reference pH	7	Internet-DrugBank (Tomlin 1997)	Measurement	True
Lipophilicity	3.46 Log Units	Publication-logP_mem_neutral (Avdeef 1998)	Measurement	True
Fraction unbound (plasma, reference value)	0.009	Publication-Takahashi 2003	Measurement	True
Specific intestinal permeability (transcellular)	0.0015 cm/min		fitted	True
Is small molecule	Yes			
Molecular weight	308.33 g/mol			
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	Charge dependent Schmitt

Processes

Systemic Process: Renal Clearances-Urine excretion data (Heimark, Toon, O'Reilly)

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.009	
Plasma clearance	0.07 ml/h/kg	
Specific clearance	0.02 1/min	Unknown

Metabolizing Enzyme: CYP2C9-HLM Mean

Molecule: CYP2C9

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	6.9 pmol/min/mg mic. protein	
Content of CYP proteins in liver microsomes	96 pmol/mg mic. protein	Unknown
Km	4.4 µmol/l	
kcat	0.2022708099 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2025-08-01 11:48

Systemic Process: Total Hepatic Clearance-Reduction to alcohool

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.009	
Lipophilicity (experiment)	3.46 Log Units	
Blood/Plasma concentration ratio	0.55	Unknown
Plasma clearance	0.14 ml/min/kg	
Specific clearance	0.02 1/min	Unknown

Metabolizing Enzyme: CYP3A4-HLM mean

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
Enzyme concentration	1 µmol/l	
Vmax	0 µmol/l/min	
Km	14.9 µmol/l	
kcat	0.0872168808 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2025-08-01 11:48

Compound: R-Warfarin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	17 mg/l	Internet-DrugBank (Tomlin 1997)	Measurement	True
Reference pH	7	Internet-DrugBank (Tomlin 1997)	Measurement	True
Lipophilicity	3.46 Log Units	Publication-logP_mem_neutral (Avdeef 1998)	Measurement	True
Fraction unbound (plasma, reference value)	0.009	Publication-Takahashi 2003	Measurement	True
Specific intestinal permeability (transcellular)	0.0015 cm/min		fitted	False
Is small molecule	Yes			
Molecular weight	308.33 g/mol			
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	Charge dependent Schmitt

Processes

Metabolizing Enzyme: CYP1A2-HLM Mean

Molecule: CYP1A2

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	775 pmol/min/mg mic. protein	
Content of CYP proteins in liver microsomes	45 pmol/mg mic. protein	Unknown
Km	648 µmol/l	

Metabolizing Enzyme: CYP2C19-HLM Mean

Molecule: CYP2C19

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	178 pmol/min/mg mic. protein	
Content of CYP proteins in liver microsomes	19 pmol/mg mic. protein	Unknown
Km	391 µmol/l	

Metabolizing Enzyme: CYP3A4-HLM Mean

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	886 pmol/min/mg mic. protein	
Km	586 µmol/l	

Systemic Process: Total Hepatic Clearance-Reduction to alcohols

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.009	
Lipophilicity (experiment)	3.46 Log Units	
Blood/Plasma concentration ratio	0.55	Unknown
Plasma clearance	0.27 ml/h/kg	

Systemic Process: Renal Clearances-Urine excretion data (Heimark, Toon, O'Reilly)

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.009	
Plasma clearance	0.07 ml/h/kg	

3.2 Diagnostics Plots S-warfarin

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in Section 2.2.2.

The first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.

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

Group	GMFE
S-Warfarin IV Administration (model verification)	1.14
S-Warfarin Oral Administration (model building)	1.23
S-Warfarin Oral Administration fasted (model verification)	1.40
S-Warfarin Oral Administration fed (model verification)	1.16
All	1.33

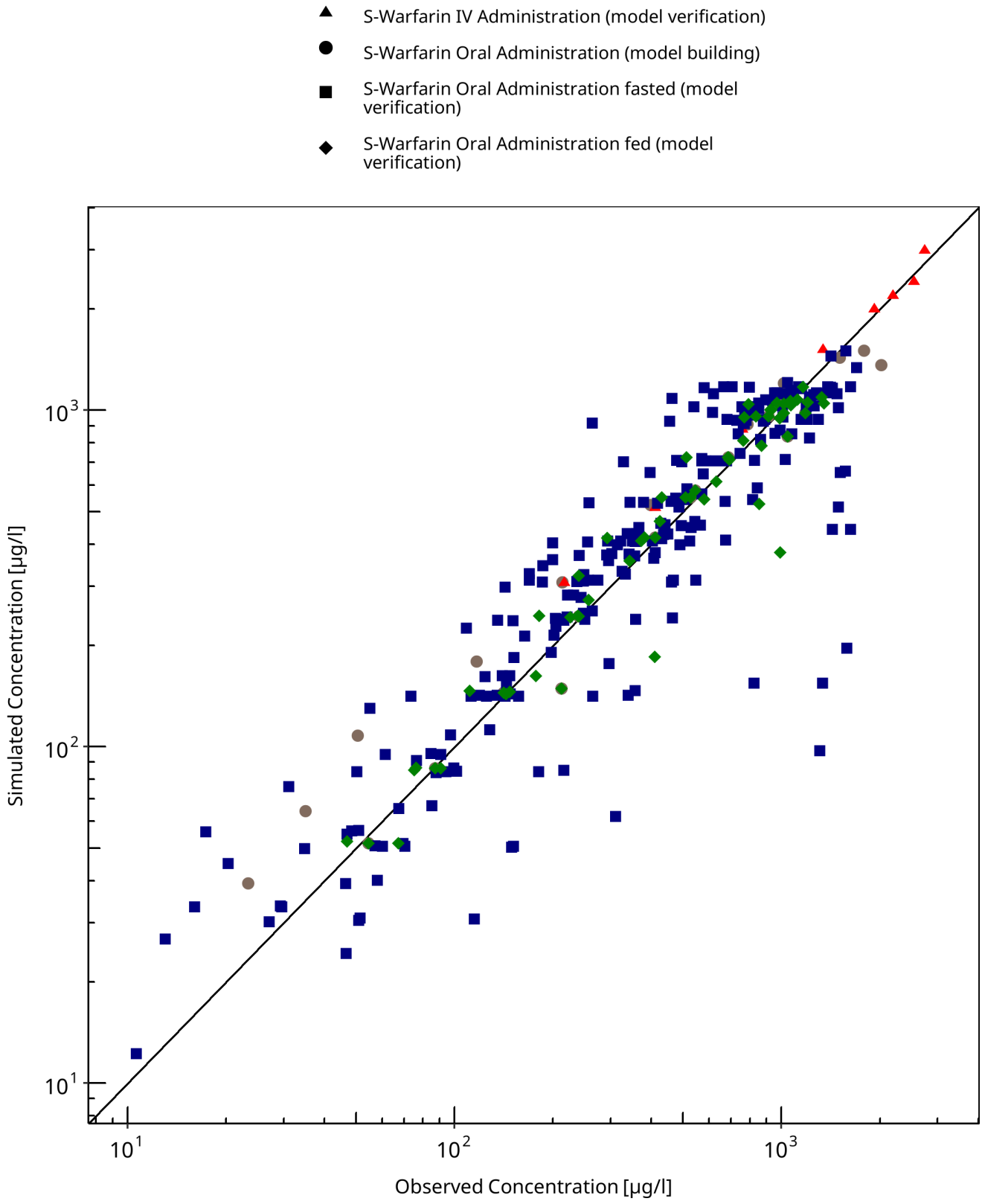

Figure 3-1: S-Warfarin Goodness of fit plot for concentration in plasma

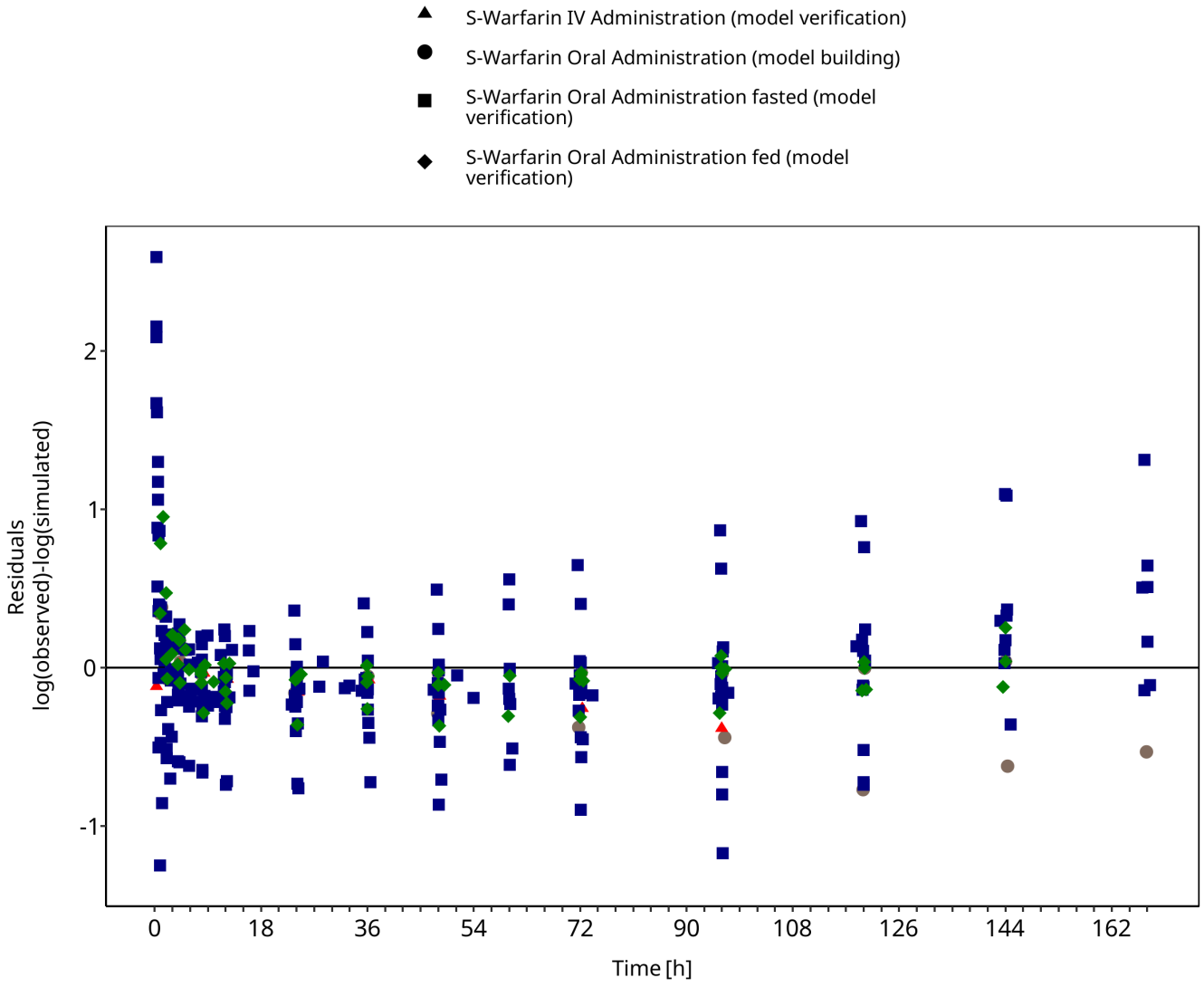

Figure 3-2: S-Warfarin Goodness of fit plot for concentration in plasma

3.3 Diagnostics Plots R-warfarin

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in Section 2.2.2.

The first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.

Table 3-2: GMFE for R-Warfarin Goodness of fit plot for concentration in plasma, R-warfarin

Group	GMFE
R-Warfarin Oral Administration (model verification)	1.32

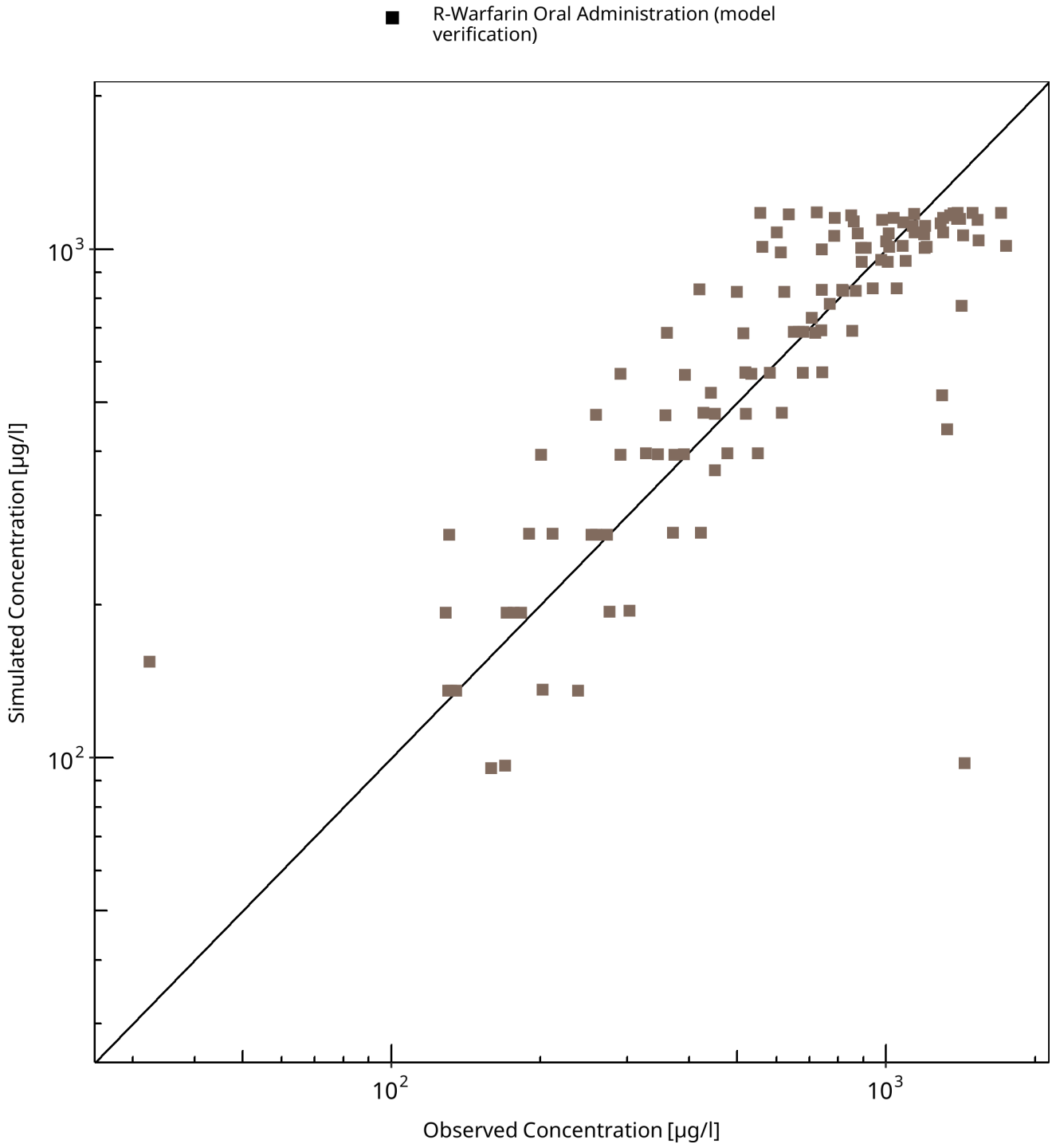

Figure 3-3: R-Warfarin Goodness of fit plot for concentration in plasma, R-warfarin

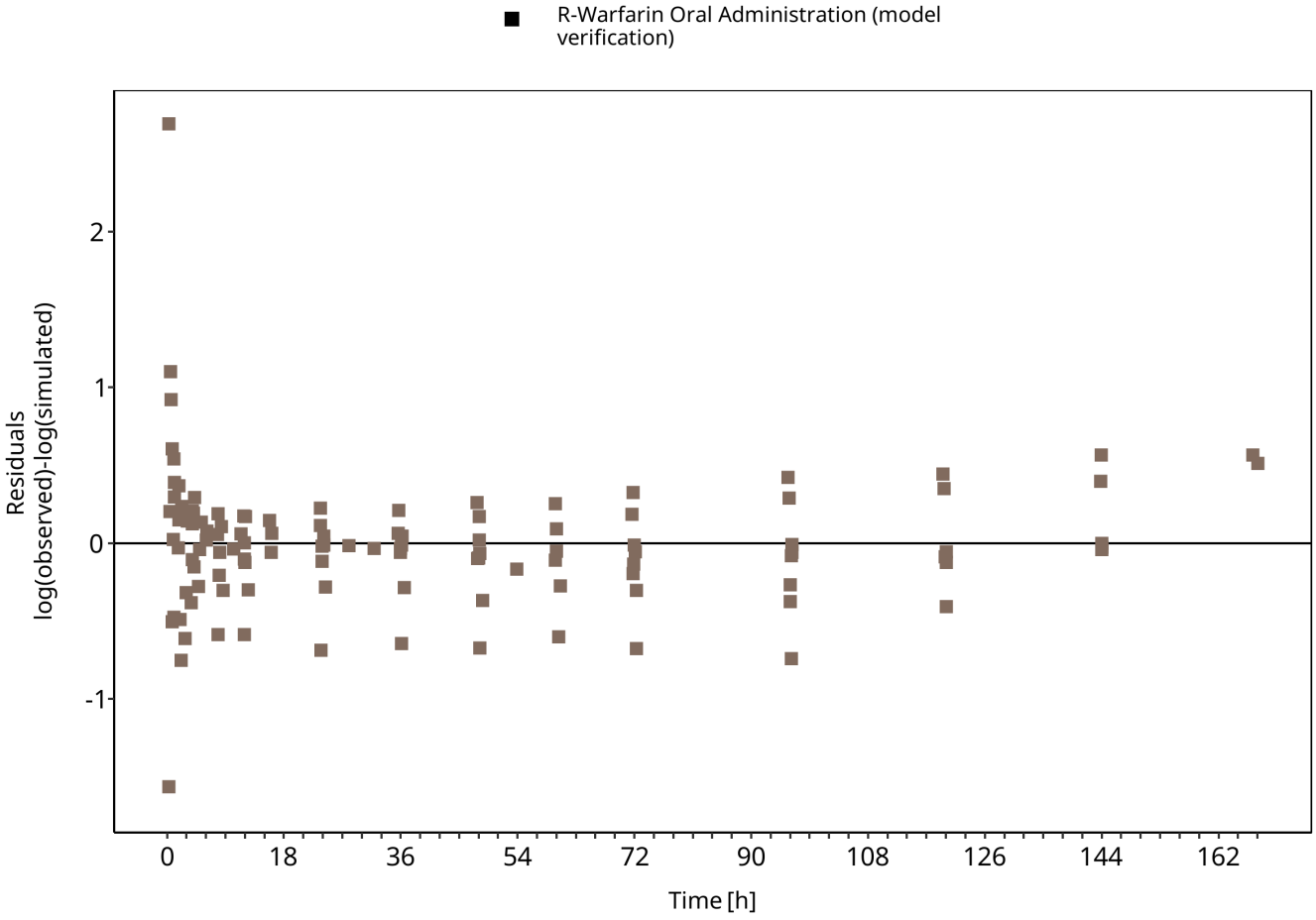

Figure 3-4: R-Warfarin Goodness of fit plot for concentration in plasma, R-warfarin

3.4 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.

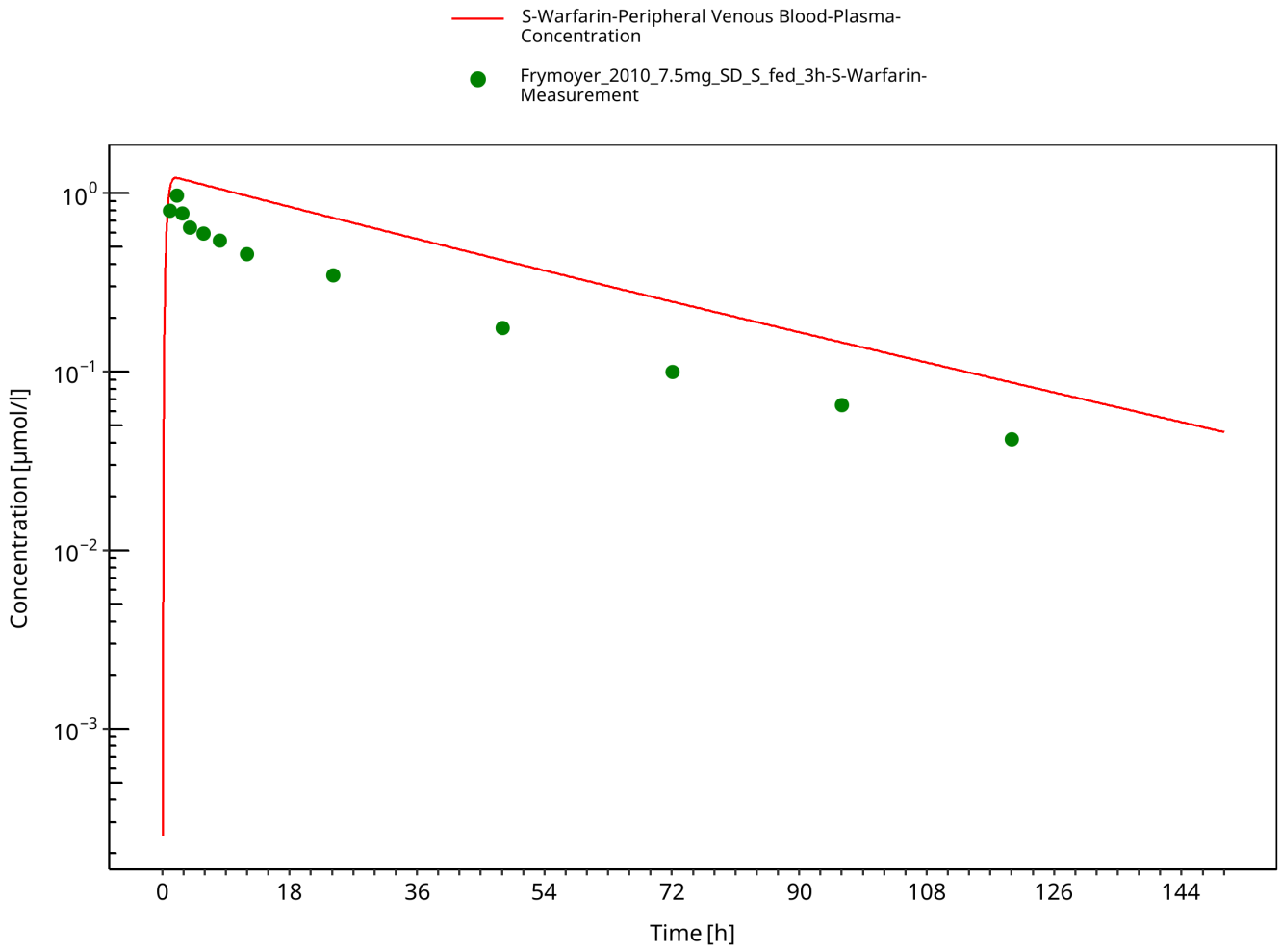

Figure 3-5: Warfarin Na 7.5mg (S-Warfarin 3.75mg) fasted + meal post-dose

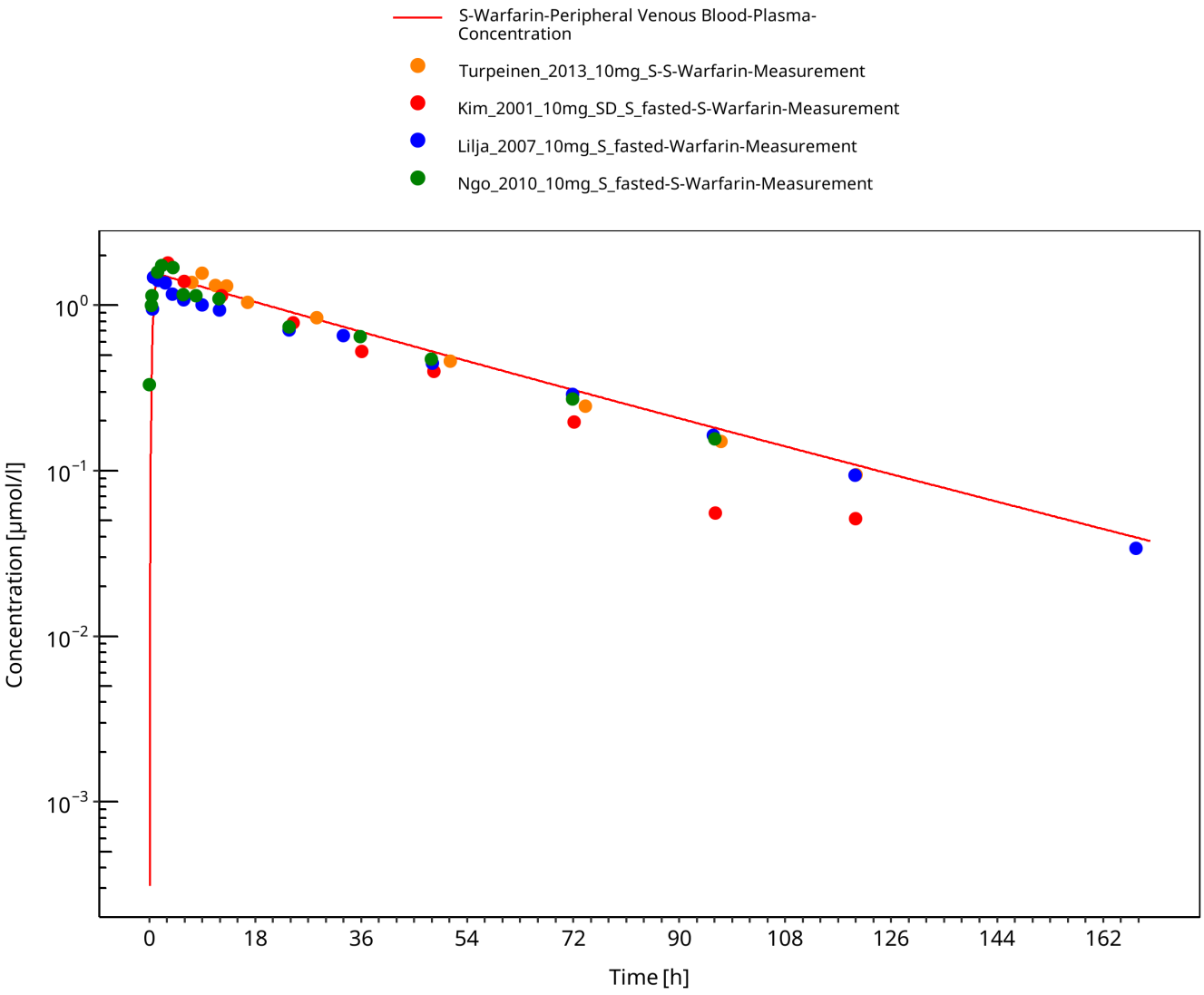

Figure 3-6: Warfarin 10mg (S-Warfarin 5mg) PO fasted

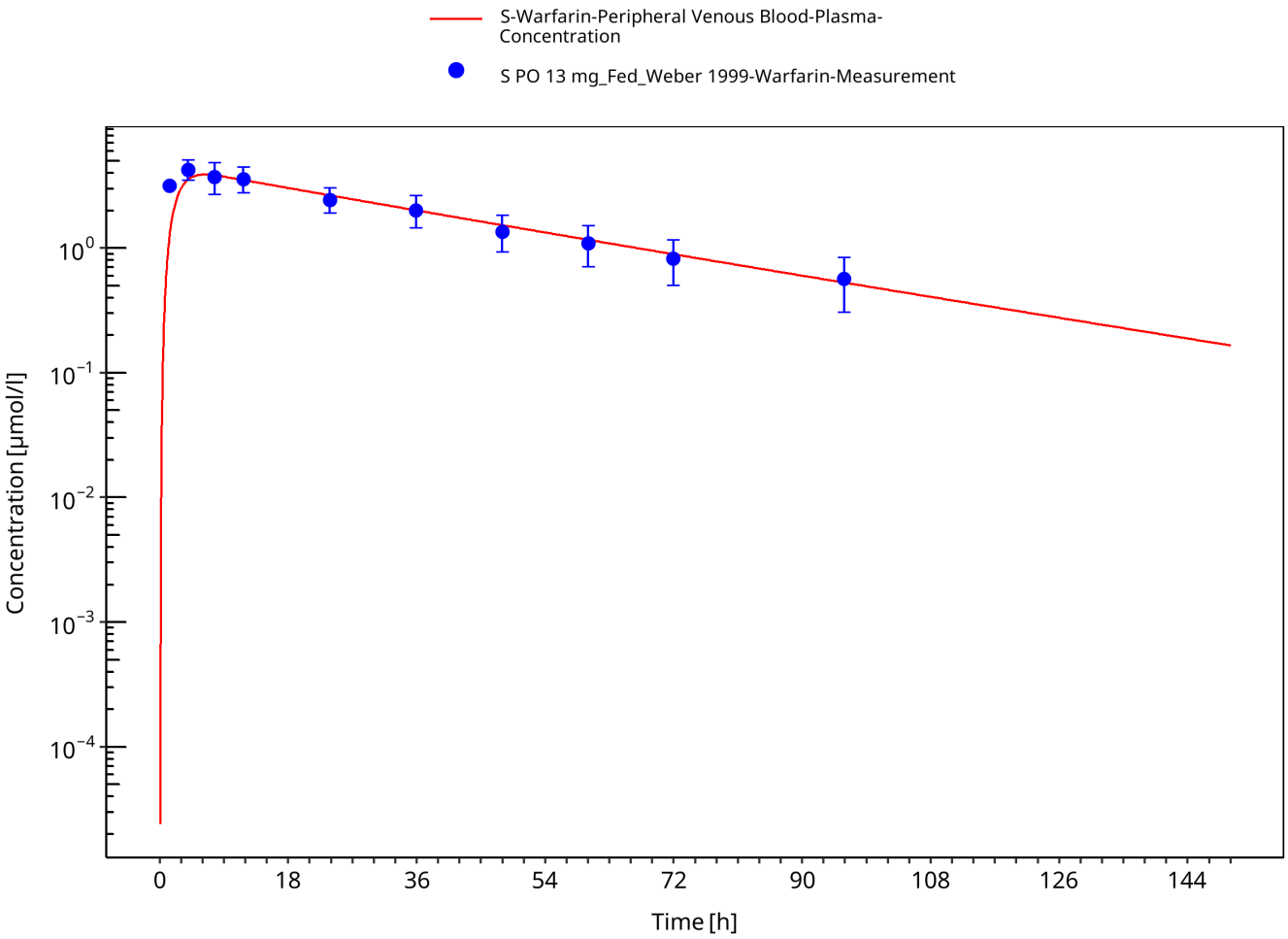

Figure 3-7: Warfarin 26mg (S-Warfarin 13mg) PO fed

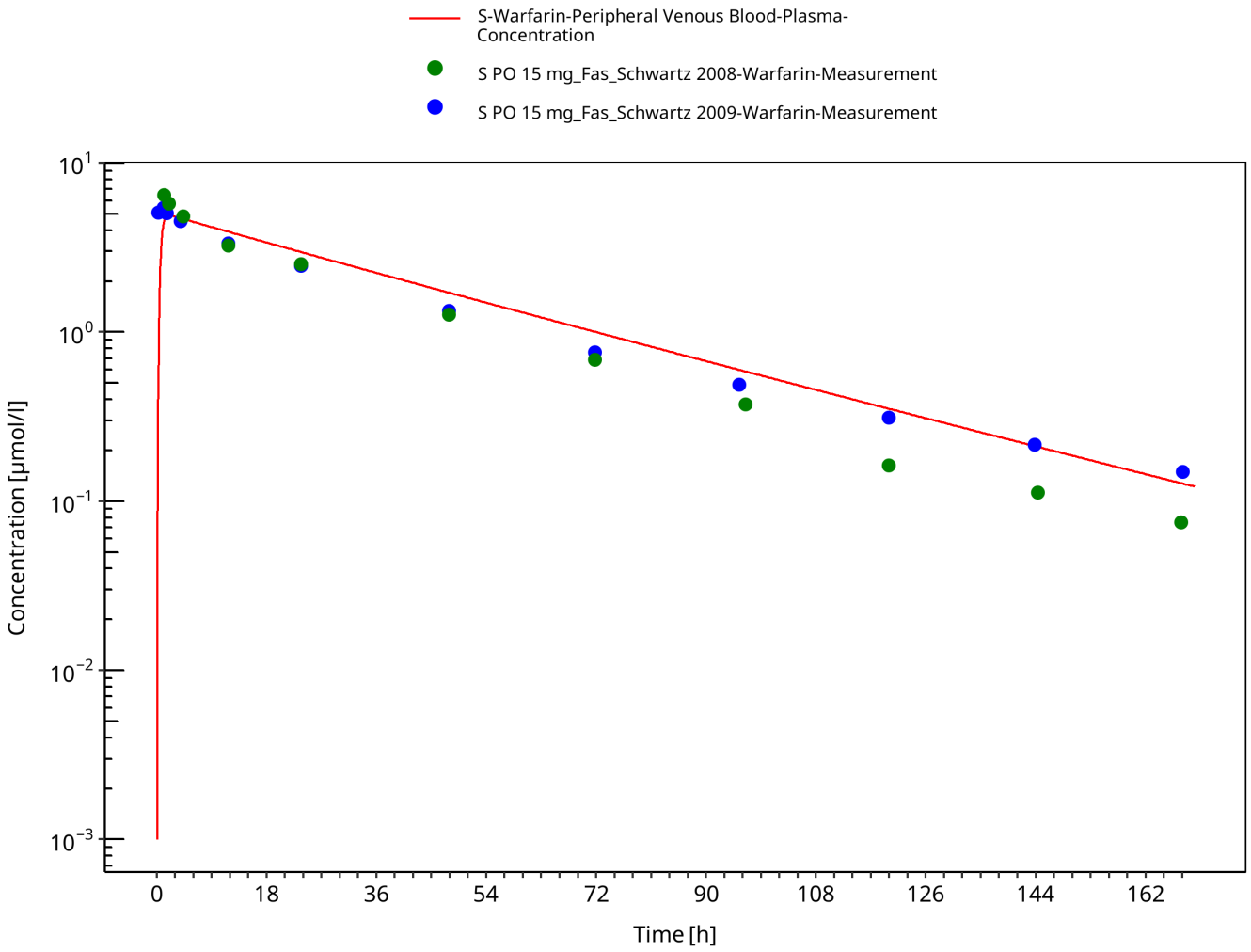

Figure 3-8: Warfarin Na 30mg (S-Warfarin 15mg) fasted

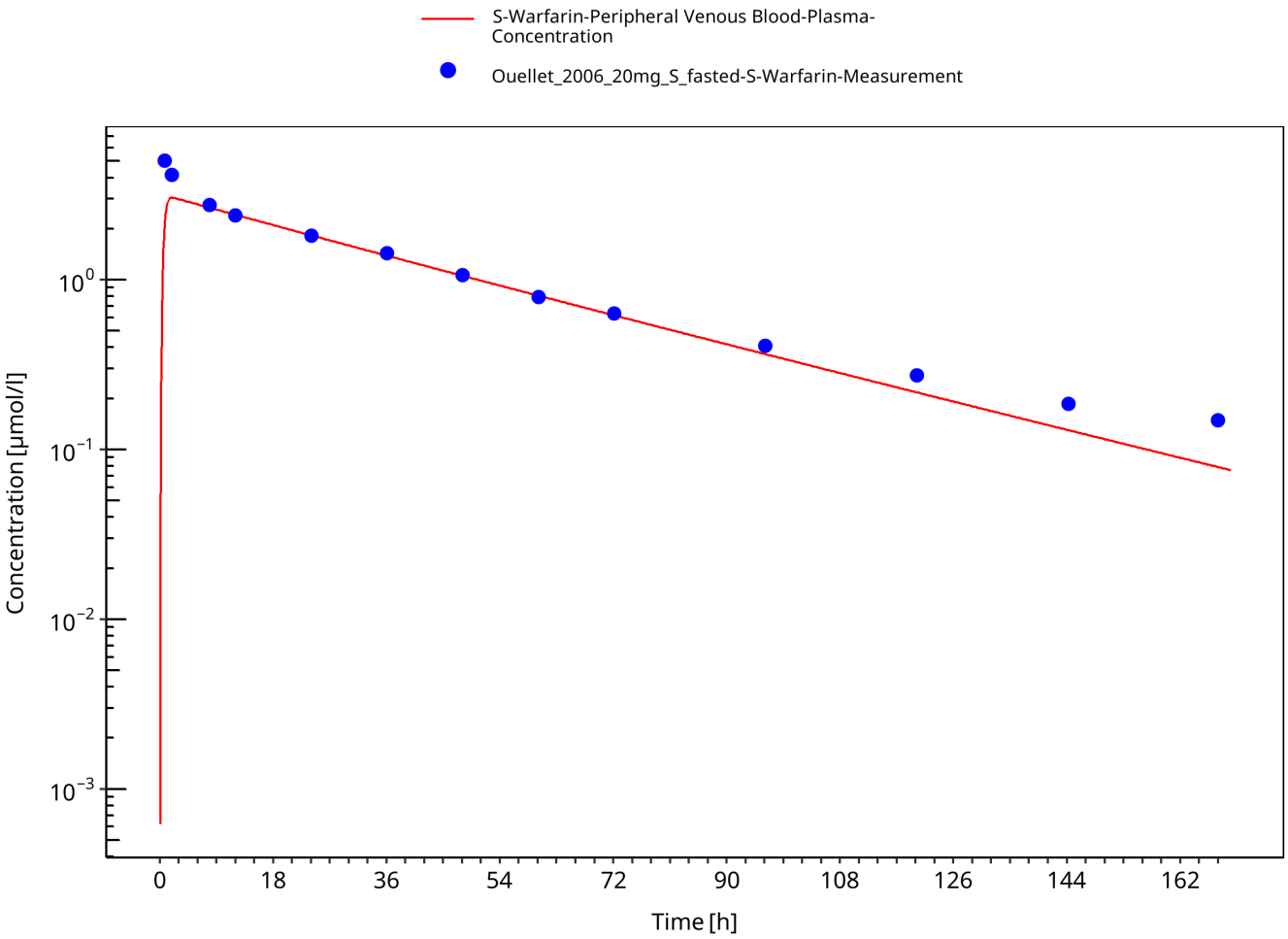

Figure 3-9: Warfarin Na 20mg (S-Warfarin 10mg) PO fasted

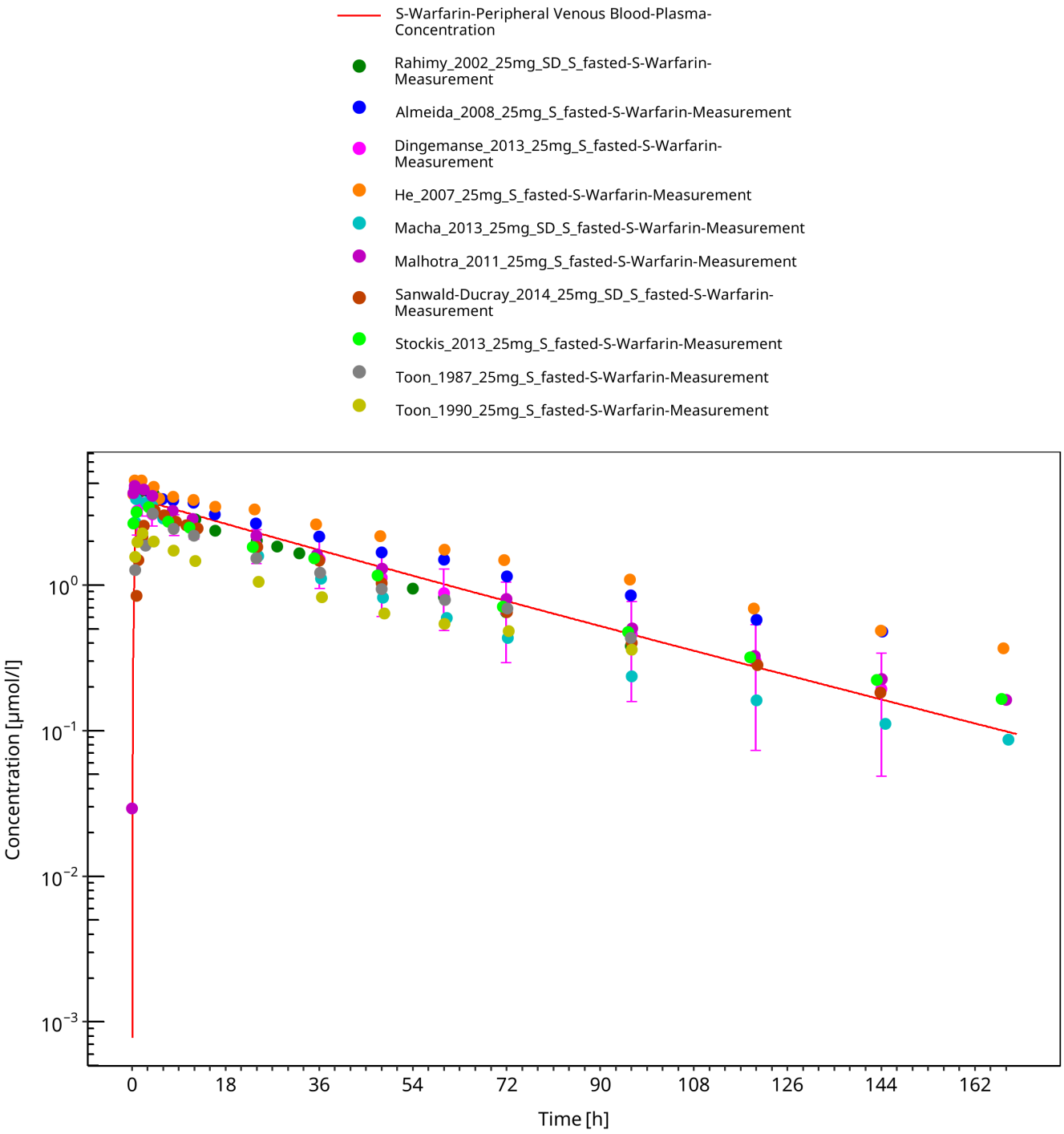

Figure 3-10: Warfarin 25mg (S-Warfarin 12.5mg) PO fasted

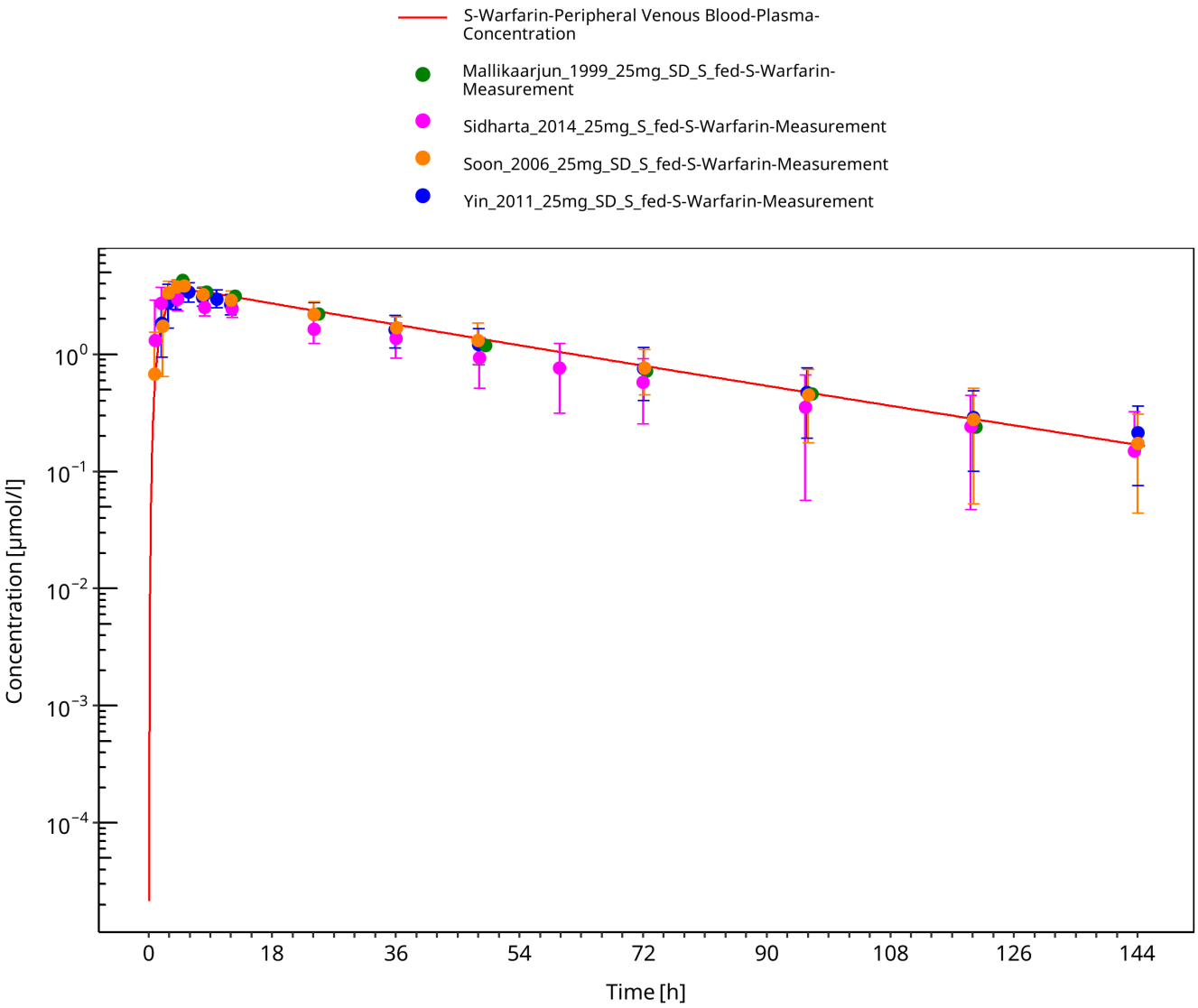

Figure 3-11: Warfarin Na 25mg (S-Warfarin 12.5mg) PO fed

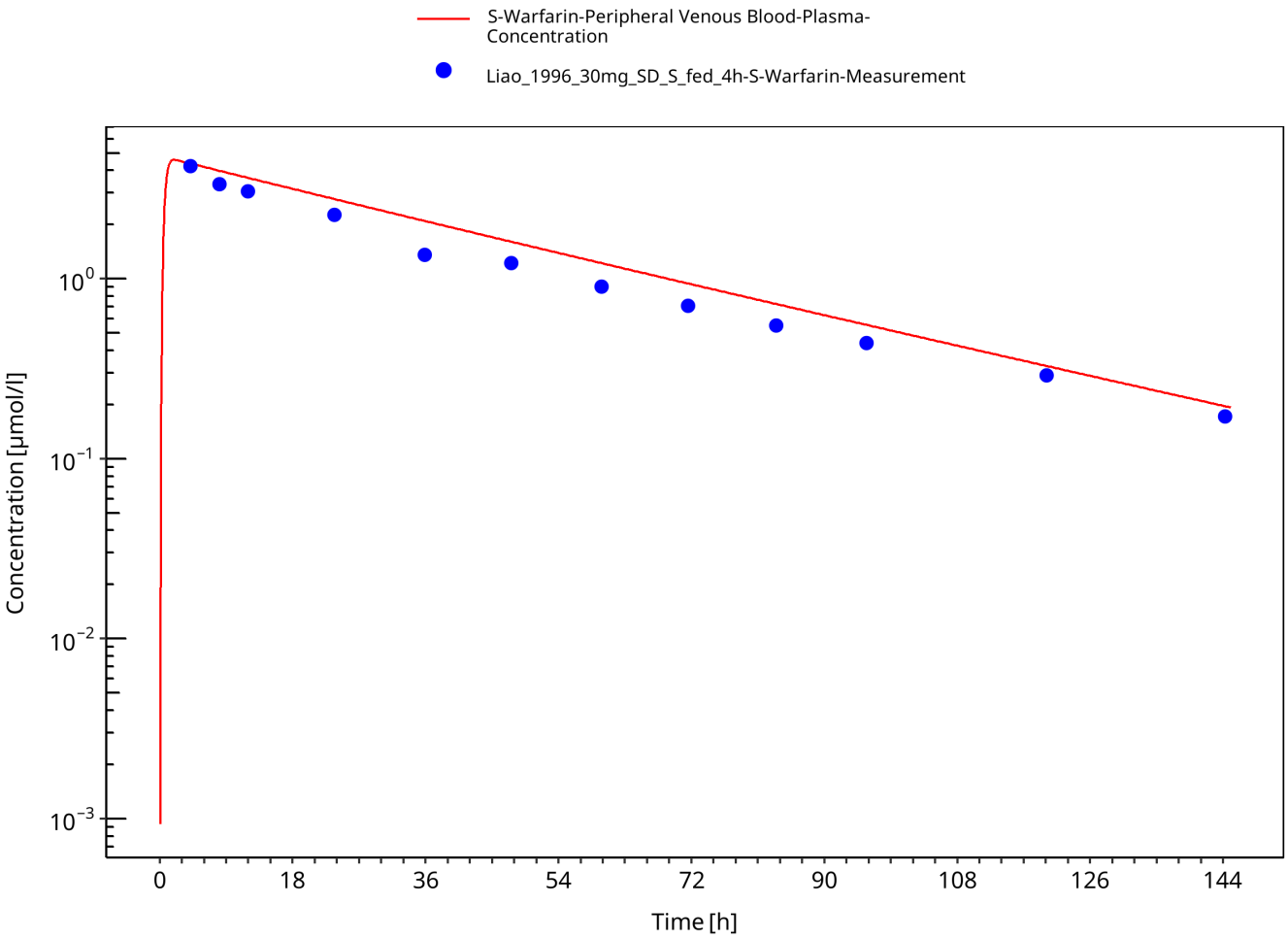

Figure 3-12: Warfarin 7.5mg (S-Warfarin 15mg) PO fasted + meal post-dose

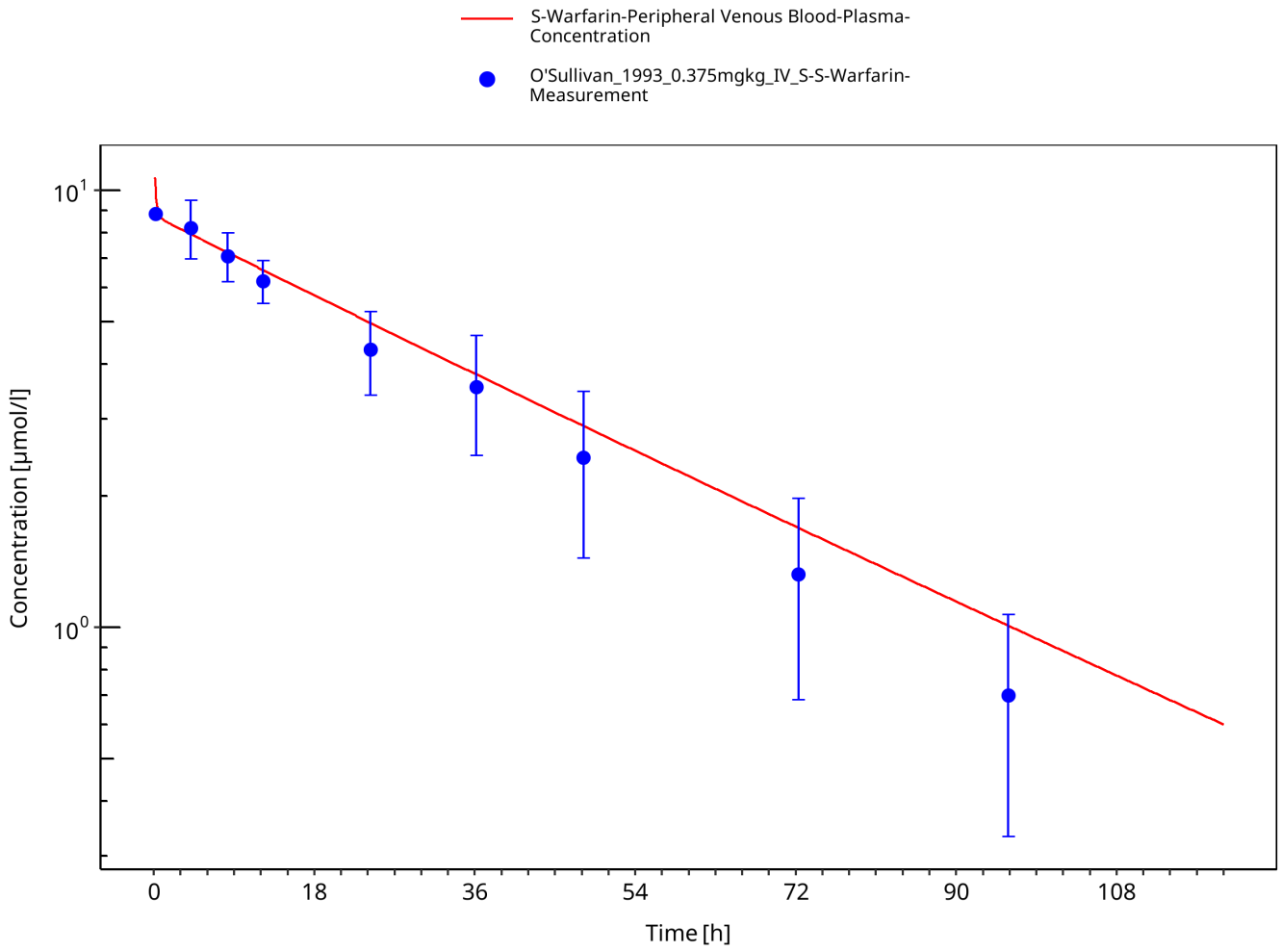

Figure 3-13: S-Warfarin 0.375mg/kg IV fasted

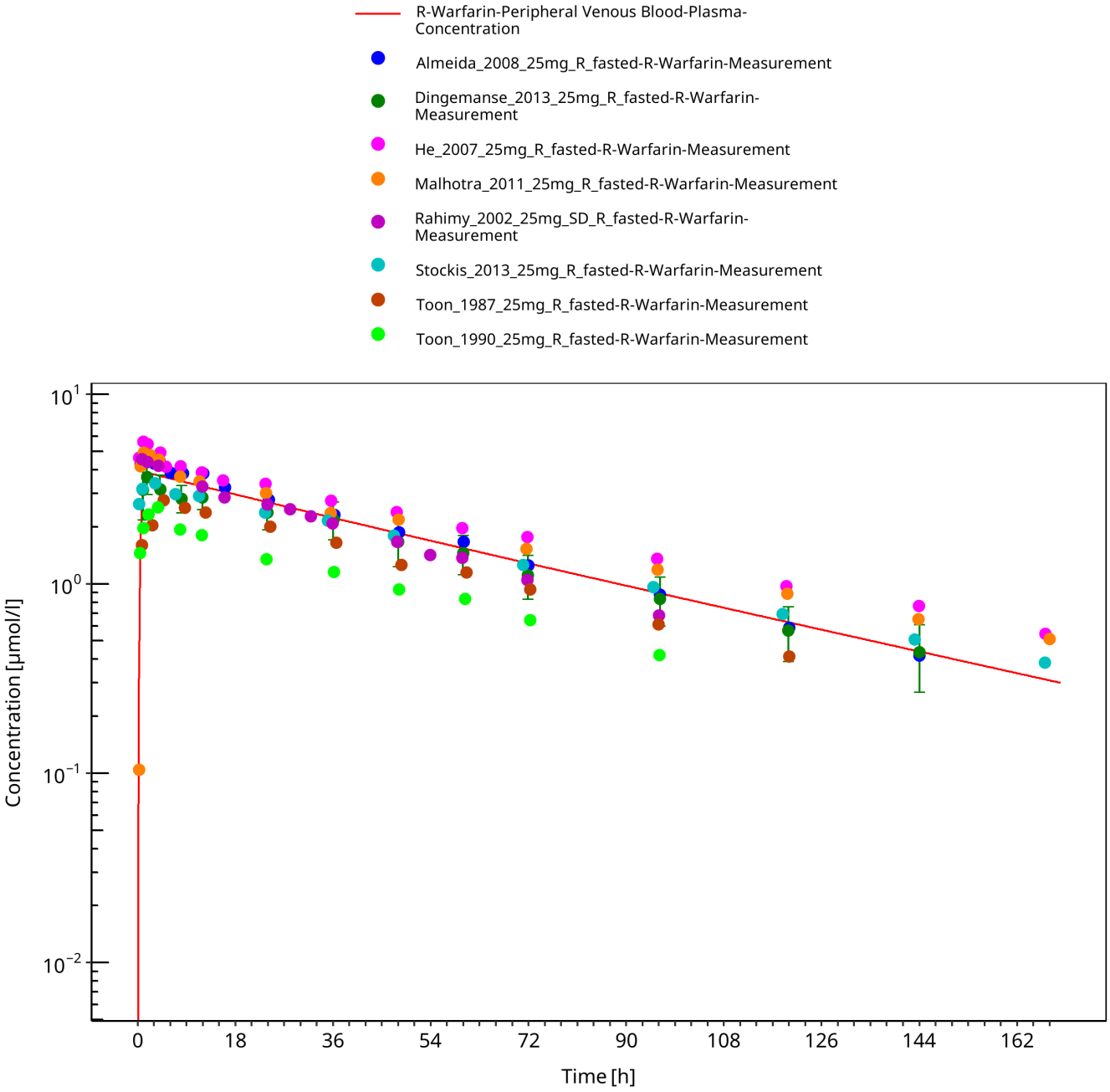

Figure 3-14: Warfarin Na 25mg (R-Warfarin 12.5mg) PO fasted

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of Warfarin in adults after iv and oral administration. Since S-warfarin is the more potent enantiomer, its model development and verification were more extensive. If modeling of R-warfarin becomes necessary in the future, additional work will be required.

5 References

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