

# Building and Evaluation of a PBPK Model for Carbamazepine in Adults

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Version	TODO
Model file and Evaluation Report	TODO
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	1.0 ( <a href="https://github.com/Open-Systems-Pharmacology/Carbamazepine-Model/releases/tag/v1.0">https://github.com/Open-Systems-Pharmacology/Carbamazepine-Model/releases/tag/v1.0</a> )
OSP Version	10.0
Qualification Framework Version	2.1
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# 1 Introduction

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Carbamazepine, sold under the trade name Tegretol® among others, is an anticonvulsant medication used primarily to treat epilepsy and neuropathic pain. Other indications include schizophrenia where it is used as an adjunctive treatment along with other medications, and bipolar disorder where it is used as a second-line agent. Carbamazepine is typically taken by mouth on empty stomach or together with meals, depending on the administered formulation. With the exception of e.g. grapefruit juice, the intake of food was generally found to have no significant impact on carbamazepine pharmacokinetics ([Tedeschi 1981](#), [McLean 2001](#)).

Carbamazepine is extensively metabolized by various enzymes including CYP2B6, 2C8, 3A4, and UGT2B7 ([Kerr 1994](#), [Pelkonen 2001](#), [Staines 2004](#)). The main metabolites are carbamazepine-10,11-epoxide which is pharmacologically active and 10,11-dihydroxycarbamazepine ([Eichelbaum 1985](#)). Following oral administration the major dose fraction is metabolized to carbamazepine-10,11-epoxide ([Eichelbaum 1985](#), [Tomson 1983](#)). This reaction is mainly catalyzed by CYP3A4, with some contribution from CYP2C8 ([Kerr 1994](#)). After oral administration, a minor fraction of the dose (approximately 1 - 3%) is excreted unchanged in urine ([Bernus 1994](#), [Morselli 1975](#)), while approximately 1% of the dose can be recovered as unchanged drug in the bile ([Terhaag 1978](#)). The primary metabolite carbamazepine-10,11-epoxide is cleared by metabolism via epoxide hydroxylase 1 (EPHX1) to its trans-diol form and by glomerular filtration ([Kitteringham 1996](#)).

Carbamazepine is classified by the U.S. Food and Drug Administration (FDA) as a strong CYP3A4 and CYP2B6 inducer (<https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions>) and hence induces its own metabolism.

The herein presented coupled parent-metabolite PBPK model for carbamazepine and carbamazepine-10,11-epoxide represents an update of the model published by Fuhr et al. ([Fuhr 2021](#)). In comparison to the published version by Fuhr et al. ([Fuhr 2021](#)), the CYP3A4 induction parameters have been updated and data from additional clinical studies were used for model evaluation.

# 2 Methods

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## 2.1 Modeling Strategy

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The general workflow for building an adult PBPK model has been described by Kuepfer et al. ([Kuepfer 2016](#)). Relevant information on the anthropometry (height, weight) was gathered from the respective clinical study, if reported. Information on physiological parameters (e.g. blood flows, organ volumes, hematocrit) in adults was gathered from the literature and has been incorporated in PK-Sim® as described previously ([Willmann 2007](#)). 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](#)).

The PBPK model was developed based on publicly available clinical data of adult healthy subjects. In a first step, a model was developed for carbamazepine-10,11-epoxide using pharmacokinetic data from three clinical studies administering carbamazepine-10,11-epoxide at an oral dose ranging from 50 to 200 mg as solution or tablet. This model includes metabolism by EPHX1 and unchanged renal excretion via passive glomerular filtration. Thereafter, a model was developed for carbamazepine that was combined with the carbamazepine-10,11-epoxide model. For the development of the parent-metabolite model, pharmacokinetic data from various clinical studies were used that covered a dosing range from 10 to 600 mg carbamazepine in different formulations (solution, immediate release and extended release formulations), administered under fasted conditions or together with food. The carbamazepine model includes metabolism by CYP2B6, 2C8, and 3A4 as well as an unspecific clearance pathway (implemented as `liver plasma clearance` process) and as minor elimination pathway unchanged renal excretion. Induction of CYP2B6, 3A4, and EPHX1 by carbamazepine was included.

Unknown parameters (see below) 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. Further details on model building are been described elsewhere ([Fuhr 2021](#)).

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

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### 2.2.1 In vitro / physicochemical Data

A literature search was performed to collect available information on physicochemical properties of carbamazepine and carbamazepine-10,11-epoxide. The information is summarized in the table below.

Parameter	Unit	Value	Source	Description
<b>Carbamazepine</b>				
MW	g/mol	236.27	DrugBank DB00564	Molecular weight
logP (calculated)		1.54	Austin 2002	Partition coefficient between octanol and water
logP (calculated)		2.1	DrugBank DB00564	Partition coefficient between octanol and water
logP (calculated)		2.77	DrugBank DB00564	Partition coefficient between octanol and water
Solubility (pH)	µg/mL	336 (6.2)	Annaert 2010	Solubility in human intestinal fluid
Solubility (pH)	µg/mL	283 (7.0)	Söderlind 2010	Solubility in human intestinal fluid
Solubility (pH)	µg/mL	306 (6.9)	Clarysse 2011	Solubility in fasted human intestinal fluid
f <sub>u</sub>		0.25	Pynnönen 1977	Fraction unbound in plasma of healthy subjects
f <sub>u</sub>		0.243 ± 0.013 [0.225 - 0.258] <sup>a</sup>	Morselli 1975	Fraction unbound in plasma of healthy male subjects
f <sub>u</sub>		0.239	Di Salle 1974	Fraction unbound in plasma of normal subjects
f <sub>u</sub>		0.237 ± 0.031 <sup>b</sup>	Vinçon 1987	Fraction unbound in plasma of epileptic patients
f <sub>u</sub>		0.182 ± 0.05 [0.103 - 0.297] <sup>a</sup>	Hooper 1975	Fraction unbound in plasma of normal subjects
K <sub>m</sub> CYP2B6	µM	420	Pearce 2002	CYP2B6 Michaelis-Menten constant
V <sub>max</sub> CYP2B6	pmol/min/pmol rec enzyme	0.429	Pearce 2002	in vitro metabolic rate constant for recombinant CYP2B6
K <sub>m</sub> CYP2C8	µM	757	Cazali 2003	CYP2C8 Michaelis-Menten constant
V <sub>max</sub> CYP2C8	pmol/min/pmol rec enzyme	0.673	Cazali 2003	in vitro metabolic rate constant for recombinant CYP2C8
K <sub>m</sub> CYP3A4 <sup>c</sup>	µM	282	Pearce 2002	CYP3A4 Michaelis-Menten constant
K <sub>m</sub> CYP3A4 (→CBZE) <sup>d</sup>	µM	248	Huang 2004	CYP3A4 Michaelis-Menten constant
K <sub>m</sub> UGT2B7	µM	214	Staines 2004	UGT2B7 Michaelis-Menten constant
V <sub>max</sub> UGT2B7	pmol/min/mg mic enzyme	0.79	Staines 2004	in vitro metabolic rate constant for microsomal enzymes
Microsomal UGT2B7	pmol/mg mic protein	82.9	Achour 2014	Content of UGT2B7 proteins in liver microsomes

Parameter	Unit	Value	Source	Description
Intestinal permeability	cm/min	0.0258	<a href="#">Lennernäs 2007</a>	Transcellular intestinal permeability
<b>Carbamazepine-10,11-epoxide</b>				
MW	g/mol	252.27	<a href="#">DrugBank DBMET00291</a>	Molecular weight
logP (calculated)		1.58	<a href="#">DrugBank DBMET00291</a>	Partition coefficient between octanol and water
logP (calculated)		1.97	<a href="#">DrugBank DBMET00291</a>	Partition coefficient between octanol and water
Solubility (pH)	µg/mL	1340 (7.0)	<a href="#">DrugBank DBMET00291</a>	Solubility
f <sub>u</sub>		0.489 ± 0.021 [0.468 - 0.518] <sup>a</sup>	<a href="#">Morselli 1975</a>	Fraction unbound in plasma of healthy male subjects
f <sub>u</sub>		0.491 ± 0.042 <sup>b</sup>	<a href="#">Vinçon 1987</a>	Fraction unbound in plasma of epileptic patients

<sup>a</sup> denotes mean ± standard deviation [range]

<sup>b</sup> denotes mean ± standard deviation

<sup>c</sup> refers to CYP3A4-mediated reaction forming other metabolites than carbamazepine-10,11-epoxide

<sup>d</sup> refers to CYP3A4-mediated reaction forming carbamazepine-10,11-epoxide

## 2.2.2 Clinical Data

A literature search was performed to collect available clinical data on carbamazepine and carbamazepine-10,11-epoxide in healthy adult subjects.

The following studies were used for model building and evaluation:

<b>Publication</b>	<b>Arm / Treatment / Information used for model building</b>
Barzaghi 1987	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Bedada 2015	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Bedada 2016	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Bernus 1994	Healthy subjects receiving two oral doses of 600 mg carbamazepine
Bianchetti 1987	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Burstein 2000	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 100 mg and escalating to 400 mg
Caraco 1995	Healthy lean subjects receiving a single oral dose of 200 mg carbamazepine
Caraco 1995	Obese but otherwise healthy subjects receiving a single oral dose of 200 mg carbamazepine
Cawello 2000	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 100 mg and escalating to 200 mg
Cotter 1977	Healthy subject receiving a single oral dose of 800 mg carbamazepine
Dalton 1985a	Healthy subjects receiving a single oral dose of 600 mg carbamazepine
Dalton 1985b	Healthy subjects receiving a single oral dose of 600 mg carbamazepine
Eichelbaum 1985	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Elqidra 2004	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
European Patent Application EP 1044681 A2	Healthy subjects receiving a single oral dose of 400 and 600 mg carbamazepine
Gérardin 1976	Healthy subjects receiving a single oral dose of 100, 200, and 600 mg carbamazepine
Gérardin 1990	Healthy subjects receiving a single oral dose of 100 mg carbamazepine concomitantly with a single intravenous dose of 10 mg carbamazepine
Ji 2008	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 200 mg and escalating to 400 mg
Kayali 1994	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Kim 2005	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Kovacević 2009	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Levy 1975	Healthy subjects receiving a single oral carbamazepine dose of 6 mg/kg body weight
McLean 2001	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Meyer 1996	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Meyer 1998	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Miles 1989	Healthy subjects receiving a multiple oral doses of 300 and 400 mg carbamazepine
Møller 2001	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 100 mg and escalating to 400 mg
Morselli 1975	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Pisani 1988	Healthy subjects receiving a single oral dose of 100 mg carbamazepine-10,11-epoxide
Pisani 1990	Healthy subjects receiving a single oral dose of 100 mg carbamazepine-10,11-epoxide

Publication	Arm / Treatment / Information used for model building
Pisani 1992	Healthy subjects receiving a single oral dose of 100 mg carbamazepine-10,11-epoxide
Pynnonen 1977	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Rawlins 1975	Healthy subject receiving a single oral dose of 50, 100, and 200 mg carbamazepine
Saint-Salvi 1987	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Stevens 1998	Healthy subjects receiving multiple oral doses of 400 mg carbamazepine
Strandjord 1975	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Sumi 1987	Healthy subjects receiving single oral doses of 200 mg carbamazepine and of 150 mg carbamazepine-10,11-epoxide
Tomson 1983	Healthy subjects receiving single oral doses of 200 mg carbamazepine and of 50, 100, and 200 mg carbamazepine-10,11-epoxide
US Patent Application - US 2009/0169619 A1	Healthy subjects receiving a single oral dose of 300 mg carbamazepine
US Patent Application - US 2014/0302138 A1	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Wada 1978	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Wong 1983	Healthy subjects receiving a single oral dose of 400 mg carbamazepine

## 2.3 Model Parameters and Assumptions

### 2.3.1 Absorption

Absorption of carbamazepine and carbamazepine-10,11-epoxide observed in clinical studies can be fully explained by passive absorption.

### 2.3.2 Distribution

For both carbamazepine and carbamazepine-10,11-epoxide, the observed clinical data was described by choosing the partition coefficient calculation by Rodgers and Rowlands and cellular permeability calculation by PK-sim standard.

### 2.3.3 Metabolism, Elimination and Induction

Carbamazepine is metabolized by CYP2B6, 2C8, 3A4, and UGT2B7 (Kerr 1994, Pelkonen 2001, Staines 2004). and a minor fraction of the dose (approximately 1%) is excreted unchanged in urine (Bernus 1994, Morselli 1975). Carbamazepine-10,11-epoxide is cleared by metabolism via epoxide hydroxylase 1 (EPHX1) and glomerular filtration (Kitteringham 1996).

Induction of CYP2B6 and 3A4 was taken into account (Eichelbaum 1985) and it was assumed that carbamazepine also induces EPHX1 (Eichelbaum 1985). Carbamazepine induces CYP2B6 and 3A4 via the CAR pathway (Faucette 2007); therefore, the same EC<sub>50</sub> value was used in the model for induction of CYP2B6, 3A4, and EPHX1. The associated E<sub>max</sub> values were optimized.

### 2.3.4 Automated Parameter Identification

The parameter identification tool in PK-Sim® has been used to estimate selected model parameters. The result of the final parameter identification is shown in the table below:

Model Parameter	Optimized Value	Unit
<b>Carbamazepine</b>		
Lipophilicity	2.00	
Specific clearance (total hepatic clearance process)	0.015	1/min
kcat (CYP3A4) <sup>a</sup>	0.200	1/min
kcat (→ CBZE via CYP3A4) <sup>b</sup>	0.750	1/min
Emax (CYP2B6)	17.0	
Emax (CYP3A4)	6.00	
Emax (EPHX1)	3.25	
GFR fraction	0.027	
Dissolution time (50% dissolved) (IR tablet, fasted)	200.0	min
Dissolution shape (IR tablet, fasted)	0.740	
Dissolution time (50% dissolved) (IR tablet, fed)	100.0	min
Dissolution shape (IR tablet, fed)	1.20	
Dissolution time (50% dissolved) (XR tablet, fasted)	767.2	min
Dissolution shape (XR tablet, fasted)	0.758	
Dissolution time (50% dissolved) (XR tablet, fed)	436.4	min
Dissolution shape (XR tablet, fed)	1.159	
Dissolution time (50% dissolved) (XR capsule, fasted)	439.5	min
Dissolution shape (XR capsule, fasted)	0.794	
Dissolution time (50% dissolved) (XR capsule, fed)	361.4	min
Dissolution shape (XR capsule, fed)	2.127	
<b>Carbamazepine-10,11-epoxide</b>		
Lipophilicity	1.16	
Specific intestinal permeability (transcellular)	0.299	cm/min
Specific clearance (EPHX1)	0.010	1/min
GFR fraction	0.213	
Dissolution time (50% dissolved)	200.0	min
Dissolution shape	0.754	

<sup>a</sup> refers to CYP3A4-mediated reaction forming other metabolites than carbamazepine-10,11-epoxide

<sup>b</sup> refers to CYP3A4-mediated reaction forming carbamazepine-10,11-epoxide

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# 3 Results and Discussion

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The PBPK model for carbamazepine was developed and evaluated using publicly available clinical pharmacokinetic data from studies listed in [Section 2.2.2](#).

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

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

### Compound: Carbamazepine

#### Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	17.7 mg/l	Internet-Assumption-assumed water solubility	DrugBank	False
Reference pH	7	Internet-Assumption-assumed water solubility	DrugBank	False
Solubility at reference pH	336 µg/ml	Publication-In Vitro-FaHIF (pH 5.4-7.1)	Annaert 2010 - FaHIF	False
Reference pH	6.2	Publication-In Vitro-FaHIF (pH 5.4-7.1)	Annaert 2010 - FaHIF	False
Solubility at reference pH	255.2 µg/ml	Publication-In Vitro-FaSSIF (pH = ???)	Annaert 2010 - FaSSIF	False
Reference pH	6.5	Publication-In Vitro-FaSSIF (pH = ???)	Annaert 2010 - FaSSIF	False
Solubility at reference pH	336 µg/ml	Parameter Identification-Parameter Identification-Value updated from '2020-01-14_' on 2020-01-15 09:37	Clarysse 2011 - FaHIF	False
Reference pH	6.2	Parameter Identification-Parameter Identification-Value updated from '2020-01-14_' on 2020-01-15 09:37	Clarysse 2011 - FaHIF	False
Solubility at reference pH	266 µg/ml	Publication-In Vitro-FaSSIF	Clarysse 2011 - FaSSIF	False
Reference pH	6.5	Publication-In Vitro-FaSSIF	Clarysse 2011 - FaSSIF	False
Solubility at reference pH	170 µg/ml	Publication-In Vitro-FaHIF (pH 6.2)	Heikkilä 2011	False
Reference pH	6.2	Publication-In Vitro-FaHIF (pH 6.2)	Heikkilä 2011	False
Solubility at reference pH	283 µg/ml	Publication-In Vitro-FaHIF (pH 6.5-7.5)	Söderlind 2010	False
Reference pH	7	Publication-In Vitro-FaHIF (pH 6.5-7.5)	Söderlind 2010	False
Solubility at reference pH	236 µg/ml	Publication-In Vitro	Söderlind 2010 - FaSSIF	False
Reference pH	6.5	Publication-In Vitro	Söderlind 2010 - FaSSIF	False
Solubility at reference pH	468 µg/ml	Publication-In Vitro-pH = ???	Clarysse 2011 - Fed HIF	False
Reference pH	7	Publication-In Vitro-pH = ???	Clarysse 2011 - Fed HIF	False
Solubility at reference pH	524 µg/ml	Publication-In Vitro	Clarysse 2011 - FeSSIF	False
Reference pH	5	Publication-In Vitro	Clarysse 2011 - FeSSIF	False
Solubility at reference pH	336 µg/ml		used in simulation	True
Reference pH	6.2		used in simulation	True

Name	Value	Value Origin	Alternative	Default
Lipophilicity	2.45 Log Units	Publication-In Vitro-logP	Dal Pozzo 1989	False
Lipophilicity	2.1 Log Units	Internet-logP	AlogPS	False
Lipophilicity	2.77 Log Units	Internet-logP	ChemAxon	False
Lipophilicity	2.77 Log Units	Publication-In Vitro-logD (6.5)	Annaert 2010	False
Lipophilicity	2.77 Log Units	Publication-In Vitro-logD (6.5)	Clarysse 2011	False
Lipophilicity	2.77 Log Units	Publication-In Vitro-logD (6.5)	Heikkilä 2011	False
Lipophilicity	2.45 Log Units	Publication-In Vitro-logP, logD(7.4)	Winiwarter 1998	False
Lipophilicity	2 Log Units	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1.' on 2020-11-04 10:58	Optimized	True
Fraction unbound (plasma, reference value)	24 %		DrugBank, FDA label	False
Fraction unbound (plasma, reference value)	25 %		Bertisson 1978	False
Fraction unbound (plasma, reference value)	21 %		Johannessen and Strandjord 1972	False
Fraction unbound (plasma, reference value)	25 %	Publication-In Vivo-determined from saliva concentration	Pynnonen 1977	False
Fraction unbound (plasma, reference value)	25 %	Other-Assumption	Optimized	True
Specific intestinal permeability (transcellular)	0.00043 cm/s	Publication-In Vitro-Lennernaes2007	Literature Lennernaes2007	True
Is small molecule	Yes			

Name	Value	Value Origin	Alternative	Default
Molecular weight	236.2686 g/mol	Internet-DrugBank		
Plasma protein binding partner	Albumin			

## Calculation methods

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

## Processes

### Metabolizing Enzyme: CYP3A4-Huang et al 2004 - CBZ-E

Molecule: CYP3A4

Metabolite: Carbamazepine 10,11-epoxide

#### Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	1 pmol/min/pmol rec. enzyme	
Km	248 µmol/l	Publication-In Vitro-Huang2004
kcat	0.75 1/min	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58

### Induction: CYP3A4-mean of literature

Molecule: CYP3A4

#### Parameters

Name	Value	Value Origin
EC50	20 µmol/l	Publication-In Vitro-mean of literature values
Emax	6	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58

### Systemic Process: Glomerular Filtration-GFR (passive reabsorption)

Species: Human

#### Parameters

Name	Value	Value Origin
GFR fraction	0.027158714	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58

### Metabolizing Enzyme: CYP2C8-Cazali 2003

Molecule: CYP2C8

#### Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.6733452272 pmol/min/pmol rec. enzyme	Publication-In Vitro-Cazali2003
Km	757 µmol/l	Publication-In Vitro-Cazali2003

### Metabolizing Enzyme: UGT2B7-Staines 2004 - mean

Molecule: UGT2B7

#### Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	0.79 pmol/min/mg mic. protein	Publication-In Vitro-Staines 2004
Content of CYP proteins in liver microsomes	82.9 pmol/mg mic. protein	Publication-In Vitro-Achour et al - 2014
Km	214 µmol/l	Publication-In Vitro-Staines2004

### Metabolizing Enzyme: CYP2B6-Pearce2002

Molecule: CYP2B6

#### Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.429 pmol/min/pmol rec. enzyme	Publication-In Vitro-Pearce2002
Km	420 µmol/l	Publication-In Vitro-Pearce 2002

### Induction: CYP2B6-Test

Molecule: CYP2B6

#### Parameters

Name	Value	Value Origin
EC50	20 µmol/l	Other-Assumption-mean of literature values of CYP3A4
Emax	17	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58

### Metabolizing Enzyme: CYP3A4-Pearce et al - 2002 - 3-hydroxy

Molecule: CYP3A4

## Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.164 pmol/min/pmol rec. enzyme	Publication-In Vitro-Pearce2002
Km	282 μmol/l	Publication-In Vitro-Pearce 2002
kcat	0.2 1/min	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58

## Induction: EPHX1-Eichelbaum

Molecule: EPHX1

## Parameters

Name	Value	Value Origin
EC50	20 μmol/l	Other-Assumption-mean of literature values for CYP3A4 induction
Emax	3.25	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58

## Systemic Process: Total Hepatic Clearance-Pearce - hydroxy processes

Species: Human

## Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.25	
Lipophilicity (experiment)	2.0000632456 Log Units	
Plasma clearance	0 ml/min/kg	
Specific clearance	0.015 1/min	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58

## Formulation: CBZ-E\_tablet

Type: Weibull

## Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	200.0000054666 min	Parameter Identification-Parameter Identification-Value updated from '2020-09-18_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_onlyTegretolIR' on 2020-09-21 11:16
Lag time	0 min	
Dissolution shape	0.7537098141	Parameter Identification-Parameter Identification-Value updated from '2020-09-18_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_onlyTegretolIR' on 2020-09-21 11:16
Use as suspension	No	

## Formulation: CBZ\_capsuleXR\_fasted (Carbatrol)

Type: Weibull

### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	439.4574099817 min	Parameter Identification-Parameter Identification-Value updated from '2020-09-15_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-10-28 17:25
Lag time	0 min	
Dissolution shape	0.7939239247	Parameter Identification-Parameter Identification-Value updated from '2020-09-15_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-10-28 17:25
Use as suspension	Yes	

## Formulation: CBZ\_capsuleXR\_fed (Carbatrol)

Type: Weibull

### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	361.3585414973 min	Parameter Identification-Parameter Identification-Value updated from '2020-09-15_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-10-28 17:25
Lag time	0 min	
Dissolution shape	2.1274794597	Parameter Identification-Parameter Identification-Value updated from '2020-09-15_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-10-28 17:25
Use as suspension	Yes	

## Formulation: CBZ\_tabletIR\_fasted (Tegretol)

Type: Weibull

### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	200 min	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58
Lag time	0 min	
Dissolution shape	0.74	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58
Use as suspension	Yes	

## Formulation: CBZ\_tabletIR\_fed (Tegretol)

Type: Weibull

### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	100 min	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58
Lag time	0 min	
Dissolution shape	1.2	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58
Use as suspension	Yes	

## Formulation: CBZ\_tabletXR\_fasted (TegretolXR)

Type: Weibull

### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	767.1608678294 min	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58
Lag time	0 min	
Dissolution shape	0.7579087507	Parameter Identification-Parameter Identification-Value updated from '2020-10-30_refit_no2C8-induction_CYP3A4-metabolism_EPHX1_' on 2020-11-04 10:58
Use as suspension	Yes	

## Formulation: CBZ\_tabletXR\_fed (TegretolXR)

Type: Weibull

### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	436.3502971601 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 6' on 2020-11-06 10:47
Lag time	0 min	
Dissolution shape	1.1593235448	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 6' on 2020-11-06 10:47
Use as suspension	Yes	

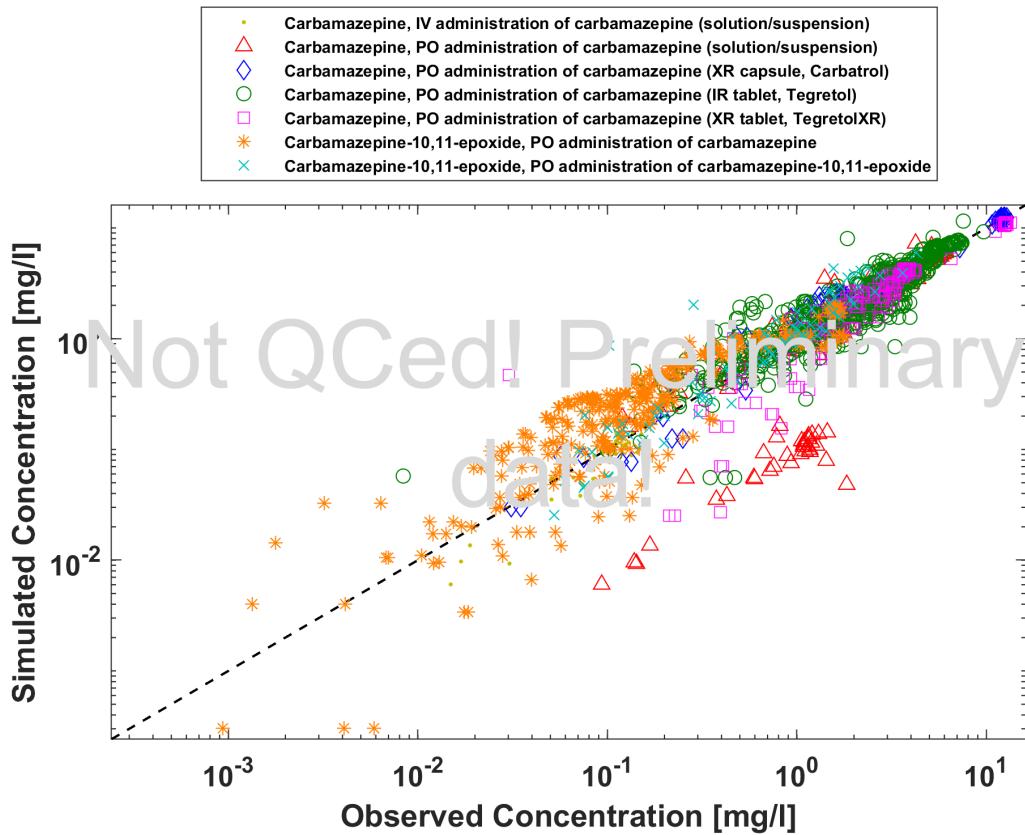
## Formulation: Solution

Type: Dissolved

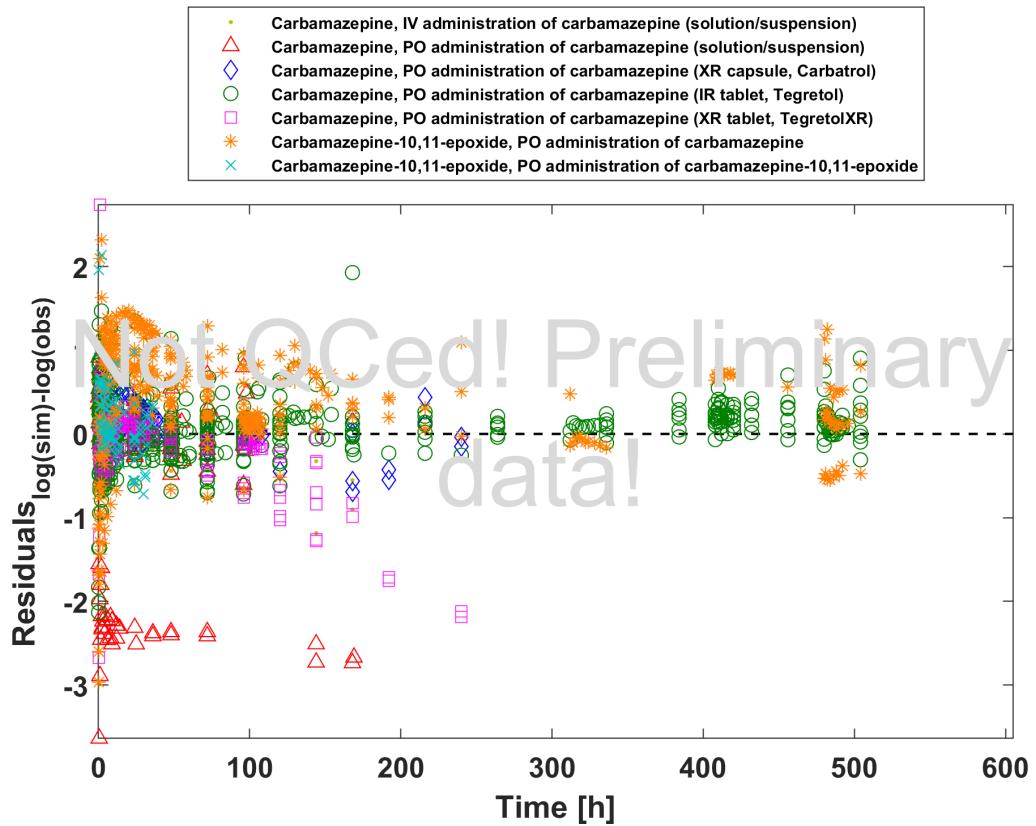
### 3.2 Diagnostics Plots

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 simulated versus observed plasma concentration, the second weighted residuals versus time.



Goodness of fit plot for concentration in plasma

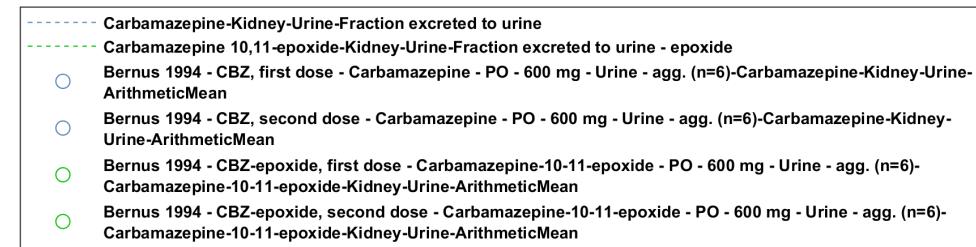


Goodness of fit plot for concentration in plasma

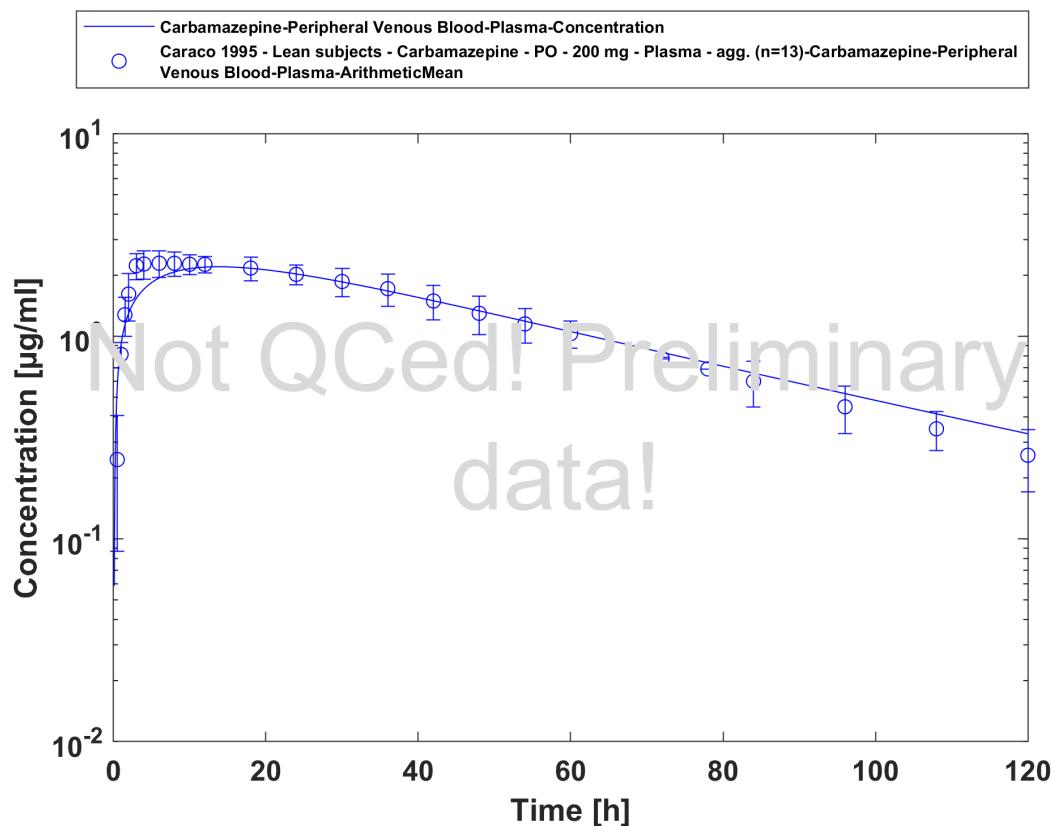
GMFE = 1.498759

### 3.3 Concentration-Time Profiles

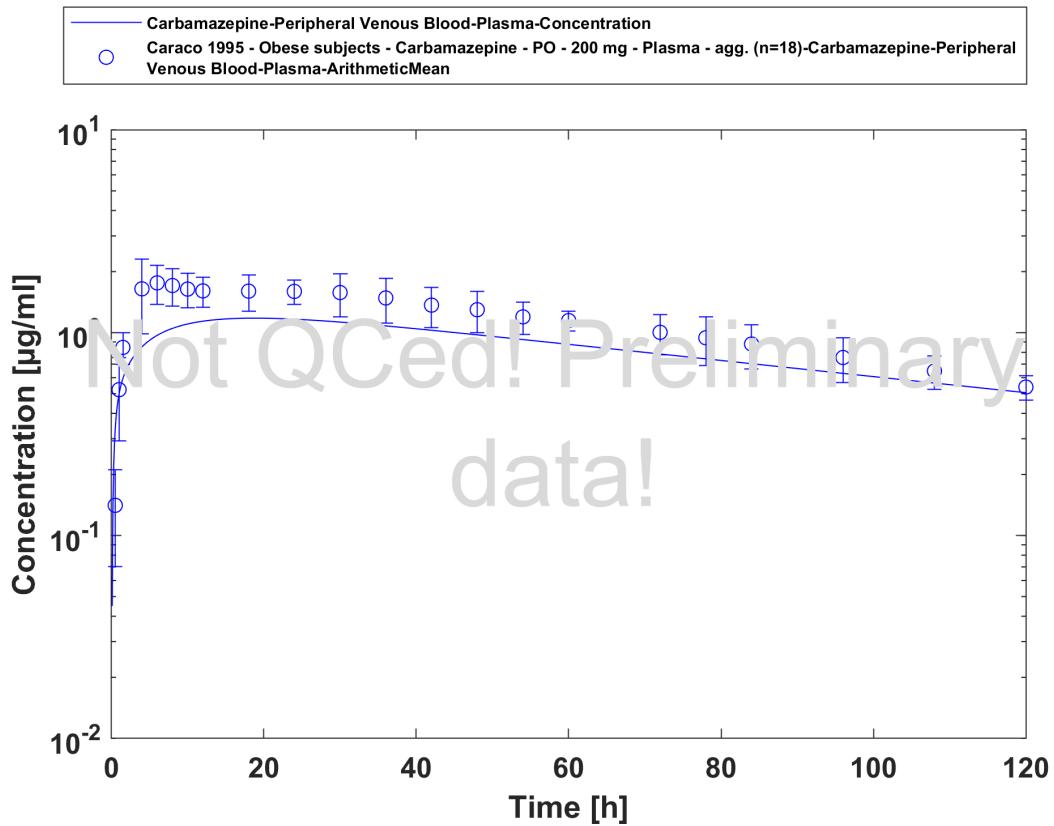
Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.



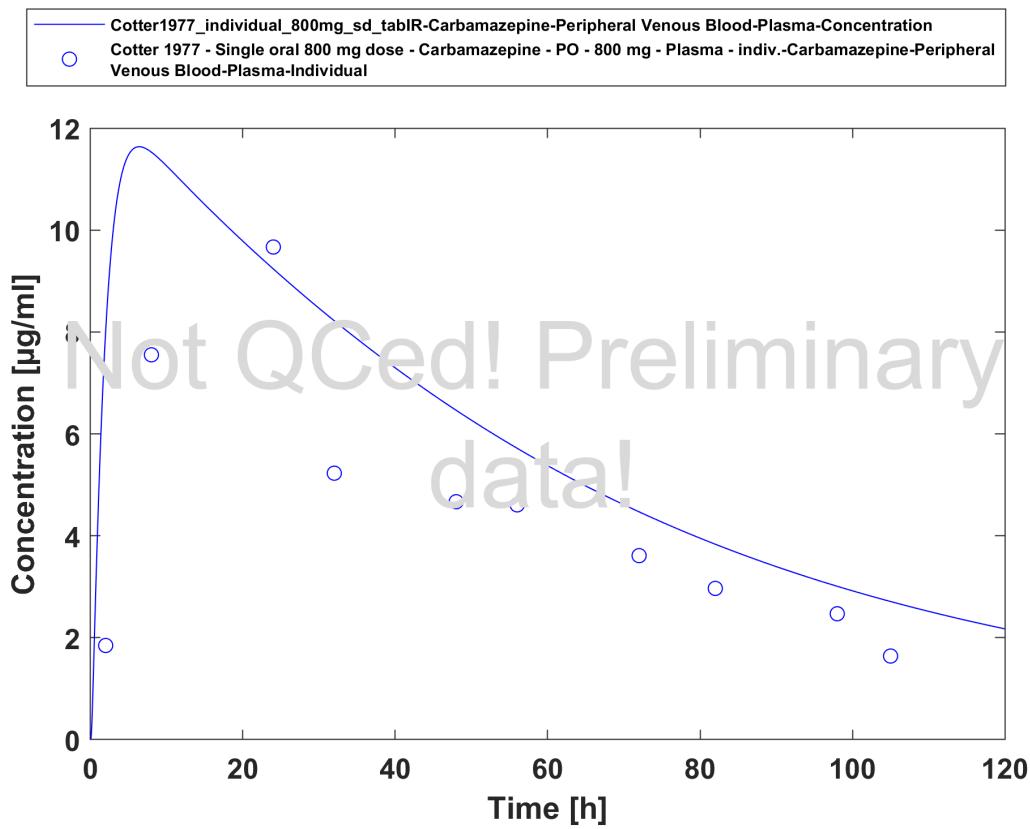
Bernus1994\_600mg\_D1+D5\_tablR - urine



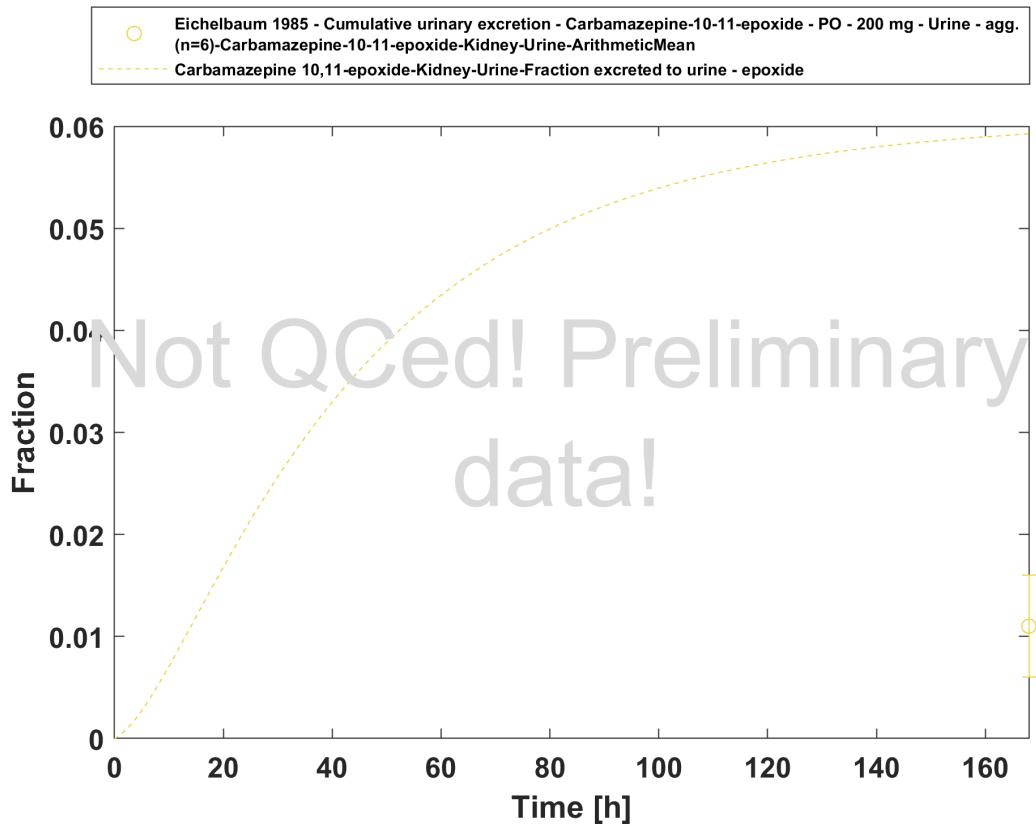
Time Profile Analysis



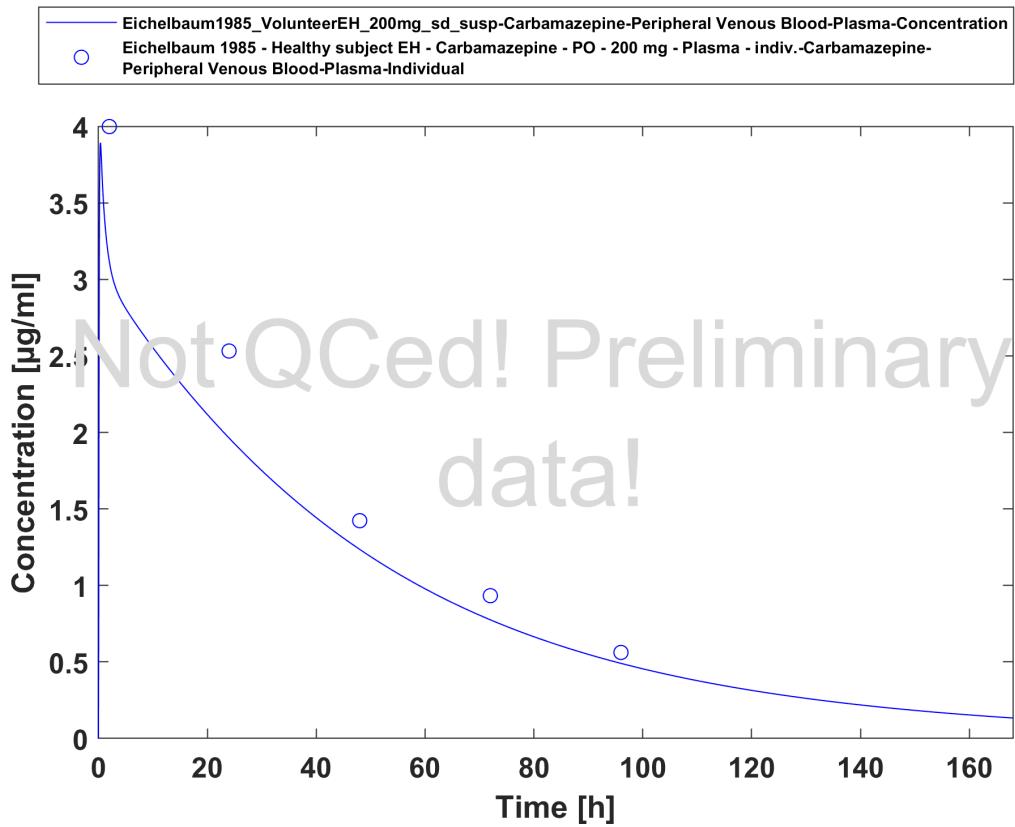
Time Profile Analysis



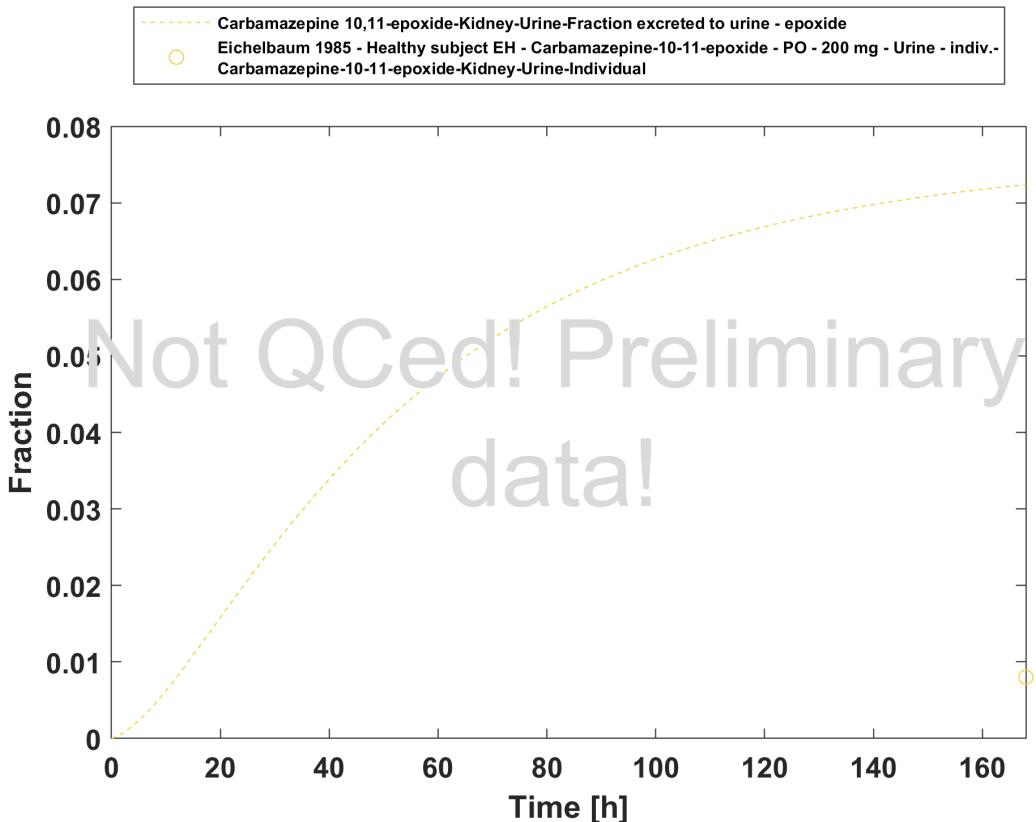
Cotter1977\_individual\_800mg\_sd\_tabIR



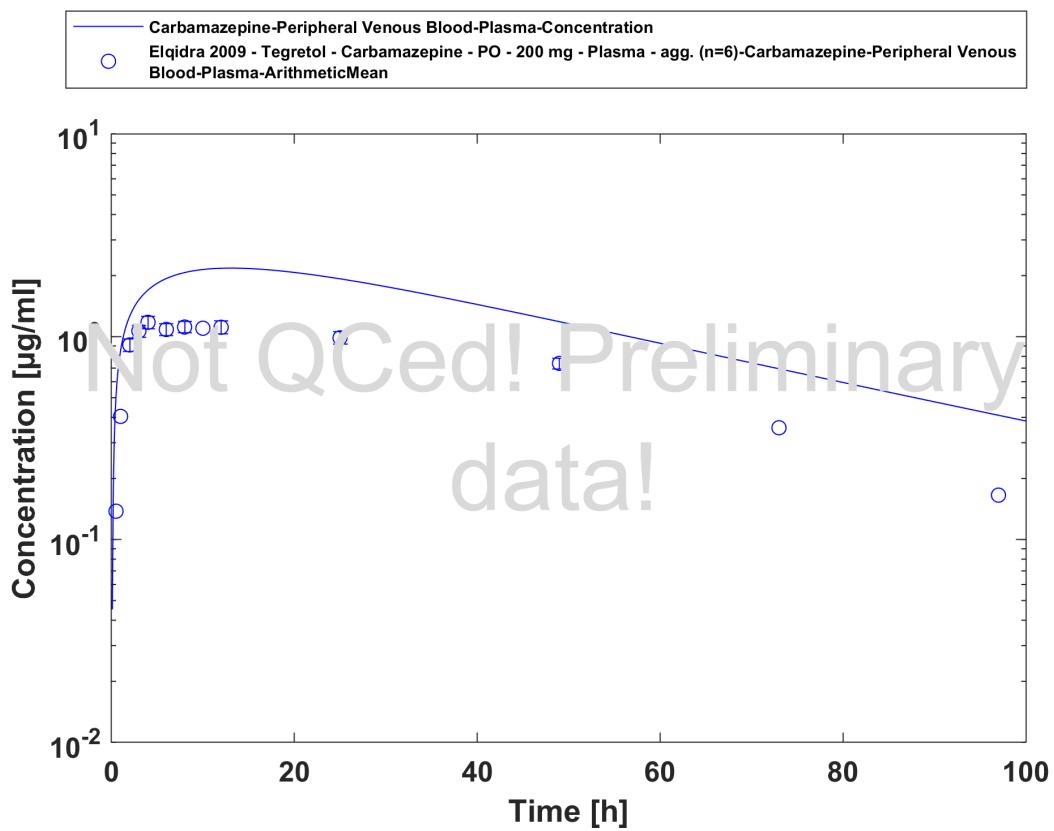
Time Profile Analysis



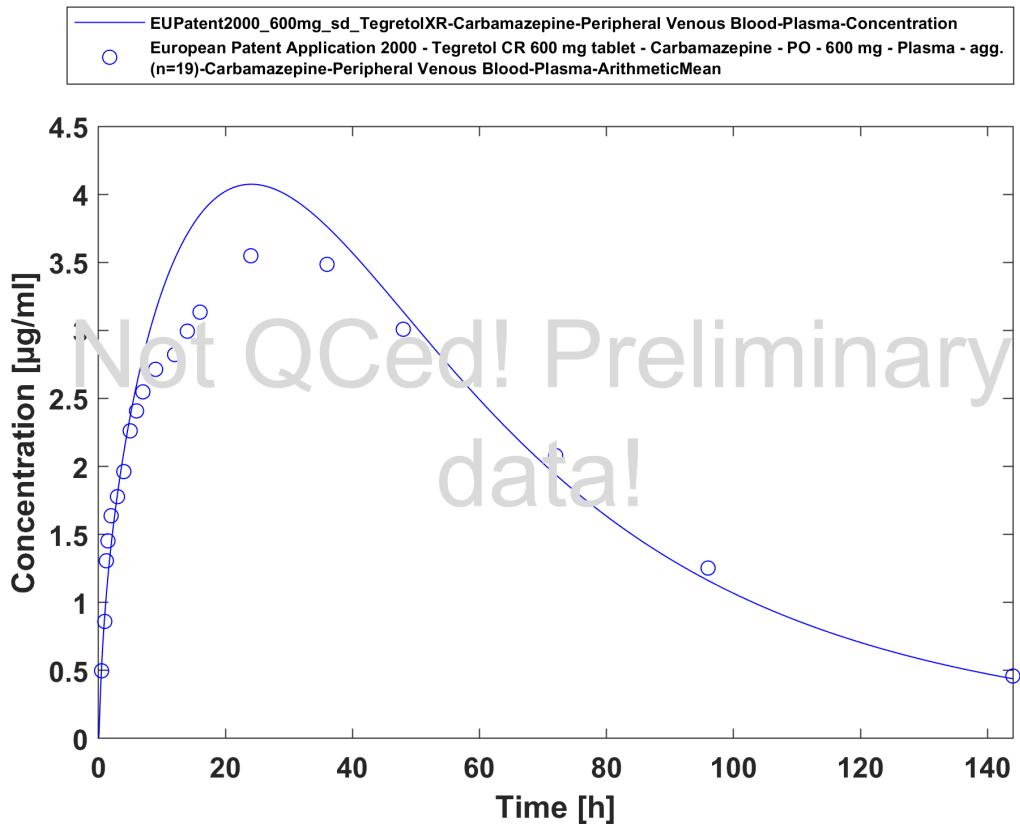
Time Profile Analysis



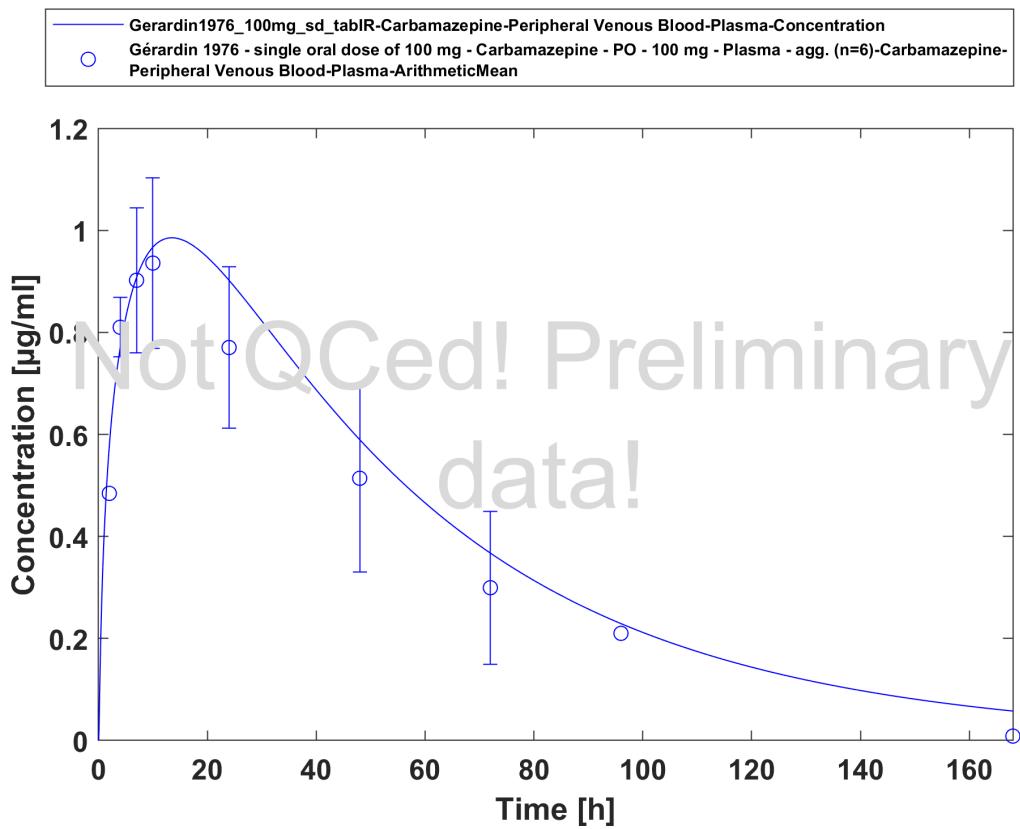
Time Profile Analysis 1



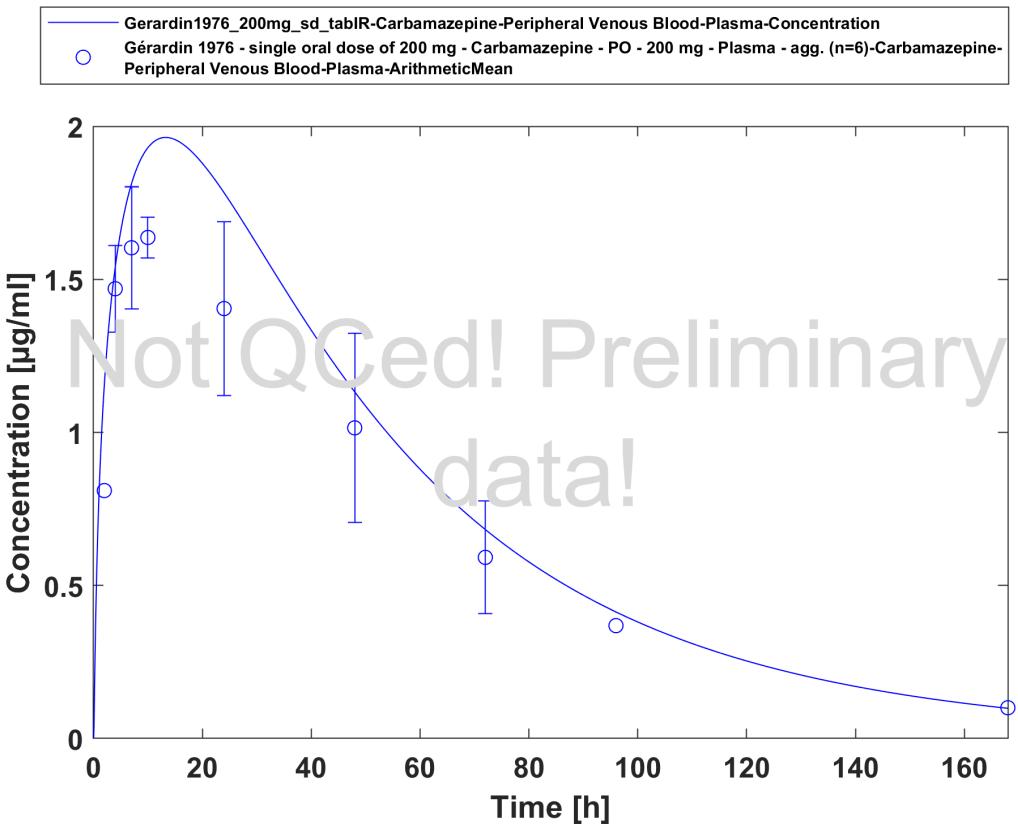
Time Profile Analysis



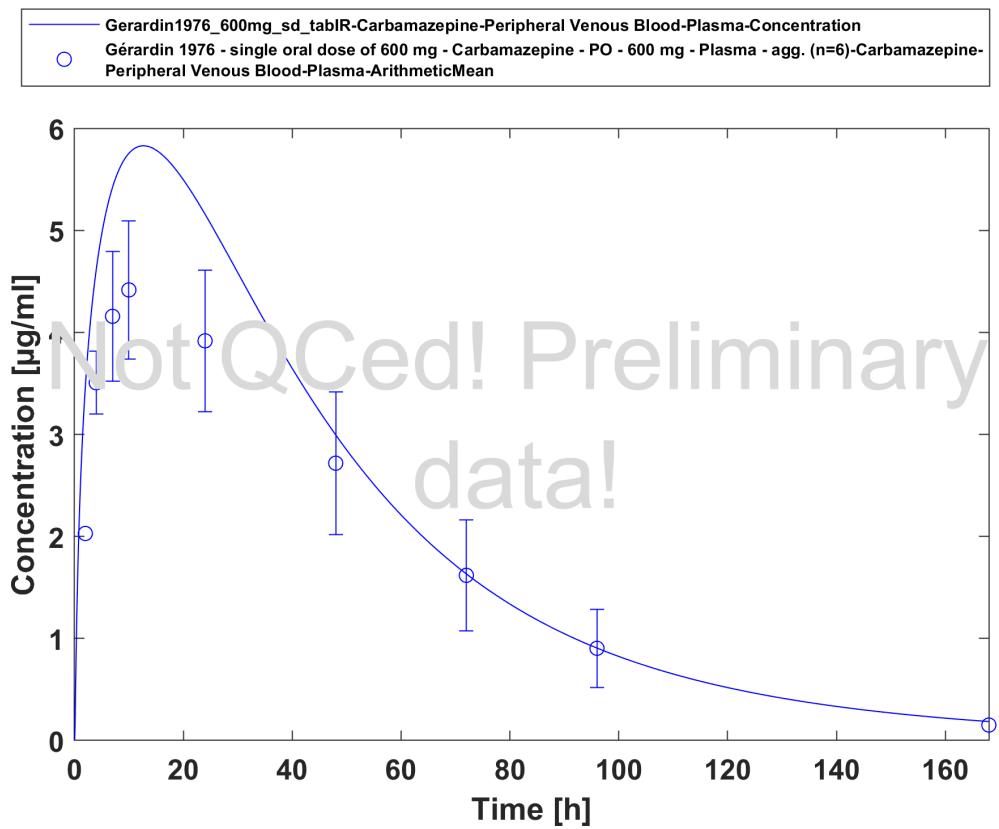
EUPatent2005\_600mg\_sd\_TegretolXR



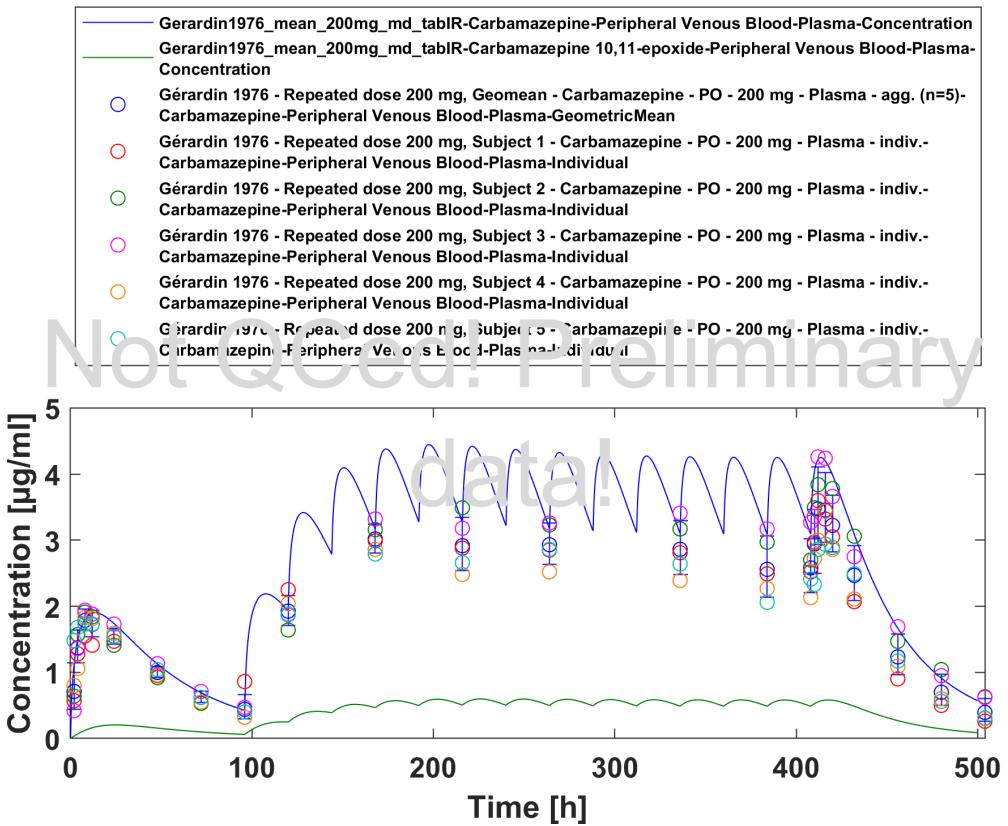
Time Profile Analysis



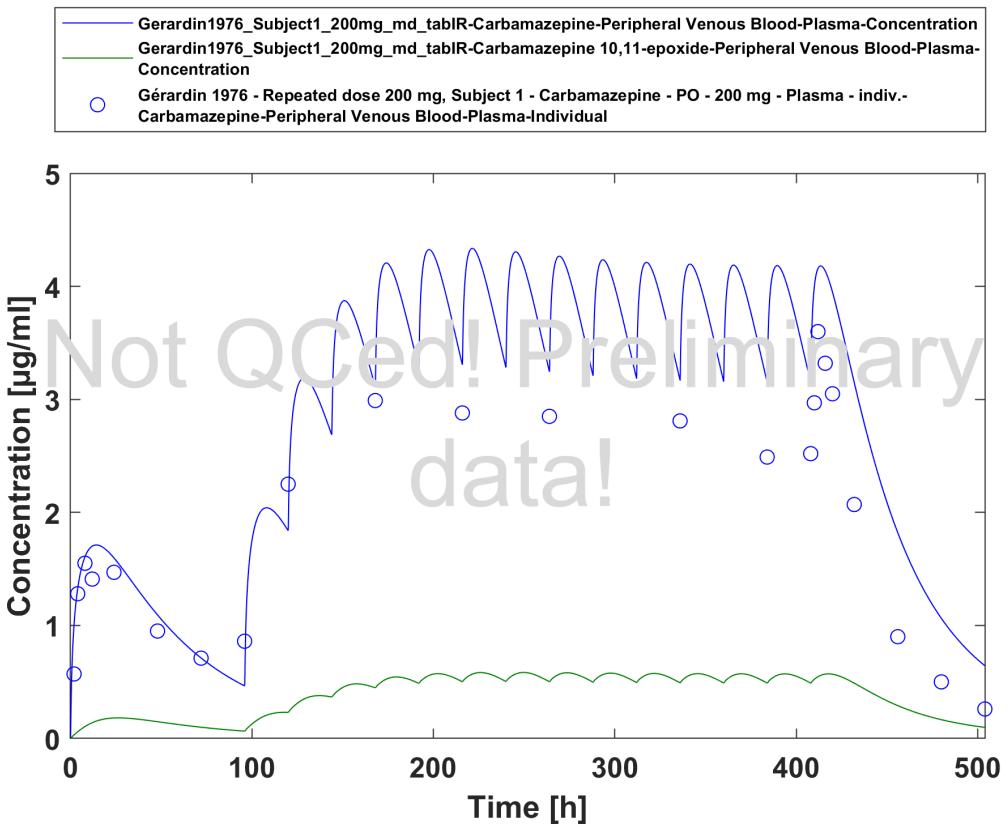
Geradin1976\_200mg\_sd\_tabIR



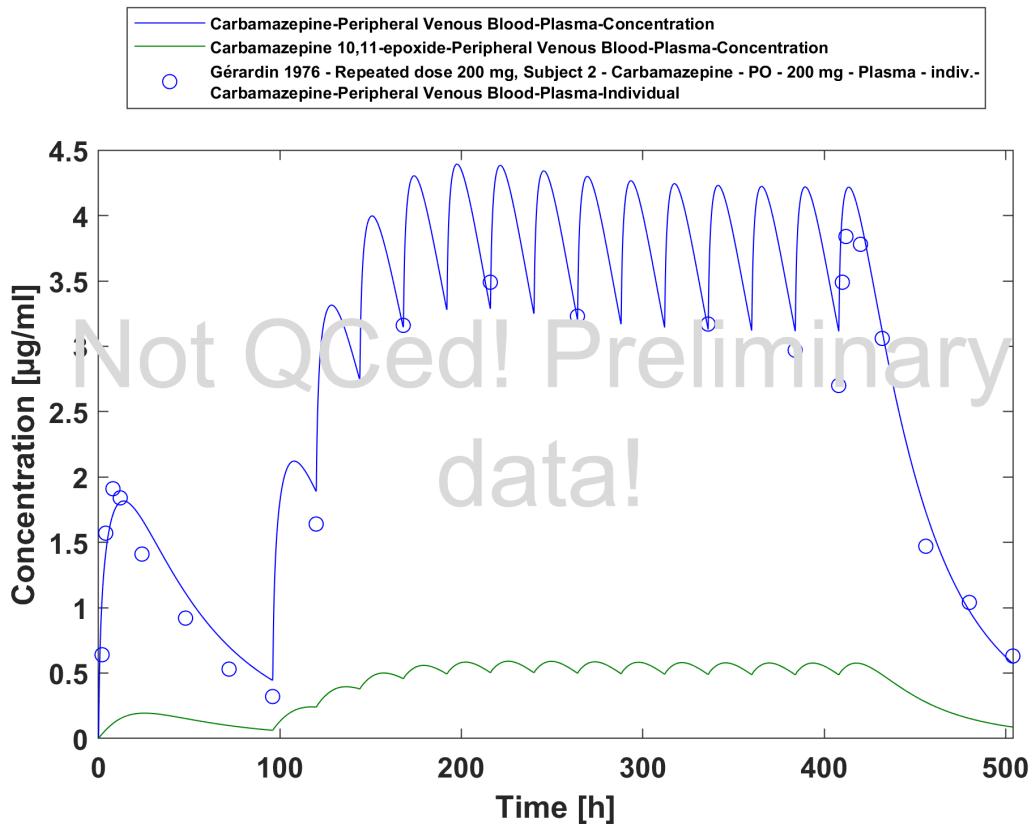
Time Profile Analysis



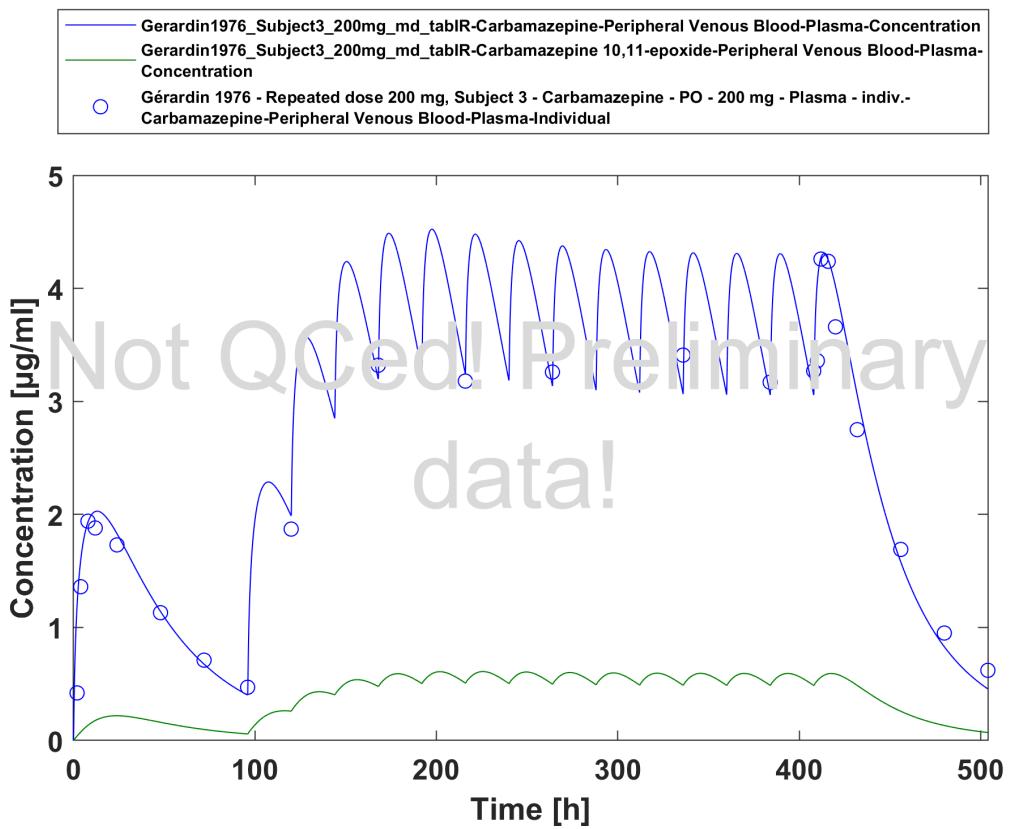
Gerardin1976\_mean\_200mg\_md\_tabIR



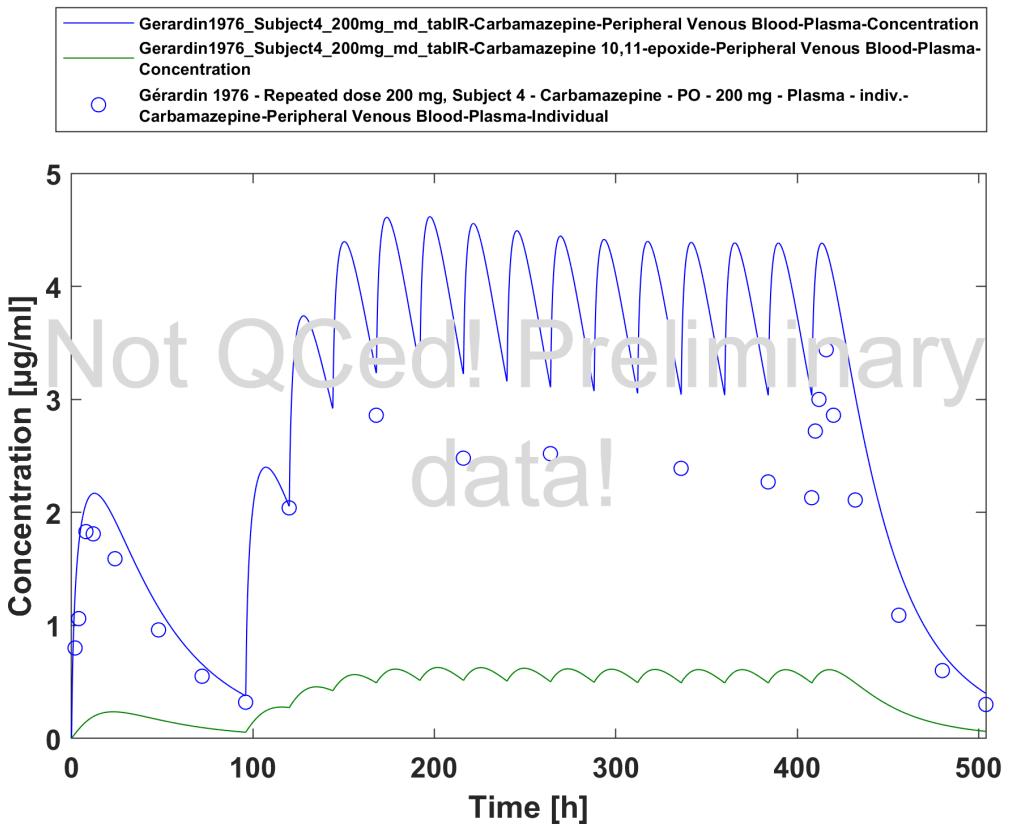
Gerardin1976\_Subject1\_200mg\_md\_tabIR



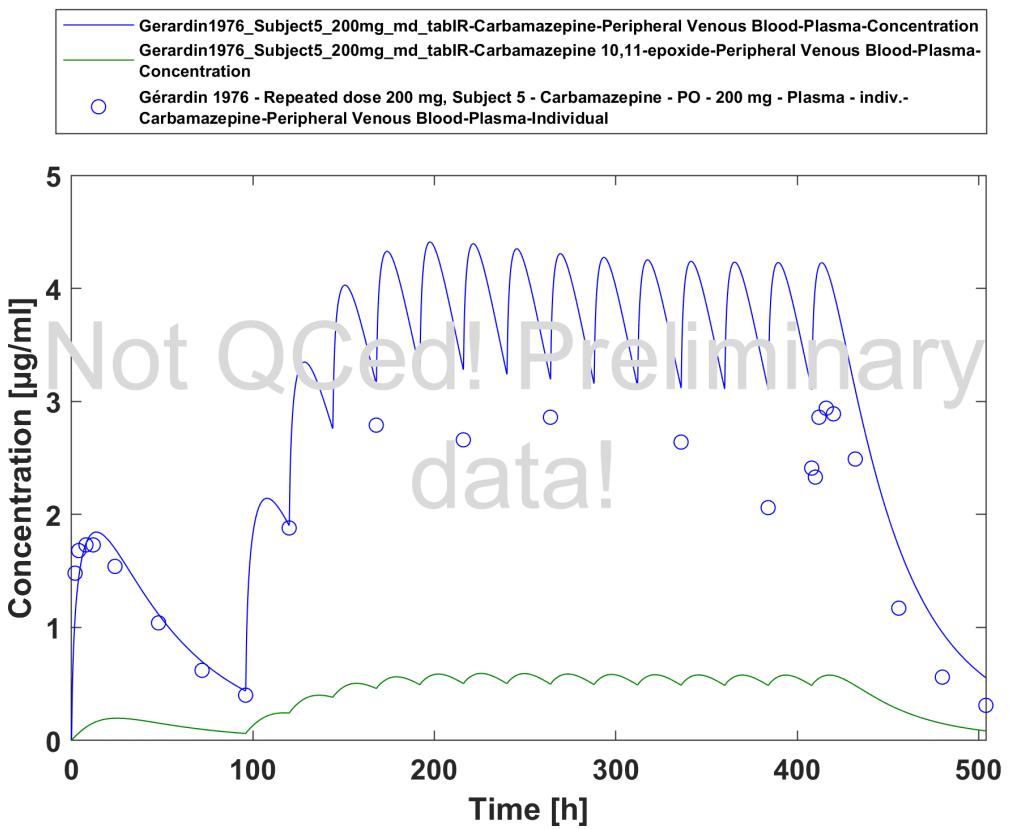
Time Profile Analysis



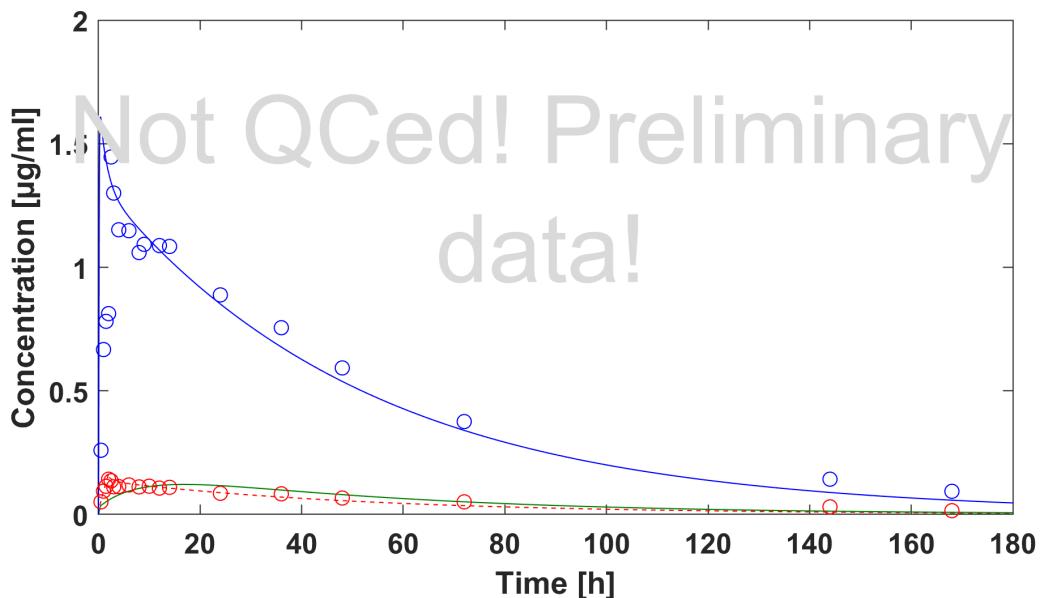
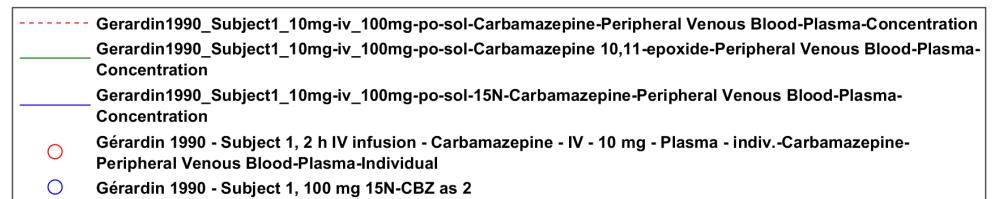
Gerardin1976\_Subject3\_200mg\_md\_tabIR



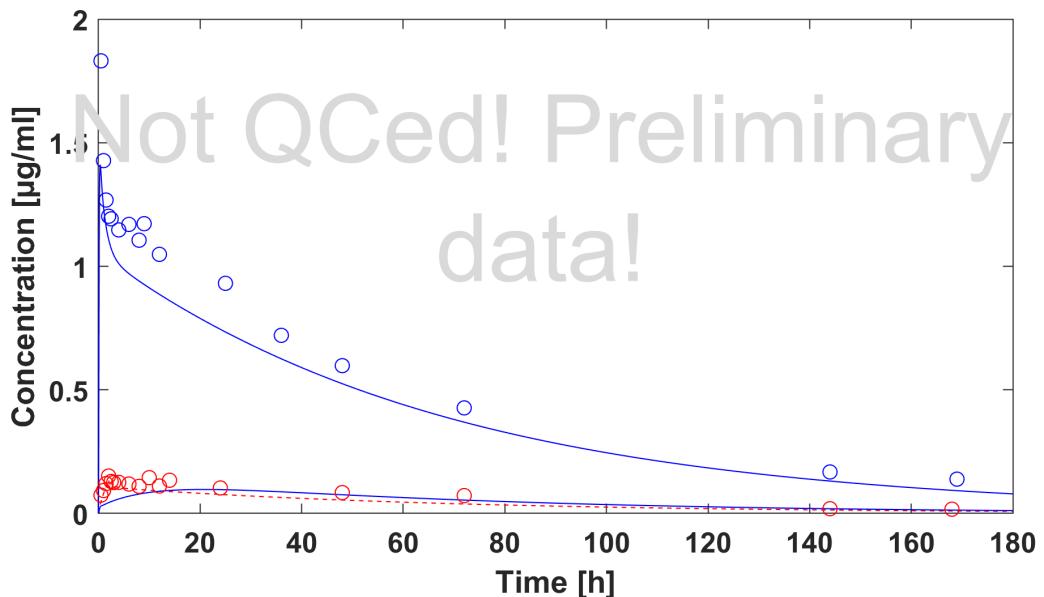
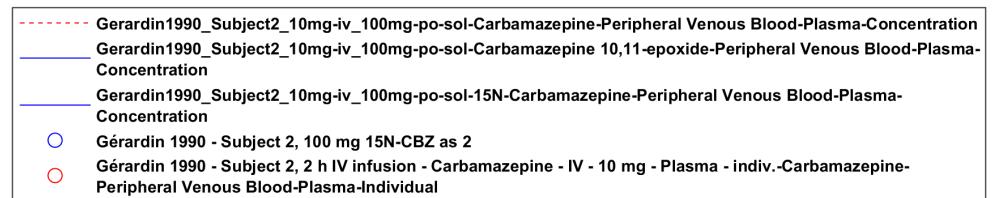
Time Profile Analysis



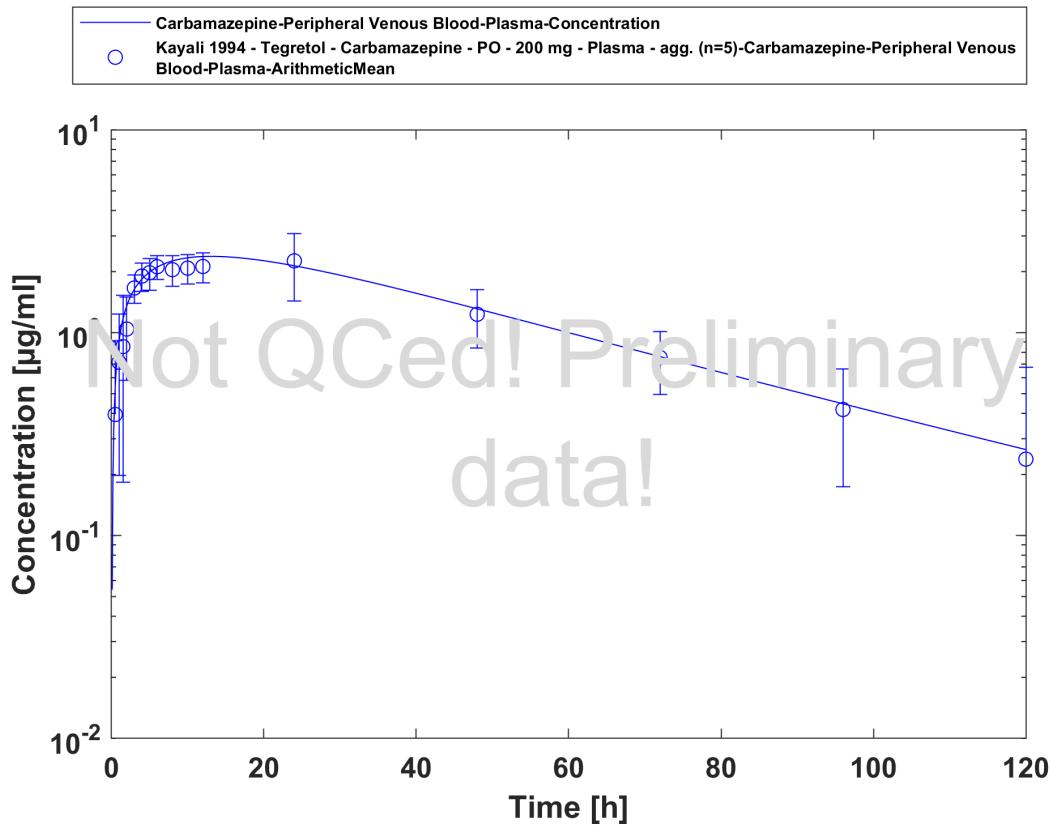
Gerardin1976\_Subject5\_200mg\_md\_tabIR



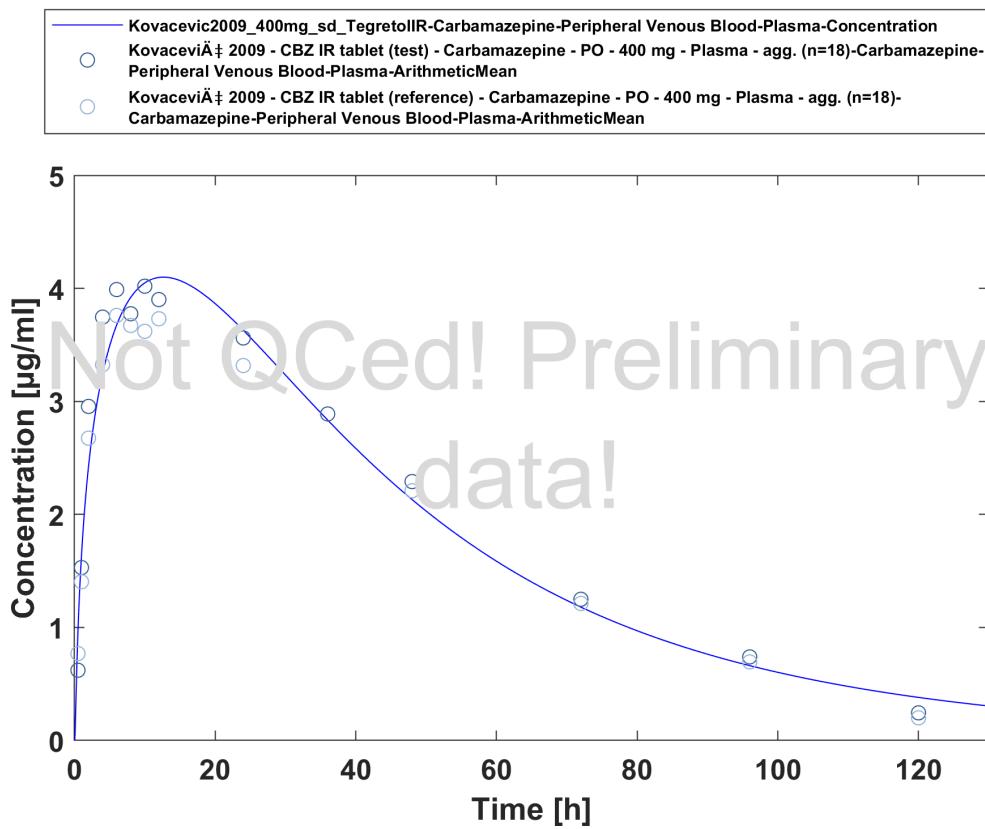
Gerardin1990\_Subject1\_100mg-iv\_100mg-po-sol



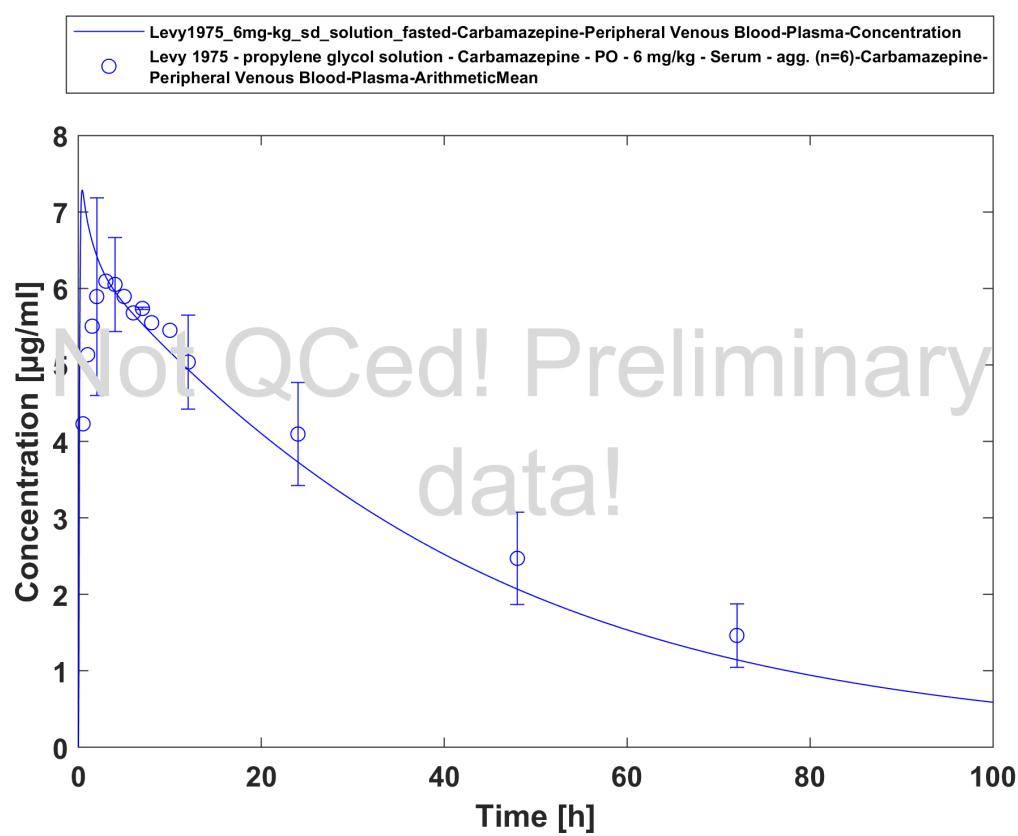
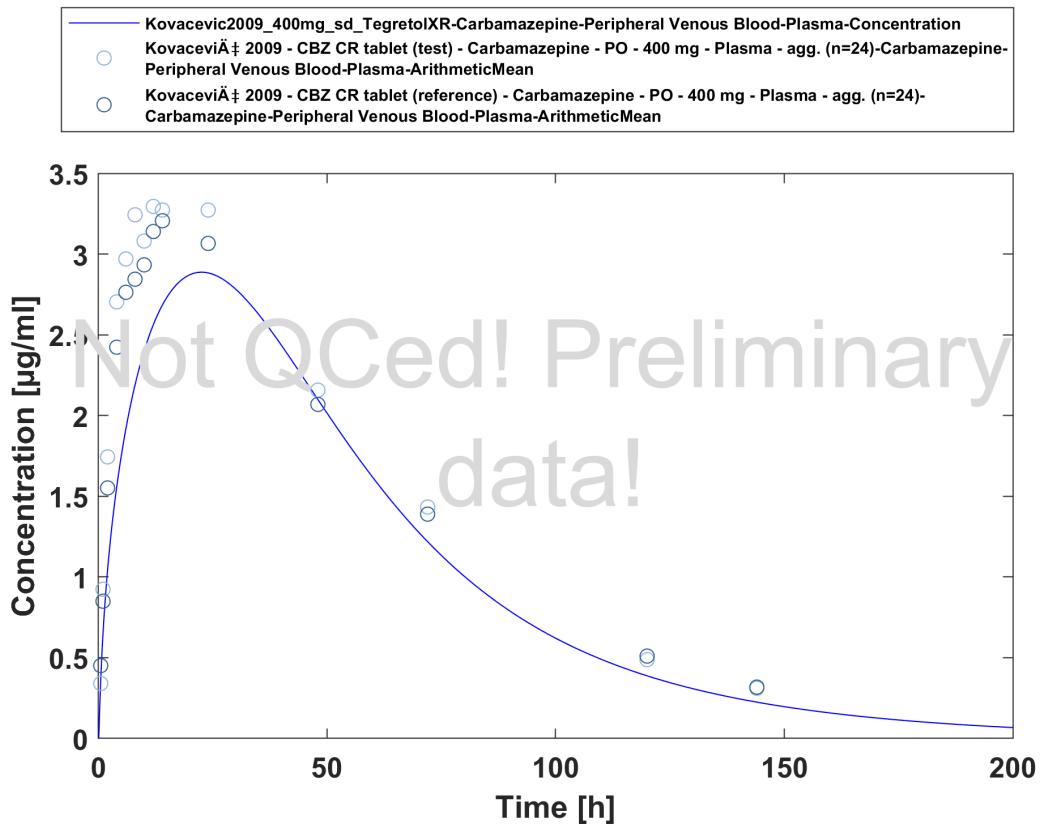
Gerardin1990\_Subject2\_100mg-iv\_100mg-po-sol

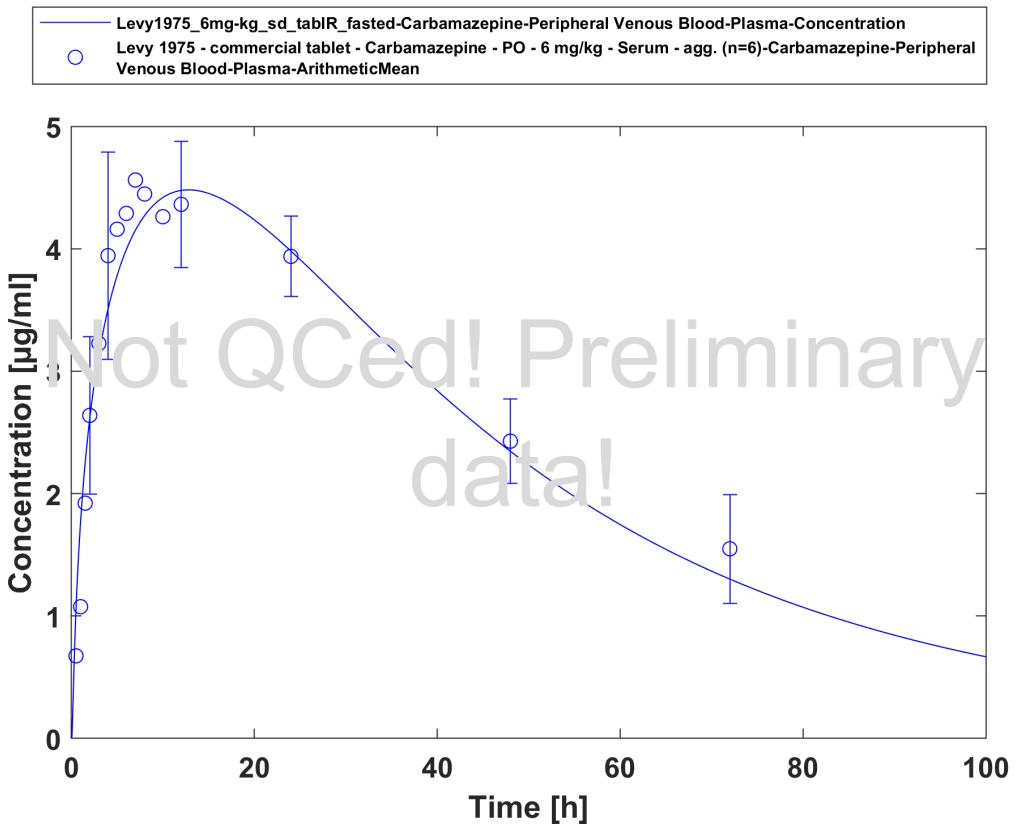


Time Profile Analysis

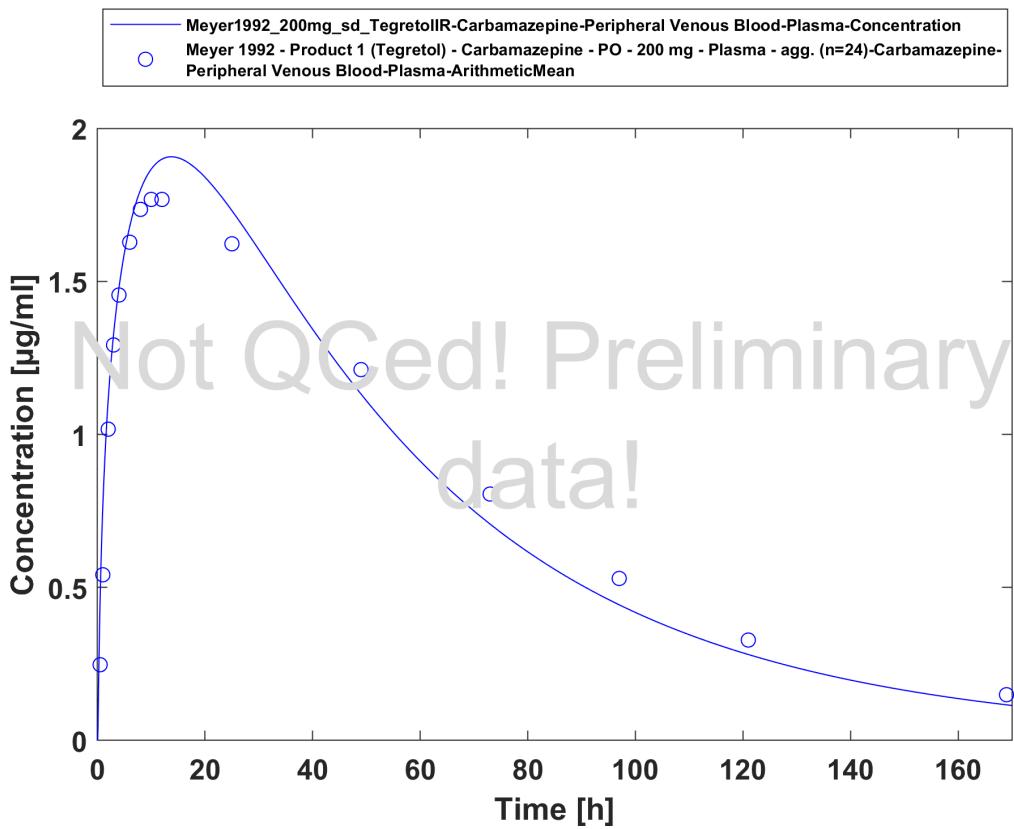


Kovacevic2009\_400mg\_sd\_TegretolIR

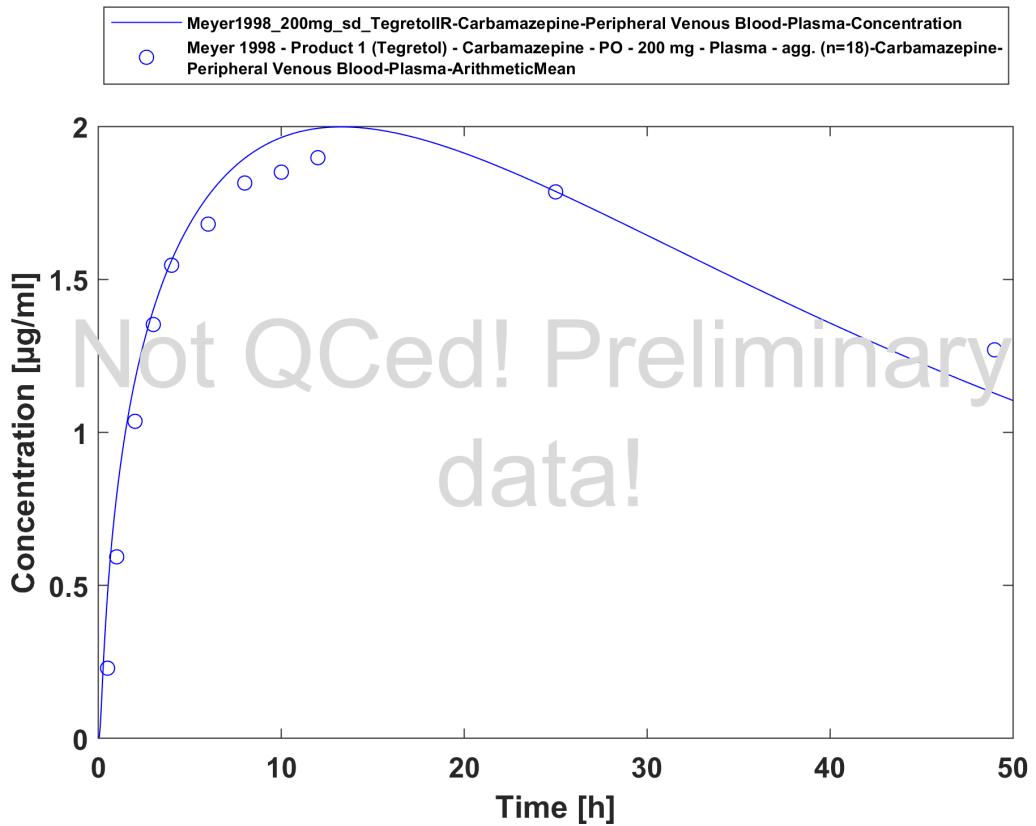




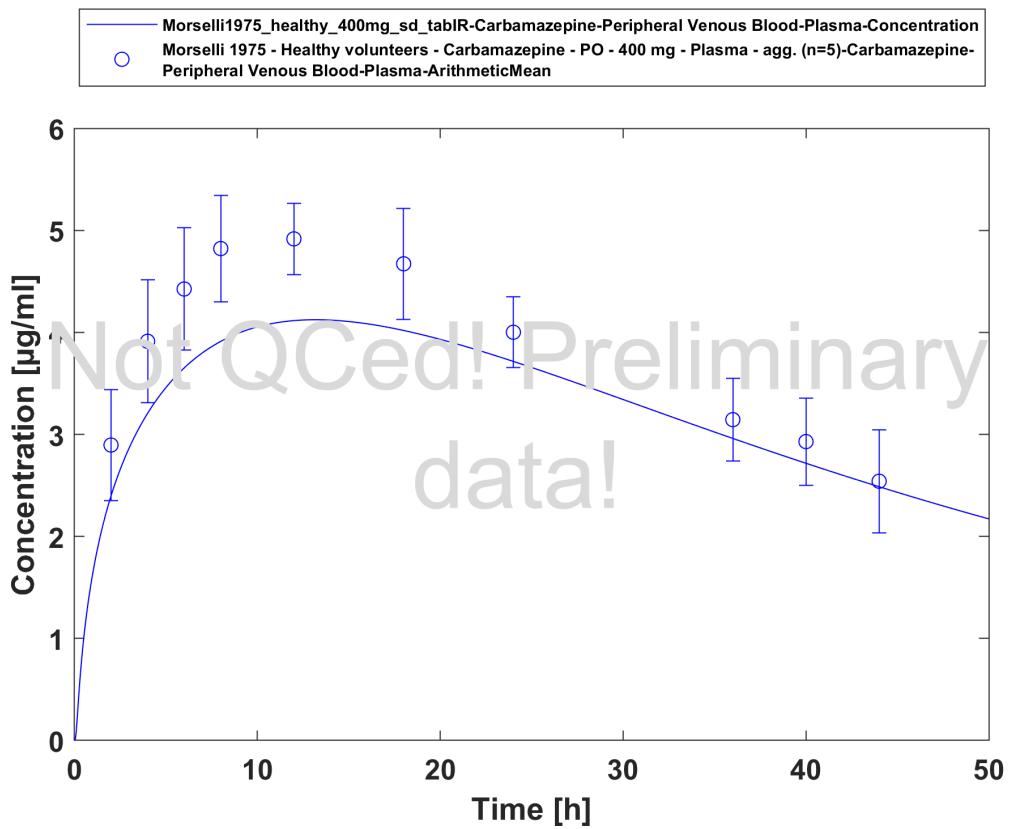
Levy1975\_6mg-kg\_sd\_tablR\_fasted



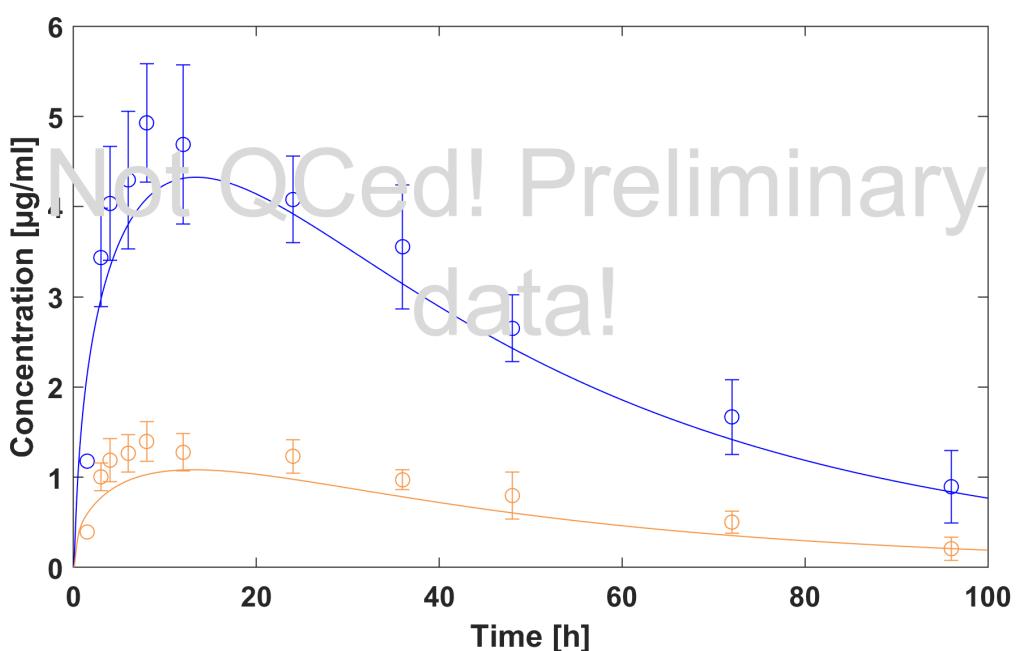
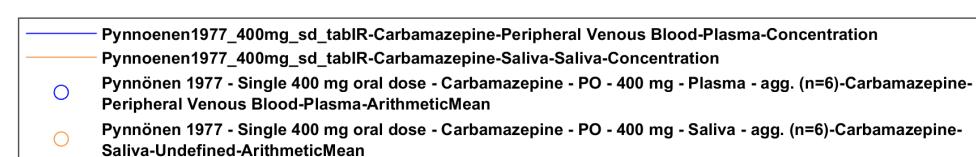
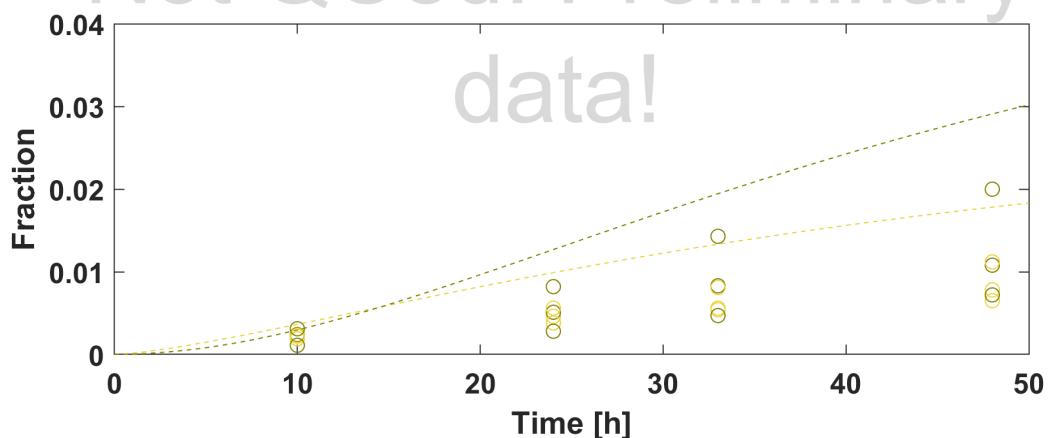
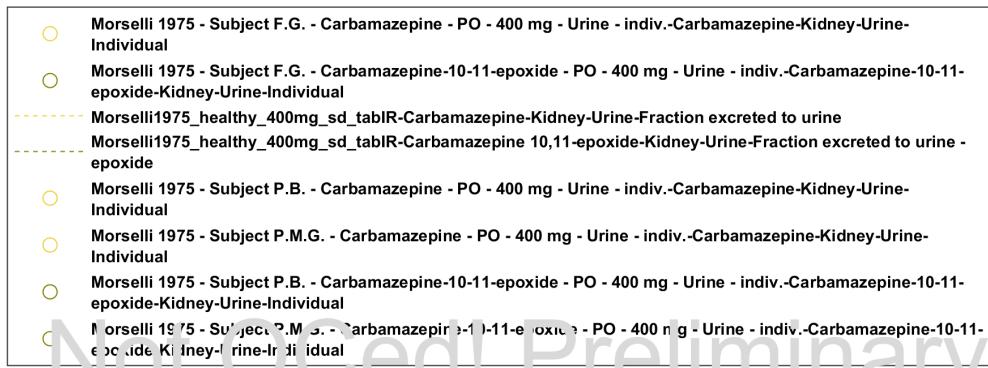
Time Profile Analysis

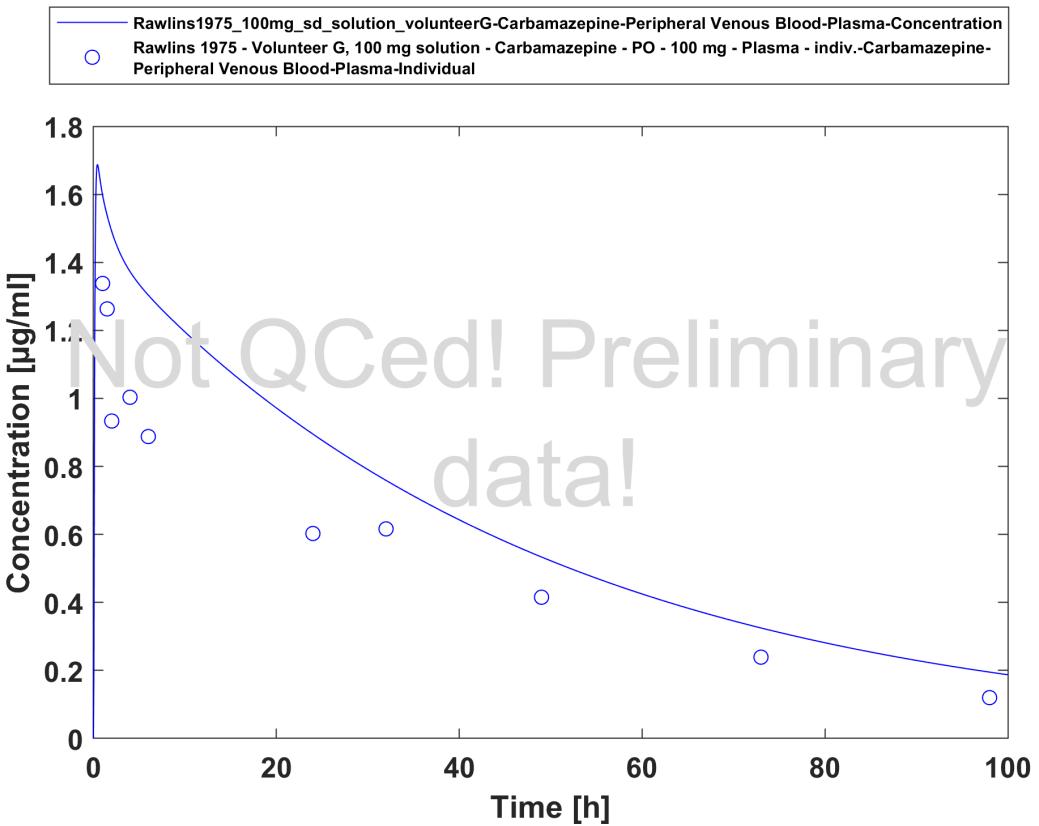


Time Profile Analysis

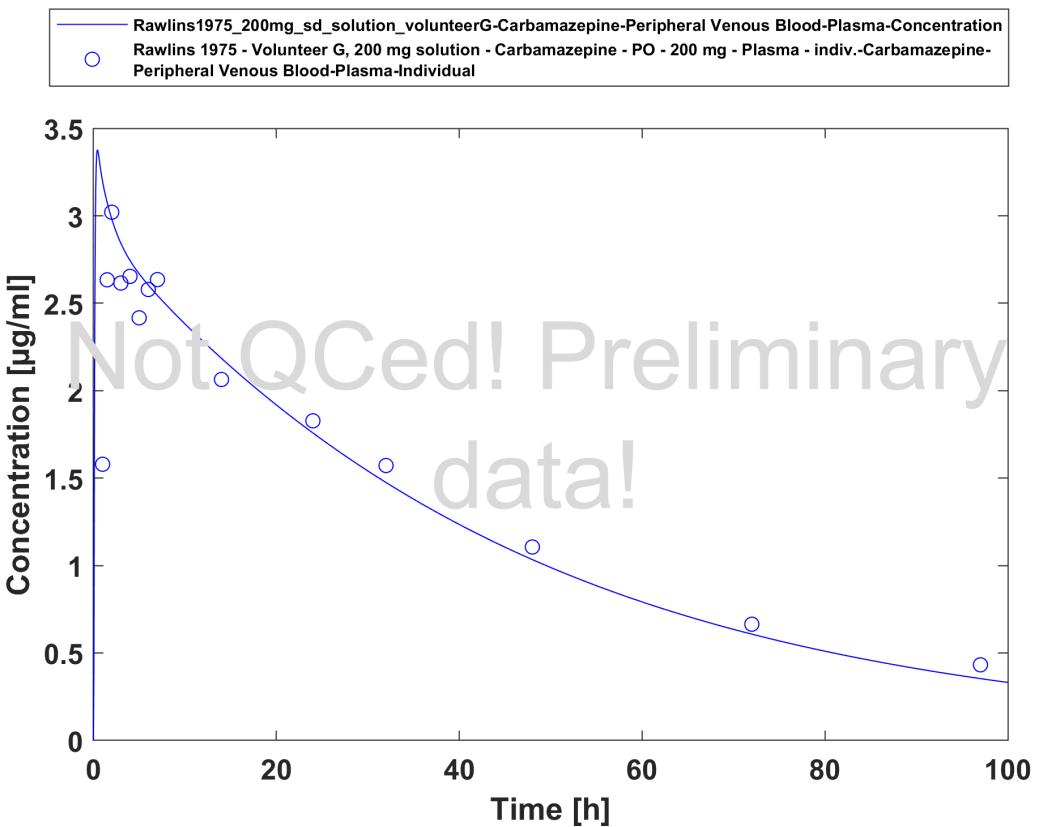


Morselli1975\_healthy\_400mg\_sd\_tabIR\_plasma

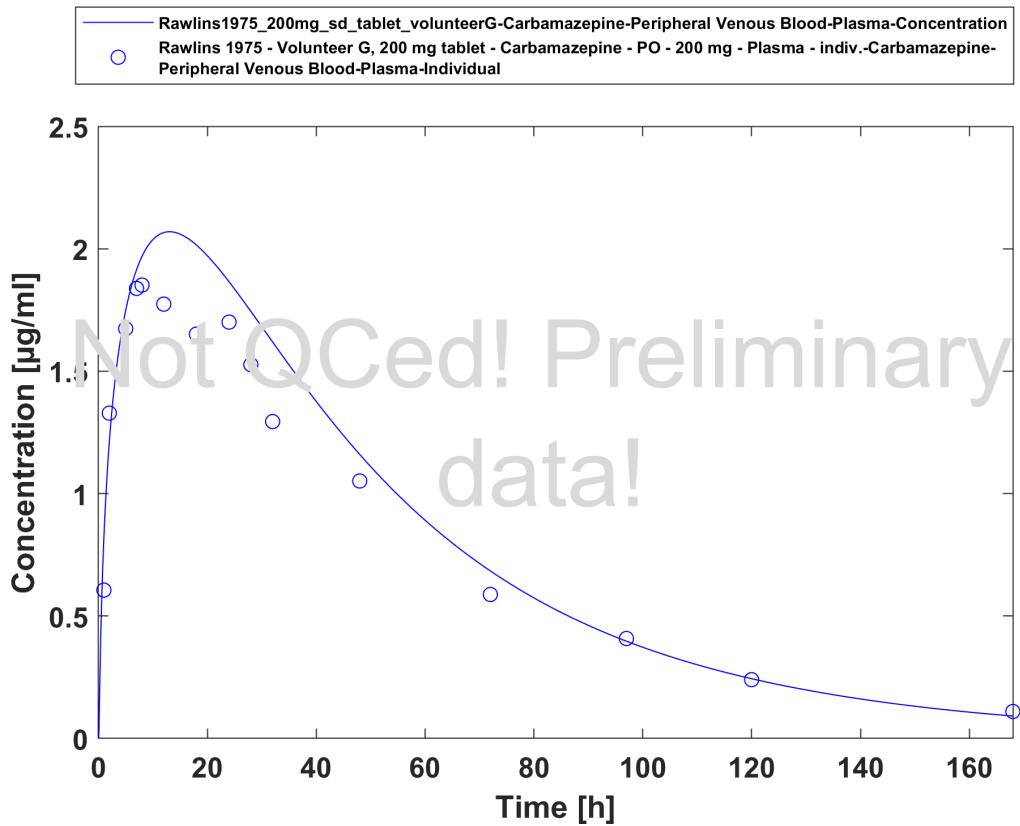




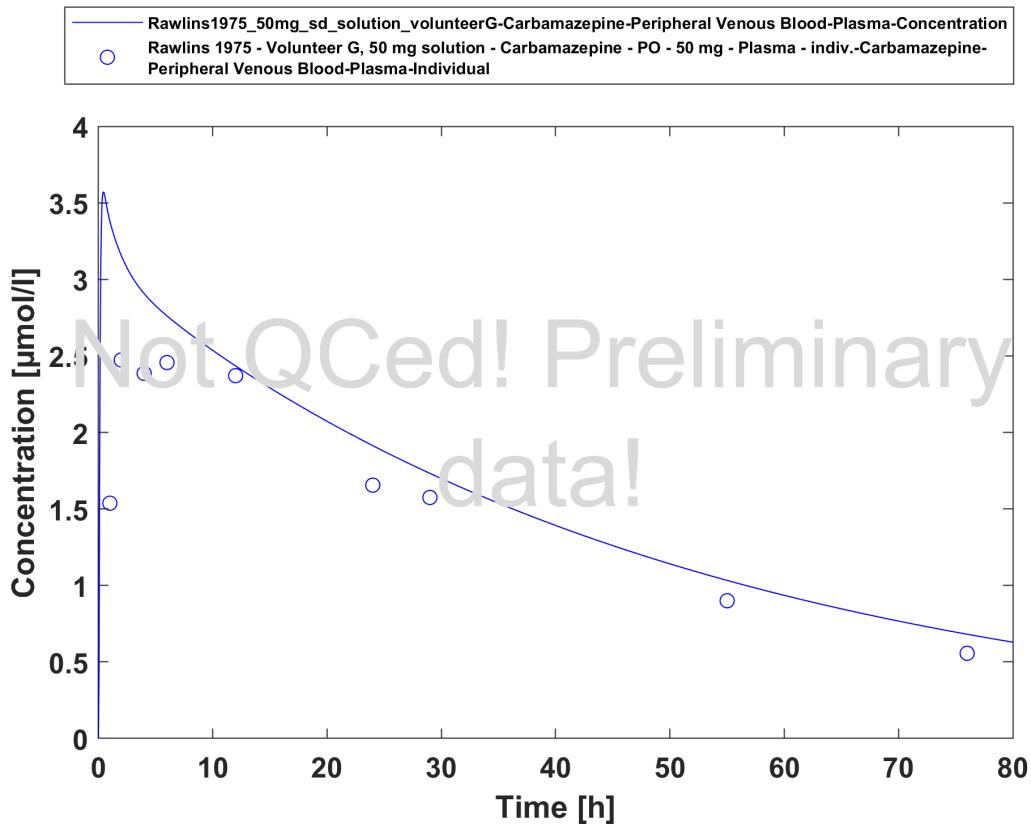
Rawlins1975\_100mg\_sd\_sol



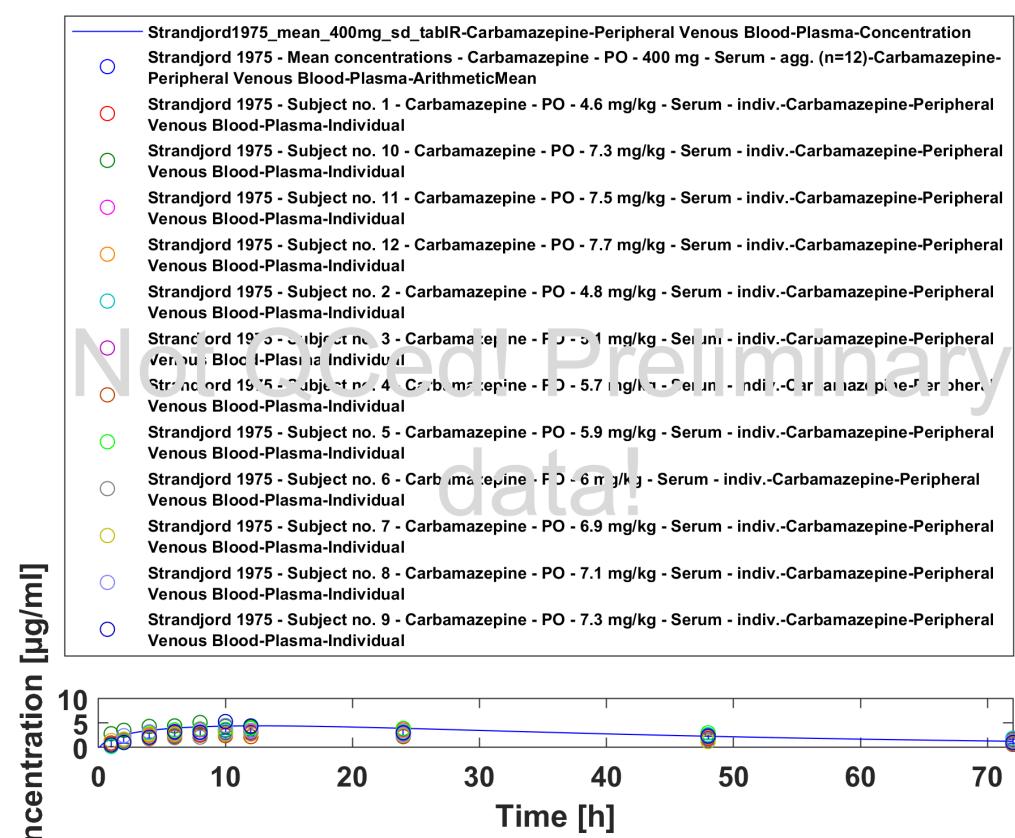
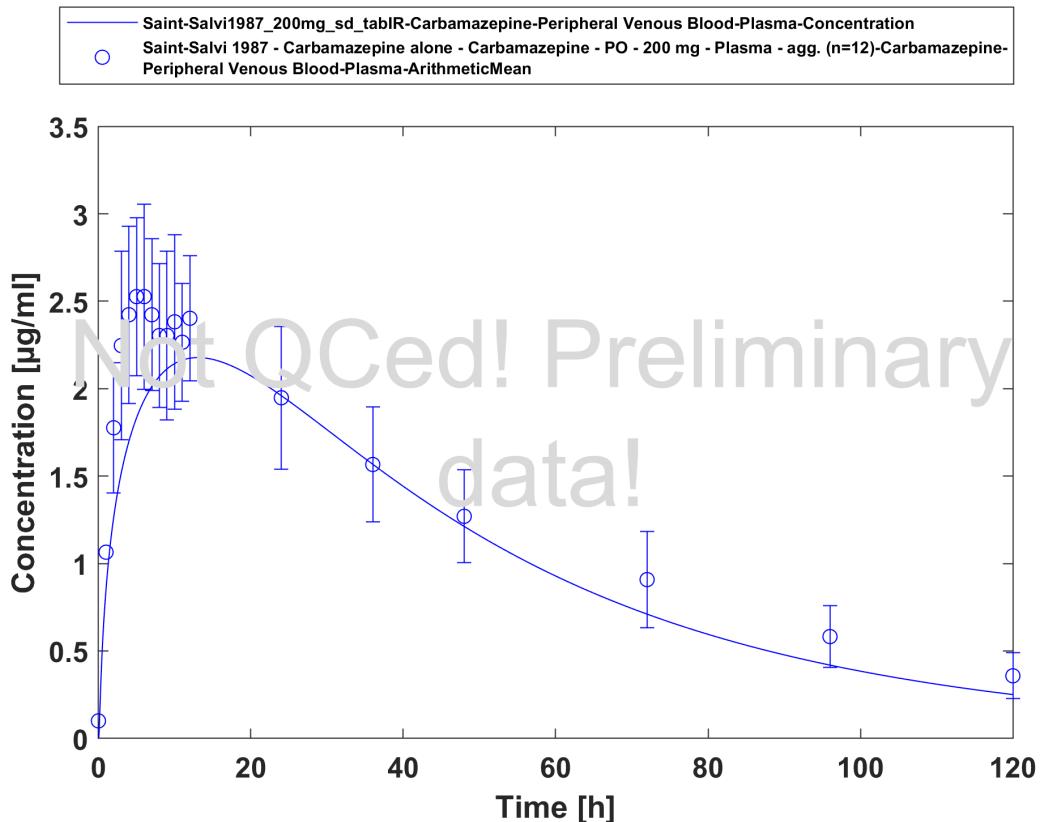
Rawlins1975\_200mg\_sd\_sol

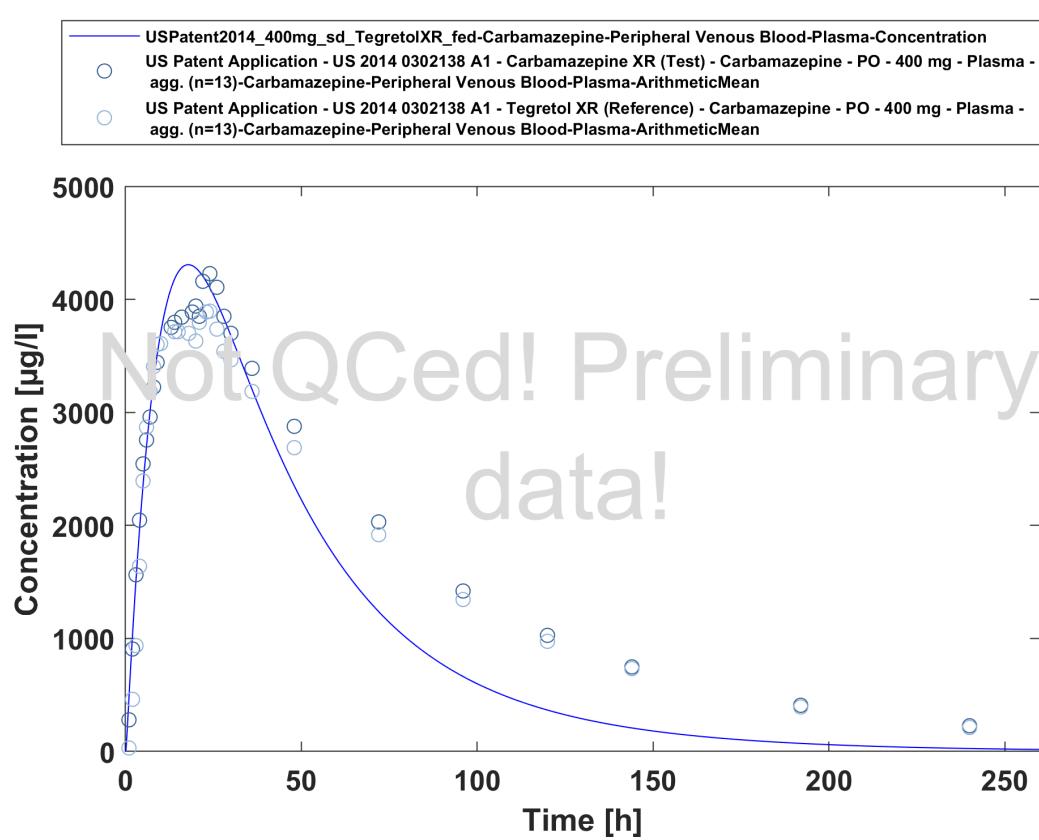
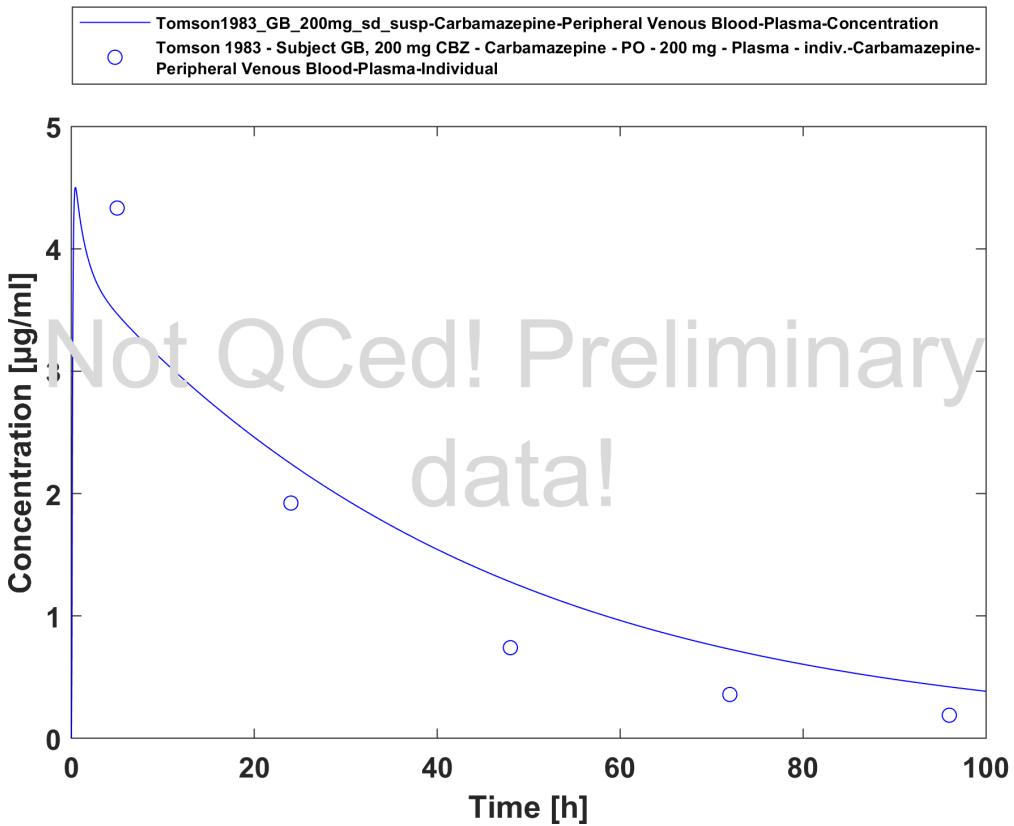


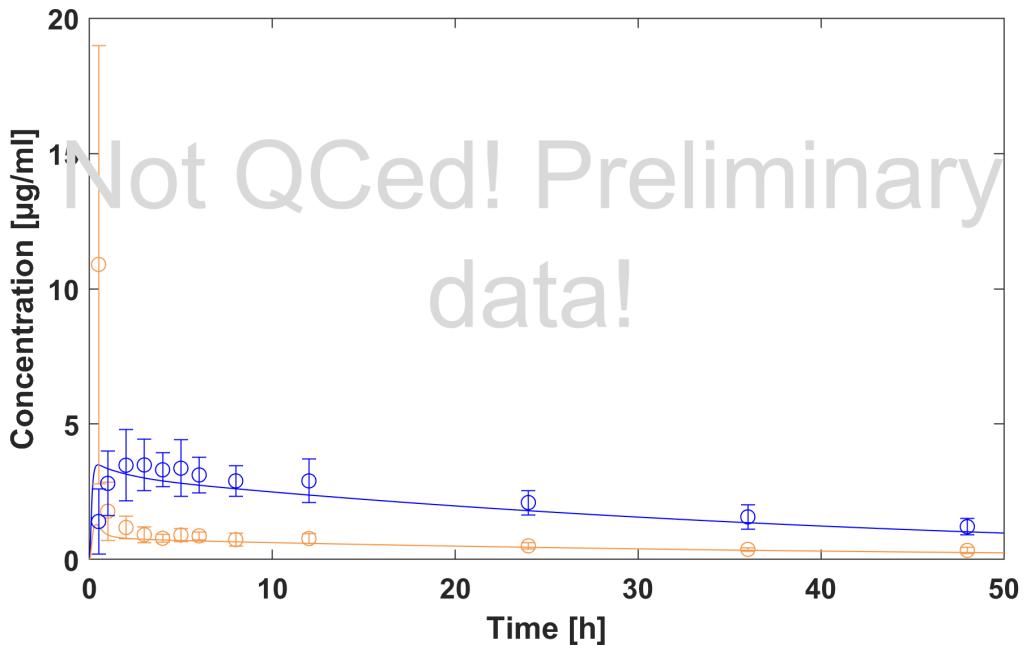
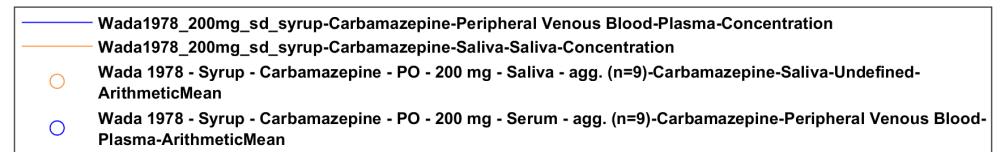
Rawlins1975\_200mg\_sd\_sol



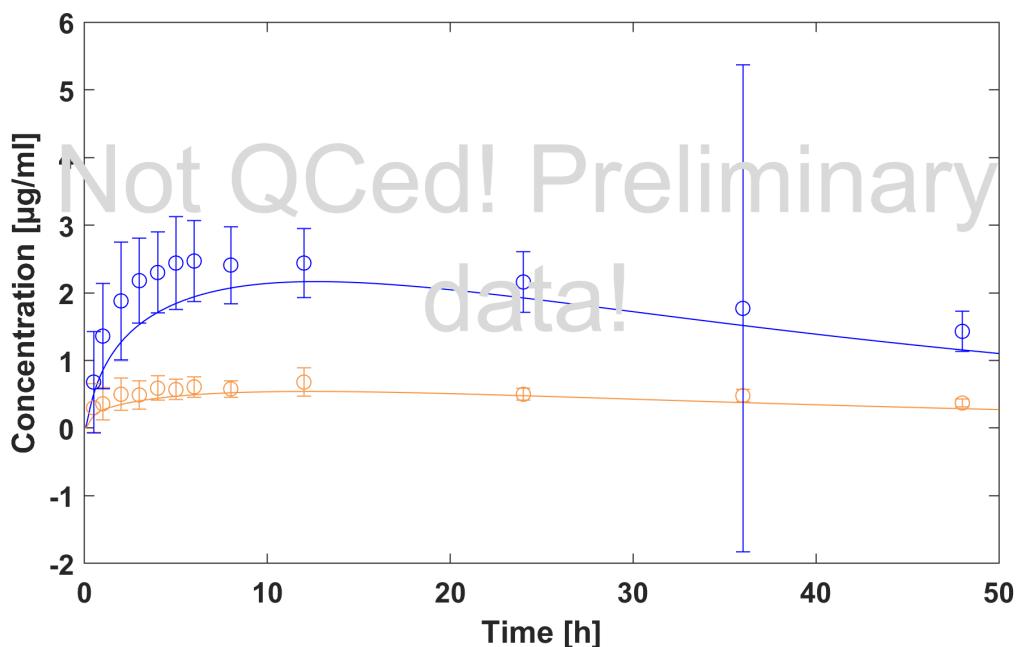
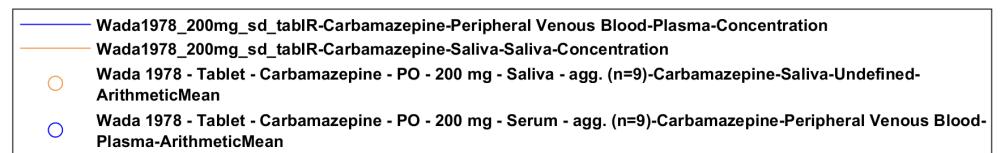
Rawlins1975\_50mg\_sd\_sol



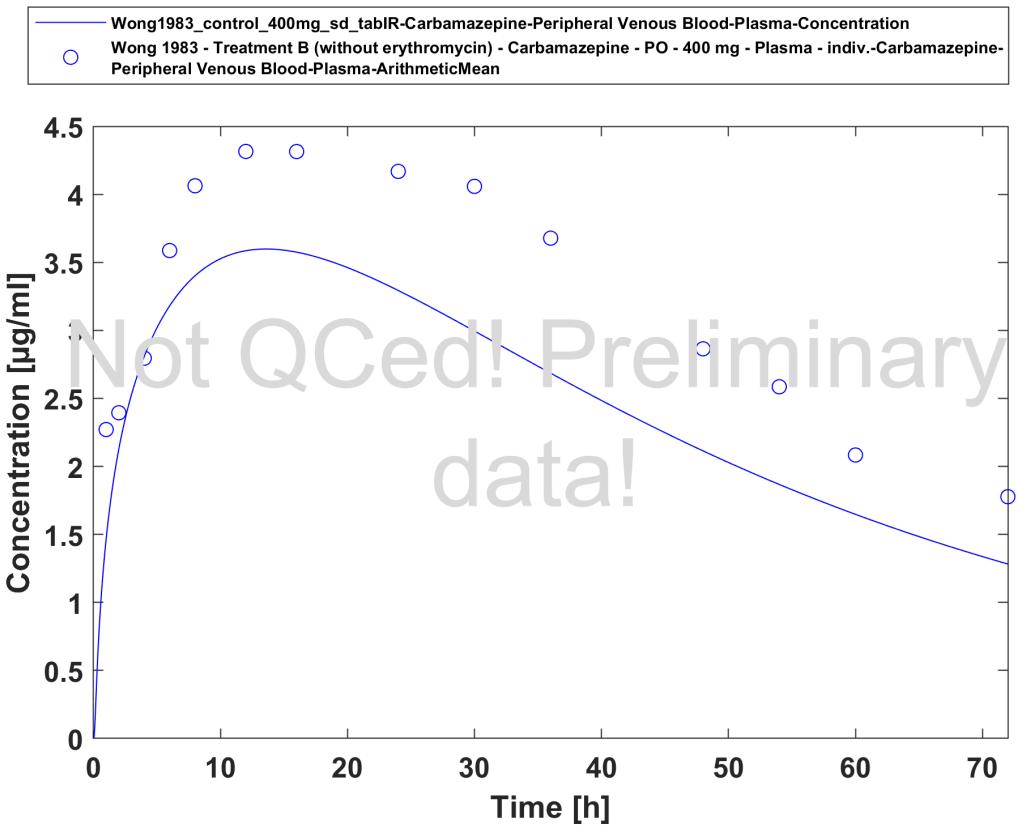




Wada1987\_200mg\_sd\_syrup



Wada1978\_200mg\_sd\_tabIR



Wong1983\_control\_400mg\_sd\_tablR

## 4 Conclusion

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The herein presented PBPK model adequately describes the pharmacokinetics of carbamazepine after single and multiple oral administration of various doses to healthy adults.

In conclusion, the presented carbamazepine PBPK model is well-suited to be applied in drug-drug-interaction scenarios.

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