Pediatric Qualification Package: CYP3A4 Ontogeny

Version	**1.1-OSP9.0**
Qualification Plan Release	https://github.com/Open-Systems-Pharmacology/Pediatric_Qualification_Package_CYP3A4_Ontogeny/releases/tag/v1.1
OSP Version	9.0
Qualification Framework Version	2.2

This qualification report is filed at:

https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports

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Chapter 1: Introduction to Pediatric Translation and CYP3A4 Ontogeny Qualification

The presented qualification report evaluates the predictive performance of the OSP suite to predict cytochrome P450 3A4 (CYP3A4)-mediated drug clearance in children.

Therefore, PBPK models of specific *in vivo* probe substances covering children aged below 6 months up to adolescents were built and evaluated. All models are whole-body PBPK models, allowing for dynamic pediatric translation in organs expressing CYP3A4. The qualification report demonstrates the level of confidence of the OSP suite with regard to reliable PBPK predictions of age-related CYP3A4-mediated drug clearance during model-informed drug development. The presented PBPK models as well as the respective qualification plan and qualification report are provided open-source and transparently documented (https://github.com/Open-Systems-Pharmacology/Pediatric-Qualification-Package-CYP3A4).

Translation of Adult PBPK to Children

Using a developed and validated (adult) PBPK model for an *in vivo* probe substance, a pediatric PBPK model can be established for children by translating physiology, clearance processes (as parameterized in the adult model) and age-dependent protein binding including the variability therein.[1]

The PBPK models are developed with clinical data of healthy adult subjects obtained from the literature, covering available dosing ranges for e.g. intravenous as well as oral administration, to capture both systemic clearance as well gut-wall metabolic clearance processes. For orally administered drugs, the same formulations that are used in children should ideally be included in the model for adults. Plasma concentrations following multiple-dose application, mass balance information and other clinical measurements need to be included for model development, if available. During model translation from adults to children for a specific substance, uncertainties in data-quality caused by impact of disease or the target study population, inaccurate in vitro assay-techniques regarding mass balance, as well as study differences may cause not being able to adequately predict the PK in children for all reported studies.

Prediction performance of the PBPK model for these probe substances in children are then shown by means of e.g. predicted versus observed area under the plasma concentration (AUC)-ratio plots, of which the results support an adequate prediction of the ontogeny function for the application of PBPK model translation of adult PBPK to children.

For qualification purpose, during the translation of adult PBPK to children the following assumptions and considerations were made:

- when translating an adult model to children, it was assumed that the metabolism and excretion pathways are qualitatively the same in children as in adults.
- no further changes to input parameters other than those for the physiology and protein binding. All other parameters (e.g. lipophilicity, intestinal permeability, solubility) were kept unchanged.

Anthropometric and Physiological Information

Regarding the age-dependencies of the relevant anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in children was gathered from the literature and has been previously published [2]. The information was incorporated into PK-Sim® and was used as default values for the simulations in children.

The applied ontogeny and variability of plasma proteins and active processes that are integrated into PK-Sim® for translation to children are described in the publicly available 'PK-Sim® Ontogeny Database Version 7.3' [3] or otherwise referenced for the specific process.

Qualification of CYP3A4 enzyme ontogeny

To qualify the OSP suite for the pediatric translation of the pharmacokinetics of new drugs that are metabolized by CYP3A4, the following set of probe substances was included:

- Alfentanil [4]
- Sufentanil [5]

References

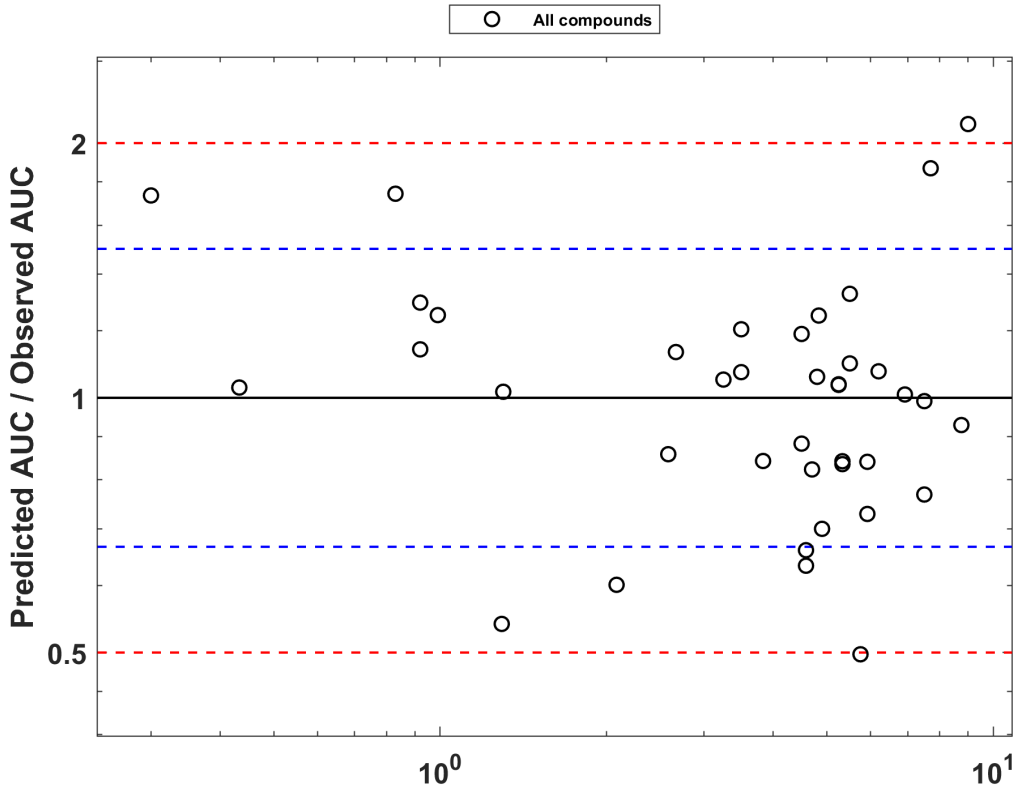
[1] Maharaj AR, Barrett JS, Edginton AN. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. The AAPS journal. 2013;15(2): 455-464.

[2] Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinet. 2006;45(10):1013-34.

[3] OSPSuite.Documentation/PK-Sim Ontogeny Database Version 7.3.pdf

[4] Alfentanil-Model, Whole-body PBPK model of Alfentanil. https://github.com/Open-Systems-Pharmacology/Alfentanil-Model

[5] Sufentanil-Model, Whole-body PBPK model of Sufentanil. https://github.com/Open-Systems-Pharmacology/Sufentanil-Model



Overall predictivity of the PBPK models. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of all drugs in children 3.6 months to 9 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

GMFE (AUC) = 1.273742

AUC	Number	Ratio [%]
Points total	39	-
Points within 1.5 fold	30	76.9231
Points within 2-fold	37	94.8718

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [mg*min/ml]	Observed AUC [mg*min/ml]	Pred/Obs AUC Ratio
Davis 1987	1.2917	8.9	0.54048	0.00082873	0.54048
Davis 1987	0.43333	5.3	1.0284	0.00054546	1.0284
Guay 1991	2.0833	12.1	0.60119	0.00010838	0.60119
Guay 1991	2.5833	16	0.85776	4.63e-05	0.85776
Guay 1991	2.6667	11.3	1.1327	8.92e-05	1.1327
Guay 1991	3.25	16	1.0509	8.26e-05	1.0509
Guay 1991	3.8333	14.2	0.84204	6.63e-05	0.84204
Guay 1991	4.5833	15	0.66053	6.73e-05	0.66053
Guay 1991	4.5833	19	0.63325	0.00013487	0.63325
Guay 1991	4.8333	17.5	1.2509	6.99e-05	1.2509
Guay 1991	5.25	18.5	1.0375	4.36e-05	1.0375
Guay 1991	5.25	19.65	1.0358	8.53e-05	1.0358
Guay 1991	5.3333	24	0.8349	0.0001355	0.8349
Guay 1991	5.3333	24	0.8415	7.55e-05	0.8415
Guay 1991	5.75	14.5	0.49761	0.00015183	0.49761
Guay 1991	5.9167	28.2	0.72904	0.00012754	0.72904
Guay 1991	5.9167	25	0.84016	5.71e-05	0.84016
Guay 1991	6.9167	29.6	1.0091	6.17e-05	1.0091
Guay 1991	7.5	23.5	0.76862	3.5e-05	0.76862
Guay 1991	7.5	15.2	0.99104	7.36e-05	0.99104
Guay 1991	8.75	22.6	0.92858	5.65e-05	0.92858
den Hollander 1992	0.92	6.5	1.141	21.1	1.141
den Hollander 1992	0.83	6.4	1.7427	14	1.7427
den Hollander 1992	0.99	8.5	1.2525	19.8	1.2525
den Hollander 1992	0.3	5.1	1.7344	18.5	1.7344
den Hollander 1992	0.92	6.149	1.2958	15.9	1.2958
den Hollander 1992	1.3	10.4	1.0166	24.3	1.0166
den Hollander 1992	9	25.6	2.1065	11.3	2.1065
den Hollander 1992	3.5	14.4	1.2051	18.6	1.2051
den Hollander 1992	5.5	19.5	1.0981	20.7	1.0981
den Hollander 1992	3.5	18.5	1.0724	22.7	1.0724
Meistelman 1987	4.7	20	0.82289	0.0058824	0.82289

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [mg*min/ml]	Observed AUC [mg*min/ml]	Pred/Obs AUC Ratio
Meistelman 1987	5.5	20	1.3271	0.0033898	1.3271
Meistelman 1987	7.7	23	1.8677	0.0024096	1.8677
Meistelman 1987	4.5	14	0.88282	0.0043478	0.88282
Meistelman 1987	4.8	24	1.0588	0.0054054	1.0588
Meistelman 1987	4.5	20	1.1898	0.0041667	1.1898
Meistelman 1987	6.2	23	1.0748	0.0045455	1.0748
Meistelman 1987	4.9	22	0.70008	0.0074074	0.70008

Chapter 2: Pediatric translation qualification results

Evaluation of Pediatric translation

All pediatric translations are pure retrospective predictions, no pediatric pharmacokinetic studies were used to inform model parameters. All parameters necessary to model the pediatric populations, such as demographics (age, weight, height), as well as dosing formulation information were taken from the respective pediatrics studies from literature in order to evaluate their predictive performance.

The models were evaluated by ratio plots of area under the plasma concentration-time curve (AUC), or clearance (CL) values resulting from our predictions to the values observed during clinical studies, and by comparison of concentration-time profiles if available. As a quantitative measure of the descriptive and predictive performance of each model, the geometric mean fold error was calculated according to Eq. 1:

Eq. 1: GMFE=10^((Σ|log10(pred PK parameter⁄obs PK parameter)|)⁄n)

with GMFE = geometric mean fold error of all AUC or CL predictions of the respective model, pred PK parameter = predicted AUC or CL, obs PK parameter = observed AUC or CL, and n = number of observed values.

The ratios of predicted over observed mean AUC or CL values from all compound were also plotted across all age groups in the figure below. As illustrated, most of the prediction were within the 0.5 to 2.0 range (2-fold error).

In the next sections the demographics as well as the evaluation results of the predictive performance of the specific compound PBPK models in children can be found.

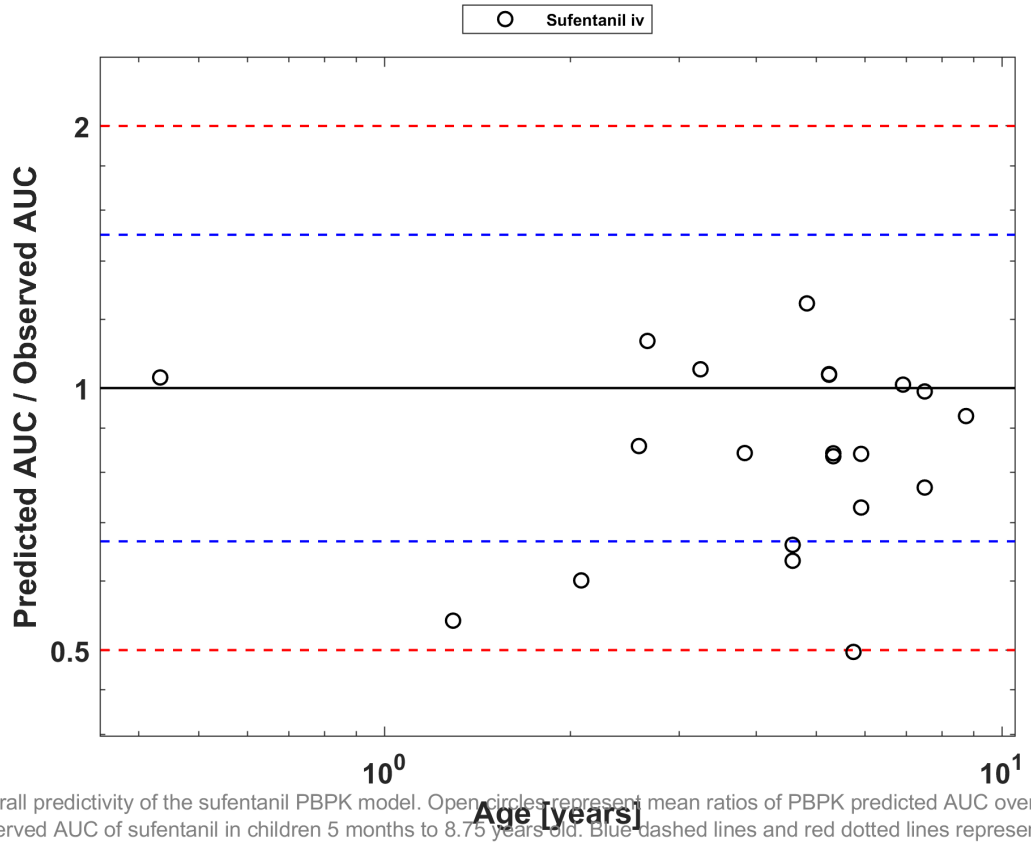
Chapter 2.1: Sufentanil PK Ratio tables and Figures

Sufentanil model

Sufentanil PBPK predictions in children were evaluated using pharmacokinetic (PK) data reported in the following studies:

- Davis PJ, Cook DR, Stiller RL, Davin-Robinson KA. Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. Anesth Analg. 1987 Mar;66(3):203-8.
- Guay J, Gaudreault P, Tang A, Goulet B, Varin F. Pharmacokinetics of sufentanil in normal children. Can J Anaesth. 1992 Jan;39(1):14-20.

The pediatric PBPK model predicted the clearance values of sufentanil observed in pediatric studies reasonably across all available age groups, ranging from 5 months to 8.75 years old. The ratios of mean predicted over observed clearance values are illustrated in the table below as well as in the predicted versus observed clearance ratio plot, showing that most predictions in children were within 2-fold error of observed values.



Overall predictivity of the sufentanil PBPK model. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of sufentanil in children 5 months to 8.75 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

GMFE (AUC) = 1.251766

AUC	Number	Ratio [%]
Points total	21	-
Points within 1.5 fold	16	76.1905
Points within 2-fold	20	95.2381

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [mg*min/ml]	Observed AUC [mg*min/ml]	Pred/Obs AUC Ratio
Davis 1987	1.2917	8.9	0.54048	0.00082873	0.54048
Davis 1987	0.43333	5.3	1.0284	0.00054546	1.0284
Guay 1991	2.0833	12.1	0.60119	0.00010838	0.60119
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Guay 1991	3.25	16	1.0509	8.26e-05	1.0509
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Guay 1991	4.5833	15	0.66053	6.73e-05	0.66053
Guay 1991	4.5833	19	0.63325	0.00013487	0.63325
Guay 1991	4.8333	17.5	1.2509	6.99e-05	1.2509
Guay 1991	5.25	18.5	1.0375	4.36e-05	1.0375
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Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [mg*min/ml]	Observed AUC [mg*min/ml]	Pred/Obs AUC Ratio
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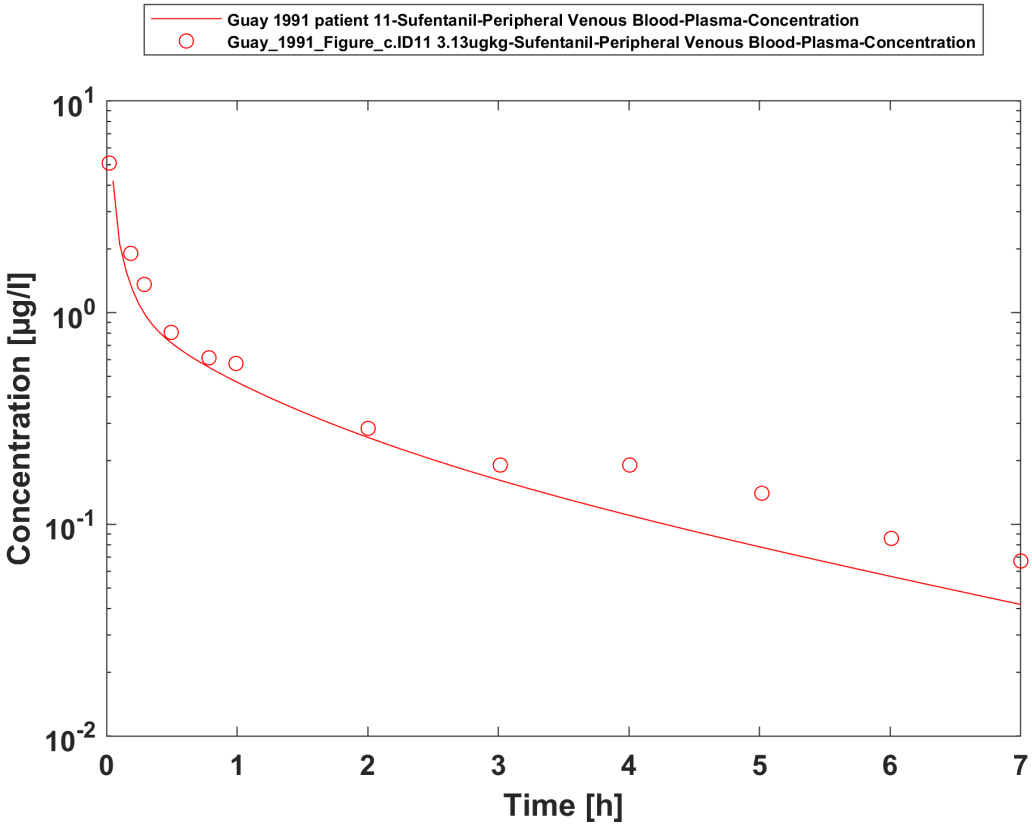
Guay 1991	5.75	14.5	0.49761	0.00015183	0.49761
Guay 1991	5.9167	28.2	0.72904	0.00012754	0.72904
Guay 1991	5.9167	25	0.84016	5.71e-05	0.84016
Guay 1991	6.9167	29.6	1.0091	6.17e-05	1.0091
Guay 1991	7.5	23.5	0.76862	3.5e-05	0.76862
Guay 1991	7.5	15.2	0.99104	7.36e-05	0.99104
Guay 1991	8.75	22.6	0.92858	5.65e-05	0.92858

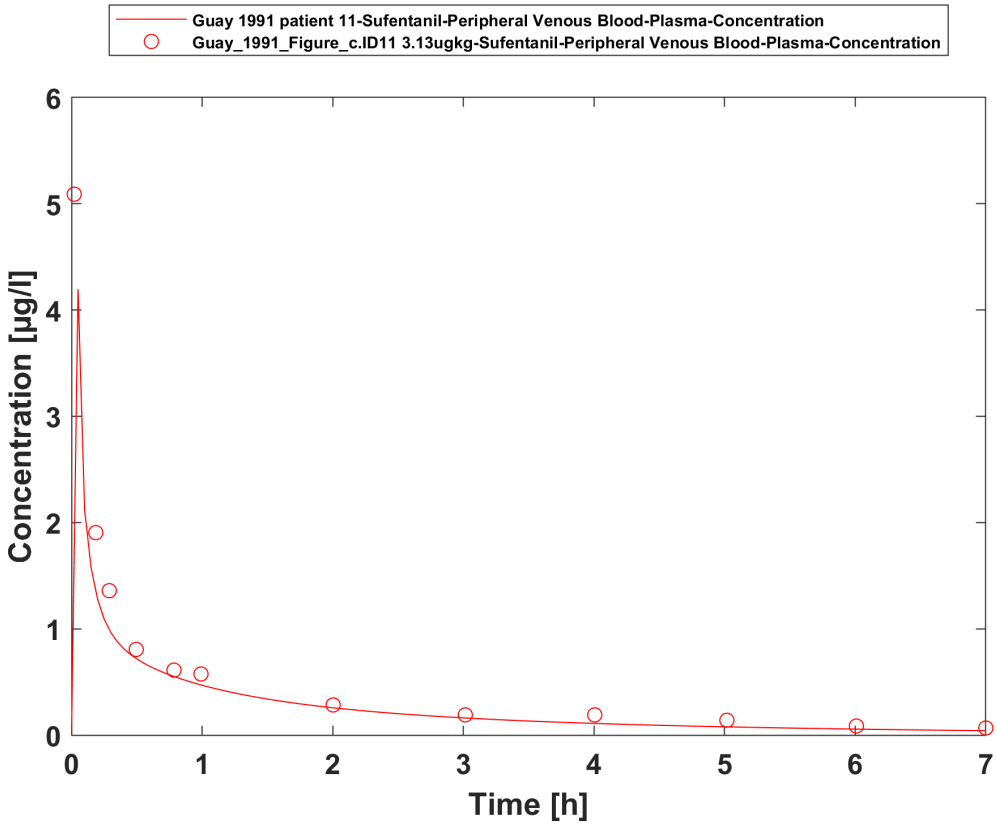
Chapter 2.2: Sufentanil Concentration-Time profiles in Children

Concentration-Time Profiles

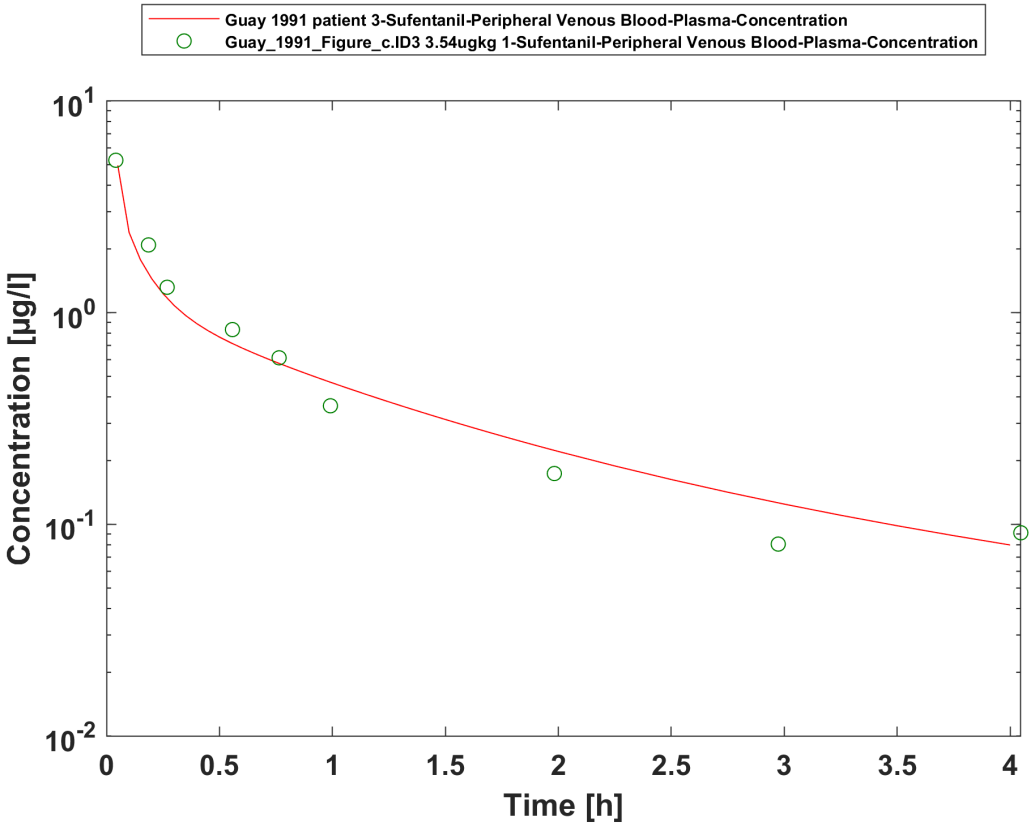
Predicted versus observed plasma concentration-time profiles are listed below. Only simulations where observed data was available for comparison are shown. Depending if the observed data were individual data or aggregated data, individual predictions or population predictions including variability are shown, respectively.



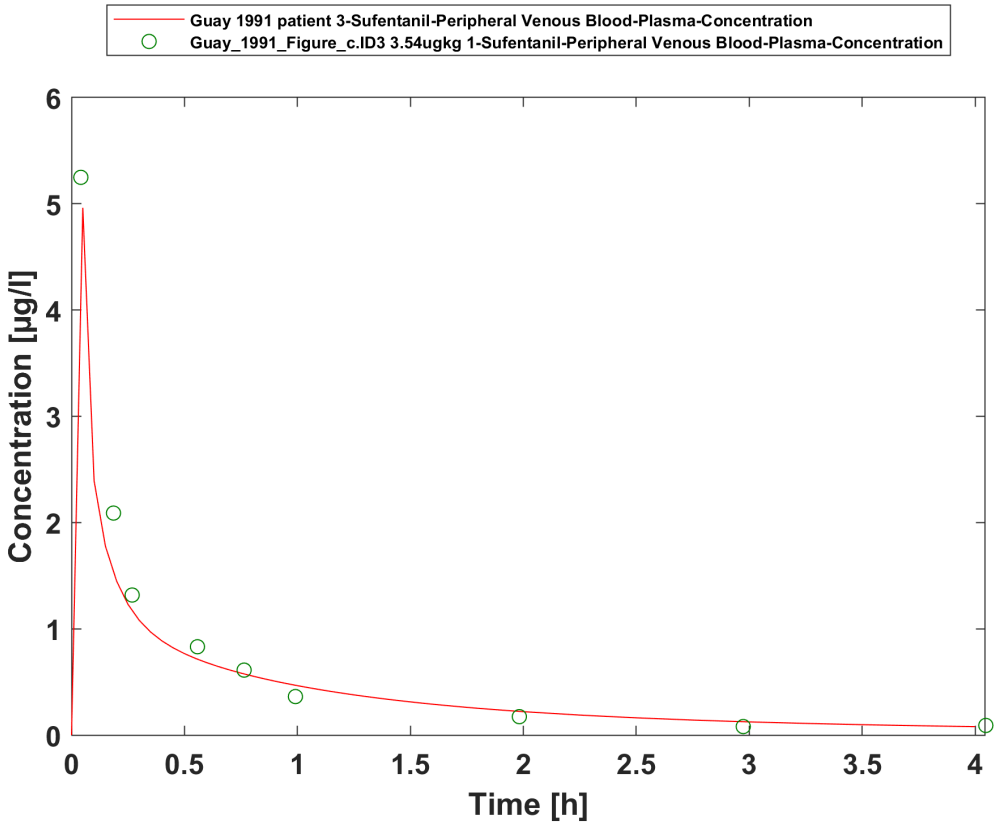
Time Profile Analysis



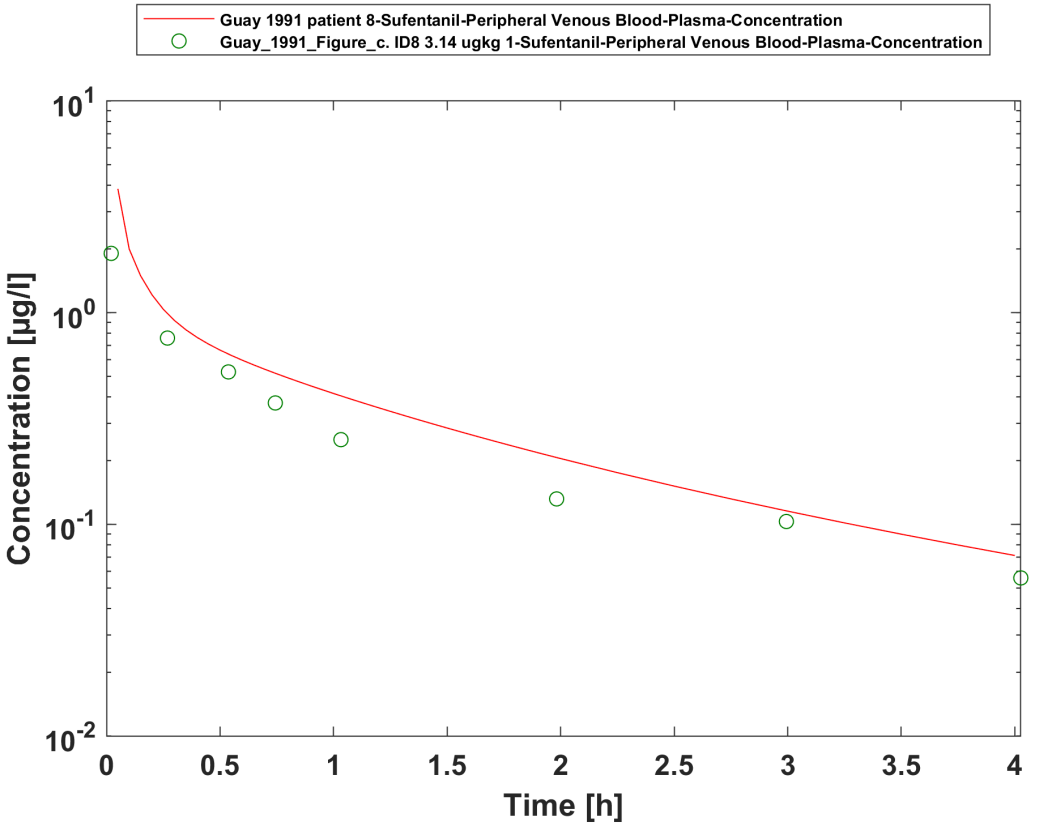
Time Profile Analysis 1



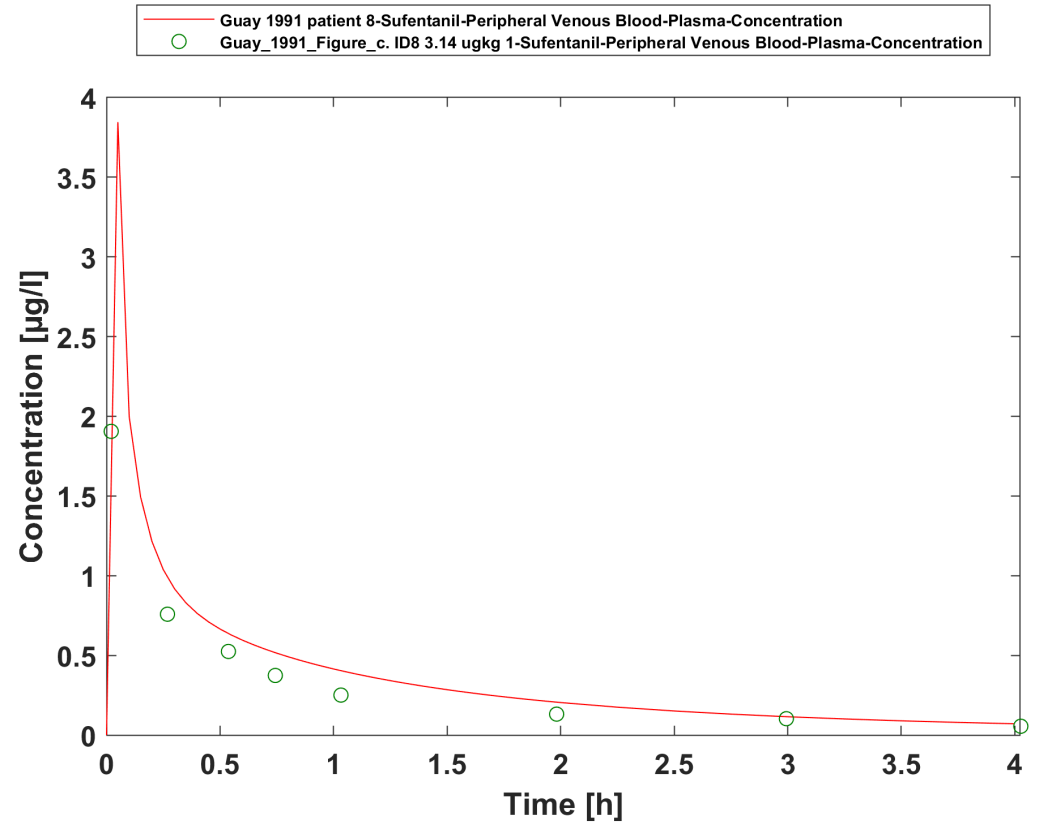
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1

Chapter 2.3: Alfentanil PK Ratio tables and Figures

Alfentanil model

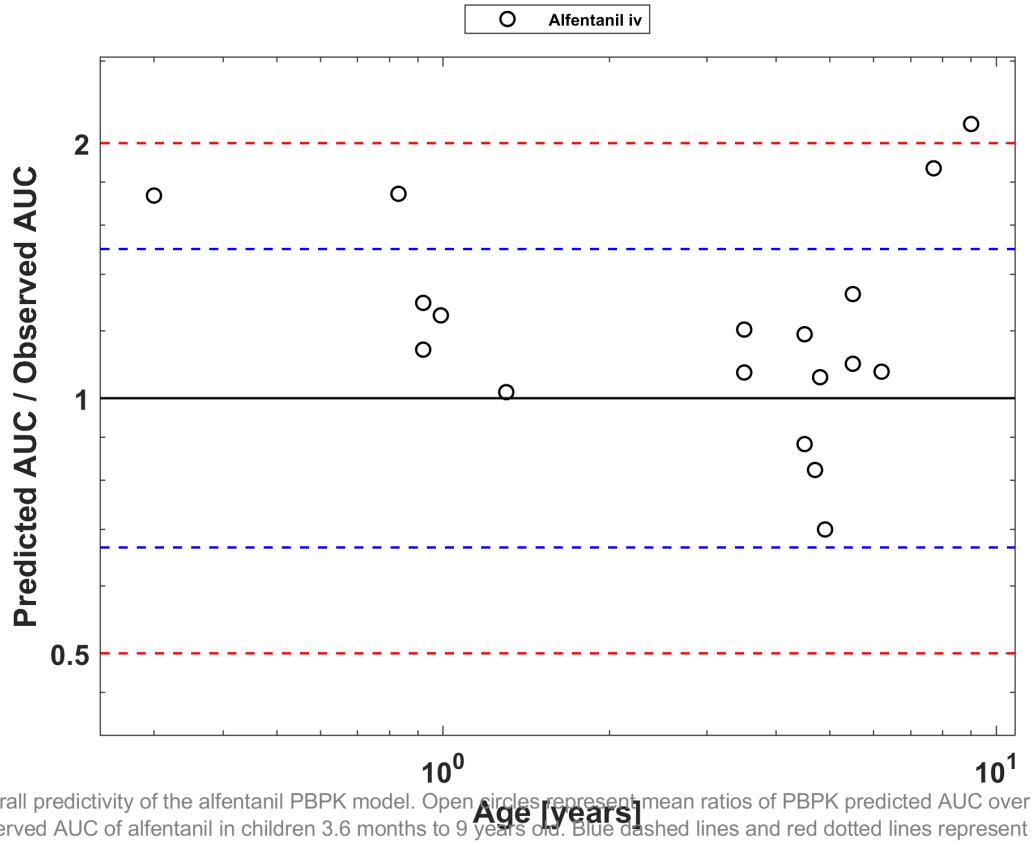
Alfentanil PBPK predictions in children were evaluated using pharmacokinetic (PK) data reported in the following studies:

- den Hollander JM, Hennis PJ, Burm AG, Vletter AA, Bovill JG. Pharmacokinetics of alfentanil before and after cardiopulmonary bypass in pediatric patients undergoing cardiac surgery: Part I. J Cardiothorac Vasc Anesth. 1992 Jun;6(3):308-12.
- Meistelman C, Saint-Maurice C, Lepaul M, Levron JC, Loose JP, Mac Gee K. A comparison of alfentanil pharmacokinetics in children and adults. Anesthesiology. 1987 Jan;66(1):13-6.

The pediatric PBPK model predicted the AUC values of alfentanil observed in pediatric studies reasonably across all available age groups, ranging from 3.6 months to 9 years old. The ratios of mean predicted over observed AUC values are illustrated in the table below as well as in the predicted versus observed AUC ratio plot, showing that most predictions in children were within 2-fold error of observed values. Another reported study on alfentanil pharmacokinetics in children [1] showed systematically higher exposure for most individuals compared to the other herein included studies. This deviation may have been caused by different impact of individual pathophysiologies of the target study population, inaccurate in vitro assay-techniques or other study differences.

References

[1] Goresky GV, Koren G, Sabourin MA, Sale JP, Strunin L., The pharmacokinetics of alfentanil in children. Anesthesiology. 1987 Nov;67(5):654-9.



Overall predictivity of the alfentanil PBPK model. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of alfentanil in children 3.6 months to 9 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

GMFE (AUC) = 1.299868

AUC	Number	Ratio [%]
Points total	18	-
Points within 1.5 fold	14	77.7778
Points within 2-fold	17	94.4444

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [mg*min/l]	Observed AUC [mg*min/l]	Pred/Obs AUC Ratio
den Hollander 1992	0.92	6.5	1.141	21.1	1.141

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [mg*min/l]	Observed AUC [mg*min/l]	Pred/Obs AUC Ratio
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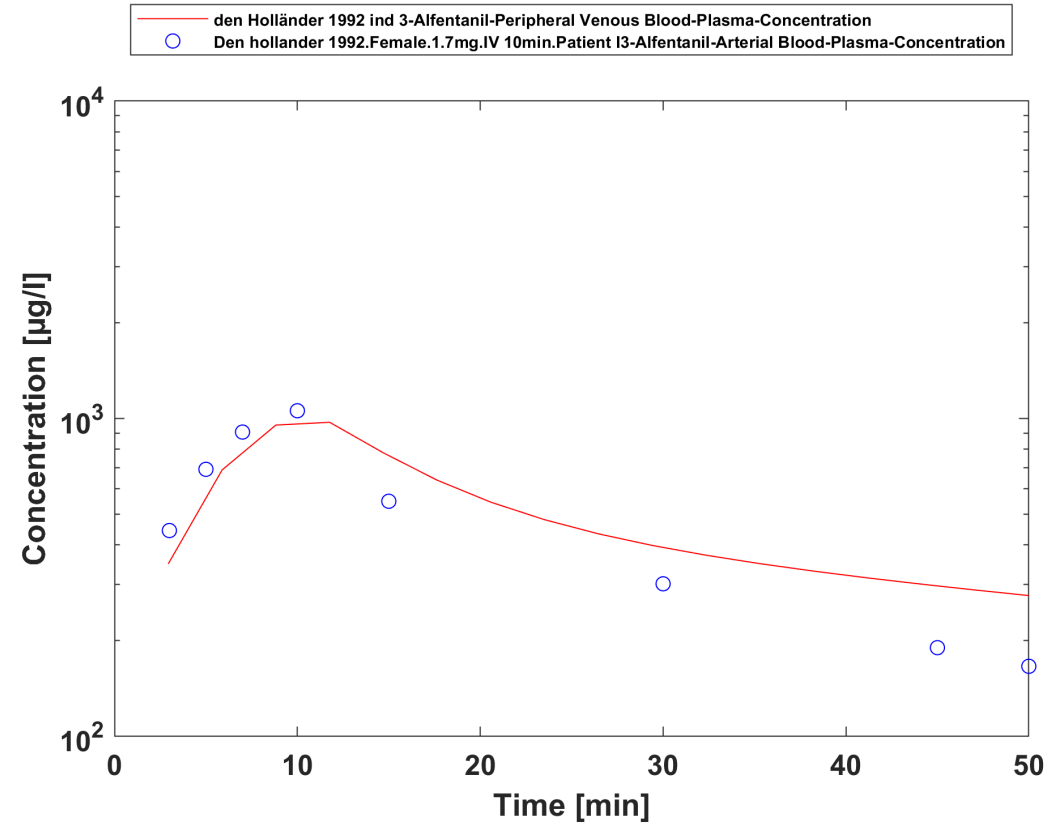
den Hollander 1992	0.3	5.1	1.7344	18.5	1.7344
den Hollander 1992	0.92	6.149	1.2958	15.9	1.2958
den Hollander 1992	1.3	10.4	1.0166	24.3	1.0166
den Hollander 1992	9	25.6	2.1065	11.3	2.1065
den Hollander 1992	3.5	14.4	1.2051	18.6	1.2051
den Hollander 1992	5.5	19.5	1.0981	20.7	1.0981
den Hollander 1992	3.5	18.5	1.0724	22.7	1.0724
Meistelman 1987	4.7	20	0.82289	0.0058824	0.82289
Meistelman 1987	5.5	20	1.3271	0.0033898	1.3271
Meistelman 1987	7.7	23	1.8677	0.0024096	1.8677
Meistelman 1987	4.5	14	0.88282	0.0043478	0.88282
Meistelman 1987	4.8	24	1.0588	0.0054054	1.0588
Meistelman 1987	4.5	20	1.1898	0.0041667	1.1898
Meistelman 1987	6.2	23	1.0748	0.0045455	1.0748
Meistelman 1987	4.9	22	0.70008	0.0074074	0.70008

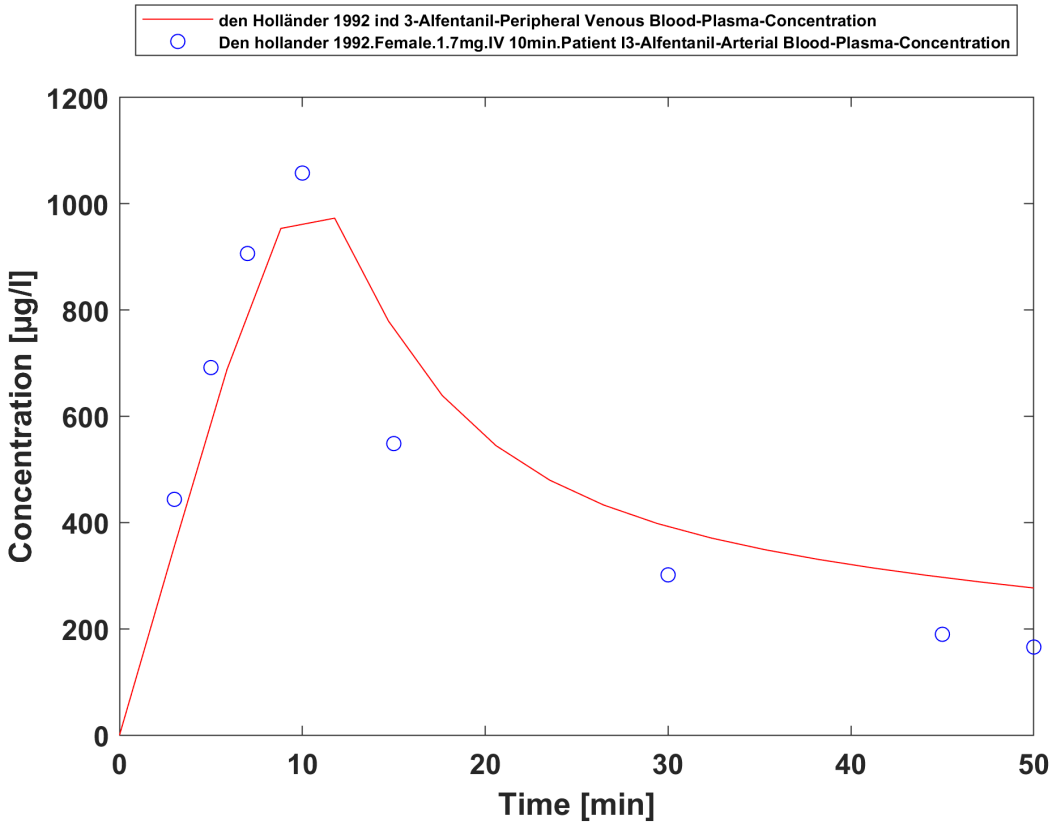
Chapter 2.4: Alfentanil Concentration-Time profiles in Children

Concentration-Time Profiles

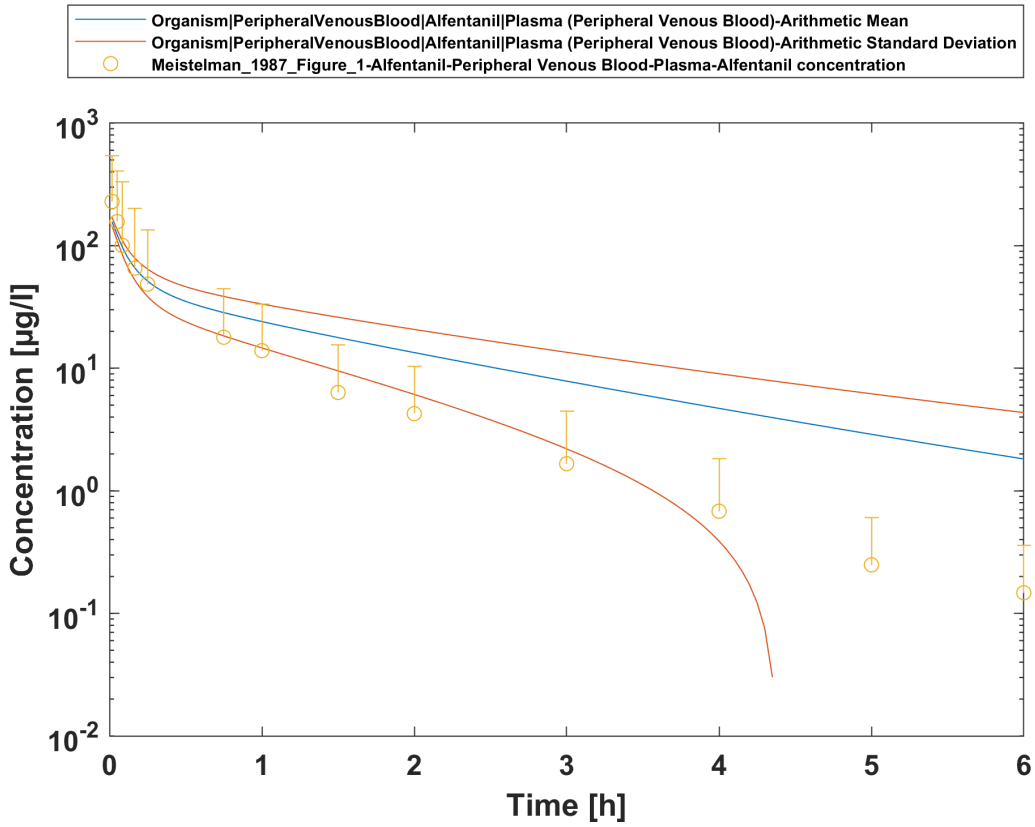
Predicted versus observed plasma concentration-time profiles are listed below. Only simulations where observed data was available for comparison are shown. Depending if the observed data were individual data or aggregated data, individual predictions or population predictions including variability are shown, respectively.



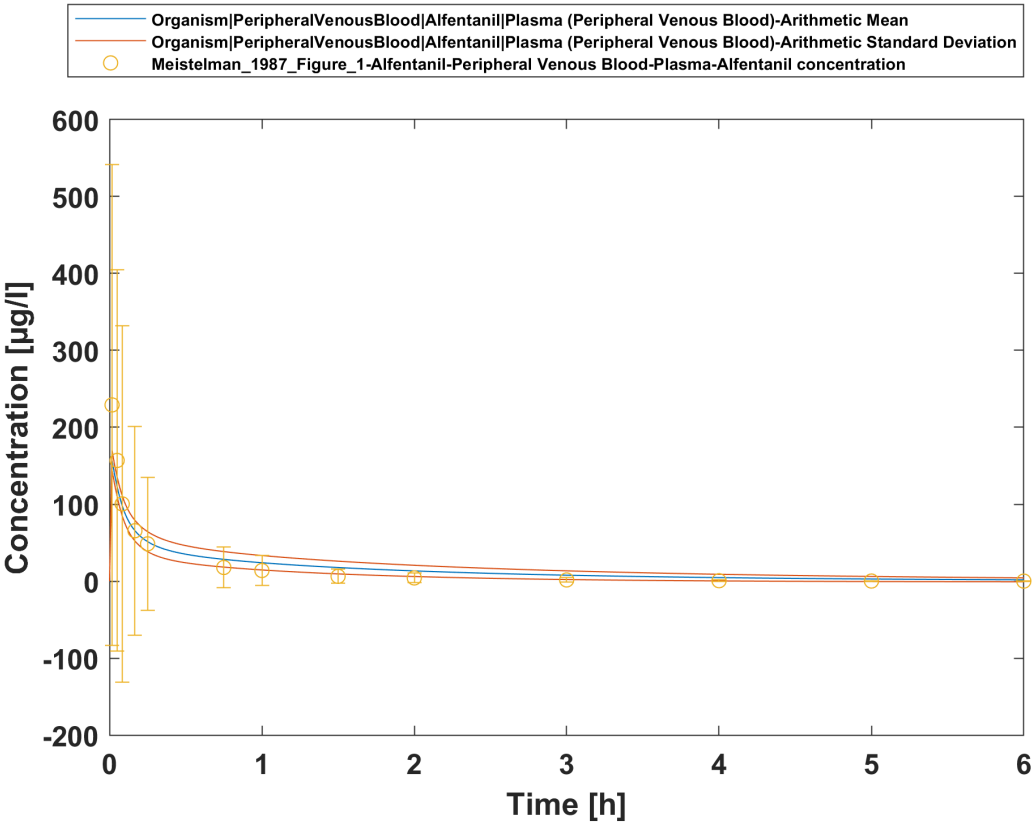
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1

Chapter 3: Adult PBPK model building and performance

Evaluation of Adult PBPK models

The PBPK models of **sufentanil** and **alfentanil** were developed with clinical pharmacokinetic data covering at least administrations given in children. Plasma concentrations following intravenous administration, oral administration, multiple dose application, fractions excreted to urine or bile and other clinical measurements were included for model development whenever available.

Chapter 3.1: Sufentanil Input Tables

Sufentanil adult PBPK model

Sufentanil is a potent synthetic opioid. Like other opioids, sufentanil creates a stable hemodynamic environment in cardiovascularly compromised pediatric patients. Sufentanil has a high lipid solubility, which accounts for the fast onset when given intravenously. The commercial solution comes as preservative-free sufentanil citrate, injectable with a pH of 4.5–7.0 (Jansen-Cilag AB, Sweden). Sufentanil is solely metabolised by CYP3A4. Due to the high hepatic extraction ratio, for the overall clearance of sufentanil both CYP3A4 values as well as liver blood flow rate play dominant roles in the elimination in adult populations. The final sufentanil model applies metabolism by CYP3A4 and glomerular filtration and adequately described the pharmacokinetics of sufentanil in adults.

The Sufentanil model was developed using data of the following publications:

- Bovill JG, Sebel PS, Blackburn CL, Oei-Lim V, Heykants JJ. The pharmacokinetics of sufentanil in surgical patients. Anesthesiology. 1984 Nov;61(5):502-6. (https://www.ncbi.nlm.nih.gov/pubmed/6238552)
- Willsie SK, Evashenk MA2, Hamel LG, Hwang SS, Chiang YK, Palmer PP. Pharmacokinetic properties of single- and repeated-dose sufentanil sublingual tablets in healthy volunteers. Clin Ther. 2015 Jan 1;37(1):145-55. doi: 10.1016/j.clinthera.2014.11.001. Epub 2014 Dec 24. (https://www.ncbi.nlm.nih.gov/pubmed/25544247)

The compound properties used for input are illustrated below.

Compound: Sufentanil

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	0.076 mg/l	Internet-Other-ROY,SD & FLYNN,GL (1988)	ROY,SD & FLYNN,GL (1988)	True
Reference pH	7	Internet-Other-ROY,SD & FLYNN,GL (1988)	ROY,SD & FLYNN,GL (1988)	True
Lipophilicity	2.896 Log Units	Parameter Identification-Parameter Identification	Fitted LogP	True
Fraction unbound (plasma, reference value)	0.075	Publication-Zhou et al. 2017	Zhou et al. 2017	True

Name	Value	Value Origin	Alternative	Default
Is small molecule	Yes			
Molecular weight	386.6 g/mol	Publication-Zhou et al. 2017		
Plasma protein binding partner	α1-acid glycoprotein			

Calculation methods

Name	Value
Partition coefficients	Schmitt
Cellular permeabilities	PK-Sim Standard

Processes

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Zhou et al. 2017

Metabolizing Enzyme: CYP3A4-Zhou et al. 2017

Species: Human
Molecule: CYP3A4

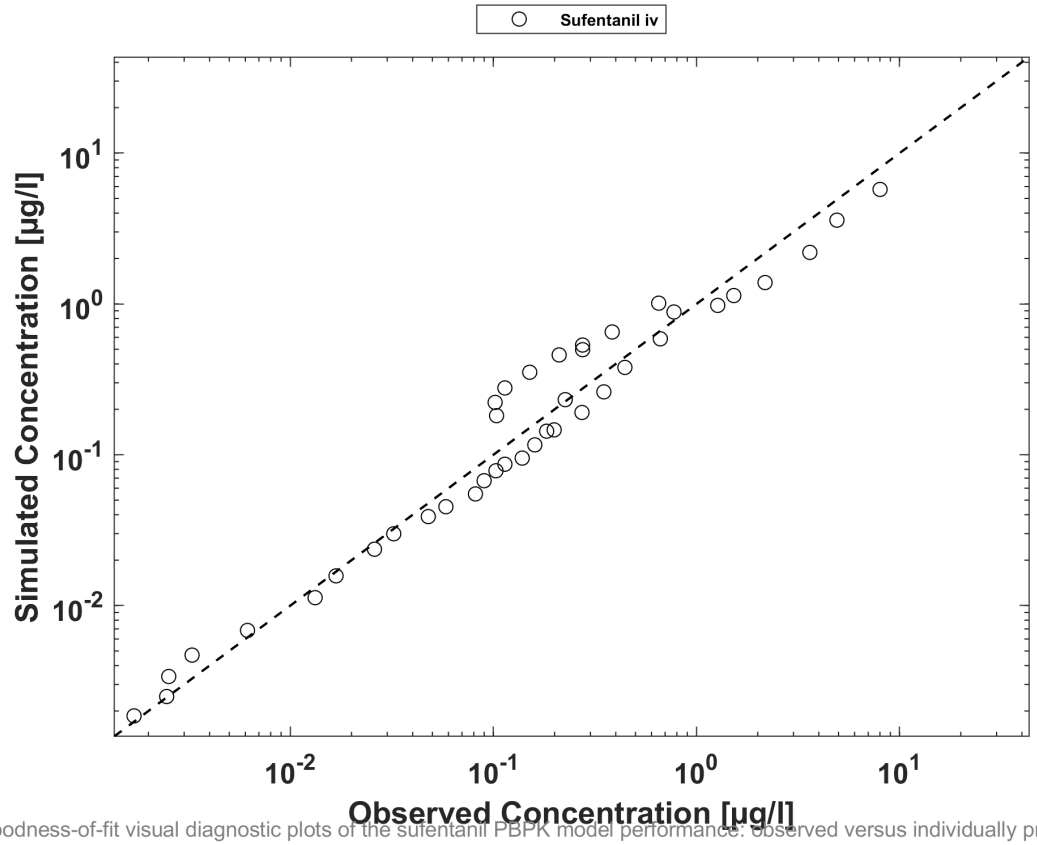
Parameters

Name	Value	Value Origin
Intrinsic clearance	9.6138746106 l/min	Parameter Identification-Parameter Identification

Chapter 3.2: Sufentanil Diagnostics Plots

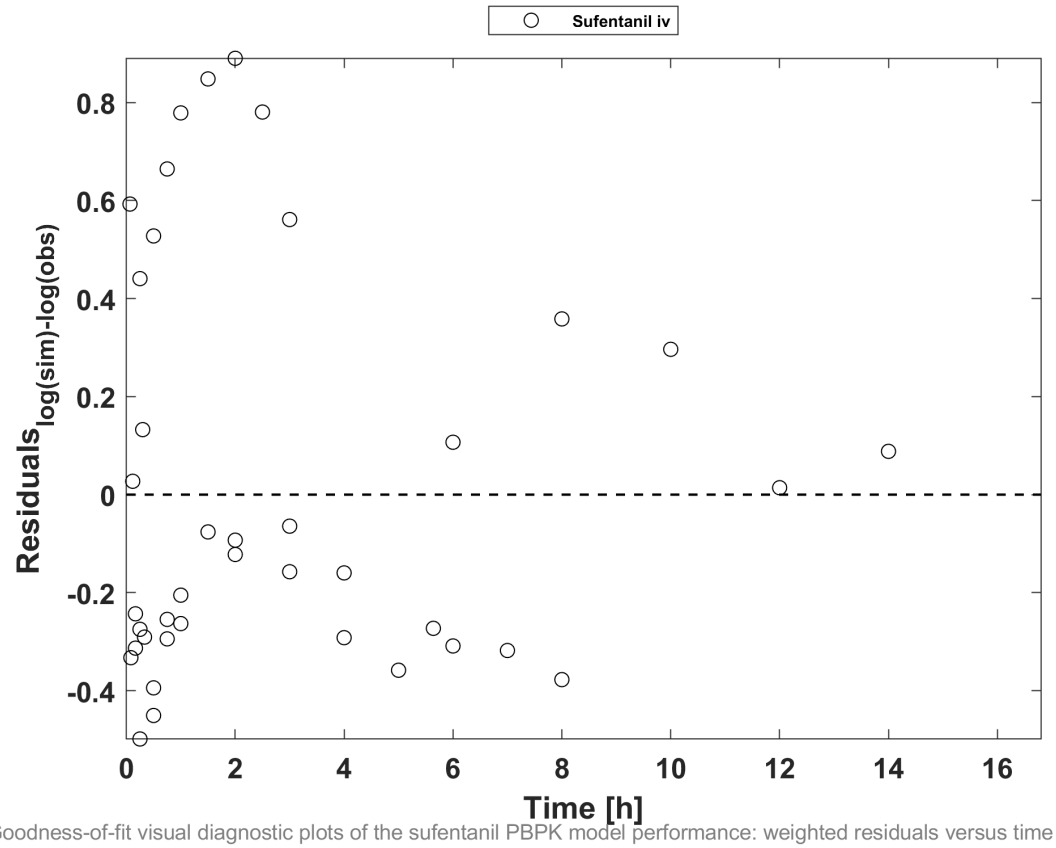
Sufentanil adult PBPK model performance

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



Goodness-of-fit visual diagnostic plots of the sufentanil PBPK model performance: observed versus individually predicted plasma concentration versus time of all adult data.

GMFE = 1.402222



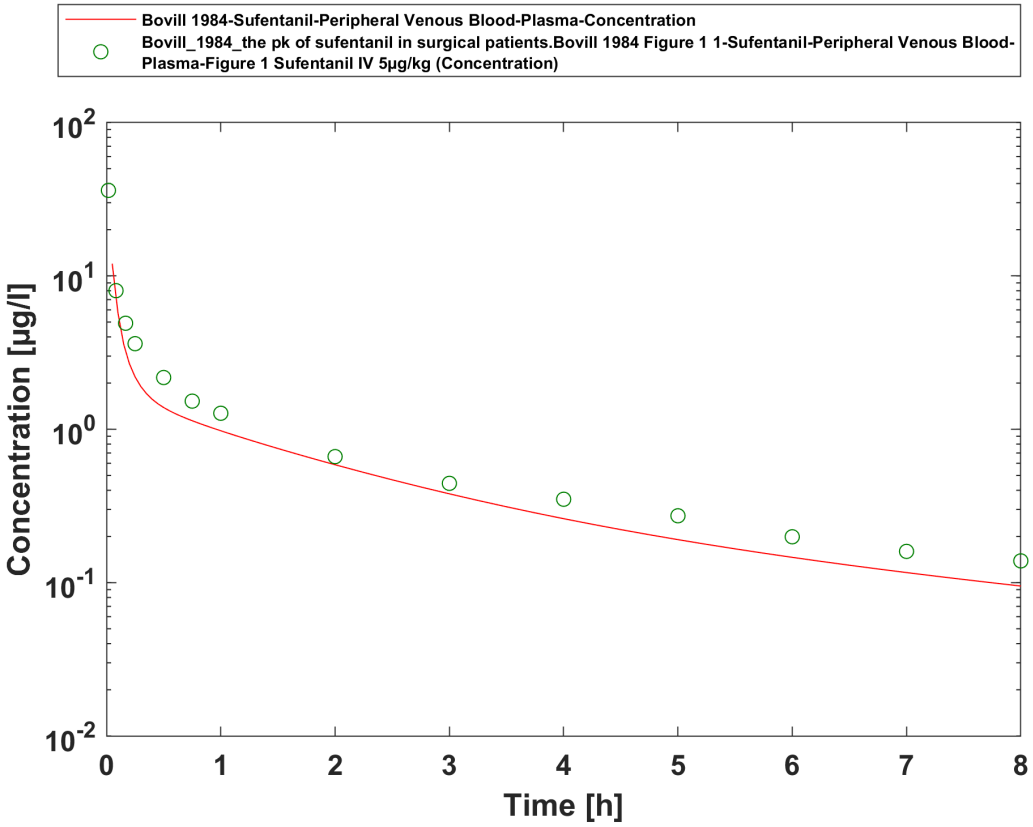
Goodness-of-fit visual diagnostic plots of the sufentanil PBPK model performance: weighted residuals versus time of all adult data.

GMFE = 1.402222

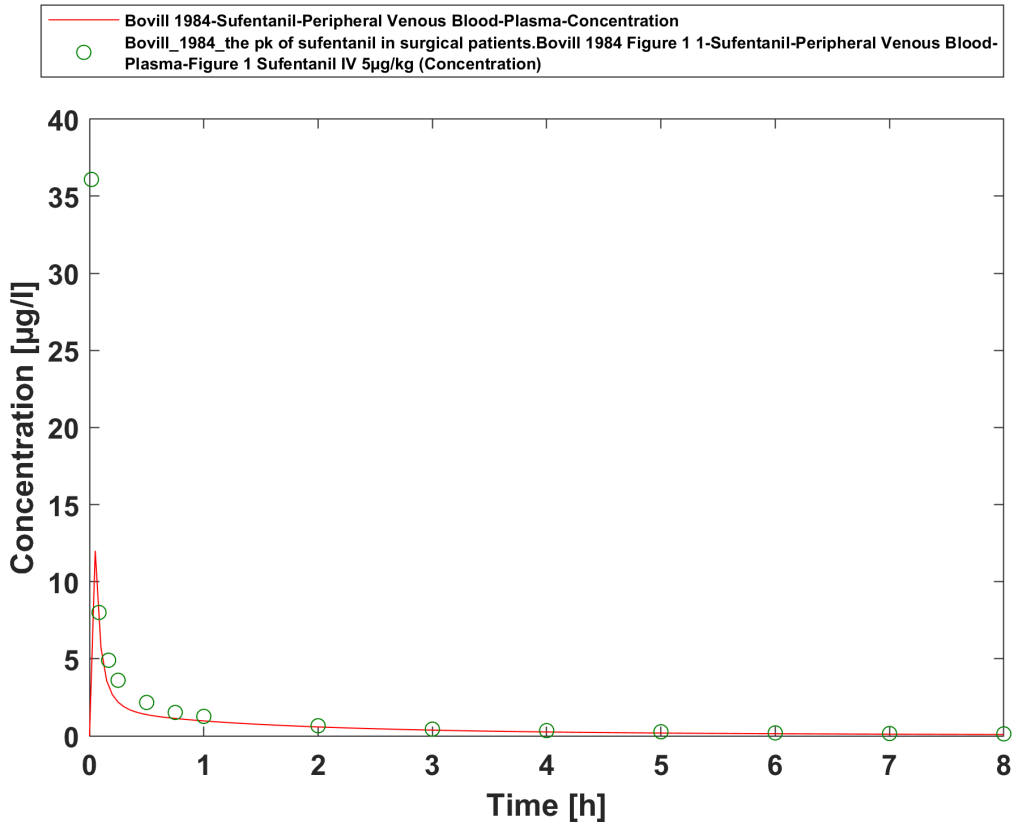
Chapter 3.3: Sufentanil Concentration-Time profiles in Adults

Concentration-Time Profiles

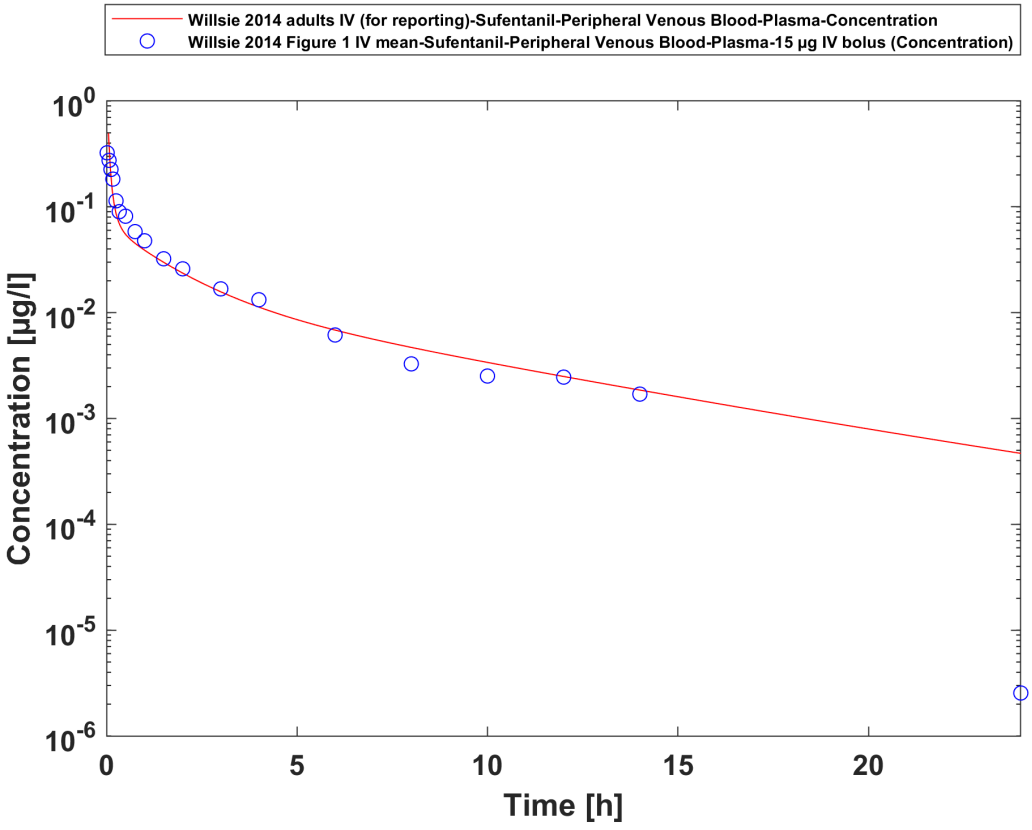
Simulated versus observed plasma concentration-time profiles of all data are listed below.



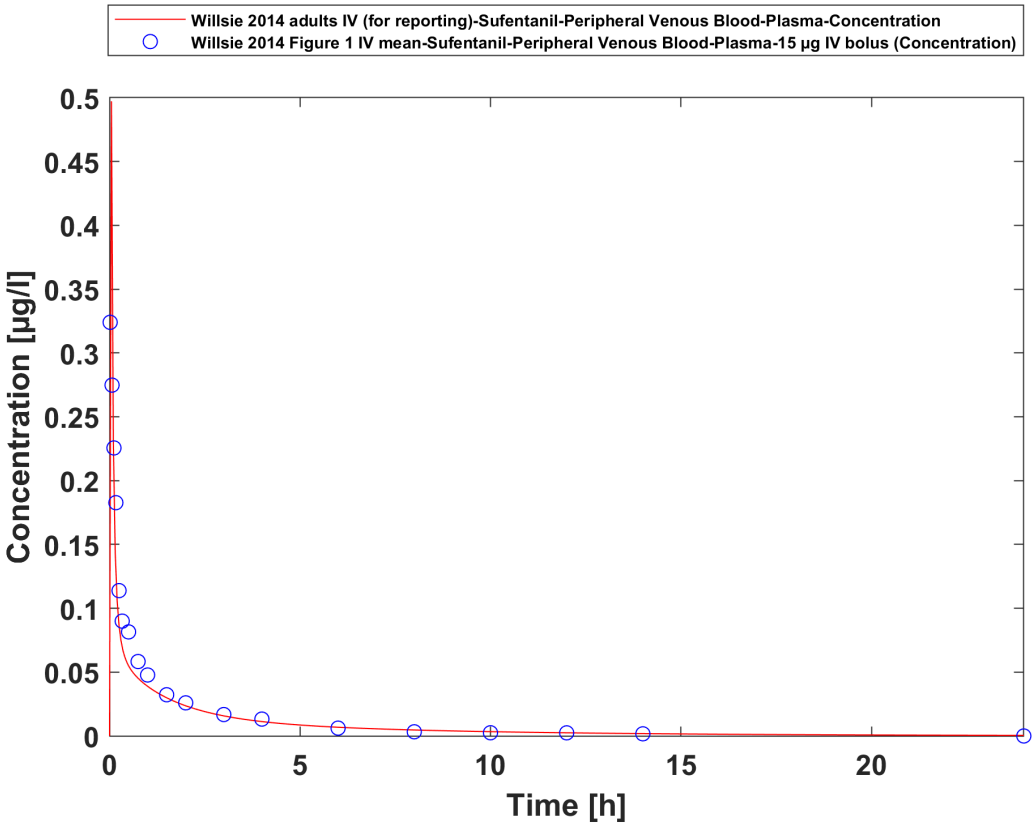
Time Profile Analysis



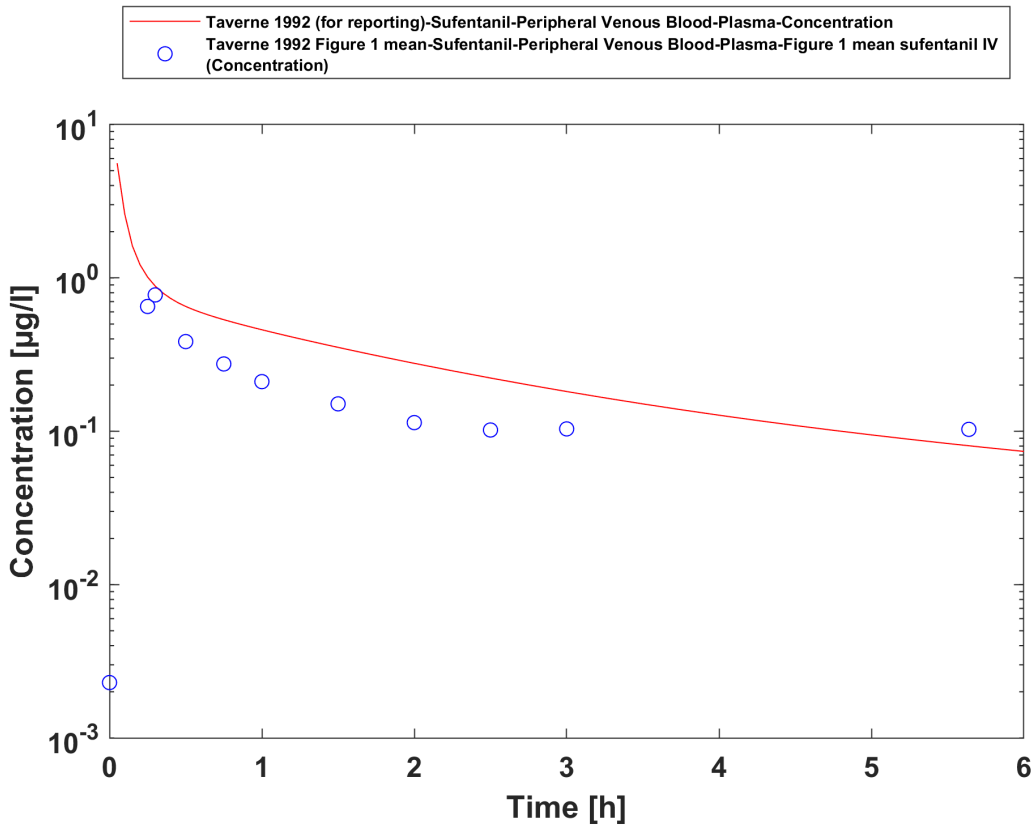
Time Profile Analysis 1



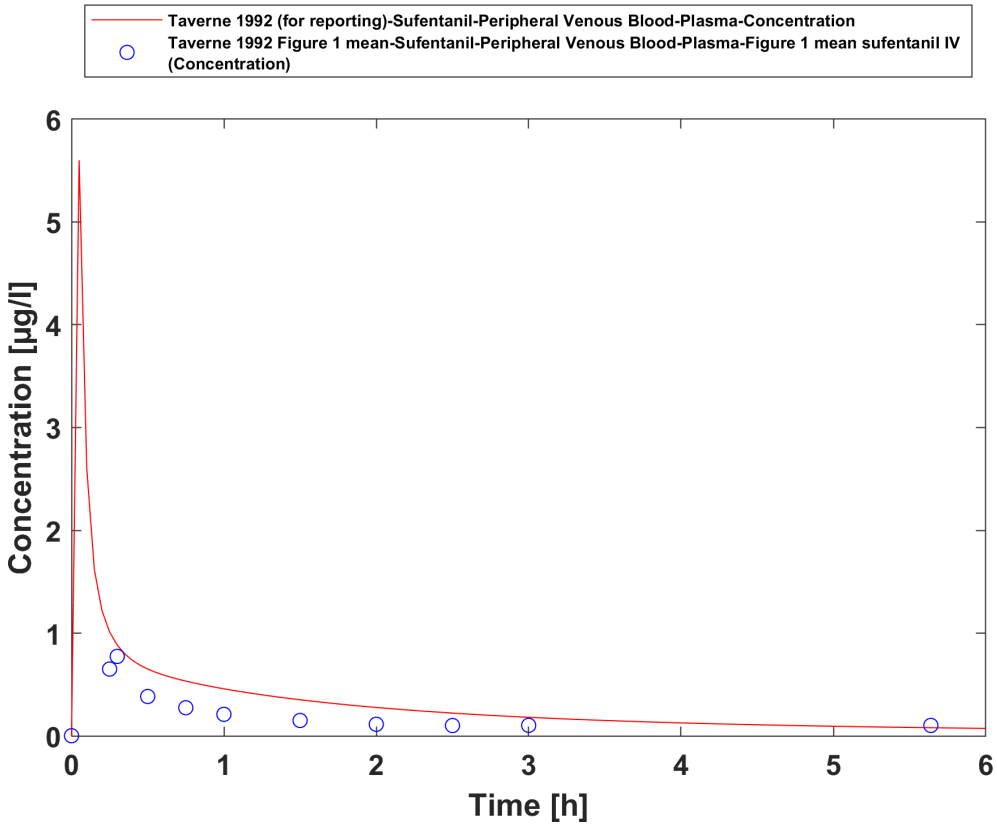
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1

Chapter 3.4: Alfentanil Input Tables

Alfentanil model

Alfentanil is another potent, short-acting synthetic opioid analgesic drug, used for anaesthesia in surgery, which is solely metabolized by CYP3A4, with less than 1% of an alfentanil dose being excreted unchanged in urine after intravenous administration. The model has been build and evaluated in healthy adults and published by Hanke et al. [1] The model applies metabolism by CYP3A4 and glomerular filtration. The alfentanil PBPK model adequately described the pharmacokinetics of alfentanil in adults.

The published alfentanil model [1] was developed using data of the following publications:

- Kharasch ED, Francis A, London A, Frey K, Kim T, Blood. Sensitivity of intravenous and oral alfentanil and pupillary miosis as minimal and noninvasive probes for hepatic and first-pass CYP3A induction. Clin Pharmacol Ther. 2011 Jul;90(1):100-8. doi: 10.1038/clpt.2011.59. Epub 2011 May 11. (https://www.ncbi.nlm.nih.gov/pubmed/21562488)
- Kharasch ED, Walker A, Hoffer C, Sheffels P. Intravenous and oral alfentanil as in vivo probes for hepatic and first-pass cytochrome P450 3A activity: noninvasive assessment by use of pupillary miosis. Clin Pharmacol Ther. 2004 Nov;76(5):452-66. (https://www.ncbi.nlm.nih.gov/pubmed/15536460)
- Phimmasone S, Kharasch ED. A pilot evaluation of alfentanil-induced miosis as a noninvasive probe for hepatic cytochrome P450 3A4 (CYP3A4) activity in humans. Clin Pharmacol Ther. 2001 Dec;70(6):505-17. (https://www.ncbi.nlm.nih.gov/pubmed/11753266)
- Kharasch ED, Russell M, Mautz D, Thummel KE, Kunze KL, Bowdle A, Cox K. The role of cytochrome P450 3A4 in alfentanil clearance. Implications for interindividual variability in

disposition and perioperative drug interactions. Anesthesiology. 1997 Jul;87(1):36-50. (https://www.ncbi.nlm.nih.gov/pubmed/9232132)

References

[1] Hanke N, Frechen S, Moj D, Britz H, Eissing T, Wendl T, Lehr T. PBPK models for CYP3A4 and P-gp DDI prediction: a modeling network of rifampicin, itraconazole, clarithromycin, midazolam, alfentanil and digoxin. CPT: Pharmacometrics & Systems Pharmacology (2018), https://doi.org/10.1002/psp4.12343.

The compound properties used for input are illustrated below.

Compound: Alfentanil

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	992 mg/l	Publication-Hanke 2018	Baneyx 2014	True
Reference pH	6.5	Publication-Hanke 2018	Baneyx 2014	True
Lipophilicity	1.75 Log Units	Publication-Hanke 2018	Fit	True
Fraction unbound (plasma, reference value)	0.1	Publication-Hanke 2018	Healthy	True
Fraction unbound (plasma, reference value)	0.27027	Publication-Hanke 2018	Child-Pugh C	False

Name	Value	Value Origin	Alternative	Default
Fraction unbound (plasma, reference value)	0.15625	Publication-Hanke 2018	Child-Pugh A	False
Fraction unbound (plasma, reference value)	0.1656	Publication-Hanke 2018	Child-Pugh B	False
Specific intestinal permeability (transcellular)	3.48E-06 cm/min	Publication-Hanke 2018	Fit	True
Is small molecule	Yes			
Molecular weight	416.52 g/mol	Publication-Hanke 2018		
Plasma protein binding partner	α1-acid glycoprotein			

Calculation methods

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

Processes

Metabolizing Enzyme: CYP3A4-1st order CL

Species: Human
Molecule: CYP3A4

Parameters

Name	Value	Value Origin
Intrinsic clearance	0.504 l/min	Publication-Hanke 2018

Systemic Process: Glomerular Filtration-GFR

Species: Human

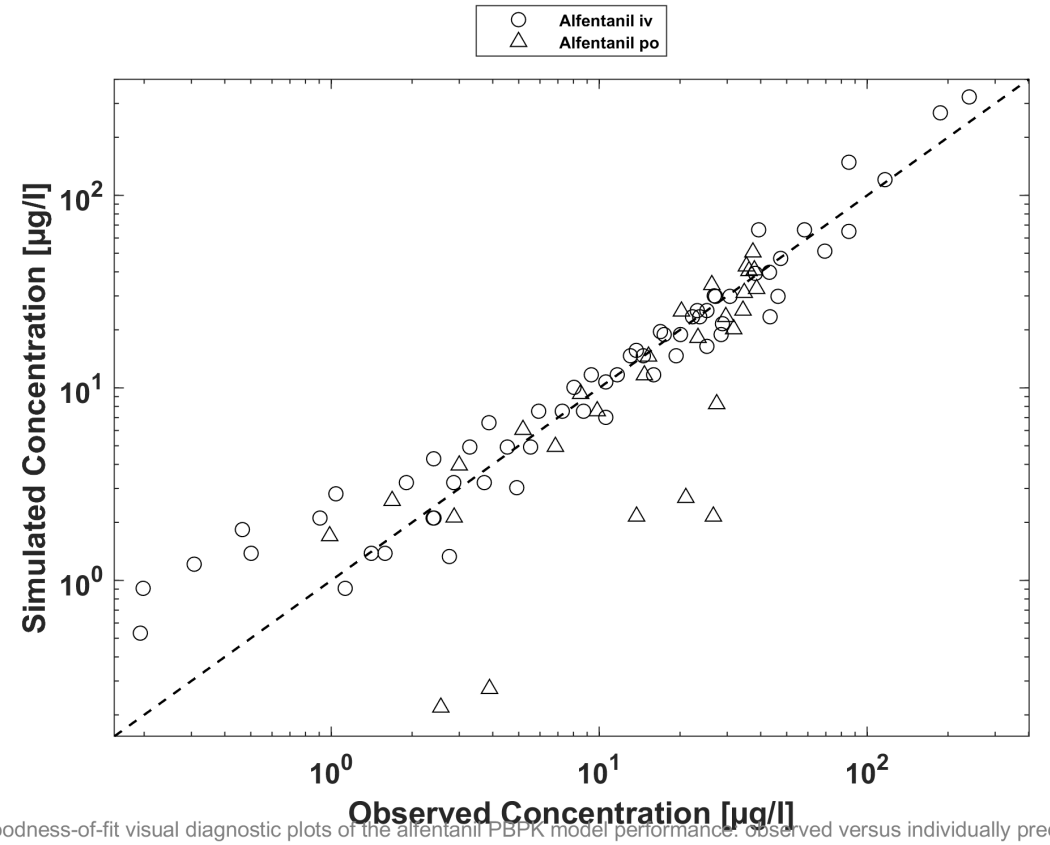
Parameters

Name	Value	Value Origin
GFR fraction	0.06	Publication-Hanke 2018

Chapter 3.5: Alfentanil Diagnostics Plots

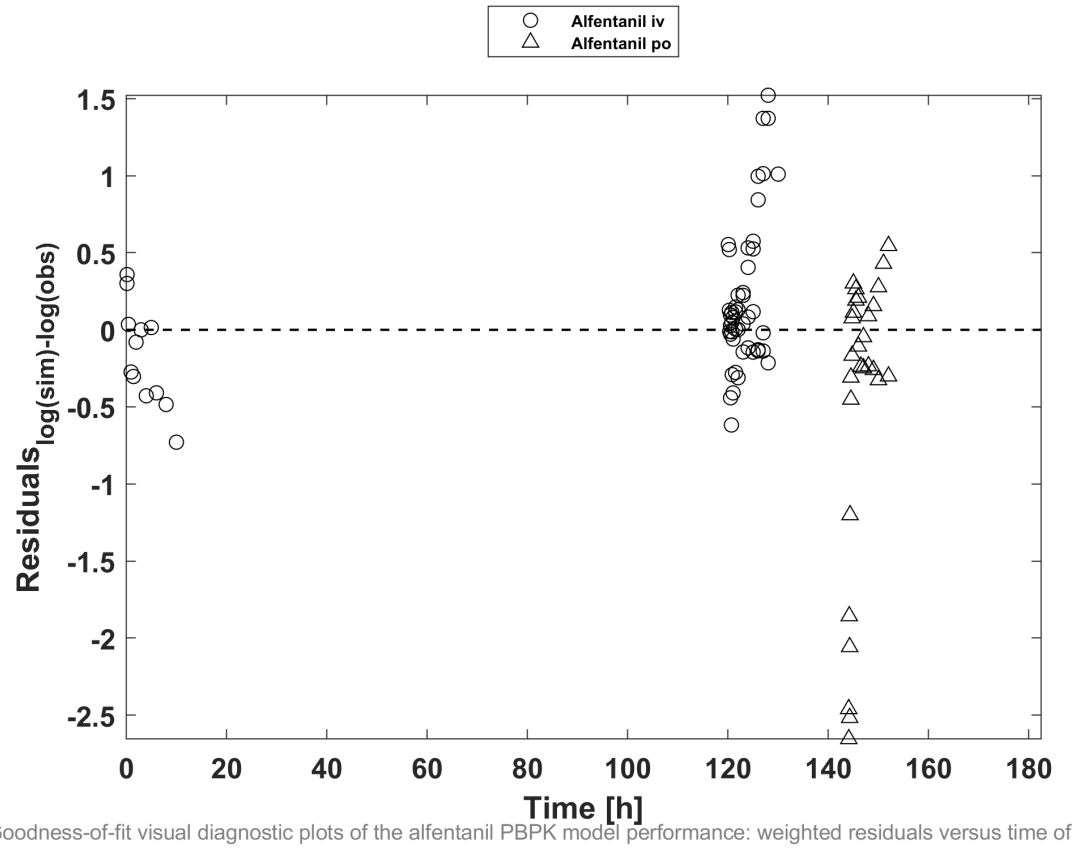
Alfentanil adult PBPK model performance

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



Goodness-of-fit visual diagnostic plots of the alfentanil PBPK model performance: observed versus individually predicted plasma concentration versus time of all adult data.

GMFE = 1.535237



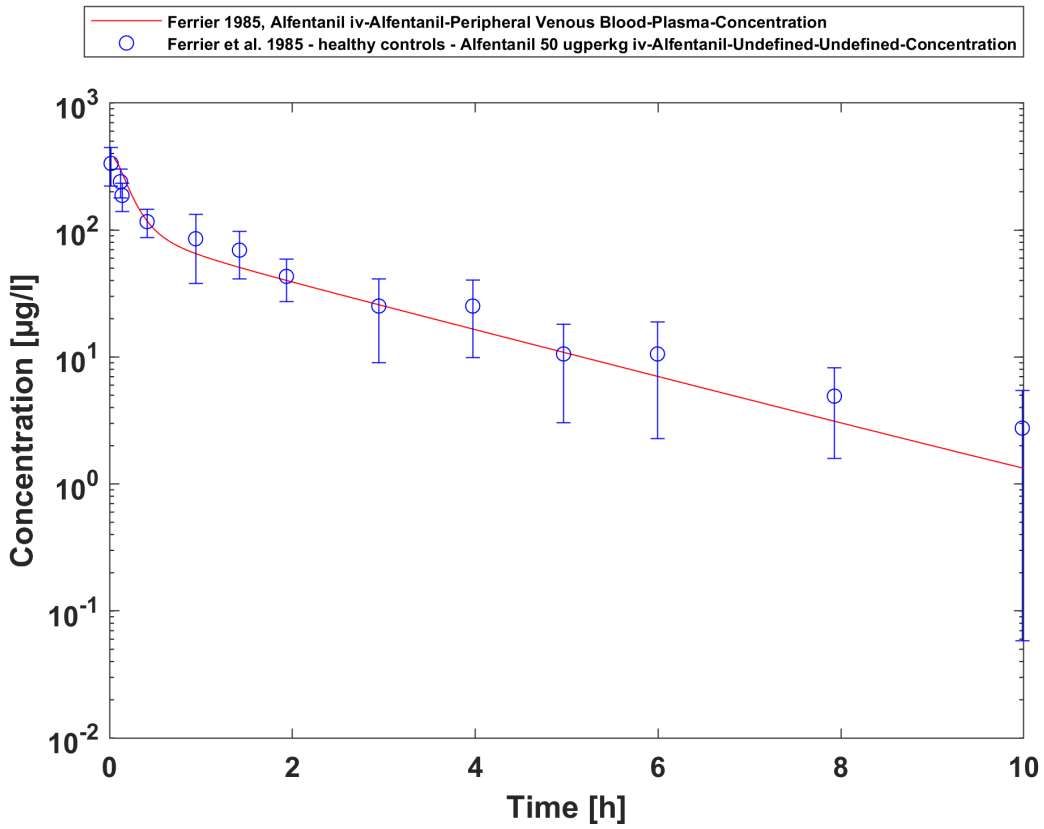
Goodness-of-fit visual diagnostic plots of the alfentanil PBPK model performance: weighted residuals versus time of all adult data.

GMFE = 1.535237

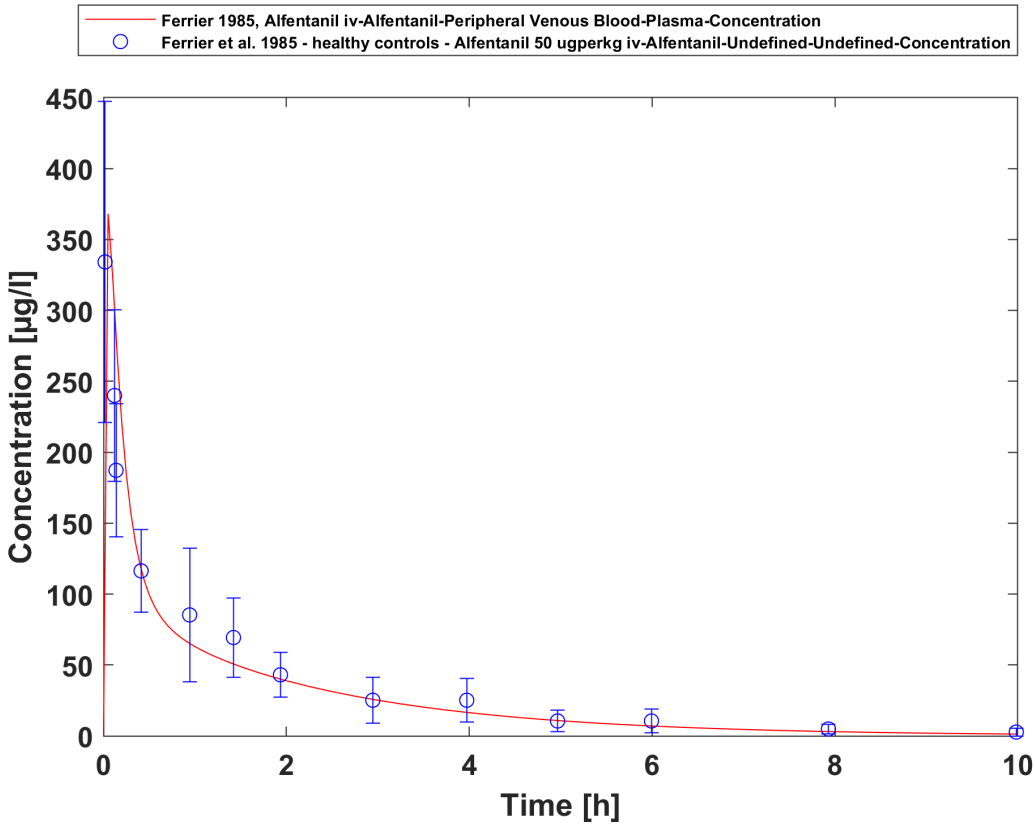
Chapter 3.6: Alfentanil Concentration-Time profiles in Adults

Concentration-Time Profiles

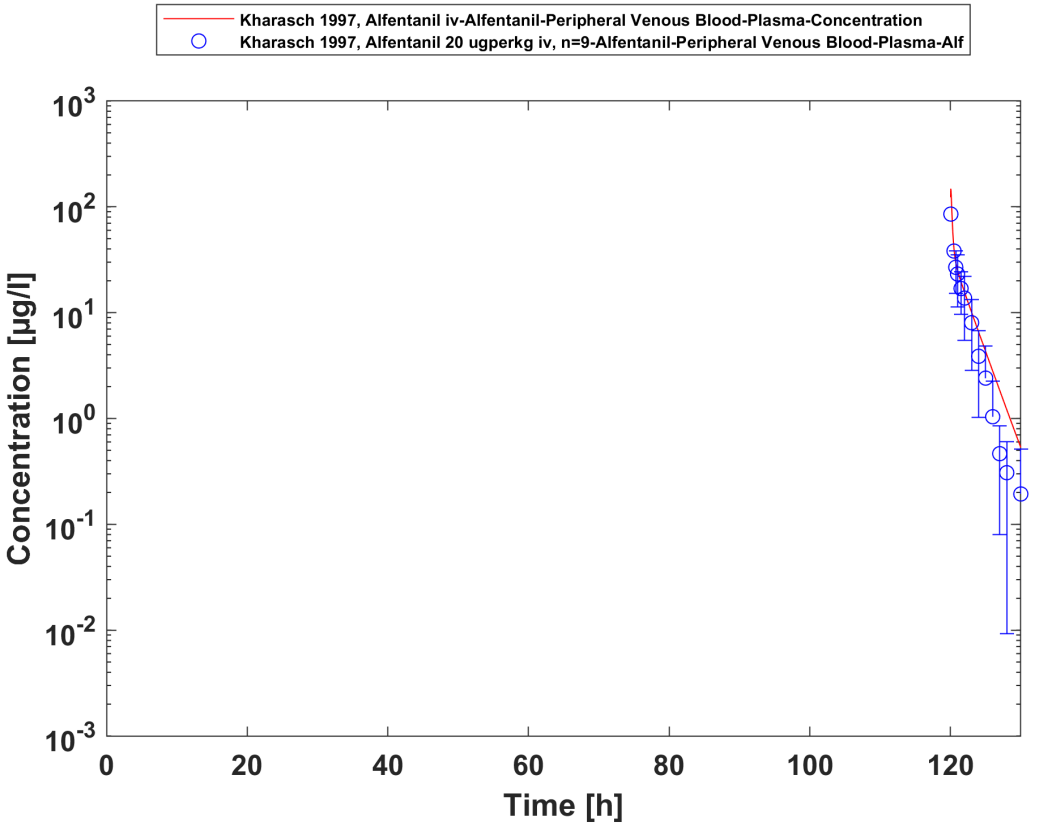
Simulated versus observed plasma concentration-time profiles of all data are listed below.



Time Profile Analysis



Time Profile Analysis 1



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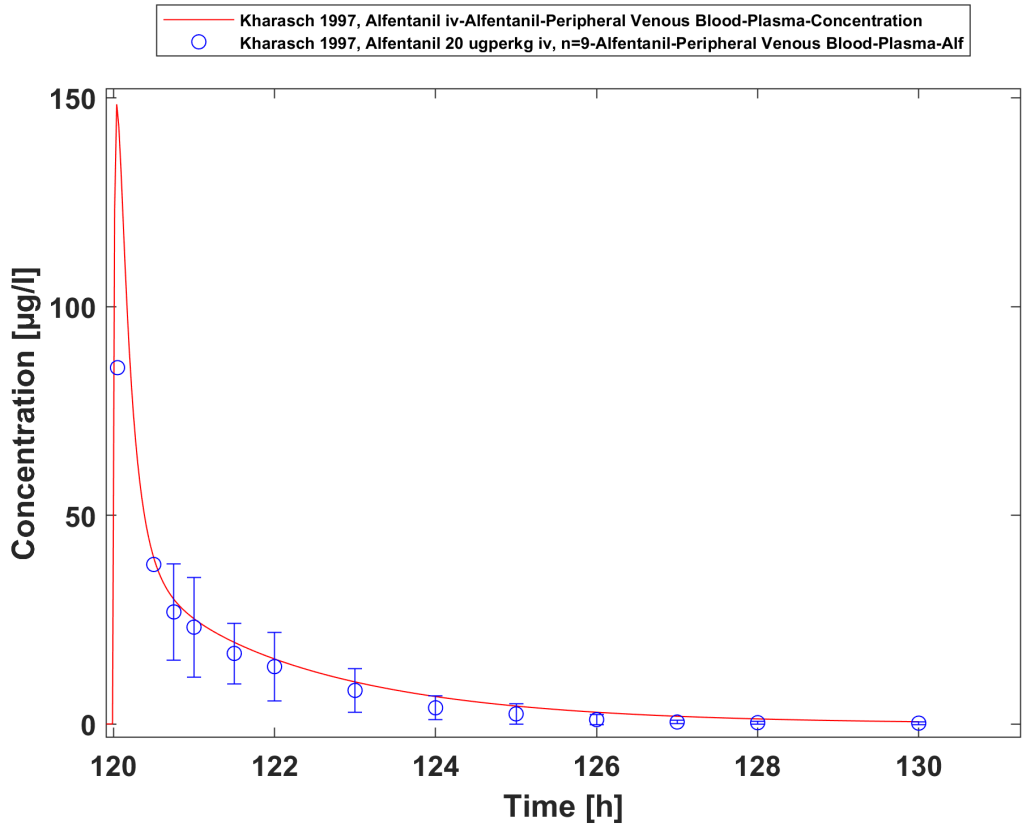

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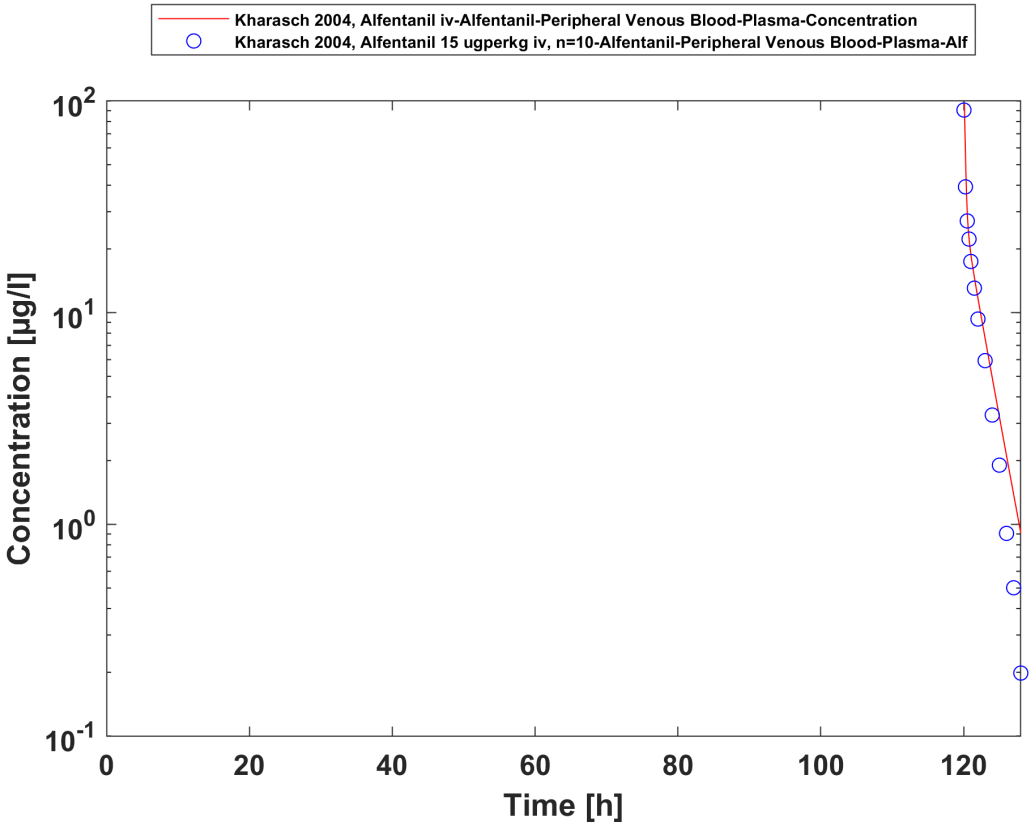

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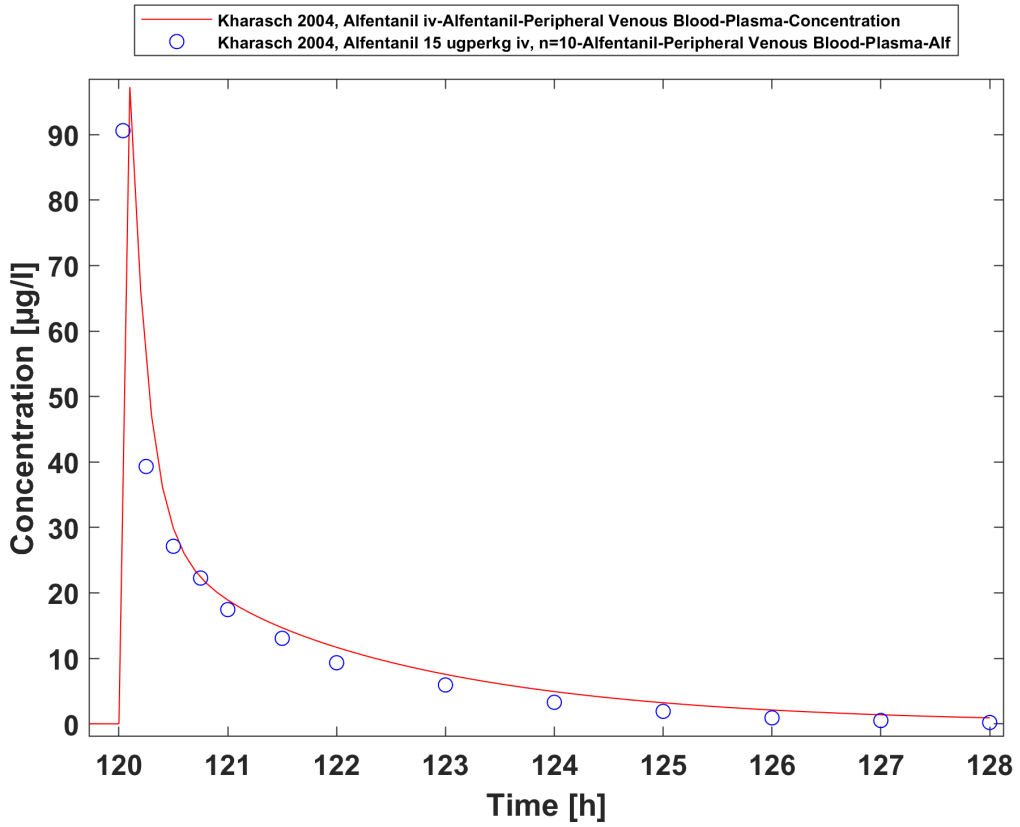

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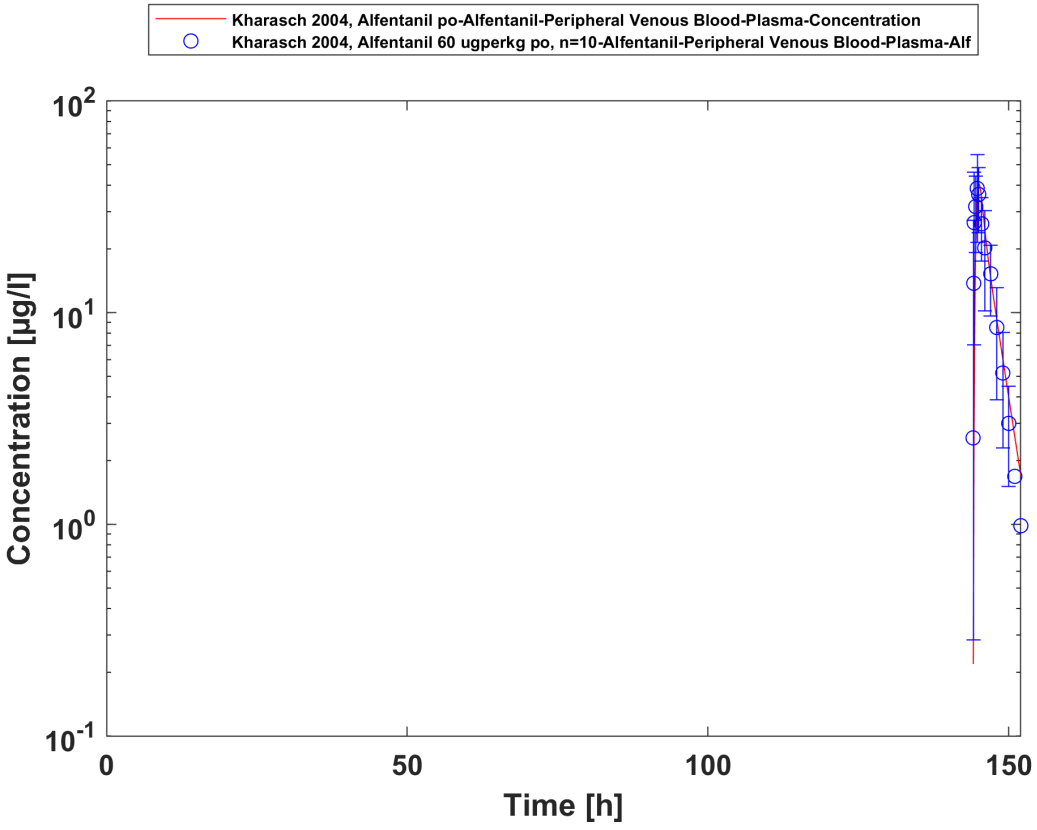

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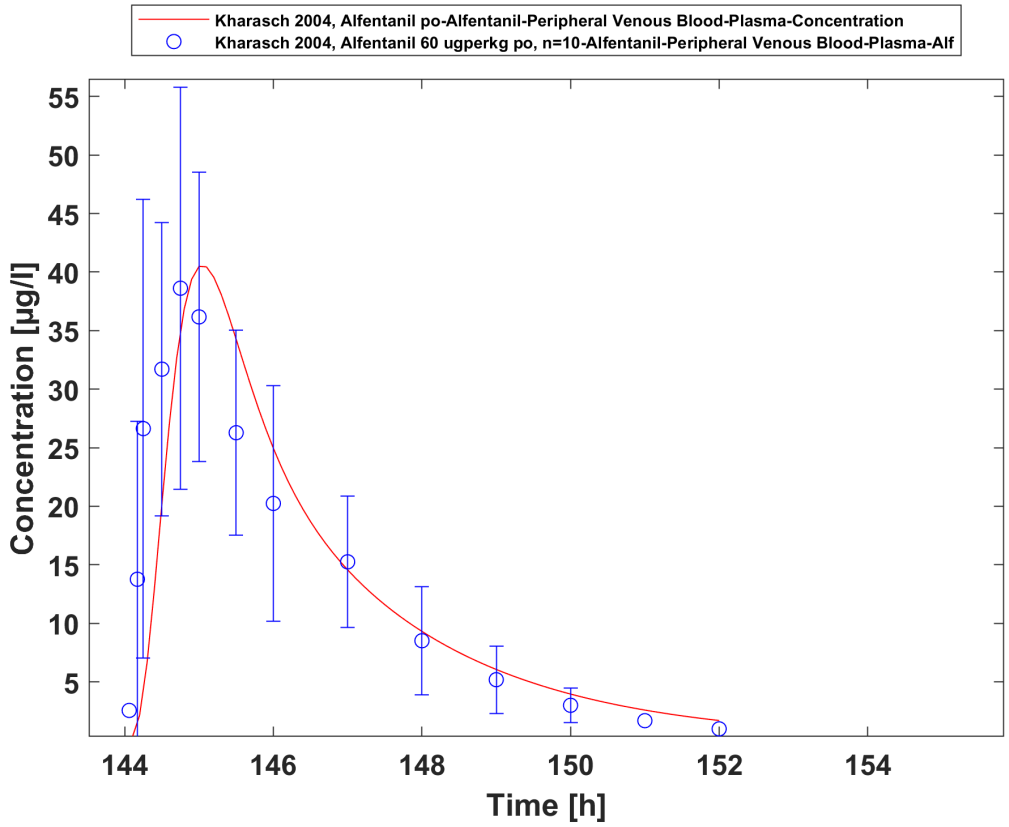
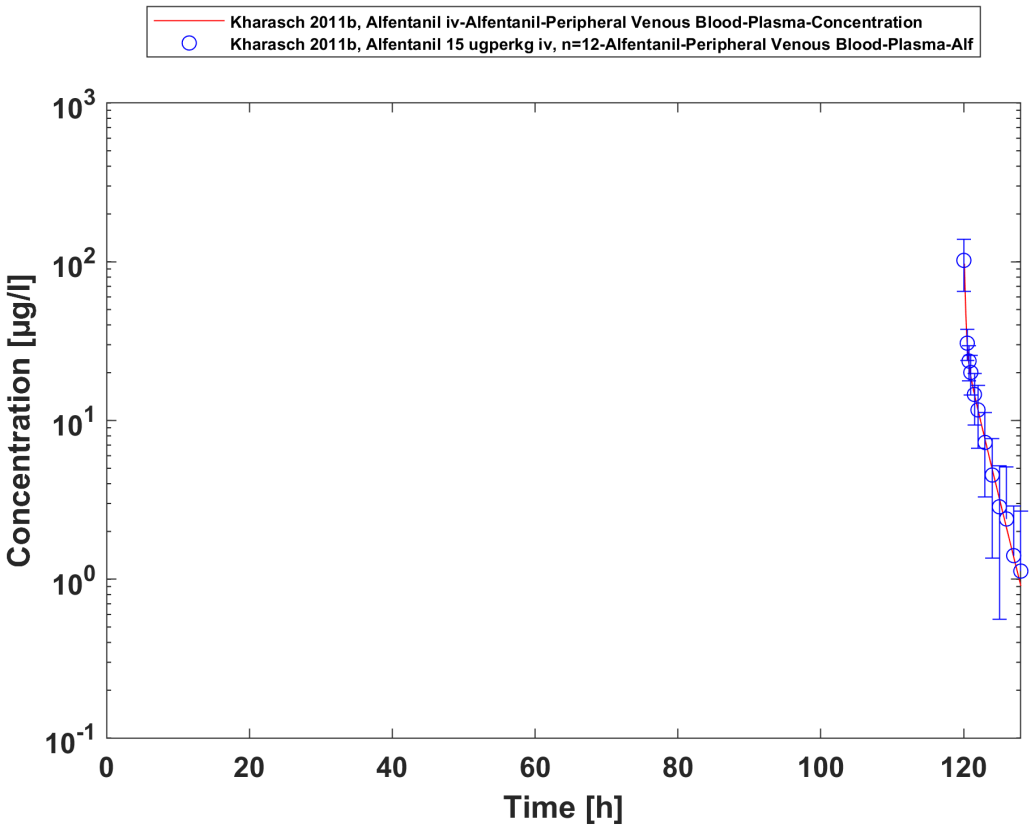


Time Profile Analysis 1



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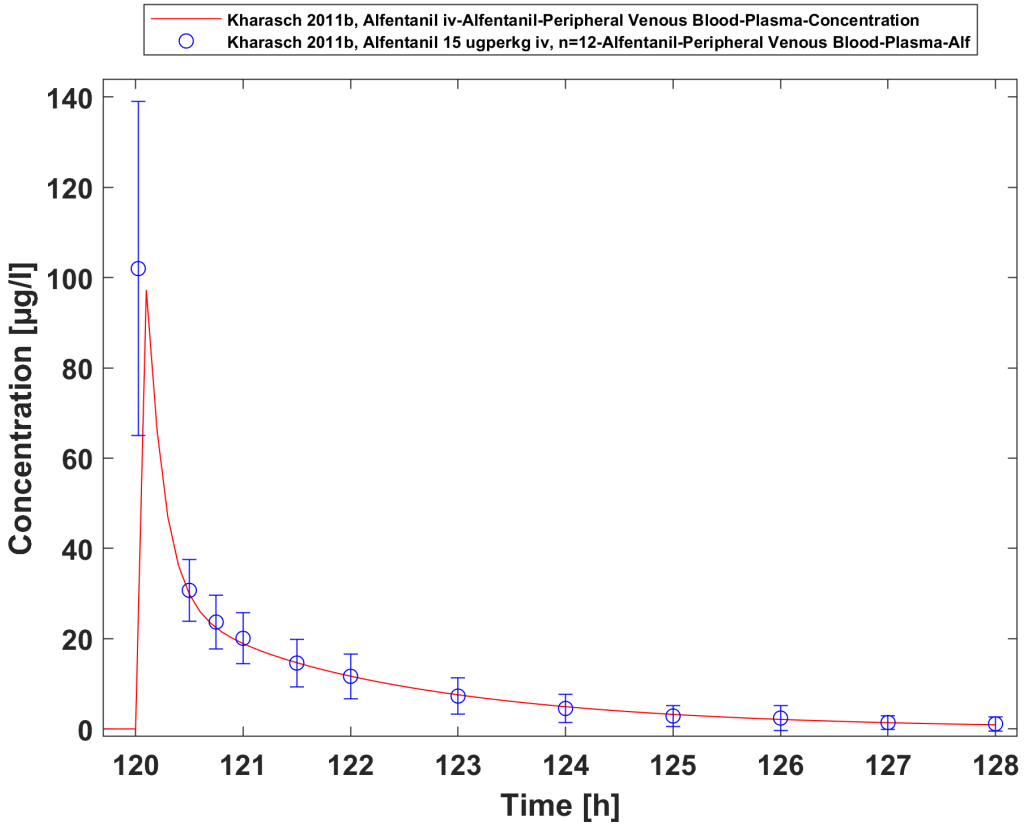
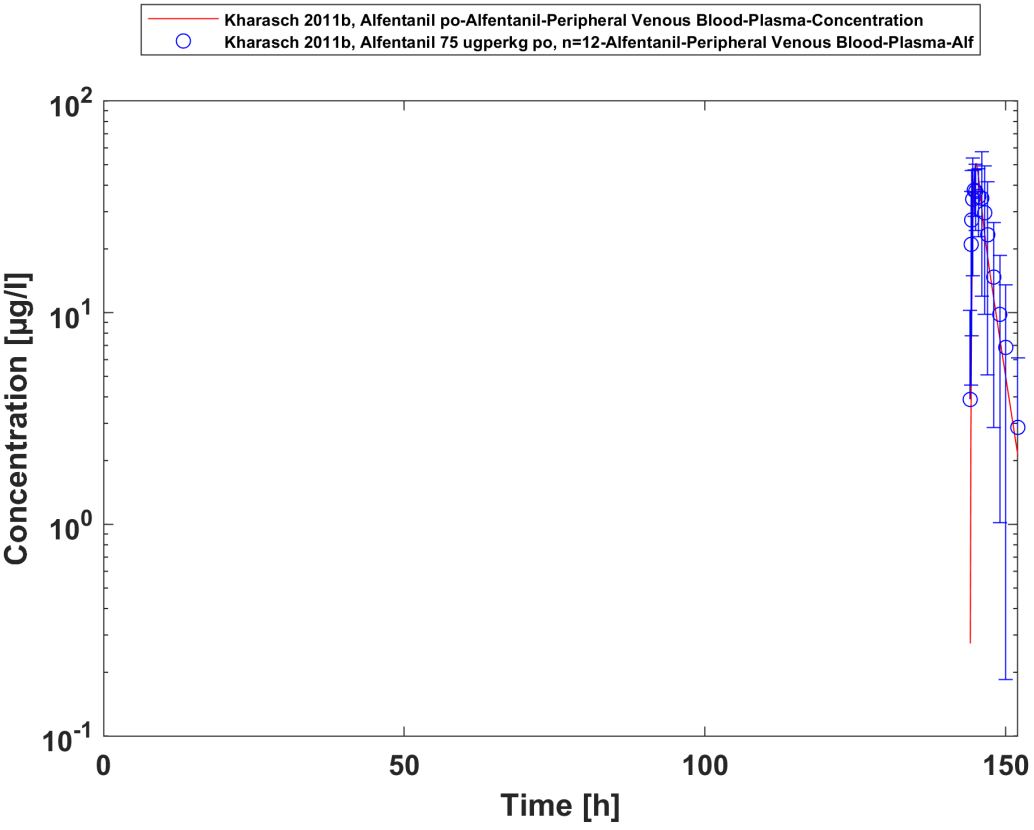
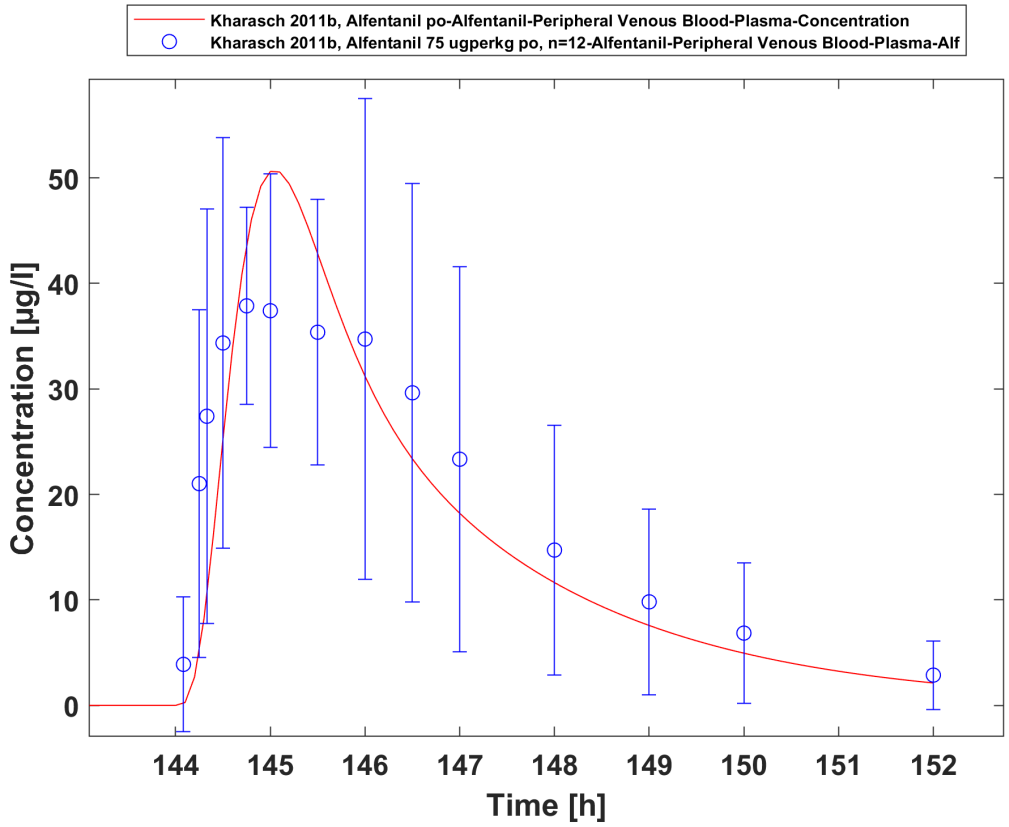


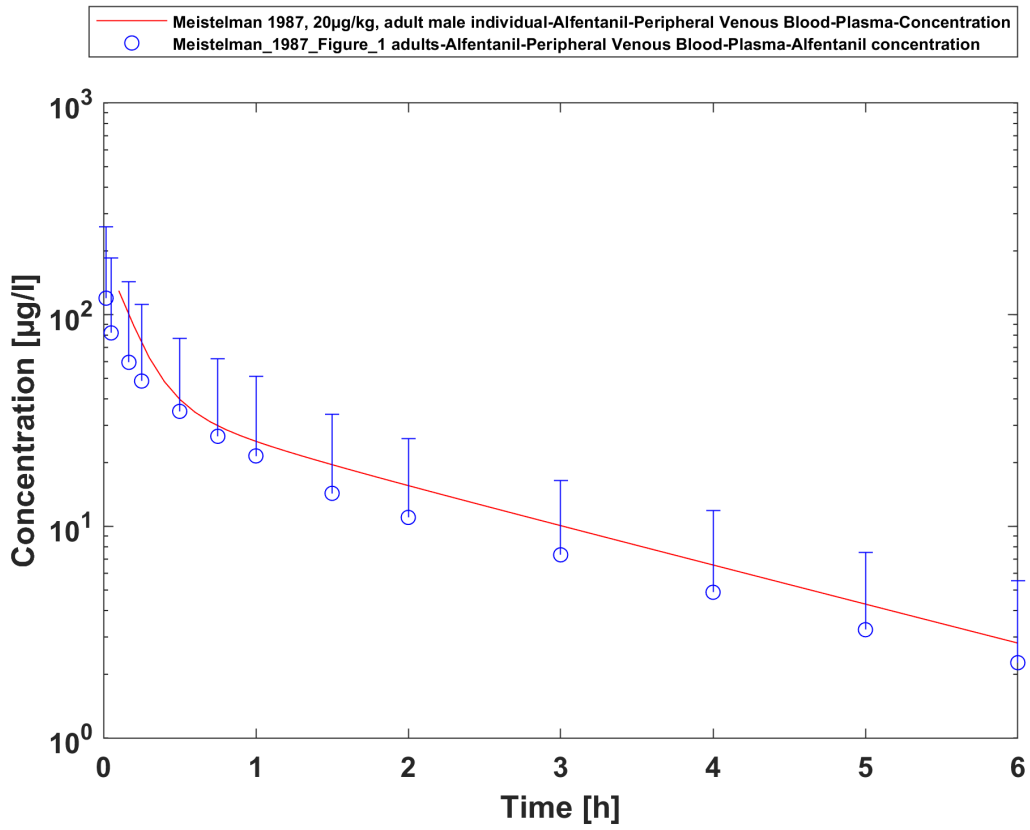
Time Profile Analysis 1



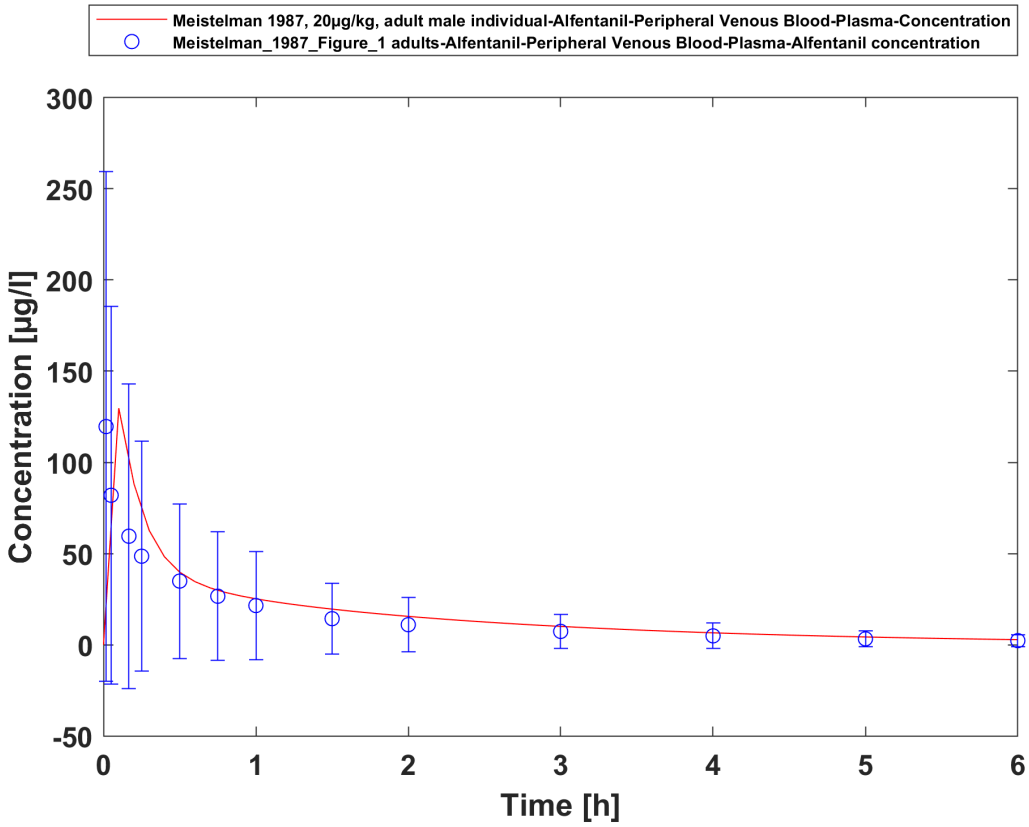
Time Profile Analysis



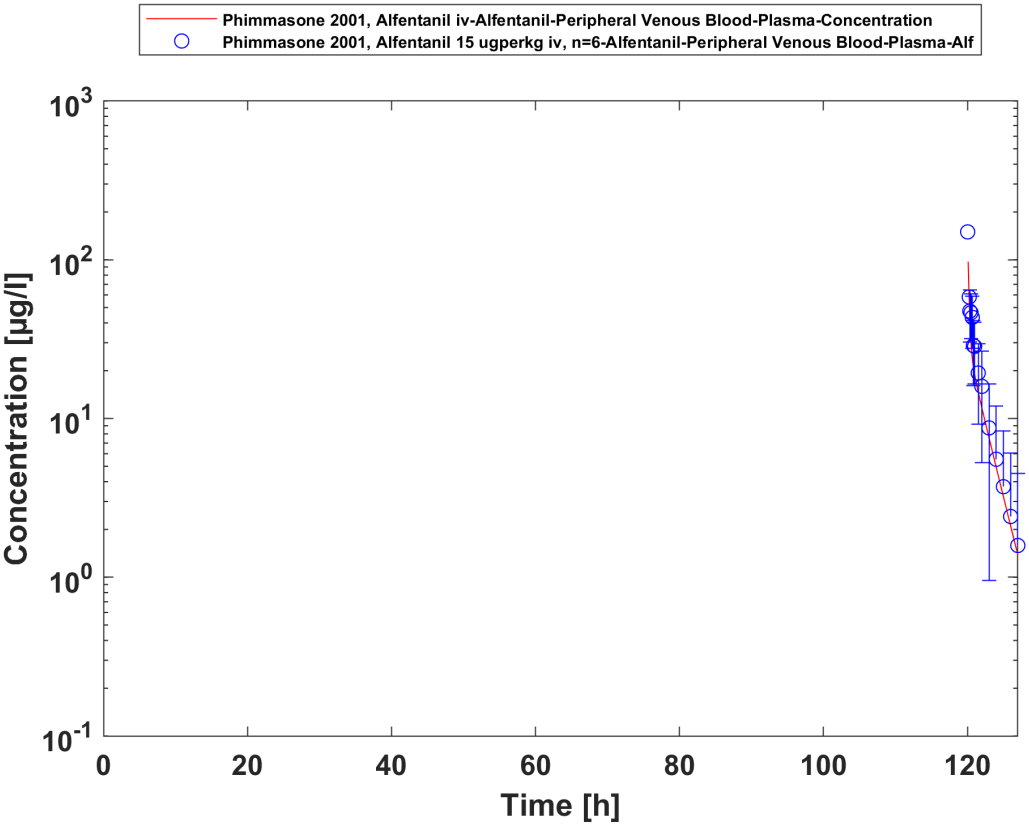
Time Profile Analysis 1



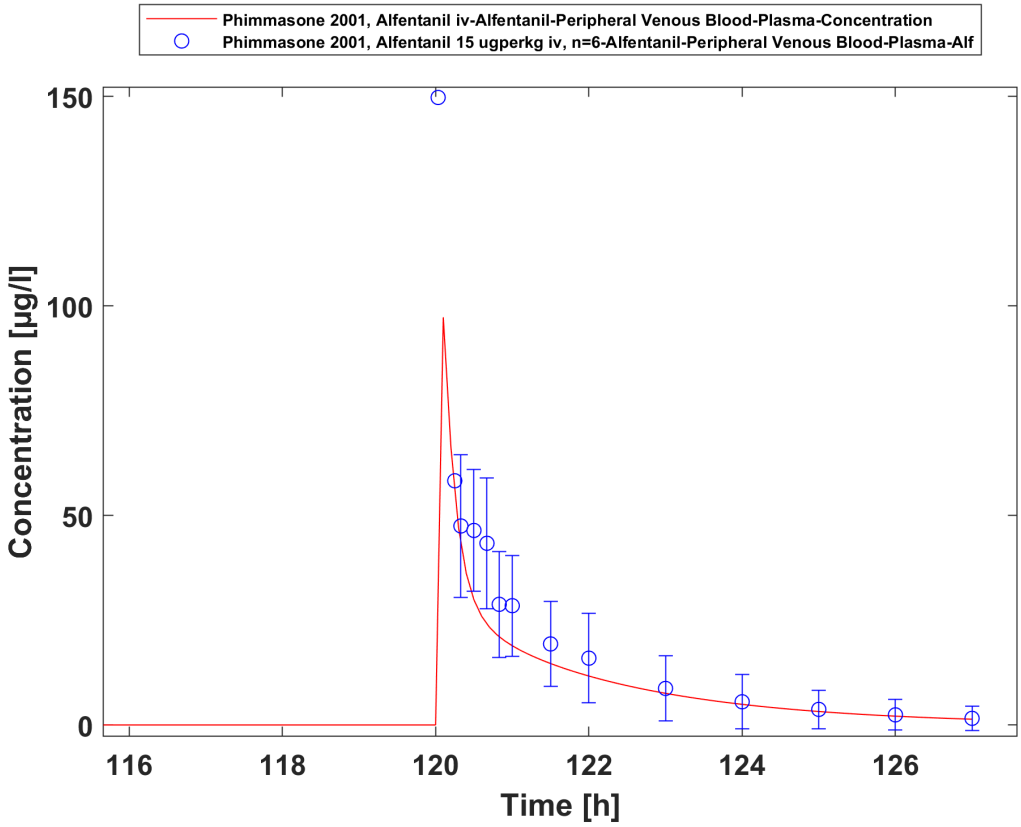
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1