

Building and Evaluation of a PBPK Model for alfentanil in Adults

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1 Introduction

Alfentanil is a potent analgesic synthetic opioid. It is fast but short-acting and used for anesthesia during surgery. Alfentanil is metabolized solely by CYP3A4 ([Phimmasone 2001](# 5 References)). Like midazolam, alfentanil is not a substrate for P-gp ([Wandel 2002](# 5 References)) and less than 1% of an alfentanil dose is excreted unchanged in urine ([Meuldemans 1988](# 5 References)).

Although in clinical use alfentanil is always administered intravenously, some DDI studies published plasma concentration-time profiles of alfentanil following oral ingestion. The presented alfentanil model was established using clinical PK data of 8 publications, covering iv and oral administration and a dosing range from 0.015 to 0.075 mg/kg as well as absolute doses of 1 mg IV and 4 mg PO. The established model is based on ([Hanke 2018](# 5 References)) and applies metabolism by CYP3A4 and glomerular filtration.

The herein presented model building and evaluation report evaluates the performance of the PBPK model for Alfentanil in (healthy) adults. The established Alfentanil PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (<https://github.com/.../Compound-model>).

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by e.g. Kuepfer et al. ([Kuepfer 2016](# 5 References)). The relevant anthropometric (height, weight) and physiological information (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](# References)). This information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

Variability of plasma proteins and CYP3A4 are integrated into PK-Sim® and described in the publicly available PK-Sim® Ontogeny Database Version 7.3 ([Schlender 2016](# 5 References)) or otherwise referenced for the specific process.

First, a base mean model was built using clinical data including selected single dose studies with intravenous and oral applications (solution) of alfentanil to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK model was developed using a typical European individual. The relative tissue specific expressions of enzymes predominantly being involved in the metabolism of alfentanil was taken from...

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.

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

Details about the structural model and its parameters can be found in [Section 2.3](#2.3 Model Parameters and Assumptions).

2.2 Data

2.2.1 In vitro / physico-chemical Data

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

Parameter	Unit	Value	Source	Description
MW	g/mol	416.52		Molecular weight
pK_a		6.5 (base)	[Jansson 2008](# 5 References)	Acid dissociation constant
Solubility (pH)	mg/L	992.0 (6.5)	[Baneyx 2014](# 5 References)	Solubility
logP		2.1, 2.2	[Baneyx 2014](# 5 References), [Jansson 2008](# 5 References)	Partition coefficient between octanol and water
fu	%	8.6, 10.0, 12.0	[Baneyx 2014](# 5 References), [Edginton 2008](#5 References), [Almond 2016](#5 References)	Fraction unbound in plasma

2.2.2 Clinical Data

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

2.2.2.1 Model Building

The following studies were used for model building:

Publication	Arm / Treatment / Information used for model building
[Ferrier 1985](#5 References)	Healthy subjects with a single iv dose of 0.05 mg/kg
[Kharasch 1997](#5 References)	Healthy subjects with a single iv dose of 0.02 mg/kg
[Kharasch 2004](#5 References)	Healthy subjects with a single iv dose of 0.015 mg/kg, healthy subjects with a single oral dose of 0.06 mg/kg
[Kharasch 2011](#5 References)	Healthy subjects with a single iv dose of 0.015 mg/kg, healthy subjects with a single oral dose of 0.075 mg/kg
[Kharasch 2011b](#5 References)	Healthy subjects with an iv dose of 1 mg, healthy subjects with an oral dose of 1 mg
[Kharasch 2012](#5 References)	Healthy subjects with a single iv dose of 0.02 mg/kg
[Meistelman 1987](#5 References)	Healthy subjects with a single dose of 0.02 mg/kg
[Phimmasone 2001](#5 References)	Healthy subjects with a single dose of 0.015 mg/kg

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Absorption observed in clinical studies can be fully explained by passive absorption.

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 PK-Sim Standard.

2.3.3 Metabolism and Elimination

Alfentanil is metabolized solely by CYP3A4.

The first model simulations showed that gut wall metabolization was too low in the PBPK model. In order to increase gut wall metabolization, the "mucosa permeability on basolateral side" was estimated. This may lead to higher gut wall concentrations and, in turn, to a higher gut wall elimination. This parameter was preferred over other parameters such as relative CYP3A4 expression or fraction unbound (fu) in the gut wall as it is technically not limited to a maximum value of 100%.

2.3.4 Automated Parameter Identification

The parameter identification tool in PK-Sim has been used to estimate selected model parameters by adjusting to PK data of the clinical studies that were used in the model building process. This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
lipophilicity	1.846	
intestinal permeability	5.737E-4	cm/min
(organ) permeability	6.875E-3	cm/min
mucosa permeability	5.415E-4	cm/min
intrinsic clearance CYP3A4	0.527	l/min

3 Results and Discussion

The PBPK model for alfentanil was developed and evaluated using publically available, clinical pharmacokinetic data from studies listed in [Section 2.2.2](#2.2.2 Clinical Data).

The next sections show:

1. the final model parameters for the building blocks: [Section 3.1](#3.1 Final Input Parameters).
2. the overall goodness of fit: [Section 3.2](#3.2 3.2 Diagnostics Plots).
3. simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: [Section 3.3](#3.3 Concentration-Time Profiles).

3.1 Final input parameters

The compound parameter values of the final PBPK model 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	1.8463211883 Log Units	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28	Fit	True
Fraction unbound (plasma, reference value)	0.1	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28	Healthy	True
Permeability	0.0068752756625 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28	fit	True
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-Drugbank		
Plasma protein binding partner	α 1-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	0.5272297928 l/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	0.06	Publication-Hanke 2018

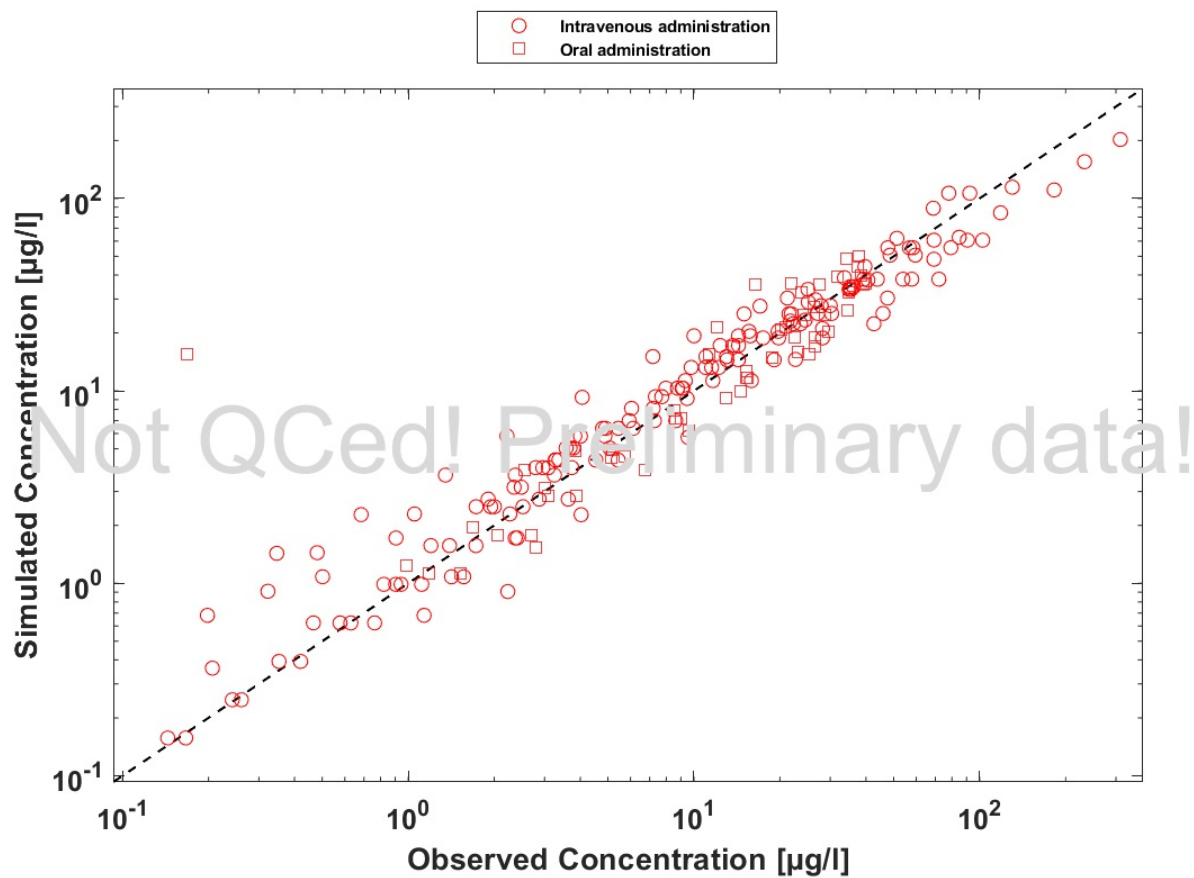
Formulation: Solution

Type: Dissolved

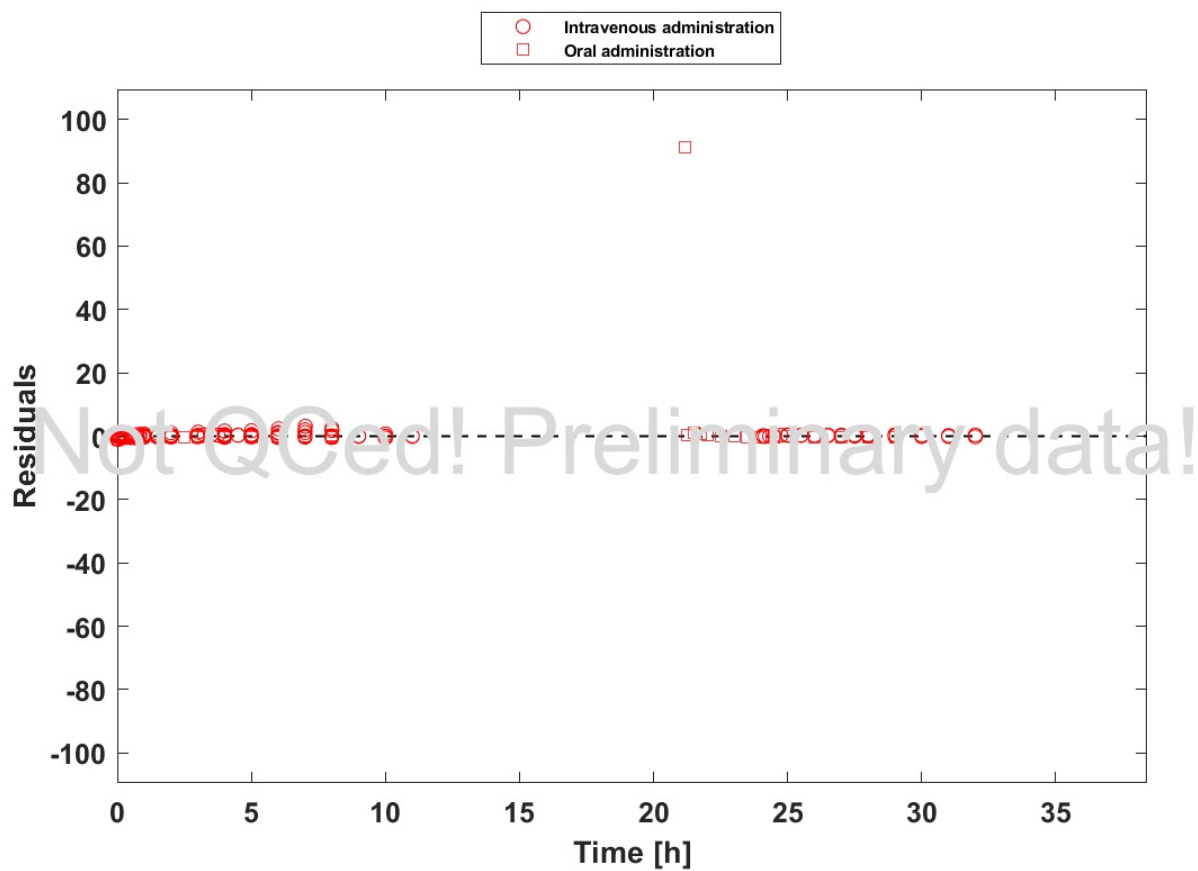
3.2 Diagnostics Plots

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](#2.2.2 Clinical Data).

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



Goodness of fit plot for concentration in plasma



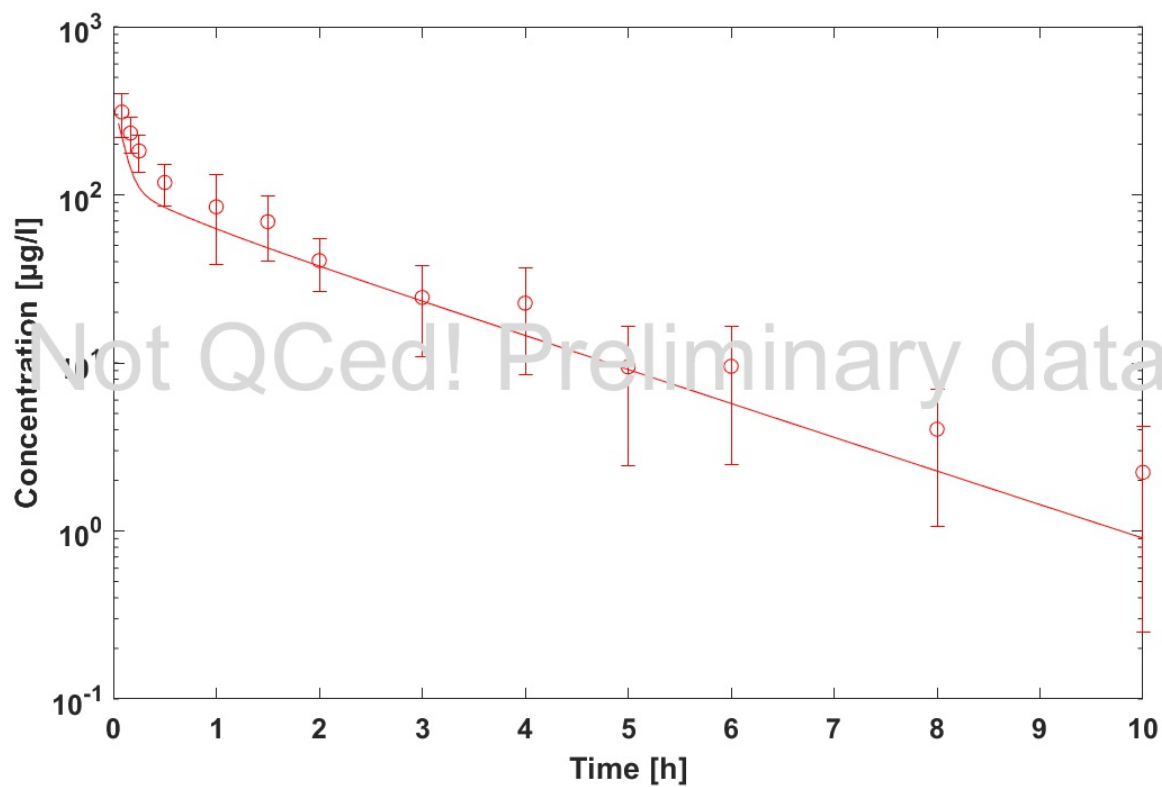
Goodness of fit plot for concentration in plasma

GMFE = 1.337255

3.3: Concentration-Time Profiles

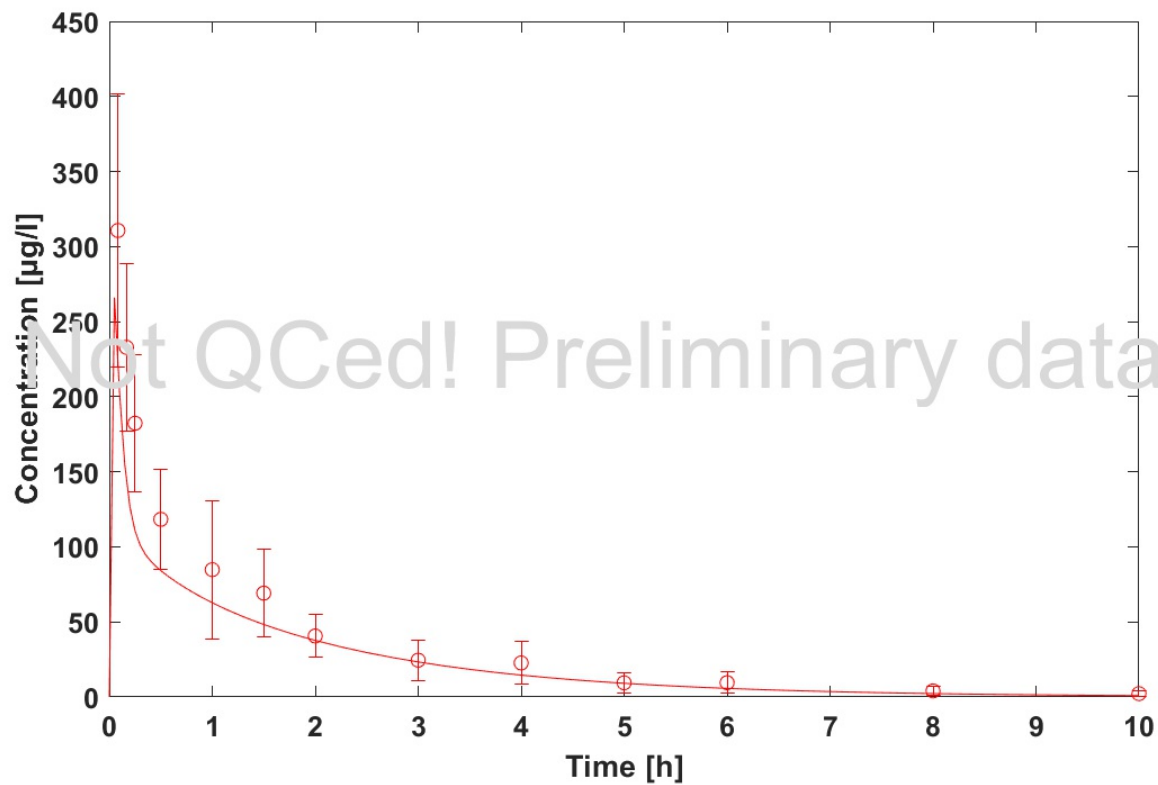
Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#2.2.2 Clinical Data) are presented below.

— Ferrier 1985, Alfentanil iv-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
○ Ferrier 1985 - healthy control patients - Alfentanil - IV - 0.05 mg/kg - Plasma - agg. (n=10)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



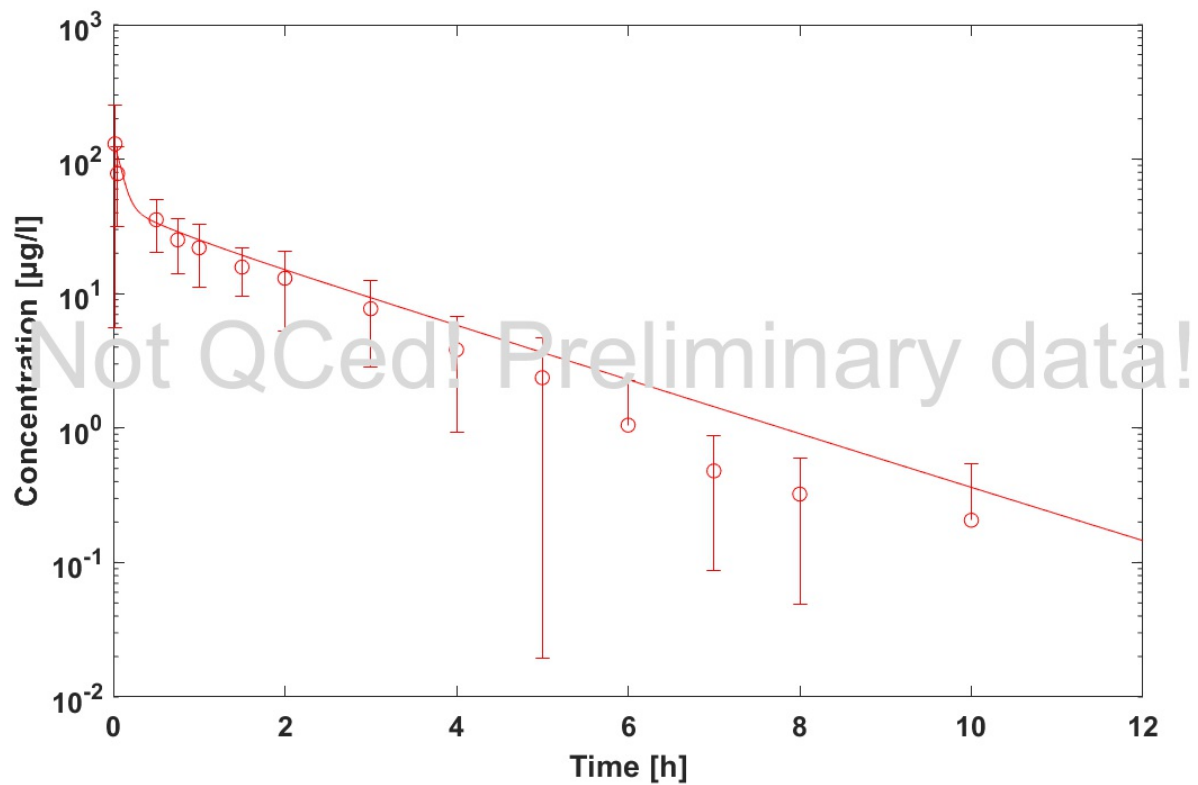
Time Profile Analysis

— Ferrier 1985, Alfentanil iv-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
○ Ferrier 1985 - healthy control patients - Alfentanil - IV - 0.05 mg/kg - Plasma - agg. (n=10)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



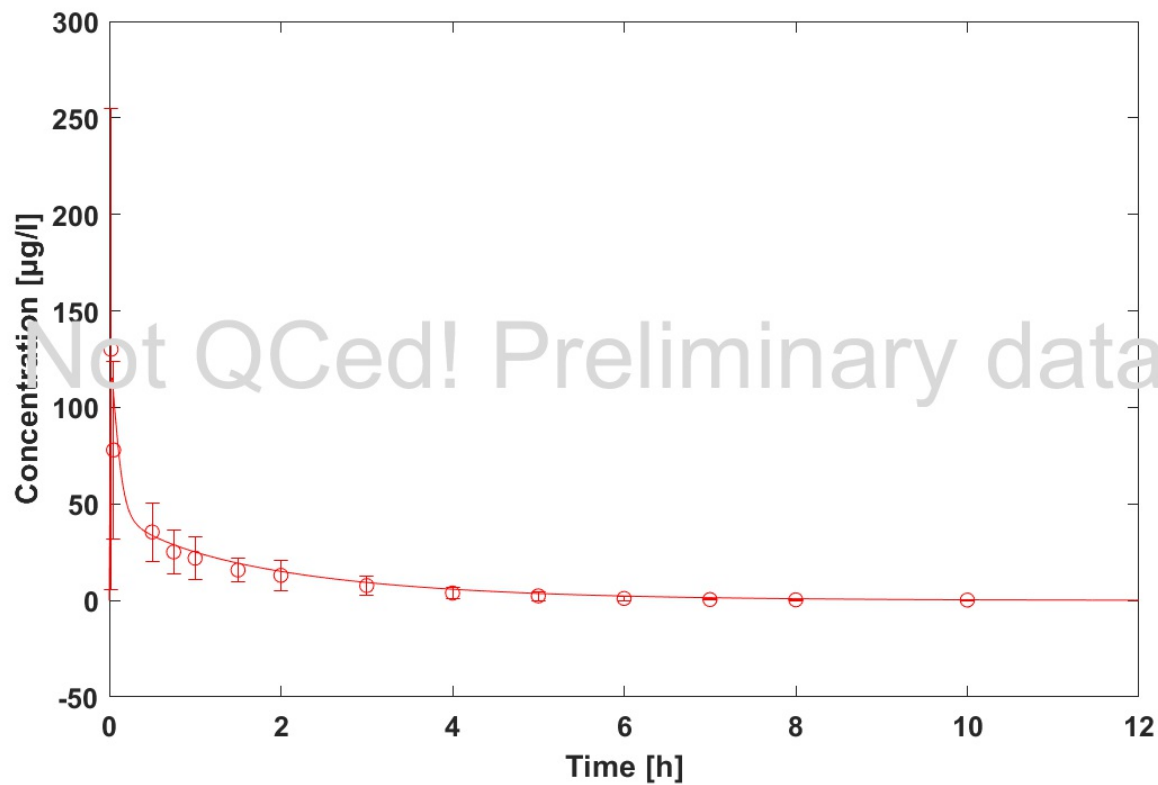
Time Profile Analysis 1

Kharasch 1997, Alfentanil iv 0.02 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
Kharasch 1997 - Control (Perpetrator Placebo) - Alfentanil - IV - 20 µg/kg - Plasma - agg. (n=9)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



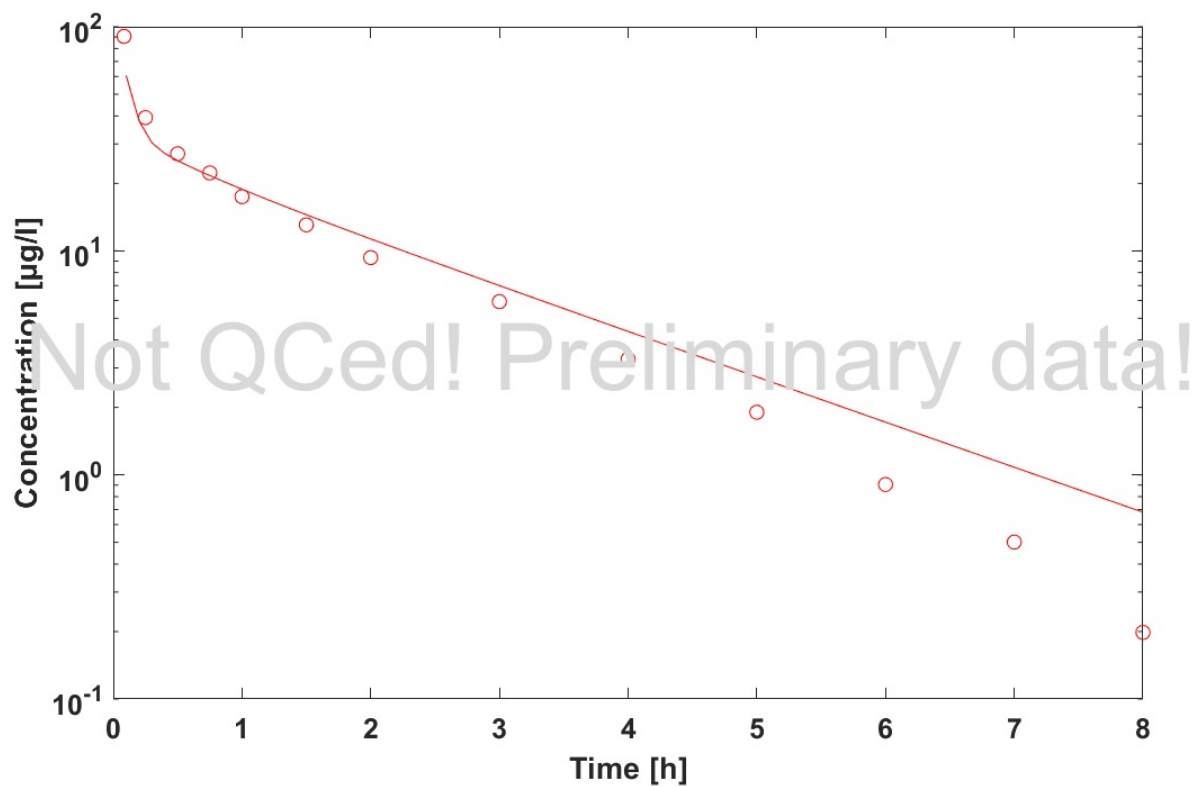
Time Profile Analysis

Kharasch 1997, Alfentanil iv 0.02 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
Kharasch 1997 - Control (Perpetrator Placebo) - Alfentanil - IV - 20 µg/kg - Plasma - agg. (n=9)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



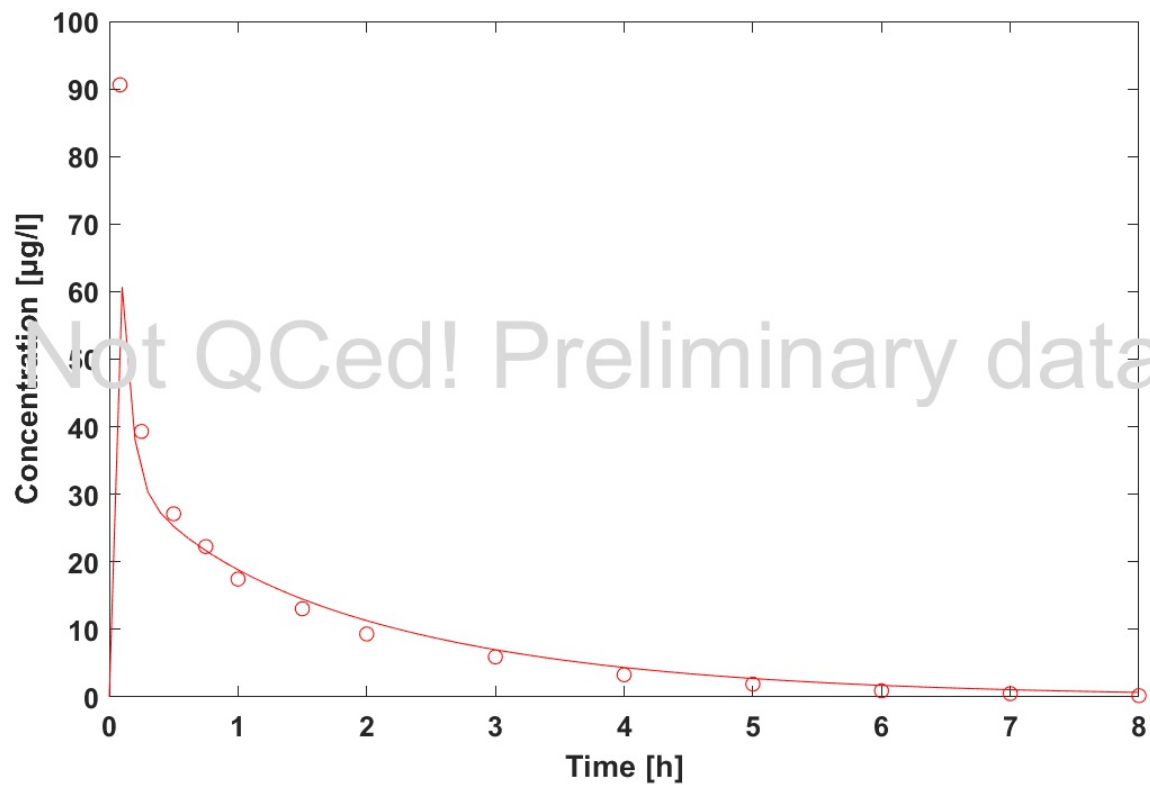
Time Profile Analysis 1

irasch 2004, Alfentanil iv 0.015 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
irasch 2004 - iv Control (Perpetrator Placebo) - Alfentanil - IV - 15 µg/kg - Plasma - agg. (n=10)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



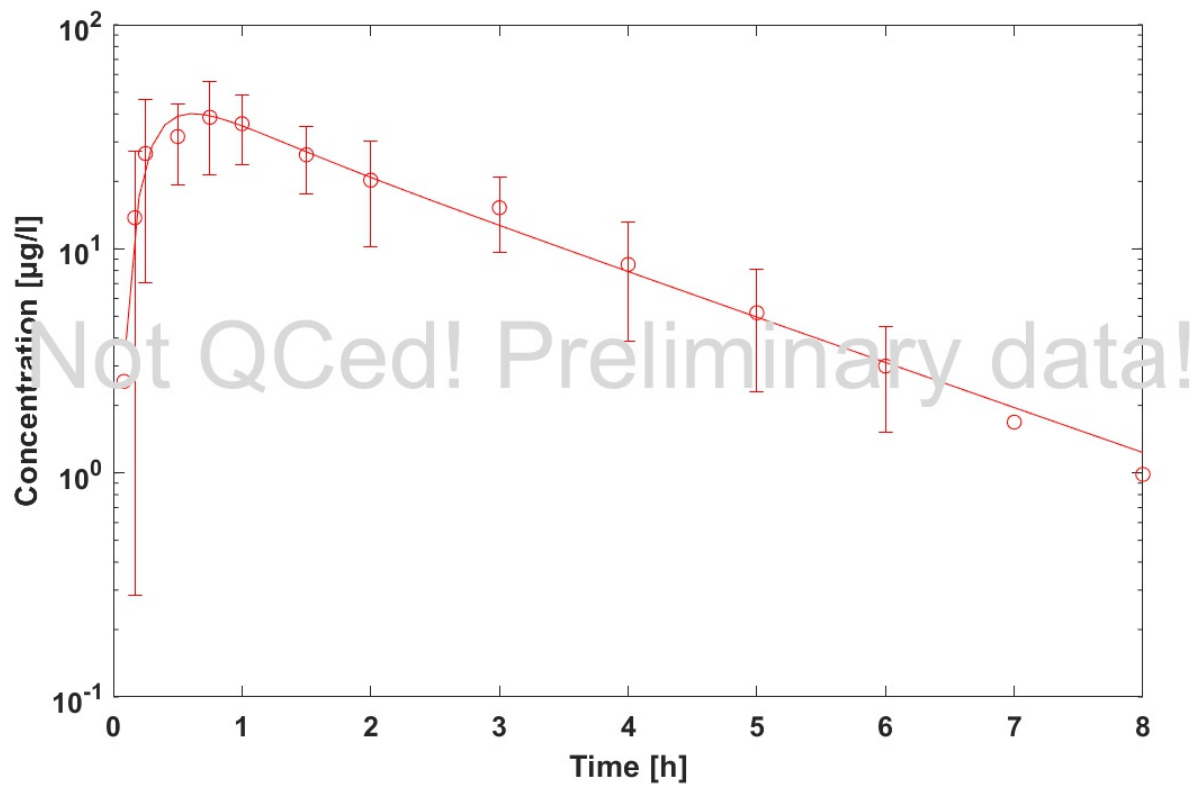
Time Profile Analysis

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irrasch 2004 - iv Control (Perpetrator Placebo) - Alfentanil - IV - 15 µg/kg - Plasma - agg. (n=10)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



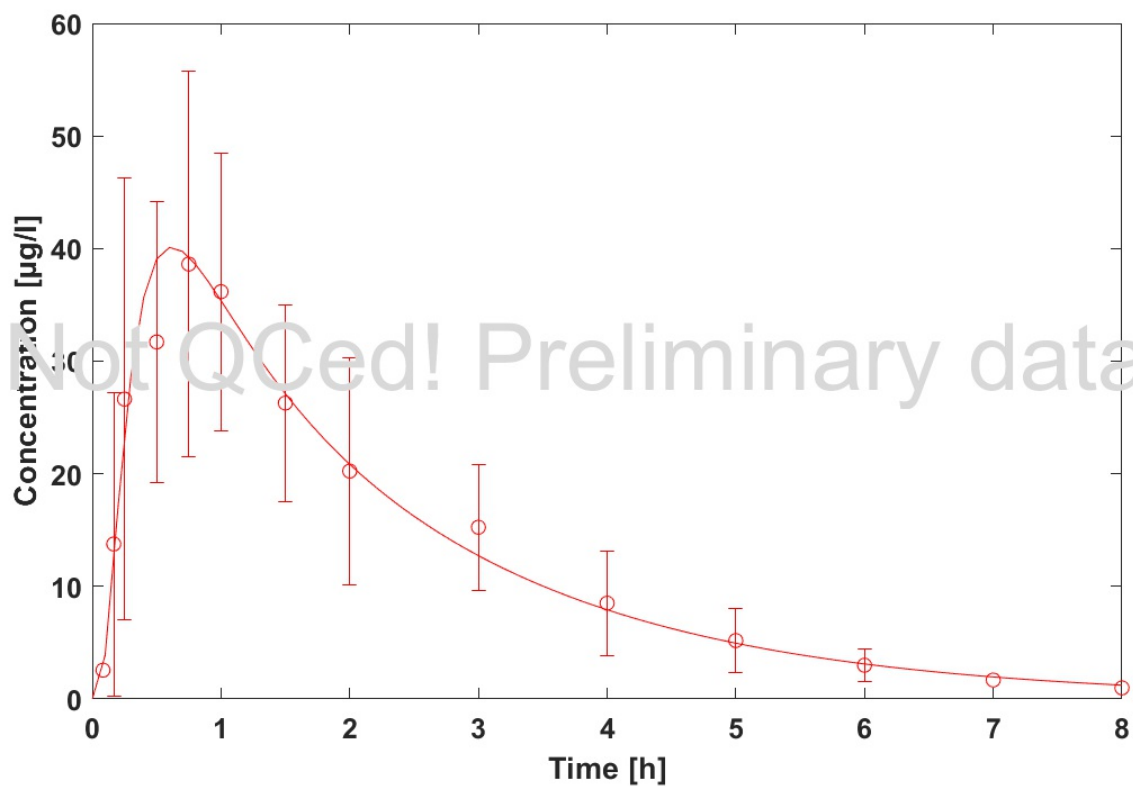
Time Profile Analysis 1

entamil po 0.06 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
#1 (60 µg/kg) Control (Perpetrator Placebo) - Alfentanil - PO - 60 µg/kg - Plasma - agg. (n=10)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



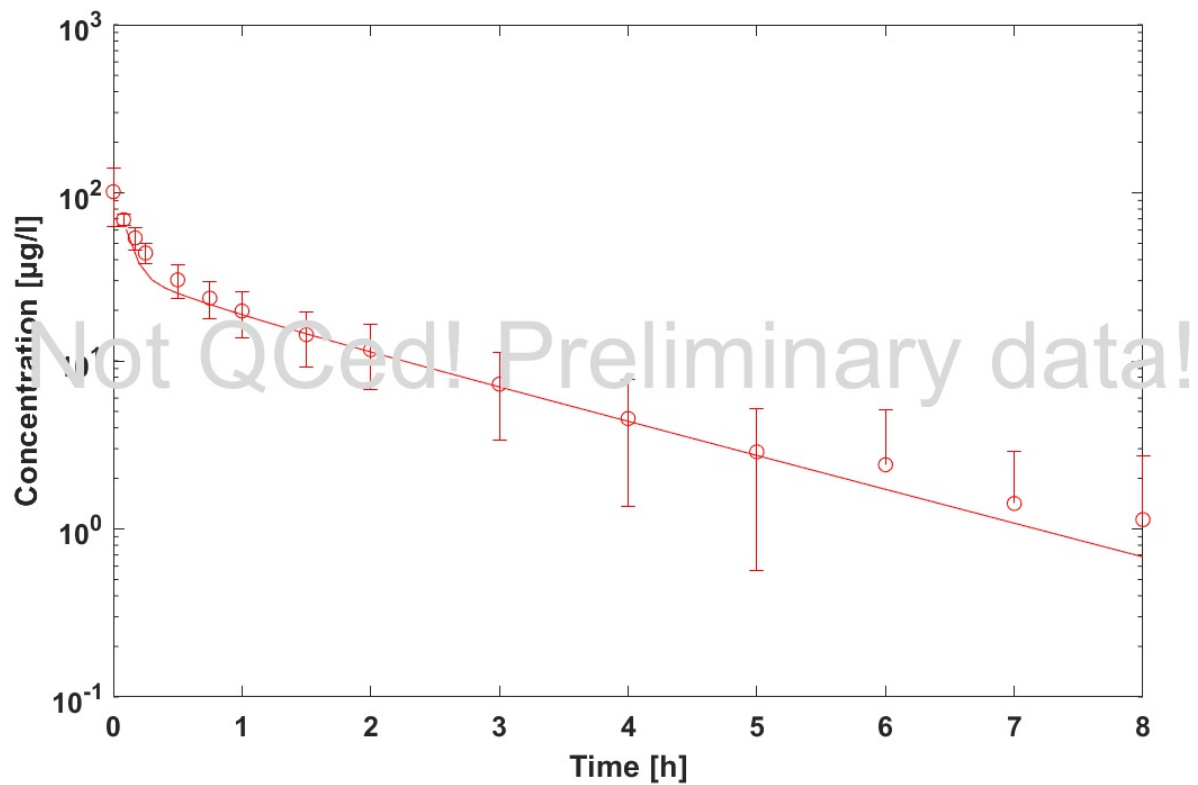
Time Profile Analysis

entamil po 0.06 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
#1 (60 µg/kg) Control (Perpetrator Placebo) - Alfentanil - PO - 60 µg/kg - Plasma - agg. (n=10)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



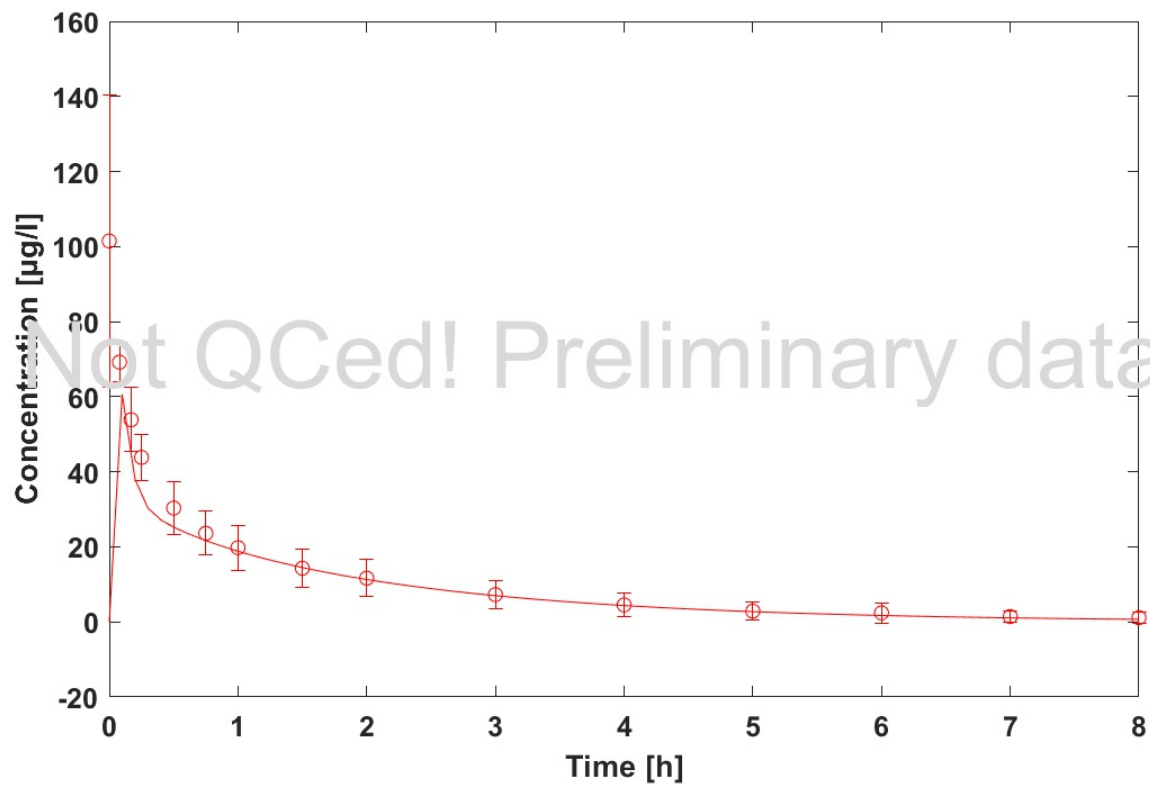
Time Profile Analysis 1

irrasch 2011, Alfentanil iv 0.015 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
irrasch 2011 - iv Control (Perpetrator Placebo) - Alfentanil - IV - 15 µg/kg - Plasma - agg. (n=12)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



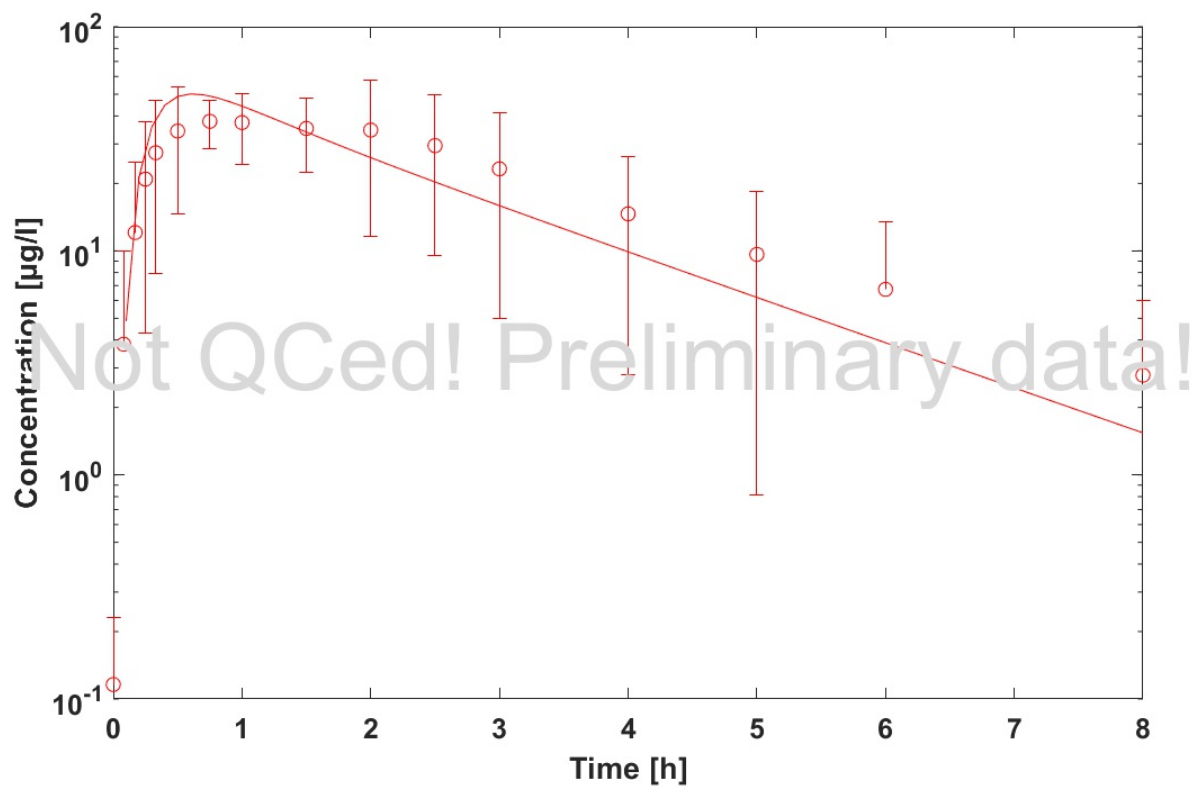
Time Profile Analysis

irrasch 2011, Alfentanil iv 0.015 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
irrasch 2011 - iv Control (Perpetrator Placebo) - Alfentanil - IV - 15 µg/kg - Plasma - agg. (n=12)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



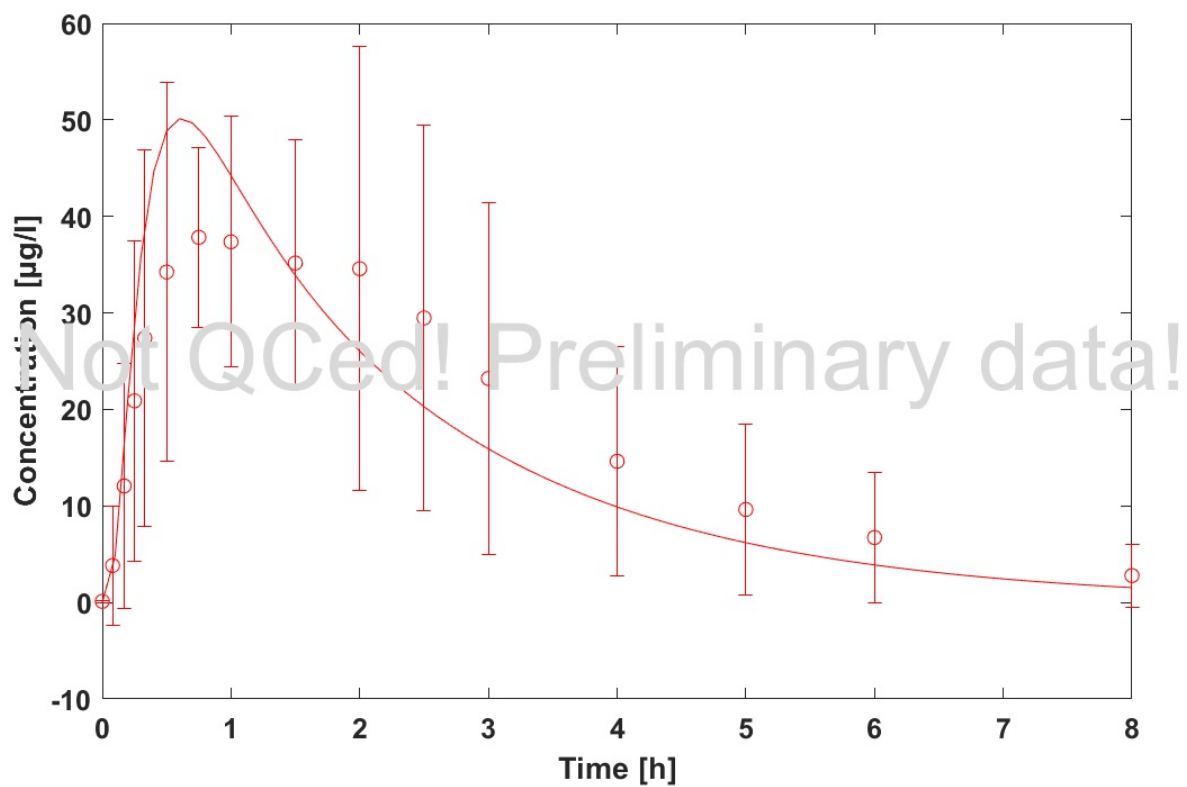
Time Profile Analysis 1

isch 2011, Alfentanil po 0.075 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
isch 2011 - po Control (Perpetrator Placebo) - Alfentanil - PO - 75 µg/kg - Plasma - agg. (n=12)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



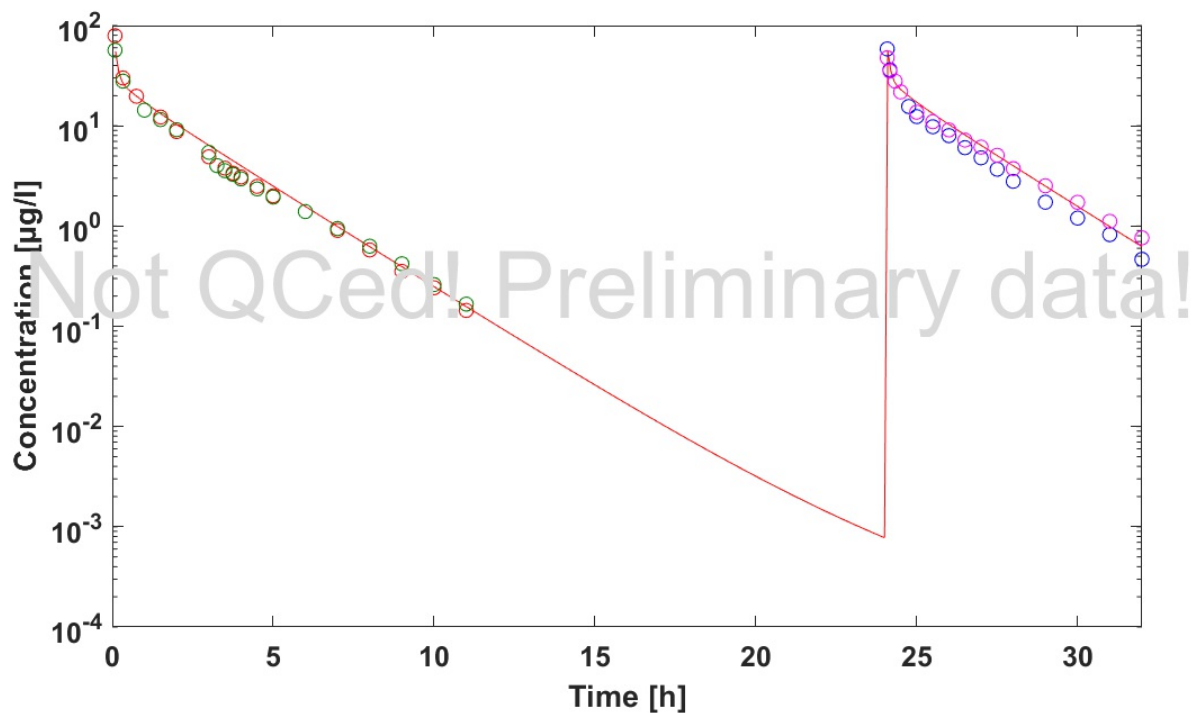
Time Profile Analysis

isch 2011, Alfentanil po 0.075 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
isch 2011 - po Control (Perpetrator Placebo) - Alfentanil - PO - 75 µg/kg - Plasma - agg. (n=12)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



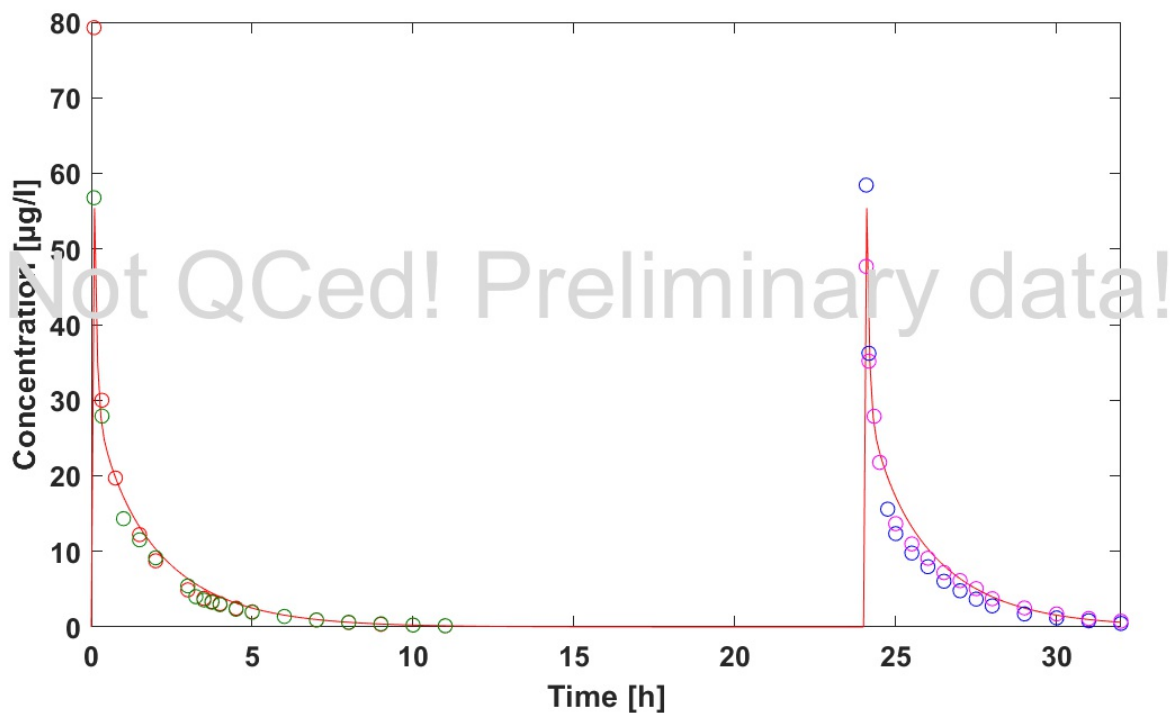
Time Profile Analysis 1

lb, Alfentanil IV 1 mg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
 lb - Alfentanil IV Control sequential - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
 lb - Alfentanil IV Control simultaneous - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
 lb - Alfentanil IV Grapefruit coadmin sequential - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
 lb - Alfentanil IV Grapefruit coadmin simultaneous - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



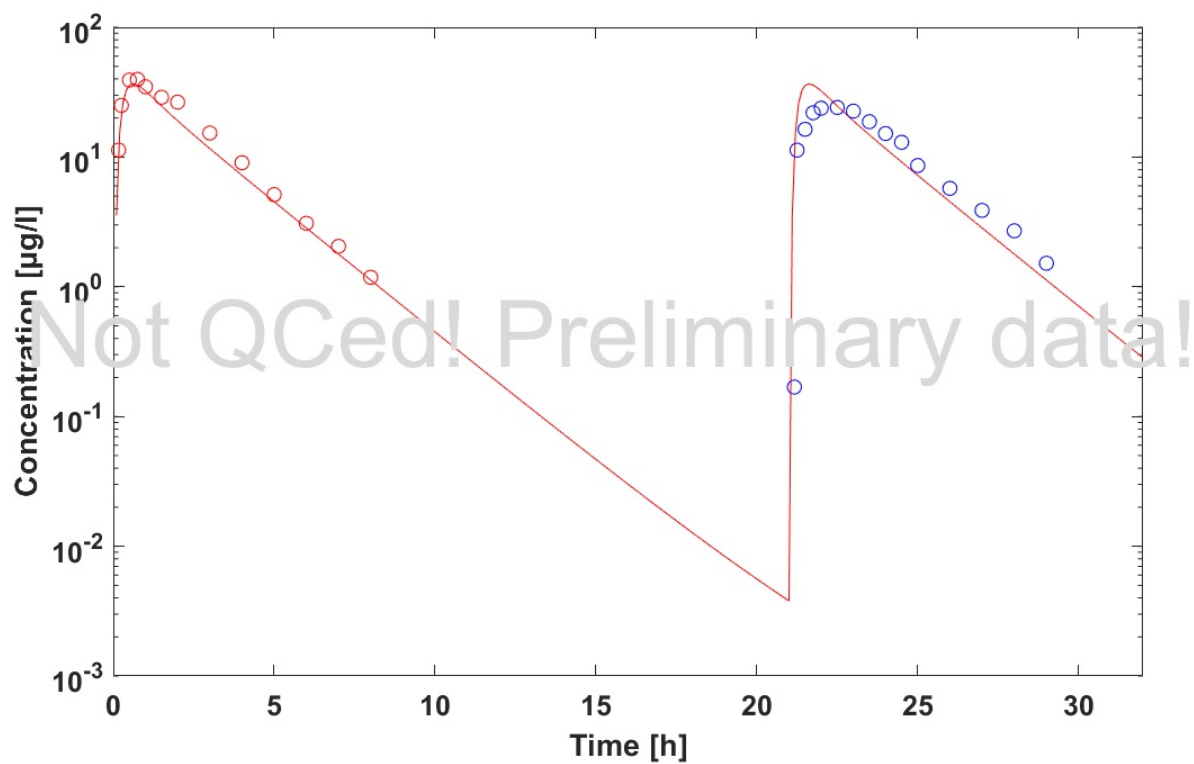
Time Profile Analysis

lb, Alfentanil IV 1 mg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
 lb - Alfentanil IV Control sequential - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
 lb - Alfentanil IV Control simultaneous - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
 lb - Alfentanil IV Grapefruit coadmin sequential - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
 lb - Alfentanil IV Grapefruit coadmin simultaneous - Alfentanil - IV - 1 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



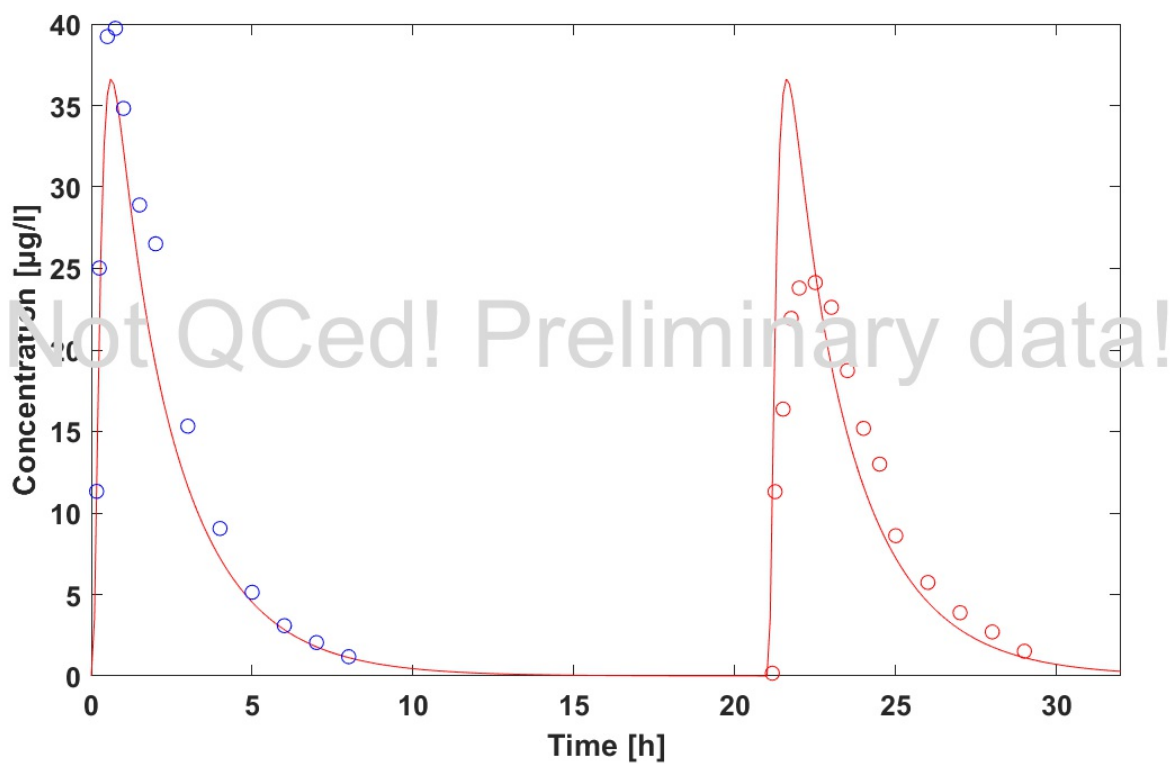
Time Profile Analysis 1

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 asch 2011b - Alfentanil PO Control simultaneous - Alfentanil - PO - 4 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
 asch 2011b - Alfentanil PO Control sequential - Alfentanil - PO - 4 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean

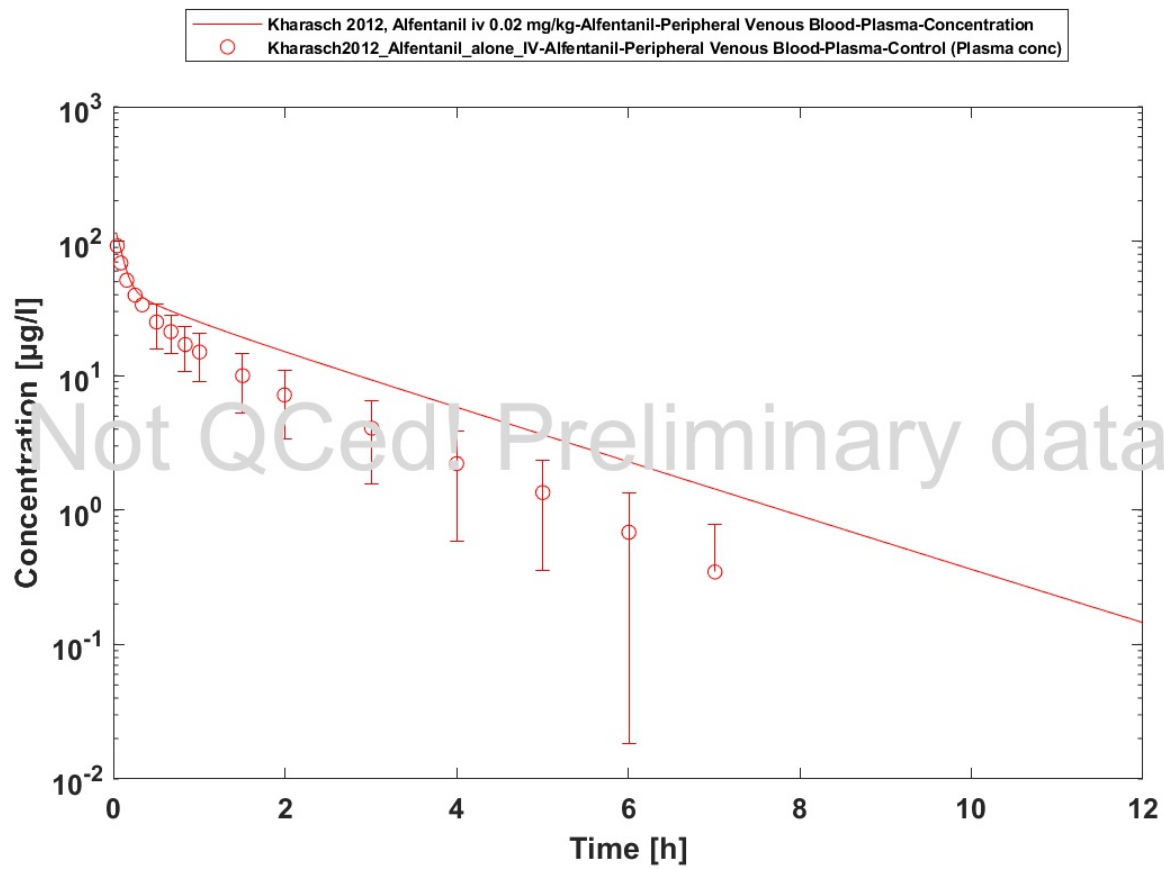


Time Profile Analysis

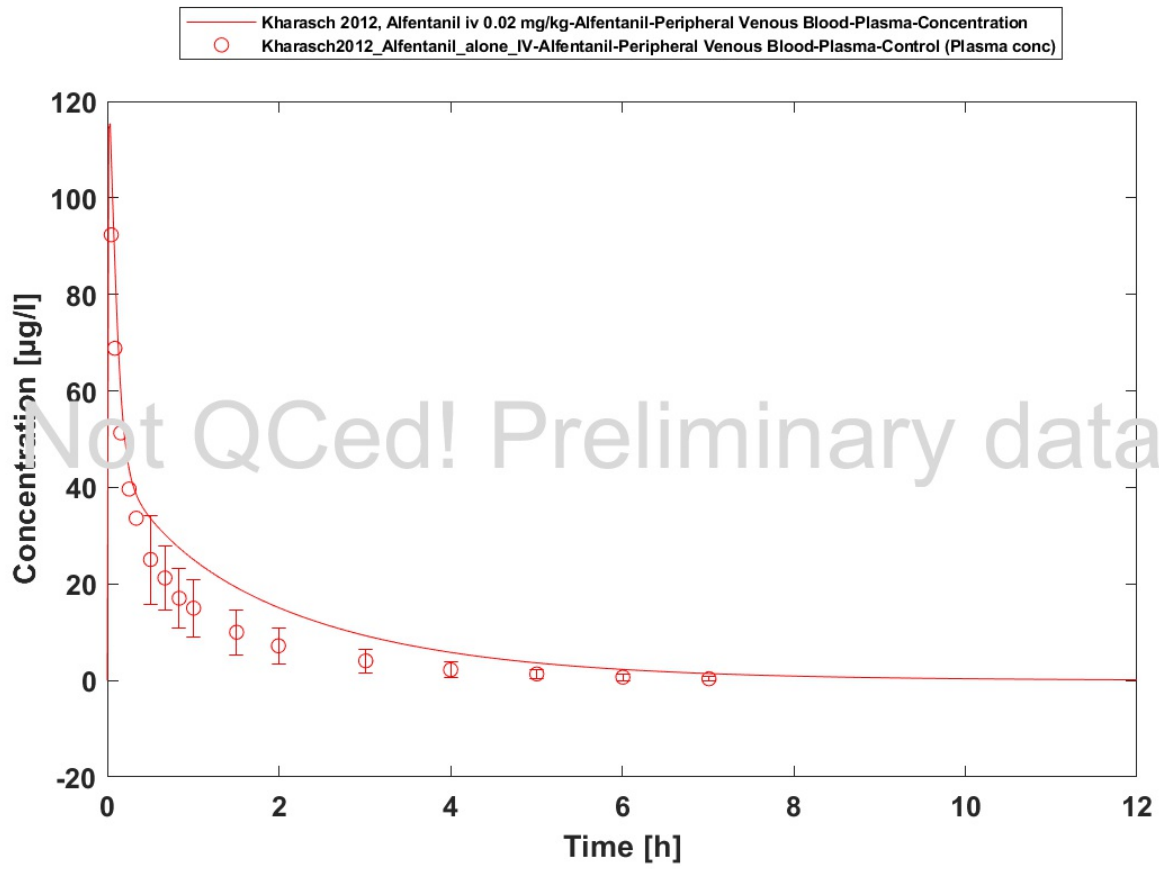
asch 2011b, Alfentanil PO 4 mg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
asch 2011b - Alfentanil PO Control simultaneous - Alfentanil - PO - 4 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean
asch 2011b - Alfentanil PO Control sequential - Alfentanil - PO - 4 mg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



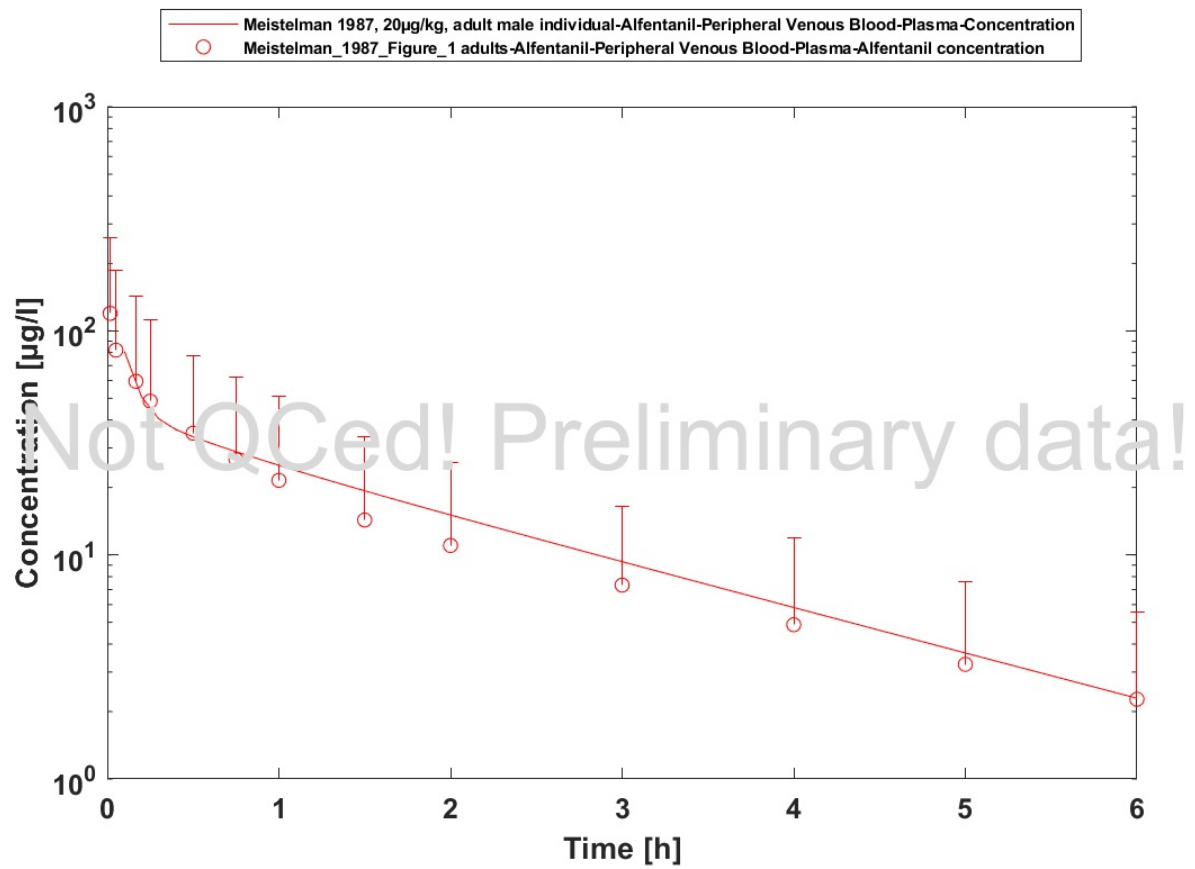
Time Profile Analysis 1



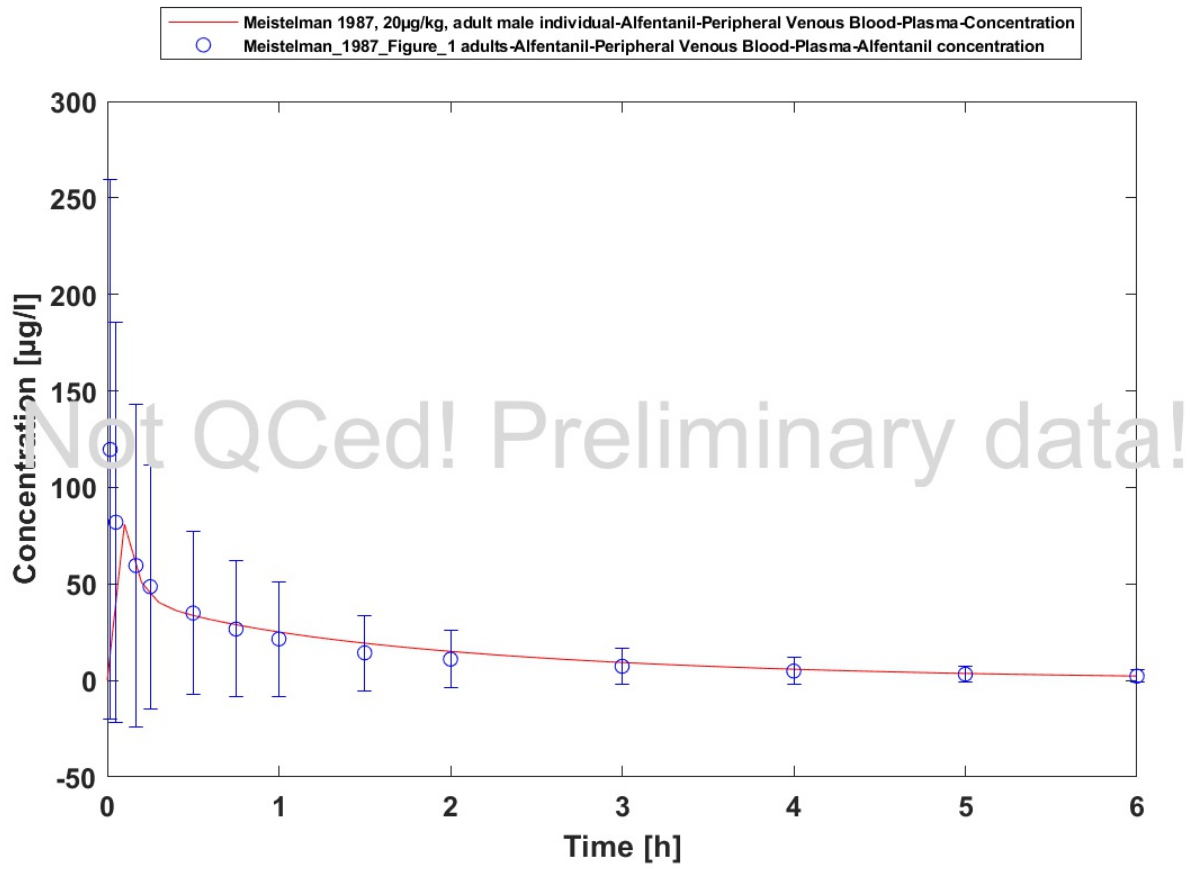
Time Profile Analysis



Time Profile Analysis 1

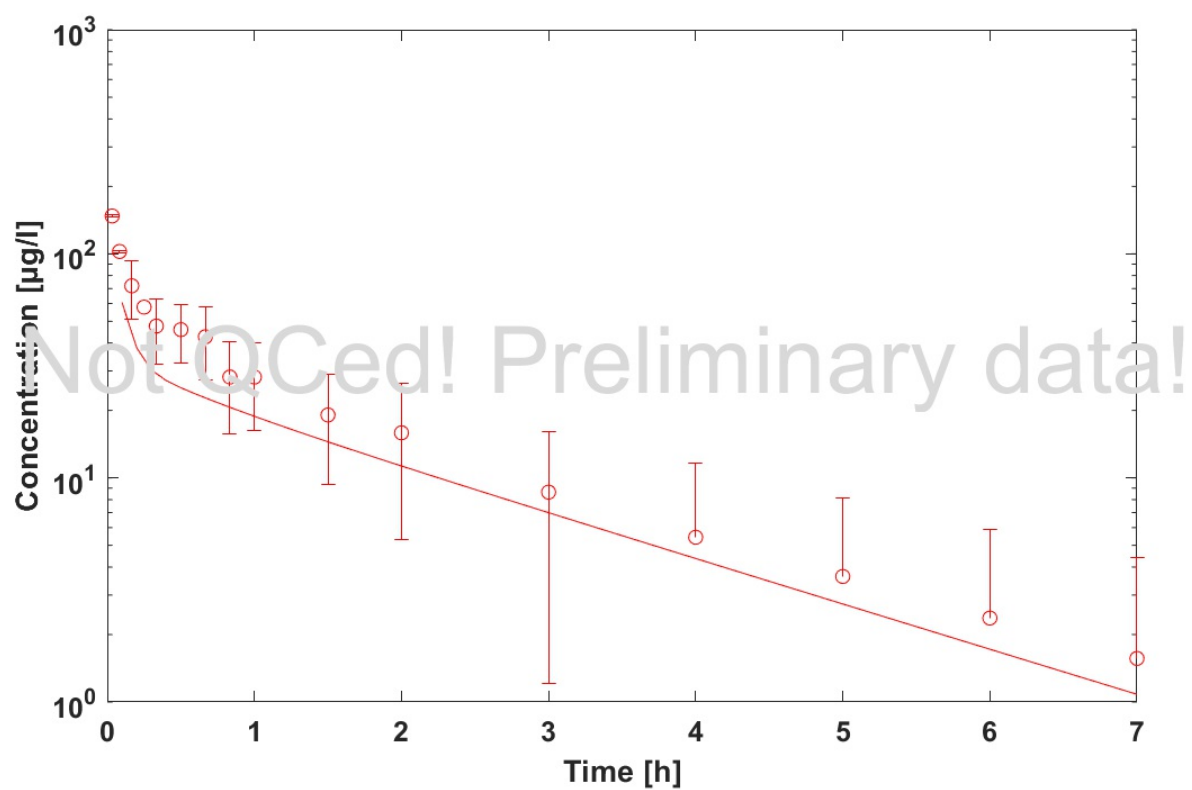


Time Profile Analysis



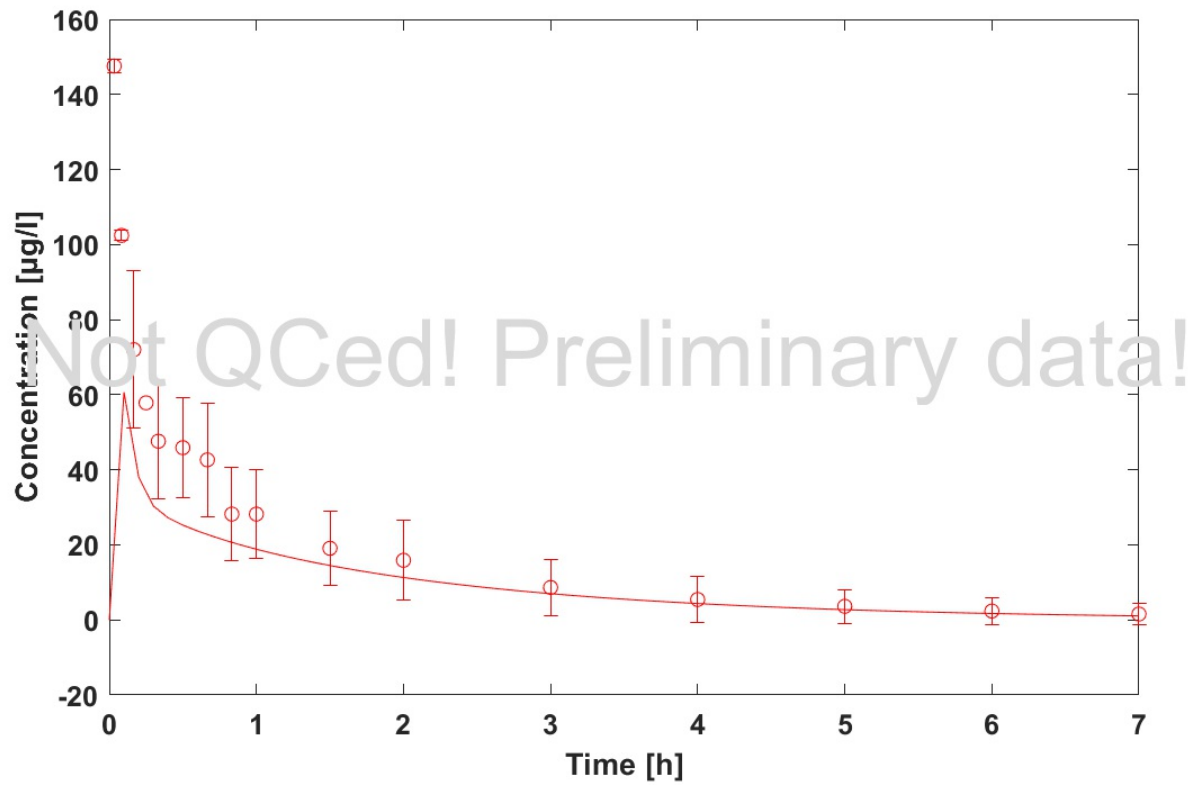
Time Profile Analysis 1

mmasone 2001, Alfentanil iv 0.015 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
mmasone 2001 - Control (Perpetrator Placebo) - Alfentanil - IV - 15 µg/kg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis

mmasone 2001, Alfentanil iv 0.015 mg/kg-Alfentanil-Peripheral Venous Blood-Plasma-Concentration
mmasone 2001 - Control (Perpetrator Placebo) - Alfentanil - IV - 15 µg/kg - Plasma - agg. (n=6)-Alfentanil-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis 1

3.3.1 Model Building

3.3.2 Model Verification

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of alfentanil in adults.

In particular, it applies quantitative ... Thus, the model is fit for purpose to be applied for...

5 References

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