

Building and Evaluation of a PBPK Model for alfentanil in Adults

| | |
|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Version | 3.0-OSP12.1 |
| based on <i>Model Snapshot</i> and <i>Evaluation Plan</i> | https://github.com/Open-Systems-Pharmacology/Alfentanil-Model/releases/tag/v3.0 |
| OSP Version | 12.1 |
| Qualification Framework Version | 3.3 |

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

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

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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](#)). Like midazolam, alfentanil is not a substrate for P-gp ([Wandel 2002](#)) and less than 1% of an alfentanil dose is excreted unchanged in urine ([Meuldermans 1988](#)).

Although in clinical use alfentanil is always administered intravenously (iv), 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 (po) 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 the model developed by Hanke *et al.* ([Hanke 2018](#)) and applies metabolism by CYP3A4 and glomerular filtration.

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](#)). 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 ([Willmann 2007](#)). 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 ([PK-Sim Ontogeny Database Version 7.3](#)) 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 were included in the model as described elsewhere ([Meyer 2012](#)).

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](#).

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

2.2 Data

2.2.1 In vitro / physicochemical Data

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

| Parameter | Unit | Value | Source | Description |
|-----------------|-------|------------|------------------|-----------------------------------------------------------|
| MW | g/mol | 416.52 | DrugBank DB00802 | Molecular weight |
| pK _a | | 6.5 (base) | Jansson 2008 | Acid dissociation constant |
| Solubility (pH) | mg/L | 992 (6.5) | Baneyx 2014 | Solubility |
| logD | | 2.1 | Baneyx 2014 | Partition coefficient between octanol and water at pH 7.4 |
| | | 2.2 | Jansson 2008 | Partition coefficient between octanol and water |
| fu | % | 8.6 | Gertz 2010 | Fraction unbound in plasma |
| | | 10.0 | Edginton 2008 | Fraction unbound in plasma |
| | | 12.0 | Almond 2016 | 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 | Healthy subjects with a single iv dose of 0.05 mg/kg |
| Kharasch 1997 | Healthy subjects with a single iv dose of 0.02 mg/kg |
| Kharasch 2004 | 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 | 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 | Healthy subjects with an iv dose of 1 mg, healthy subjects with an oral dose of 1 mg. Publication compares sequential and simultaneous dosing of oral deuterated and intravenous unlabeled alfentanil. Furthermore, IV and oral administration of alfentanil is combined with grapefruit juice. Grapefruit juice is considered to have no effect on hepatic clearance, and, hence, no effect on IV administered alfentanil |
| Kharasch 2012 | Healthy subjects with a single iv dose of 0.02 mg/kg, healthy subjects with a single oral dose of 0.043 mg/kg |
| Meistelman 1987 | Healthy subjects with a single iv dose of 0.02 mg/kg |
| Phimmasone 2001 | Healthy subjects with a single iv 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 tissue-specific CYP3A4 expression implemented in the model is based on high-sensitive real-time RT-PCR (Nishimura 2013).

The first model simulations showed that gut wall metabolism was too low in the PBPK model. In order to increase gut wall metabolism, the “mucosa permeability on basolateral side” (jointly the model parameters in the mucosa: $P_{(interstitial \rightarrow intracellular)}$ and $P_{(intracellular \rightarrow interstitial)}$) was estimated. This may lead to higher gut wall concentrations and, in turn, to a higher gut wall elimination.

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification:

| Model Parameter | Optimized Value | Unit |
|----------------------------------------------------------------------------------------------------------------------------------------|-----------------|--------|
| Lipophilicity | 1.846 | |
| Specific intestinal permeability | 5.737E-4 | cm/min |
| Specific organ permeability | 6.875E-3 | cm/min |
| Basolateral mucosa permeability ($P_{(interstitial \rightarrow intracellular)}$, $P_{(intracellular \rightarrow interstitial)}$) | 5.415E-4 | cm/min |
| CYP3A4 - 1st order CL - intrinsic clearance | 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](#).

The next sections show:

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

3.1 Final input parameters

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

Compound: 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 | Optimized | True |
| Specific intestinal permeability (transcellular) | 0.00057373577138 cm/min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28 | Optimized | True |
| Is small molecule | Yes | | | |
| Molecular weight | 416.52 g/mol | Publication-Drugbank | | |
| 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 | 0.5272297928 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](#).

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

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

| Group | GMFE |
|----------------------------|------|
| Intravenous administration | 1.26 |
| Oral administration | 1.45 |
| All | 1.32 |

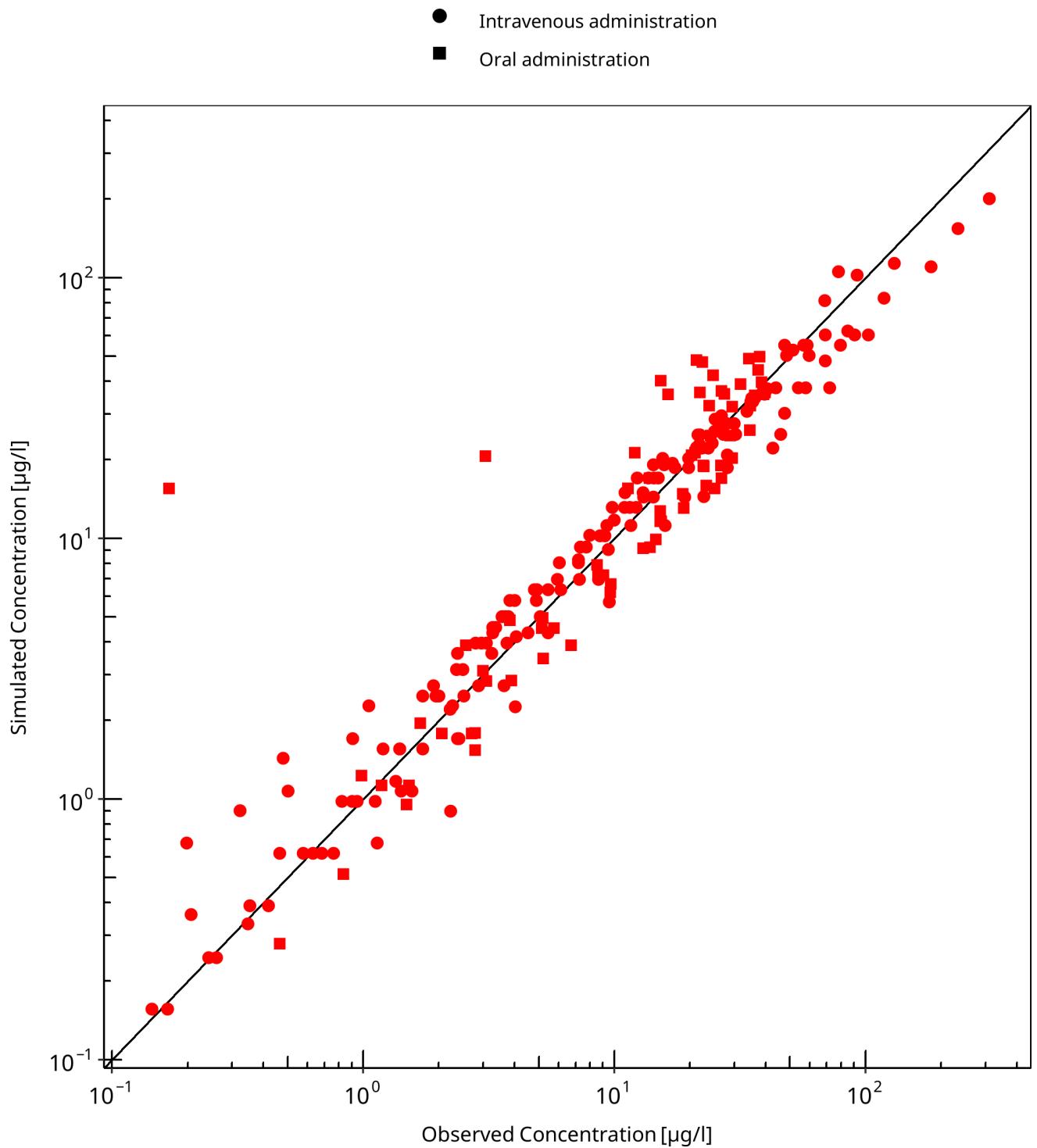


Figure 3-1: Goodness of fit plot for concentration in plasma

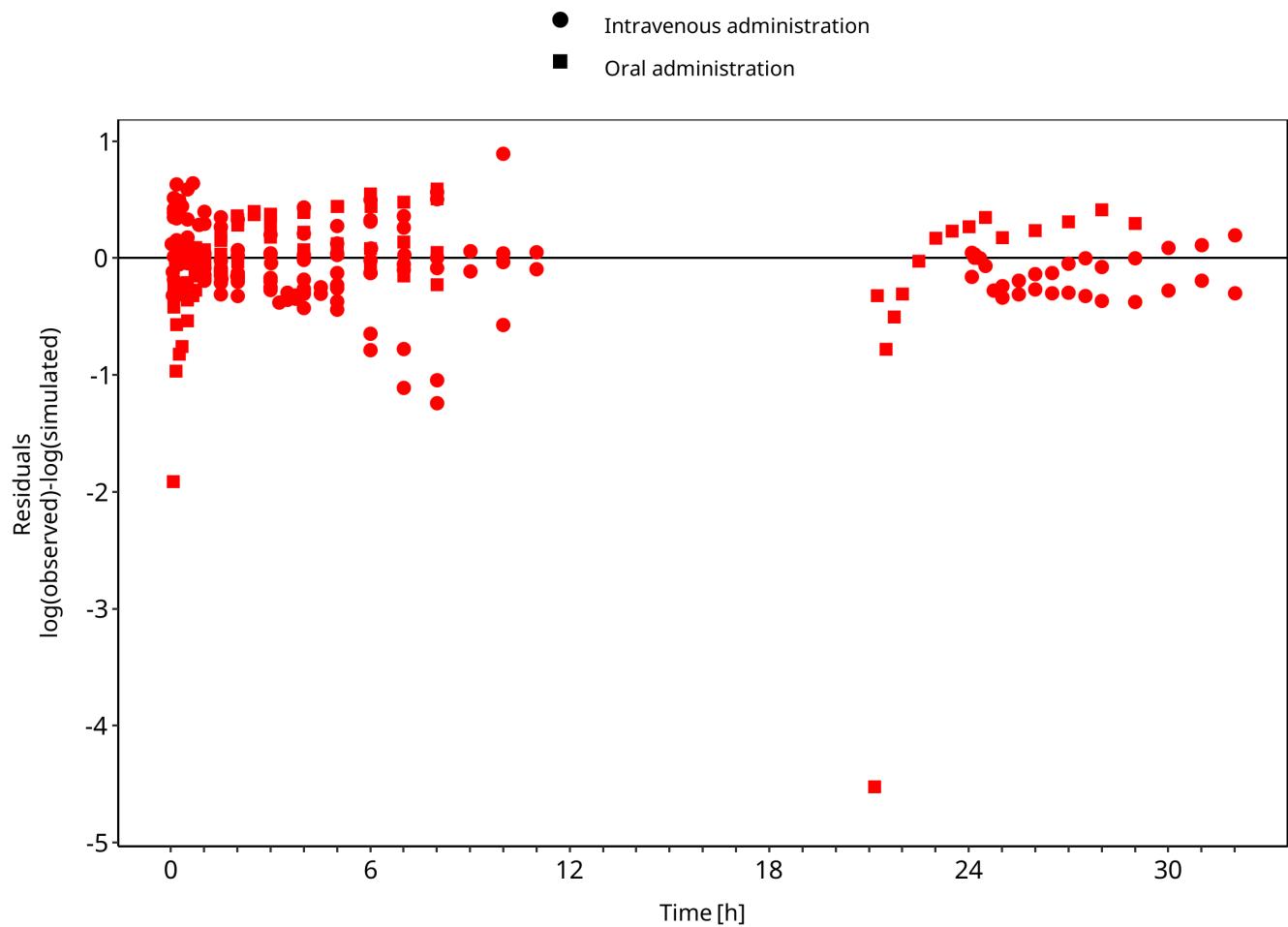


Figure 3-2: Goodness of fit plot for concentration in plasma

3.3 Concentration-Time Profiles

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

3.3.1 Model Building

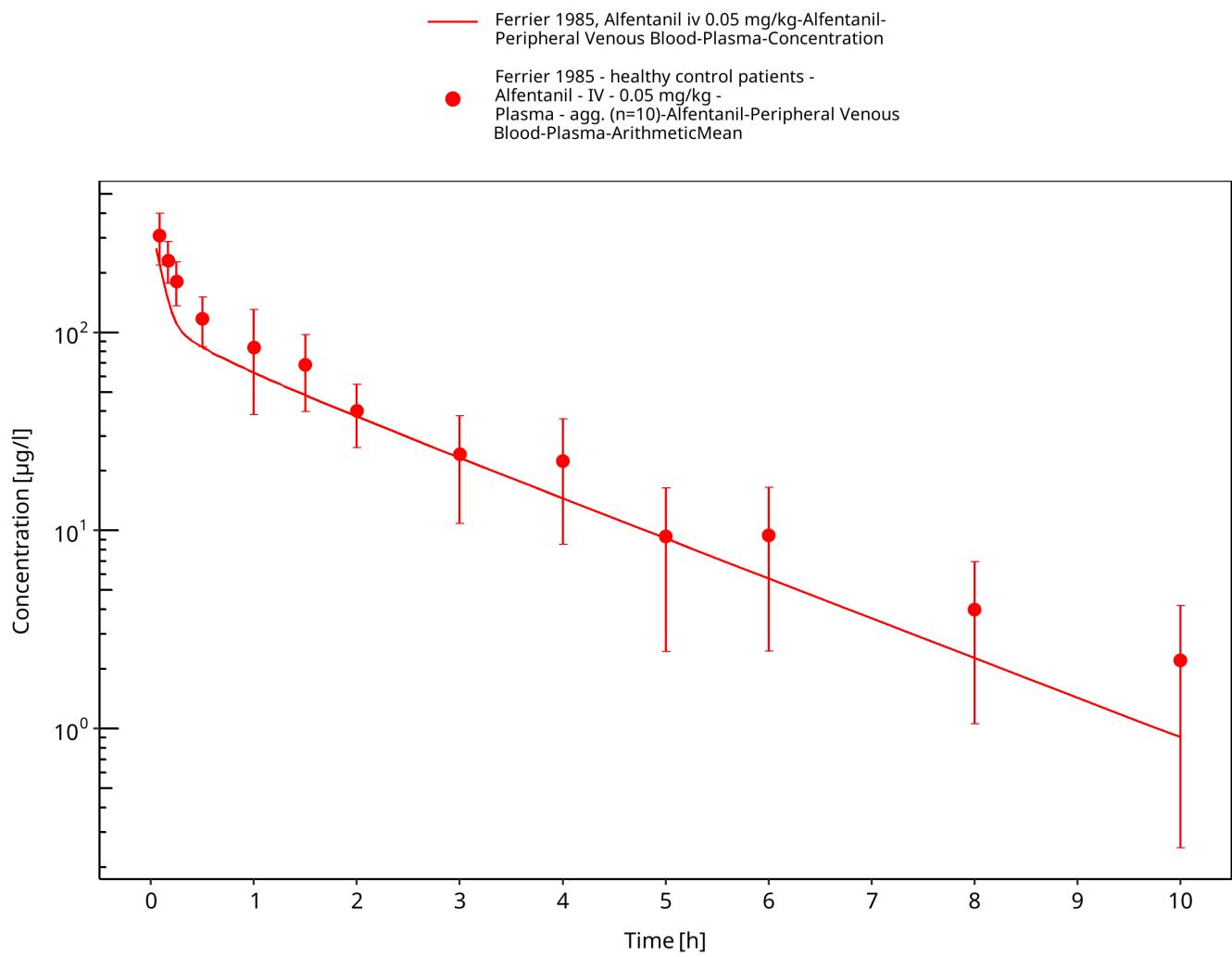


Figure 3-3: Ferrier 1985, Alfentanil iv 0.05 mg/kg - log

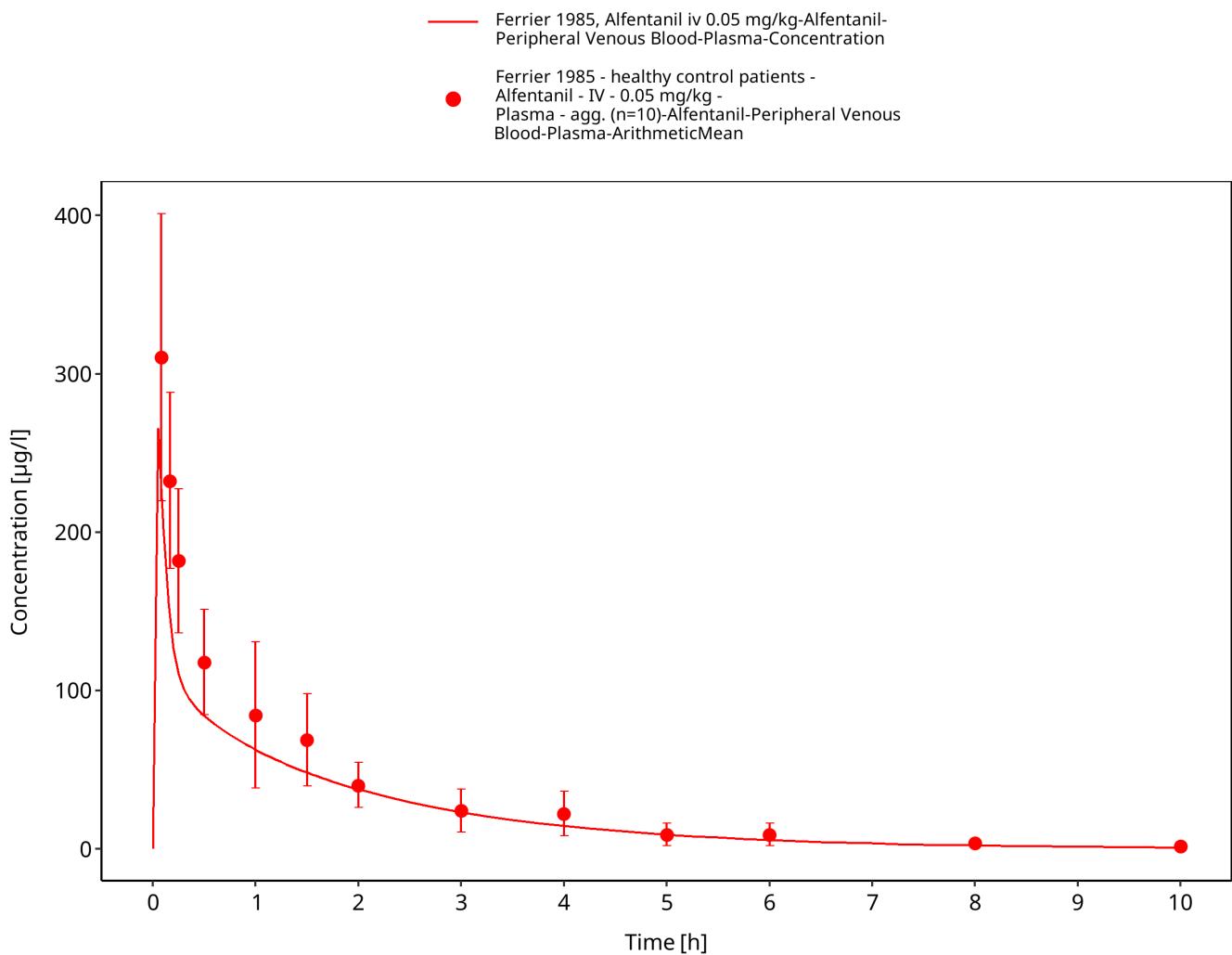


Figure 3-4: Ferrier 1985, Alfentanil iv 0.05 mg/kg - linear

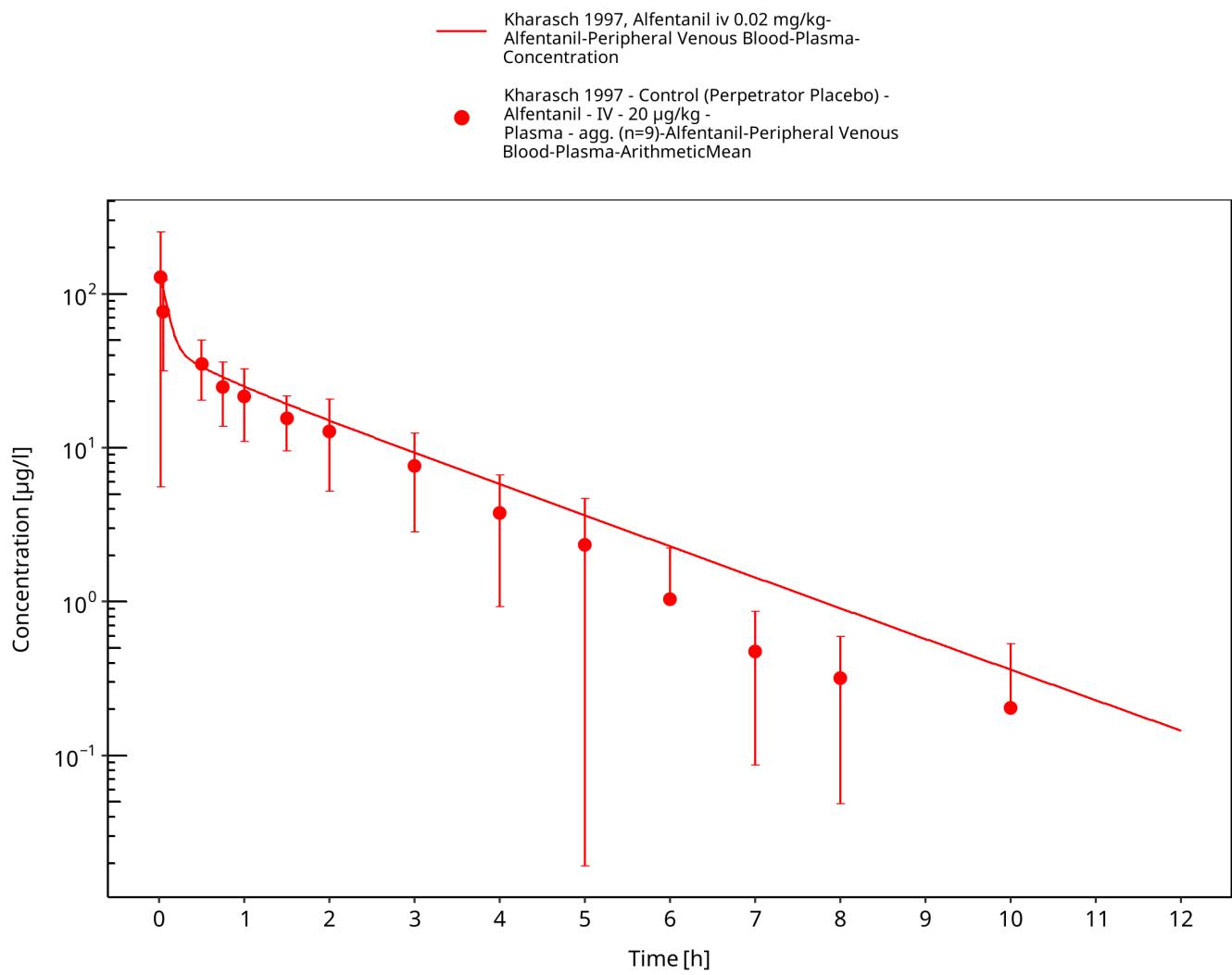


Figure 3-5: Kharasch 1997, Alfentanil iv 0.02 mg/kg - log

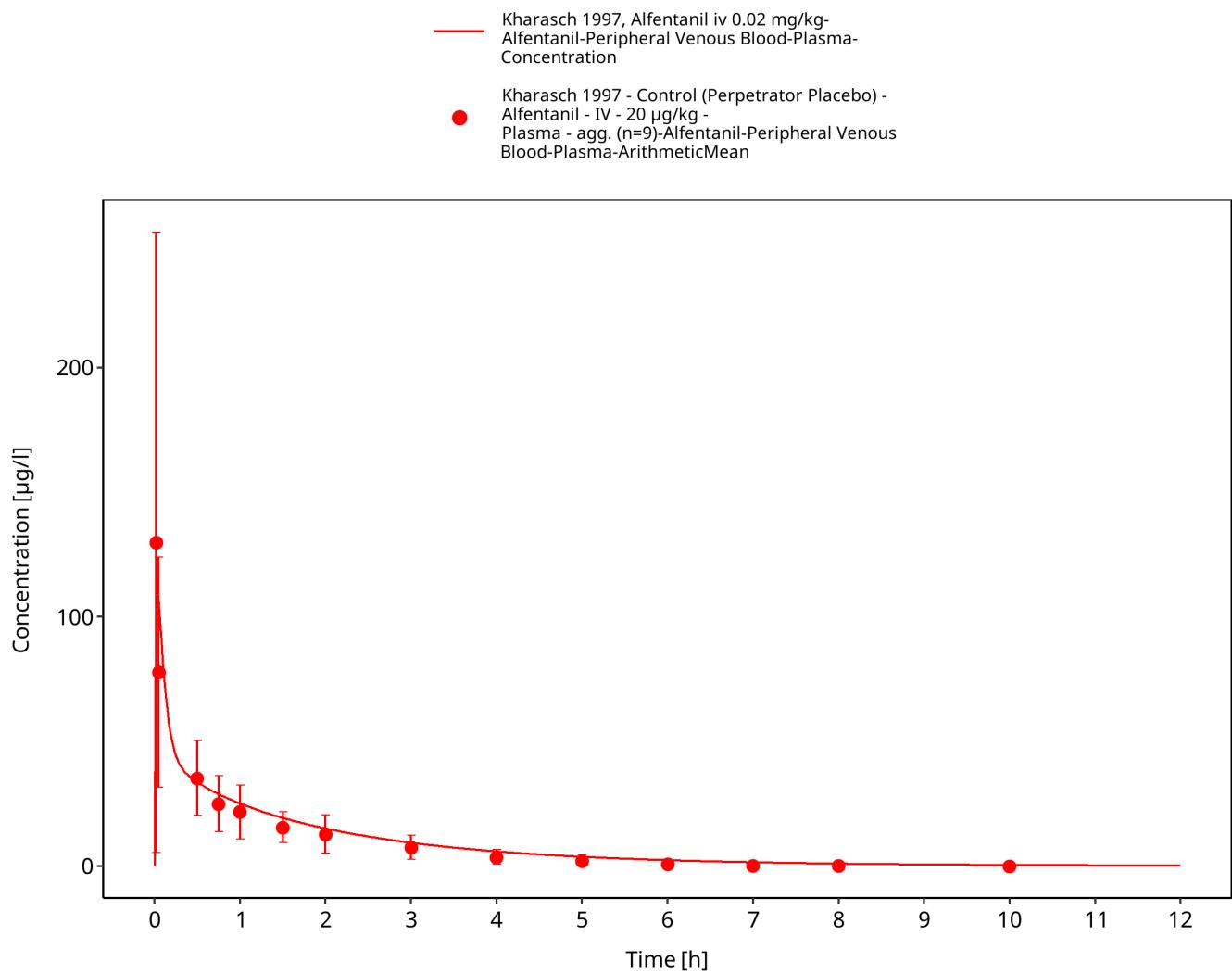


Figure 3-6: Kharasch 1997, Alfentanil iv 0.02 mg/kg - lin

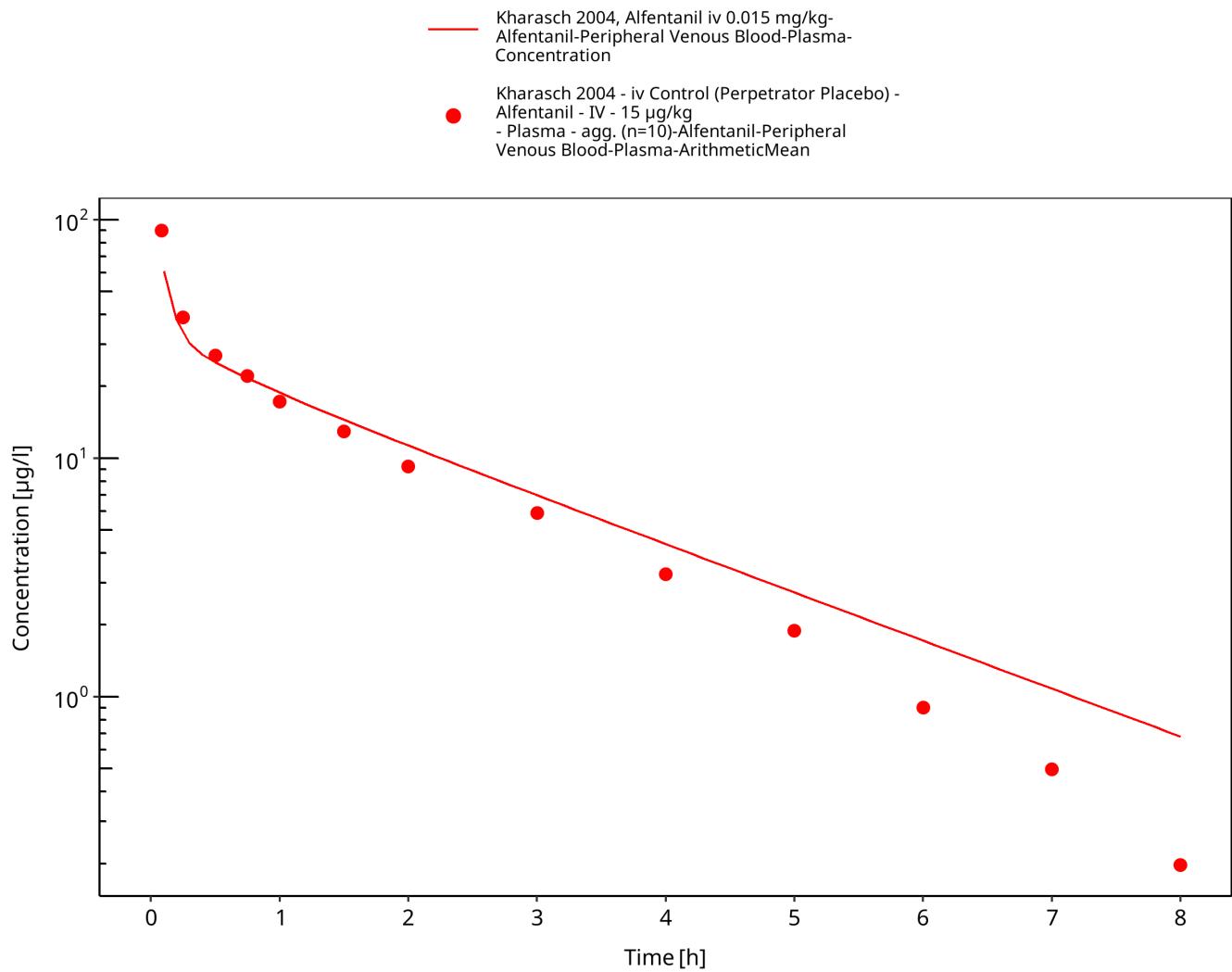


Figure 3-7: Kharasch 2004, Alfentanil iv 0.015 mg/kg - log

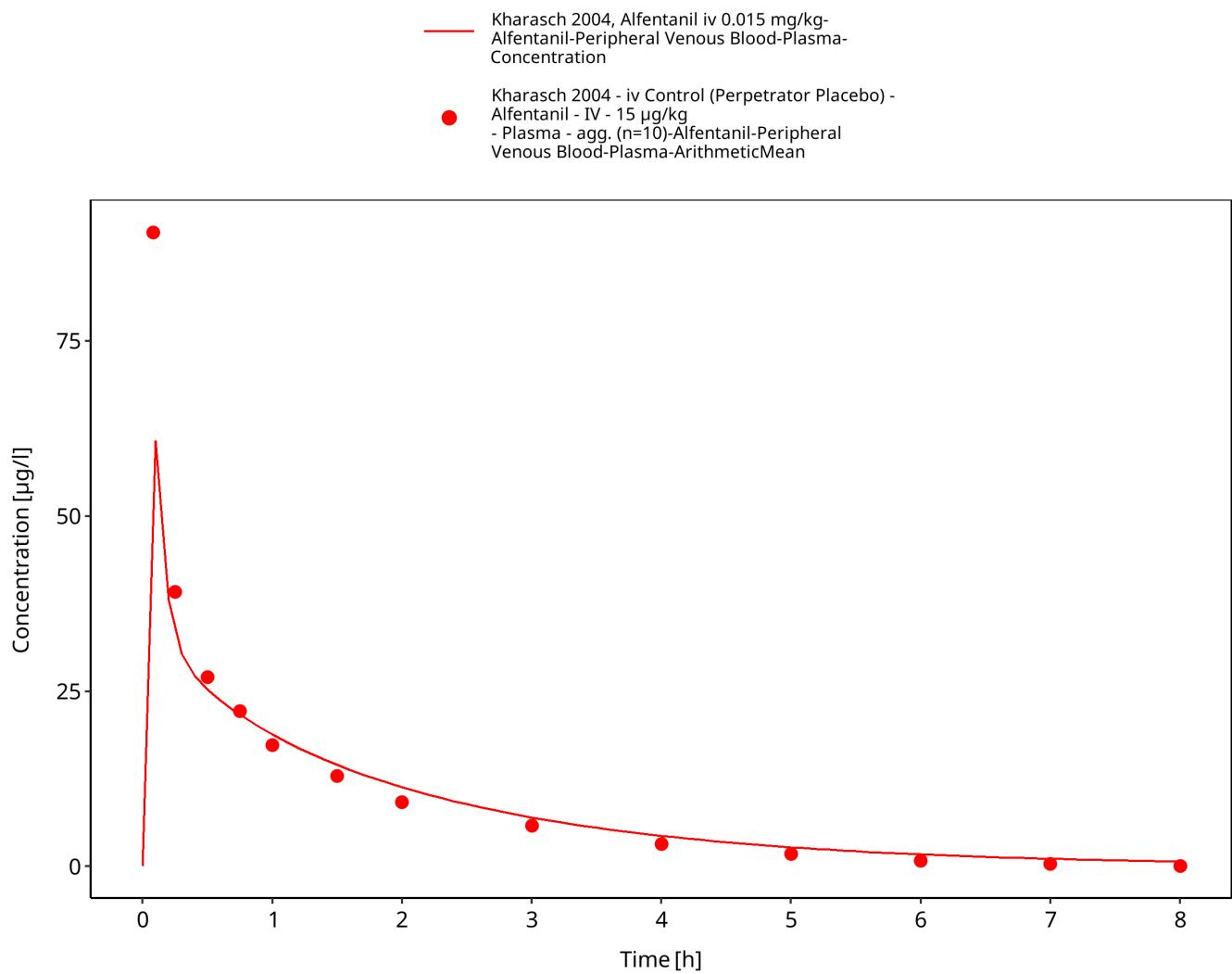


Figure 3-8: Kharasch 2004, Alfentanil iv 0.015 mg/kg - lin

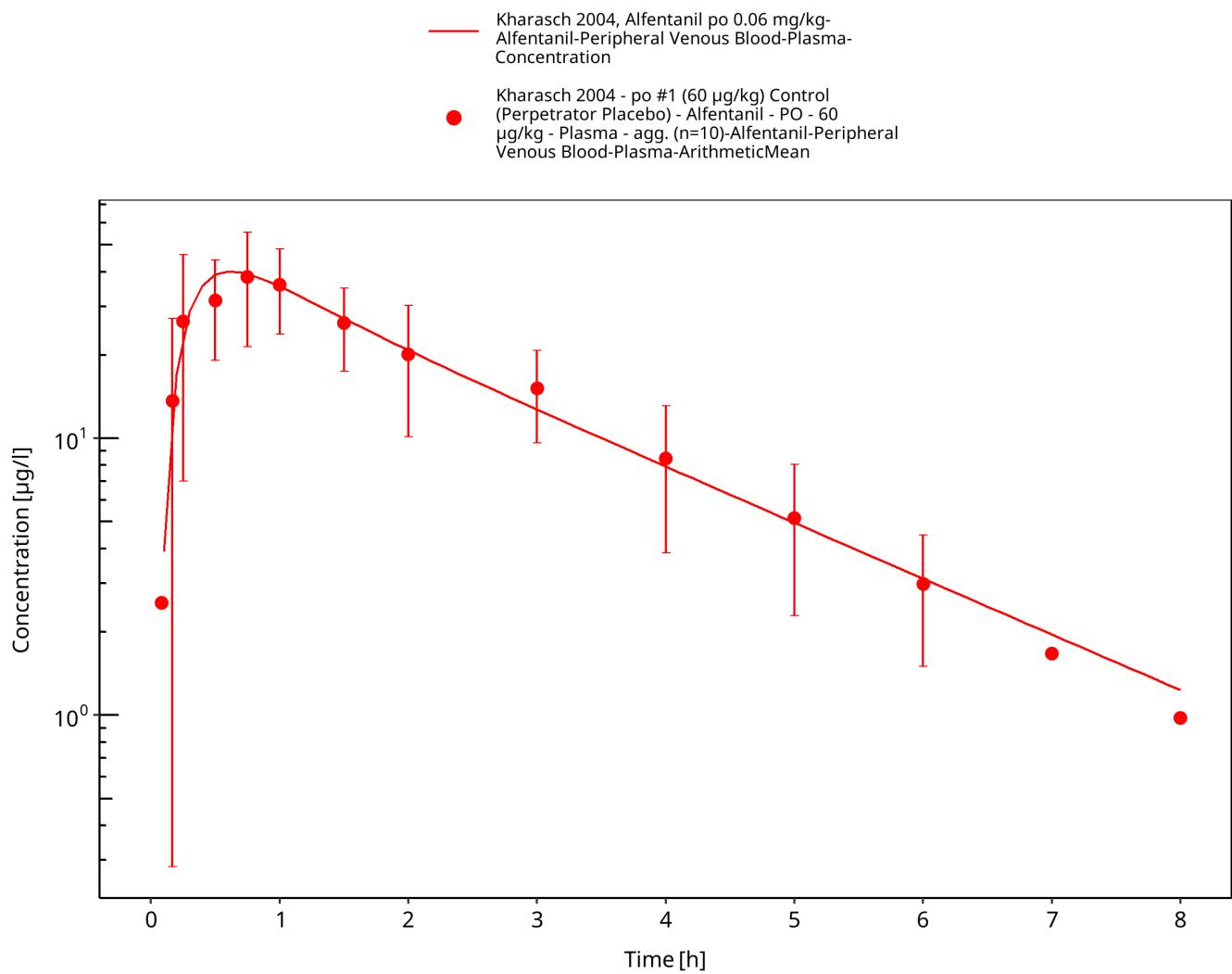


Figure 3-9: Kharasch 2004, Alfentanil po 0.06 mg/kg - log

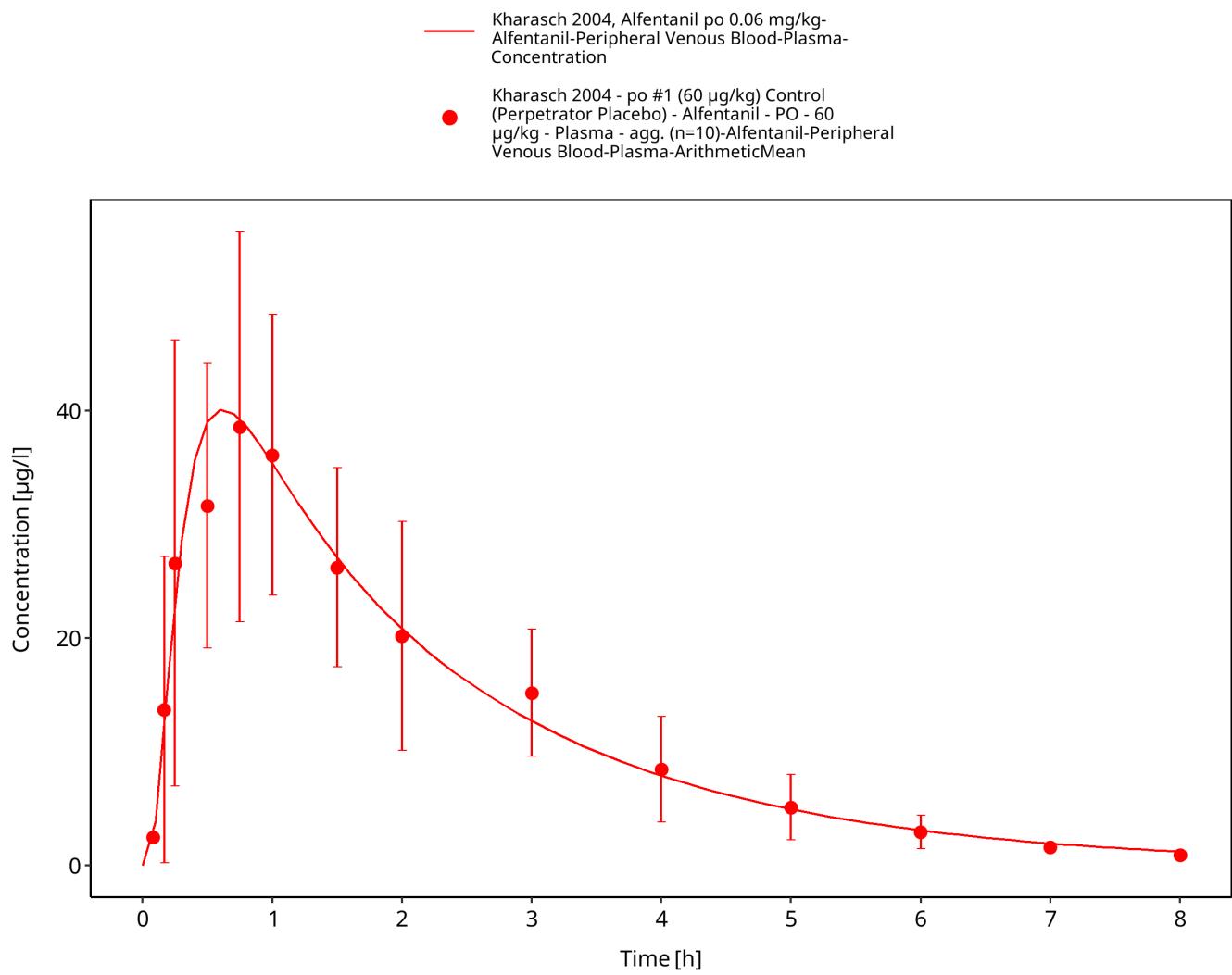


Figure 3-10: Kharasch 2004, Alfentanil po 0.06 mg/kg - lin

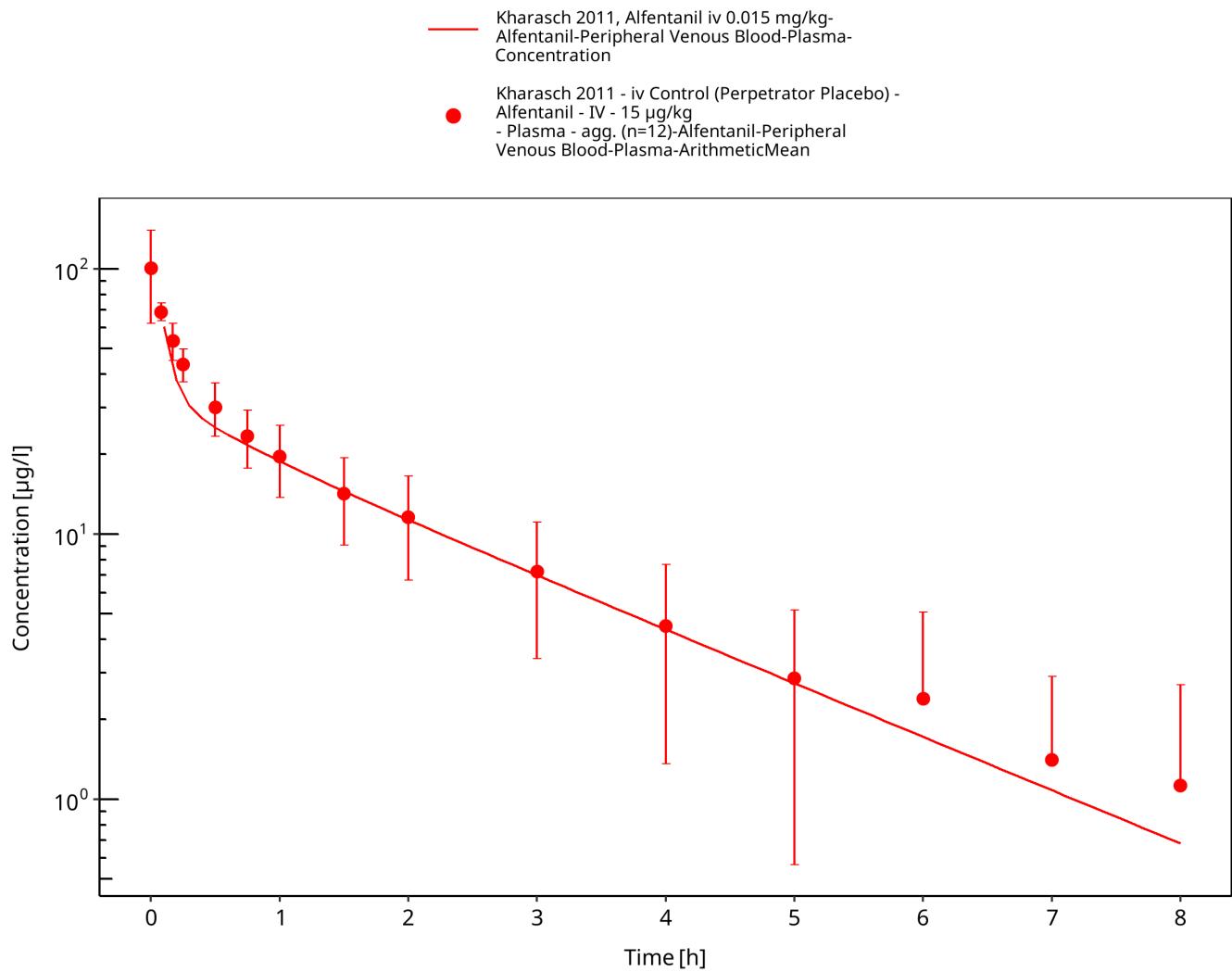


Figure 3-11: Kharasch 2011, Alfentanil iv 0.015 mg/kg - log

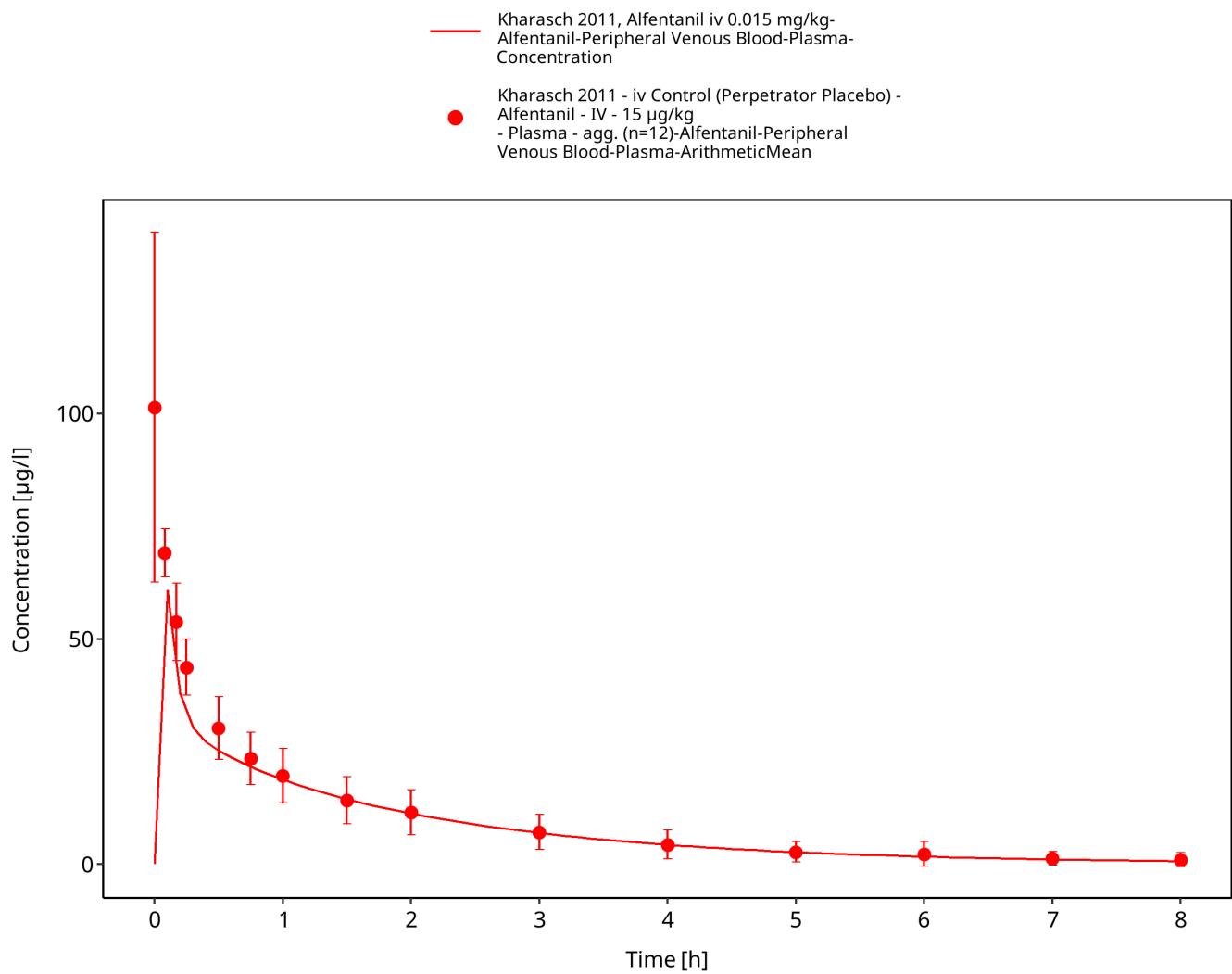


Figure 3-12: Kharasch 2011, Alfentanil iv 0.015 mg/kg - lin

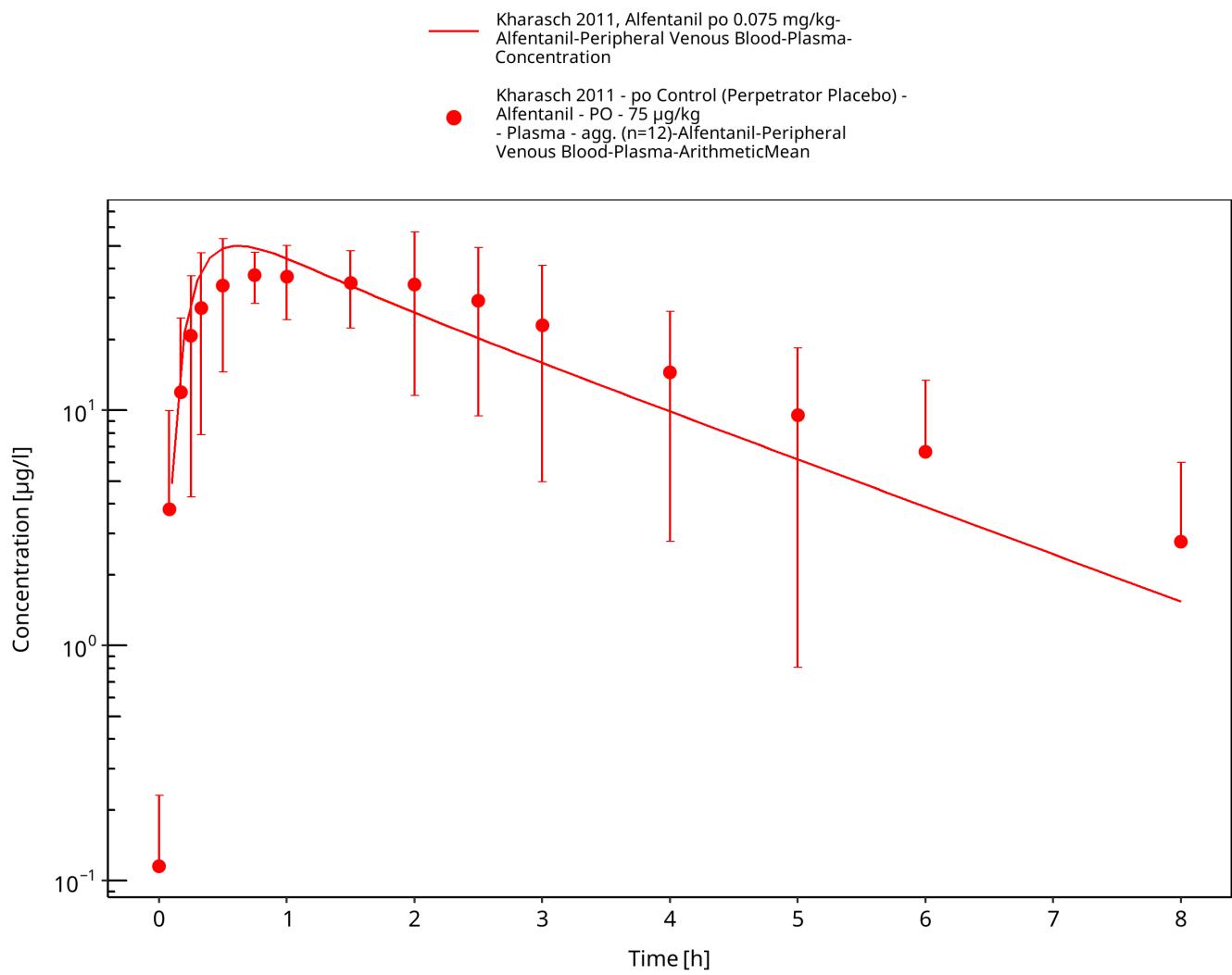


Figure 3-13: Kharasch 2011, Alfentanil po 0.075 mg/kg - log

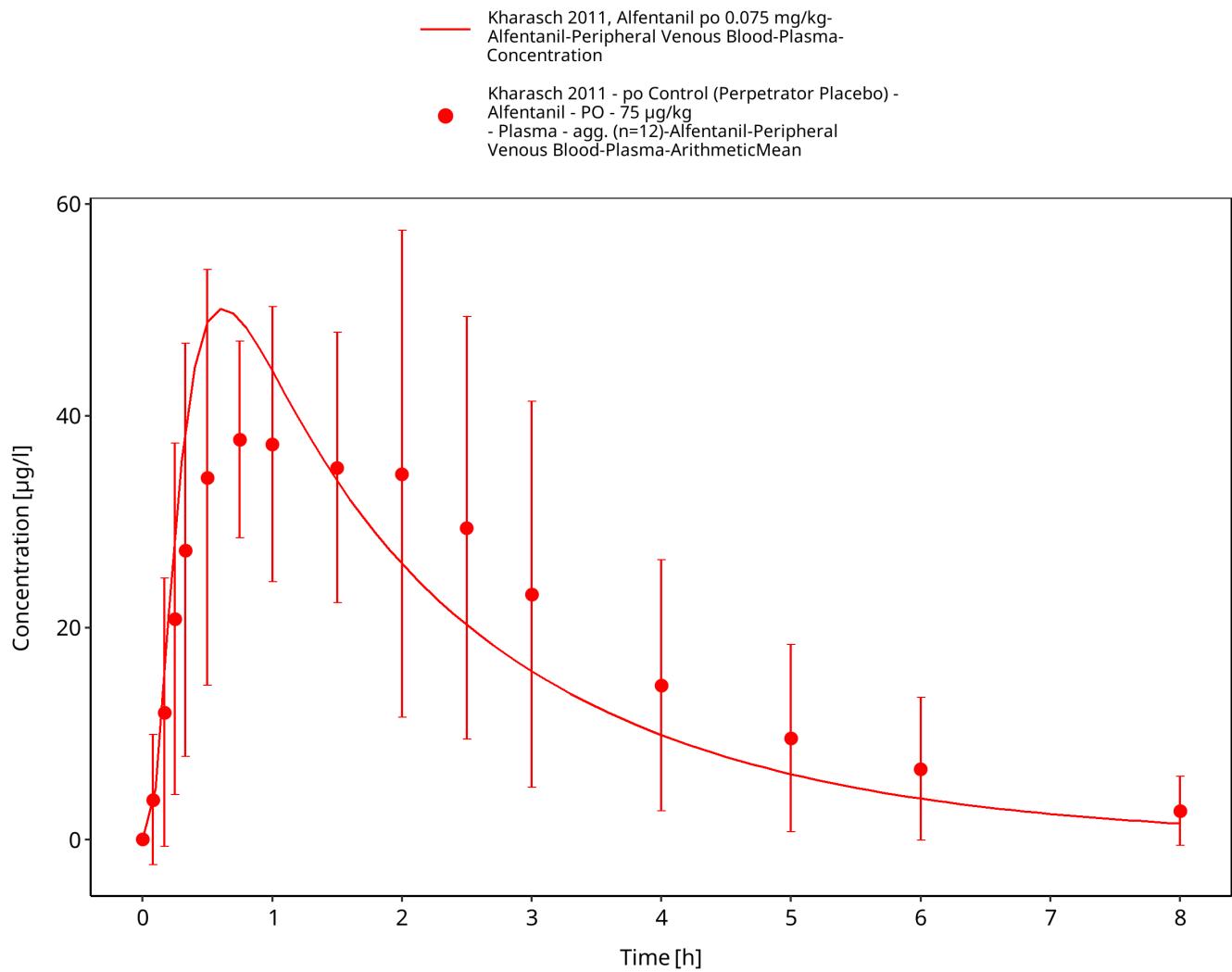


Figure 3-14: Kharasch 2011, Alfentanil po 0.075 mg/kg - lin

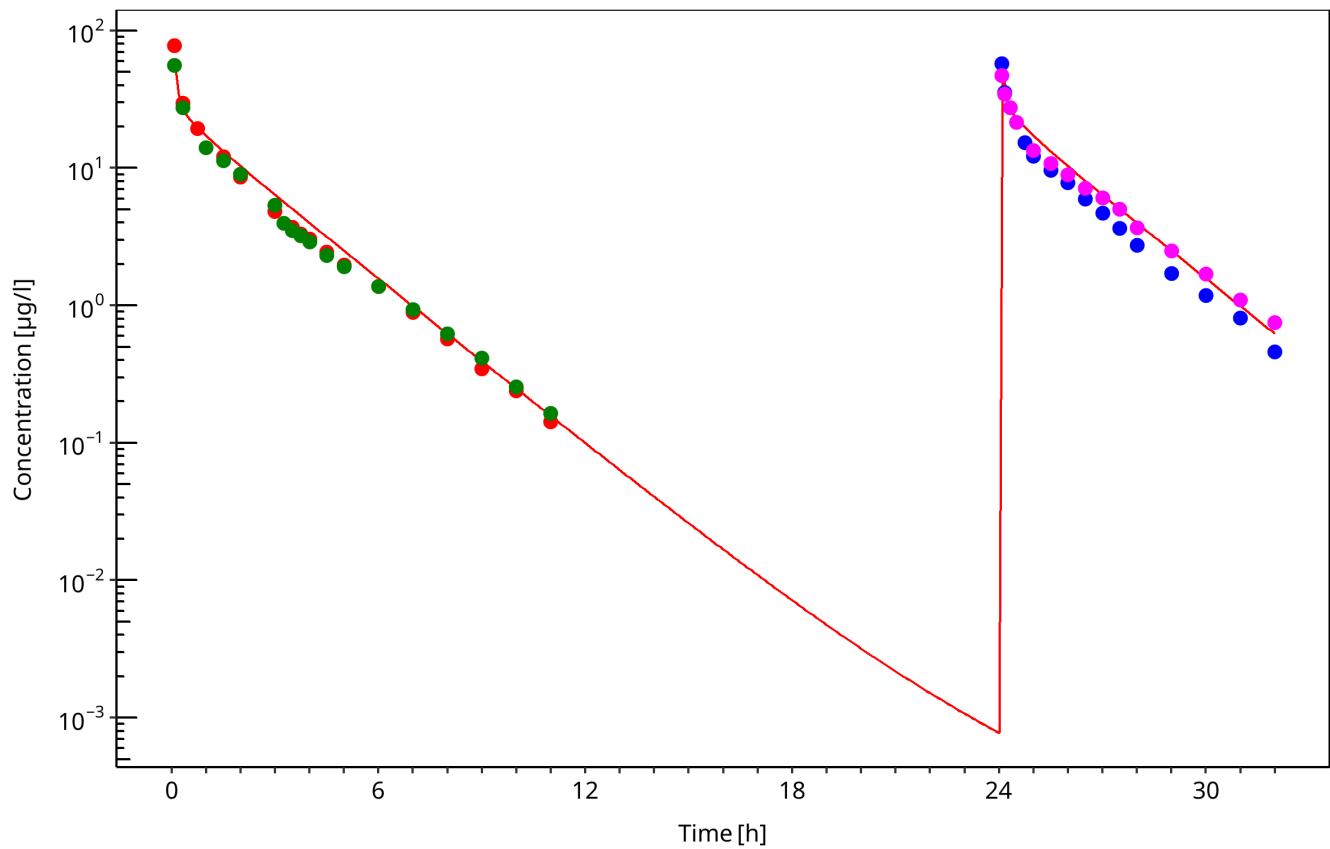
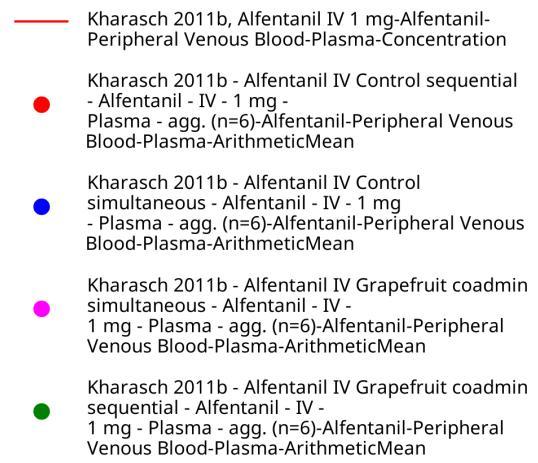


Figure 3-15: Kharasch 2011b, Alfentanil IV 1 mg - log

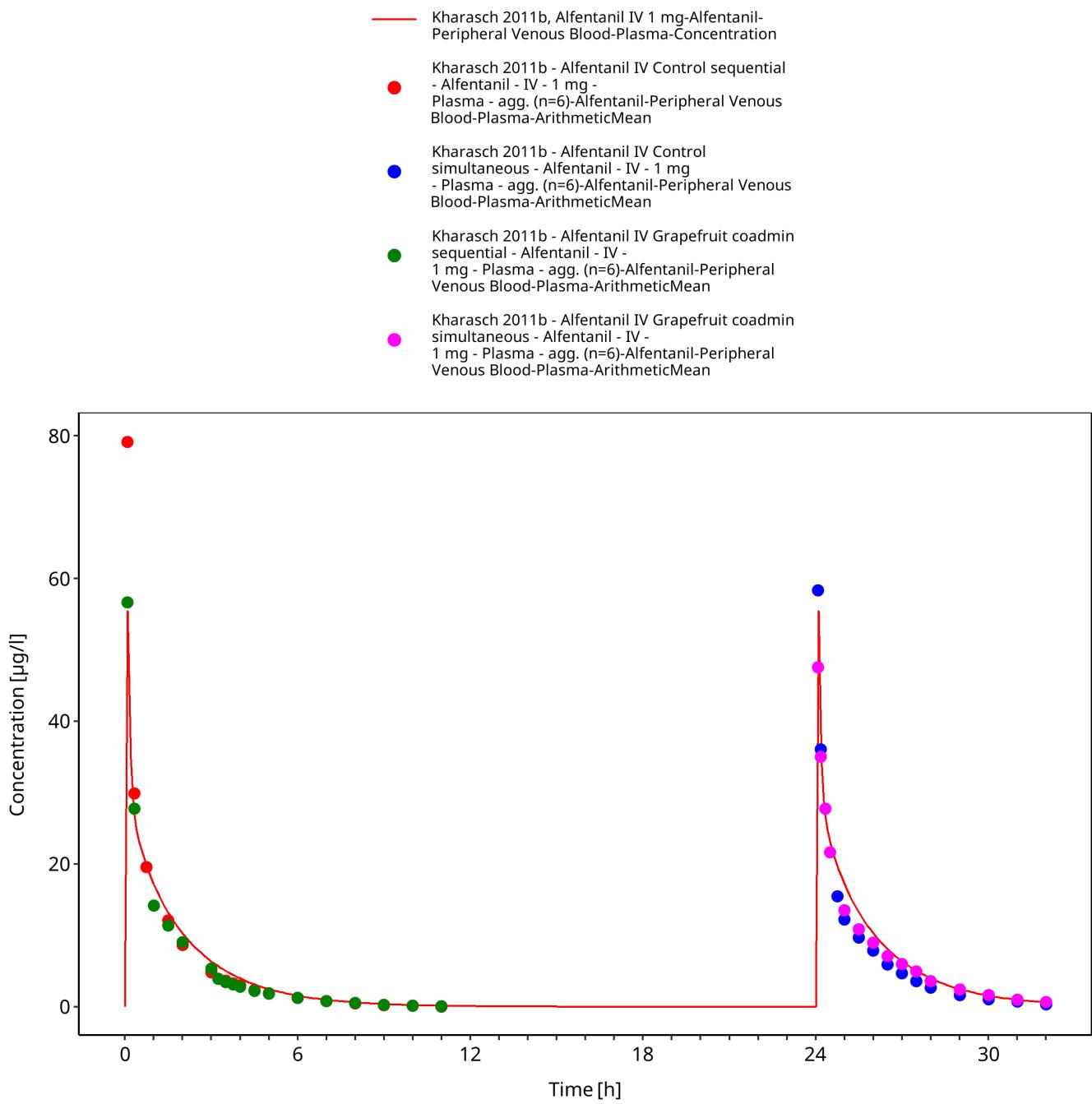


Figure 3-16: Kharasch 2011b, Alfentanil IV 1 mg - lin

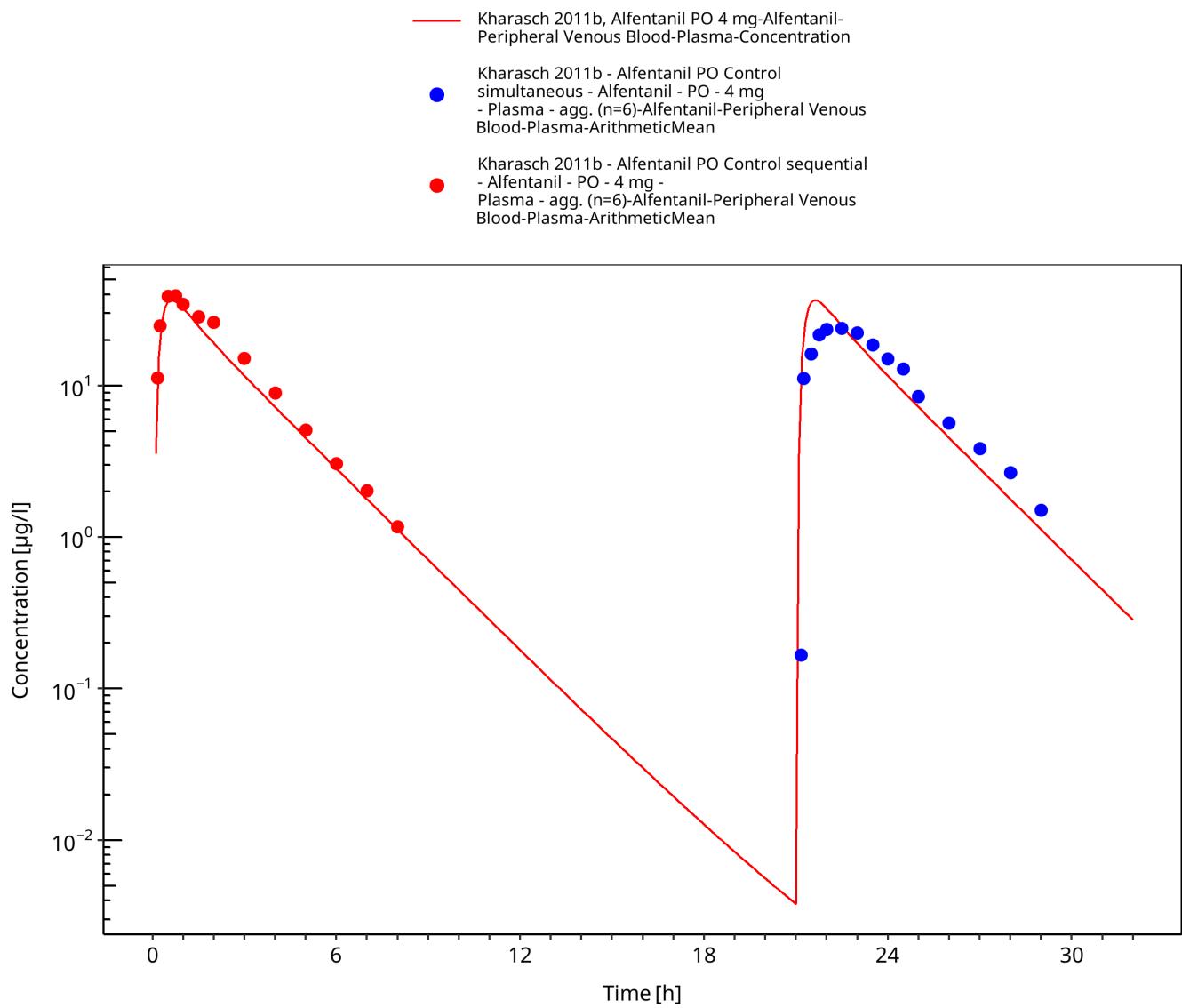


Figure 3-17: Kharasch 2011b, Alfentanil PO 4 mg - log

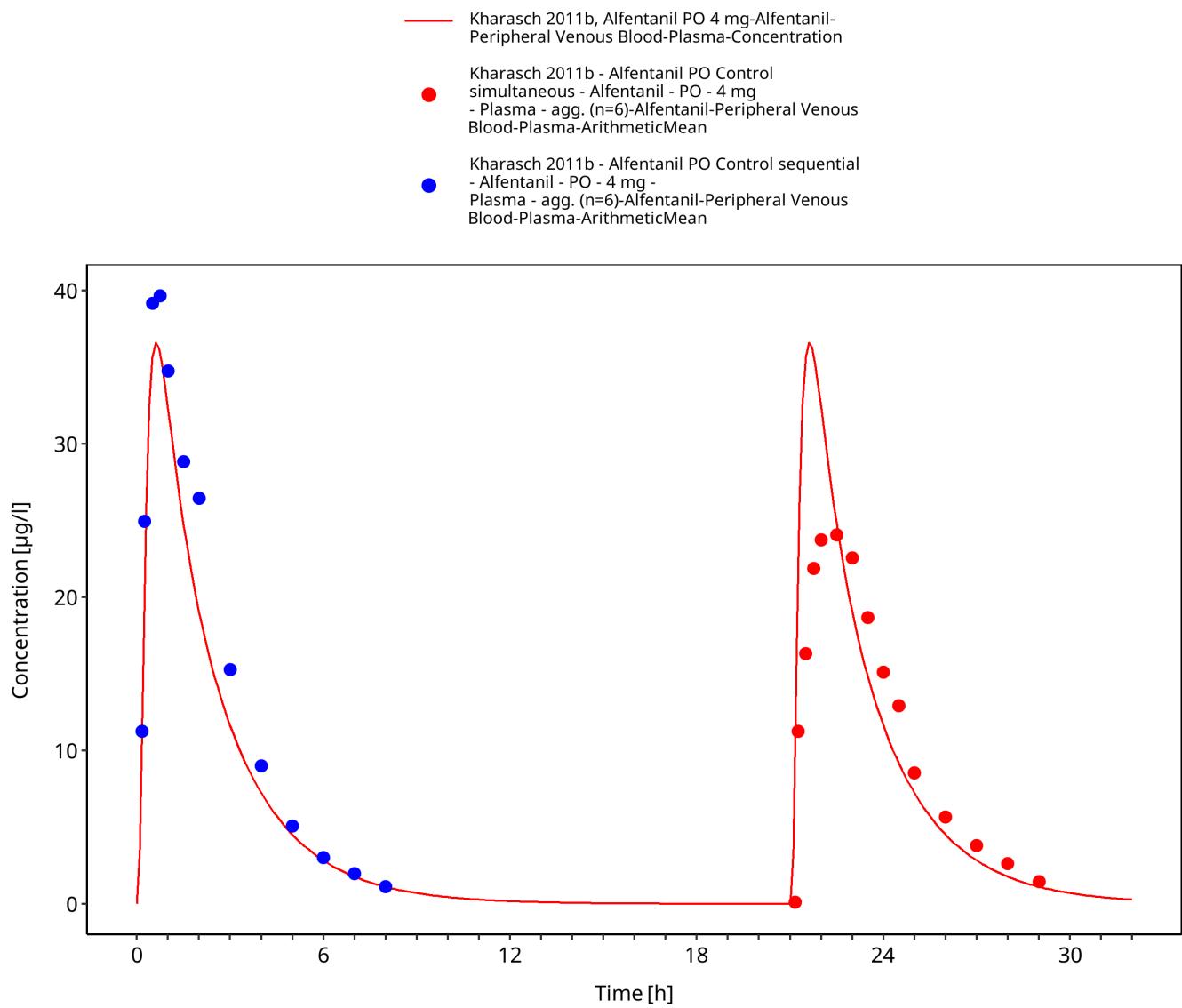


Figure 3-18: Kharasch 2011b, Alfentanil PO 4 mg - lin

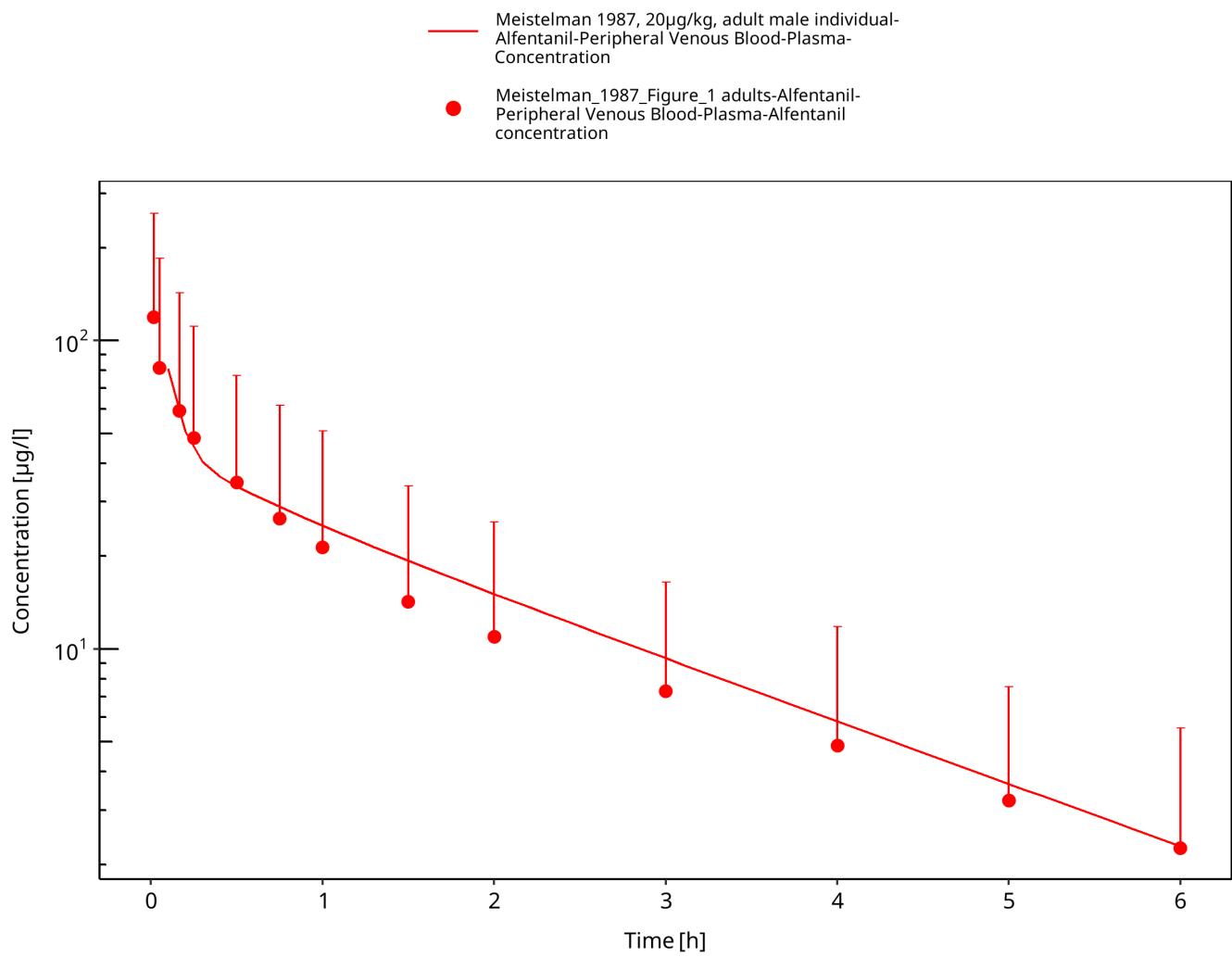


Figure 3-19: Meistelman 1987, 20 μ g/kg, adult male individual - log

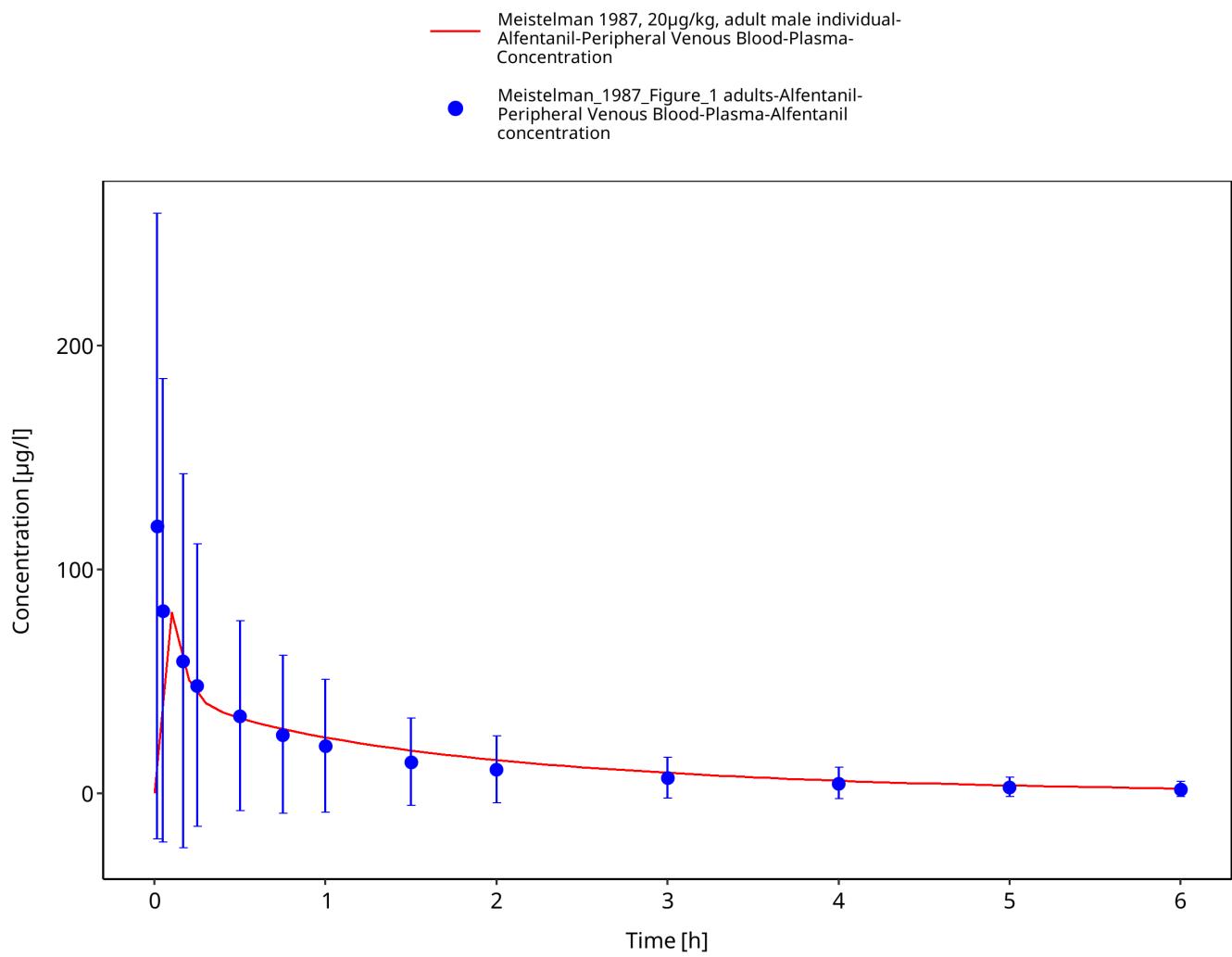


Figure 3-20: Meistelman 1987, 20 $\mu\text{g}/\text{kg}$, adult male individual - lin

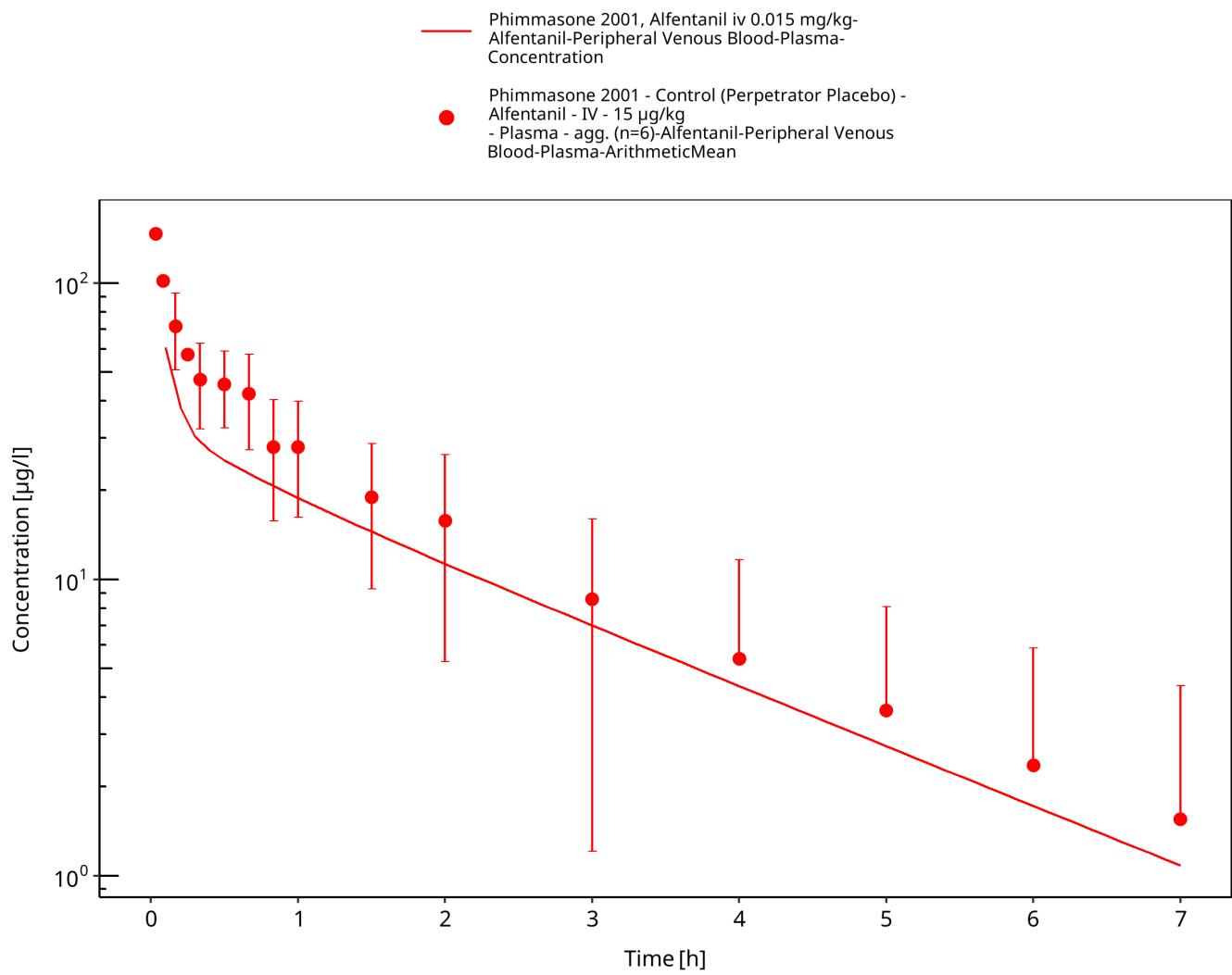


Figure 3-21: Phimmasone 2001, Alfentanil iv 0.015 mg/kg - log

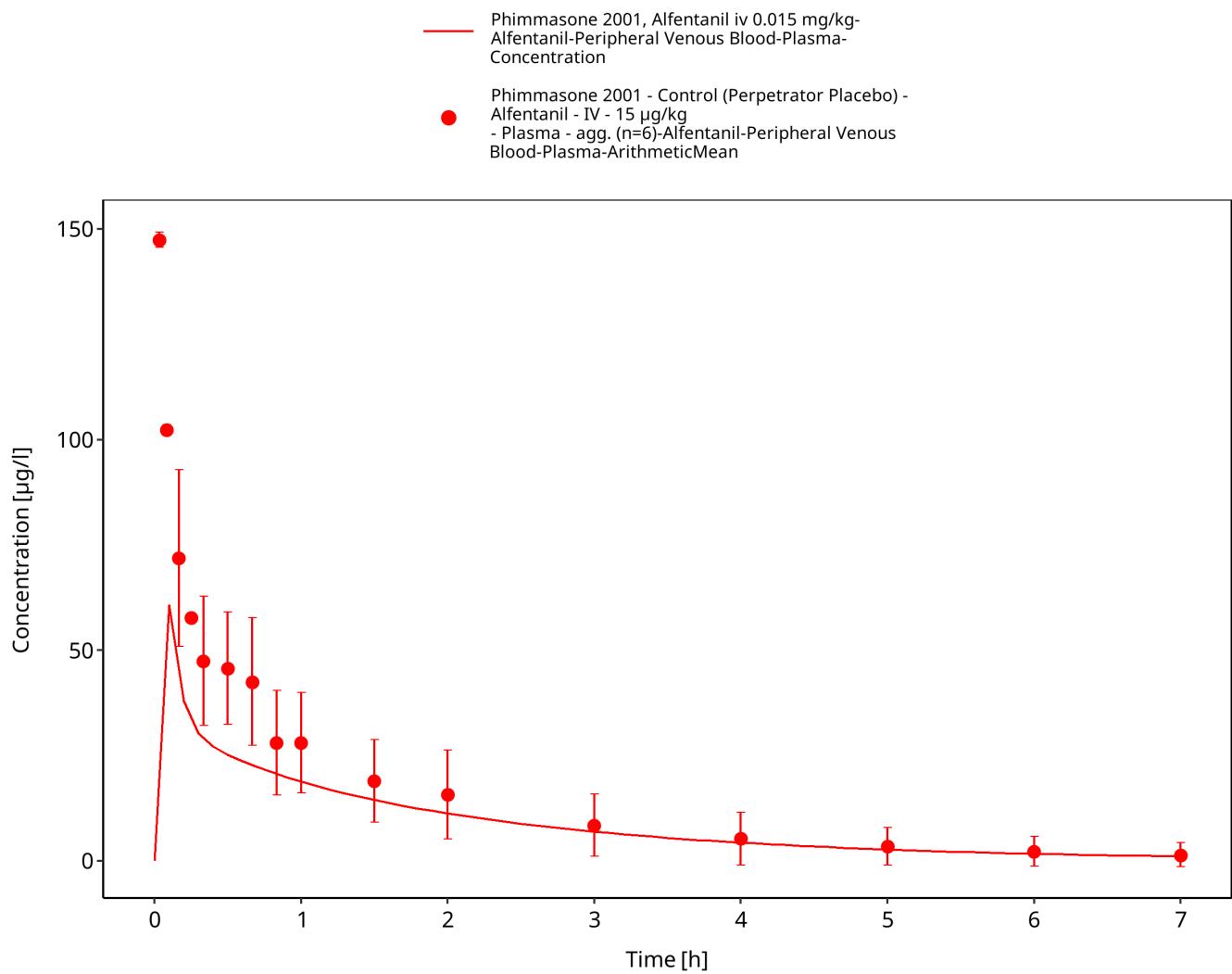


Figure 3-22: Phimmasone 2001, Alfentanil iv 0.015 mg/kg - lin

3.3.2 Model Verification

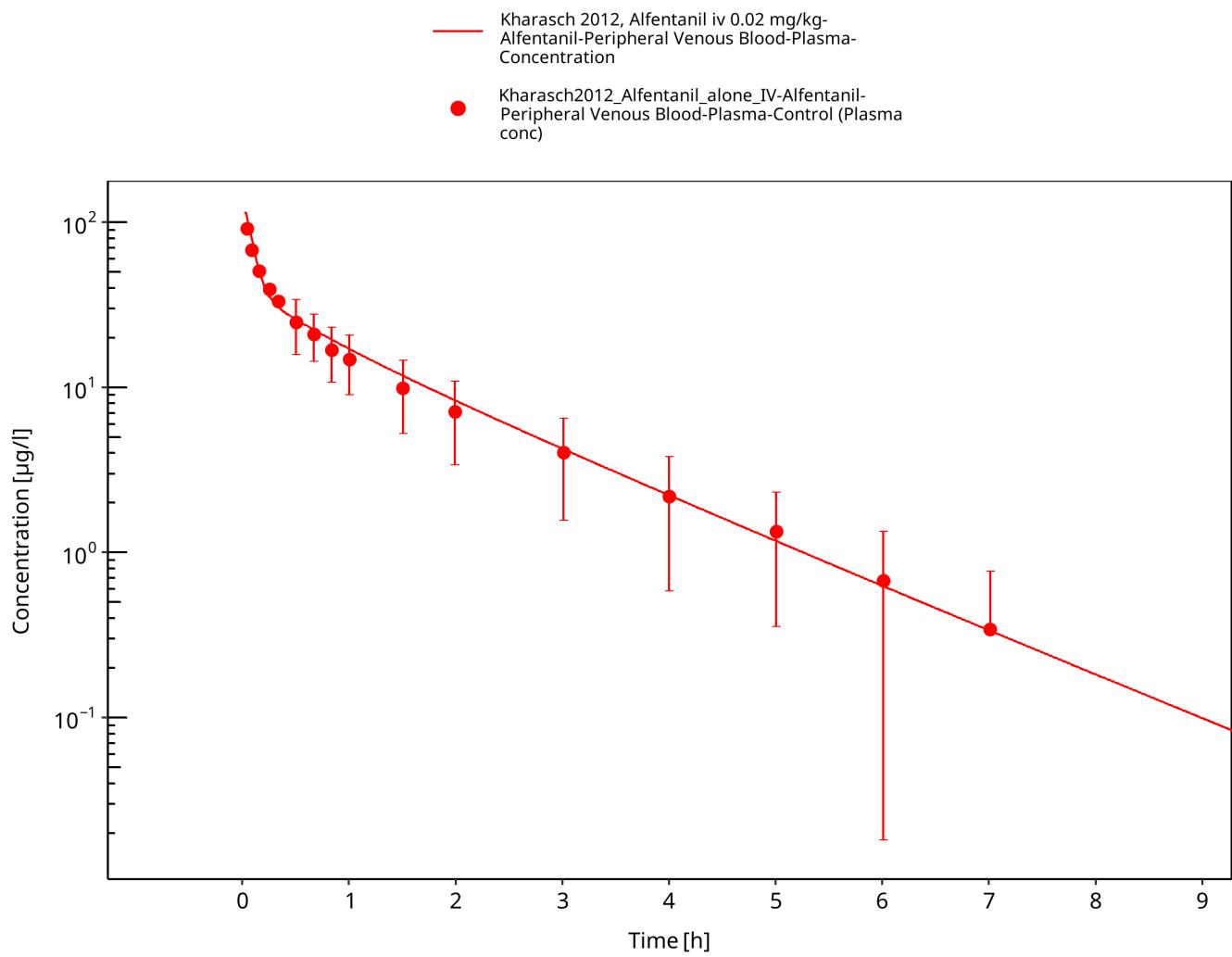


Figure 3-23: Kharasch 2012, Alfentanil iv 0.02 mg/kg - log

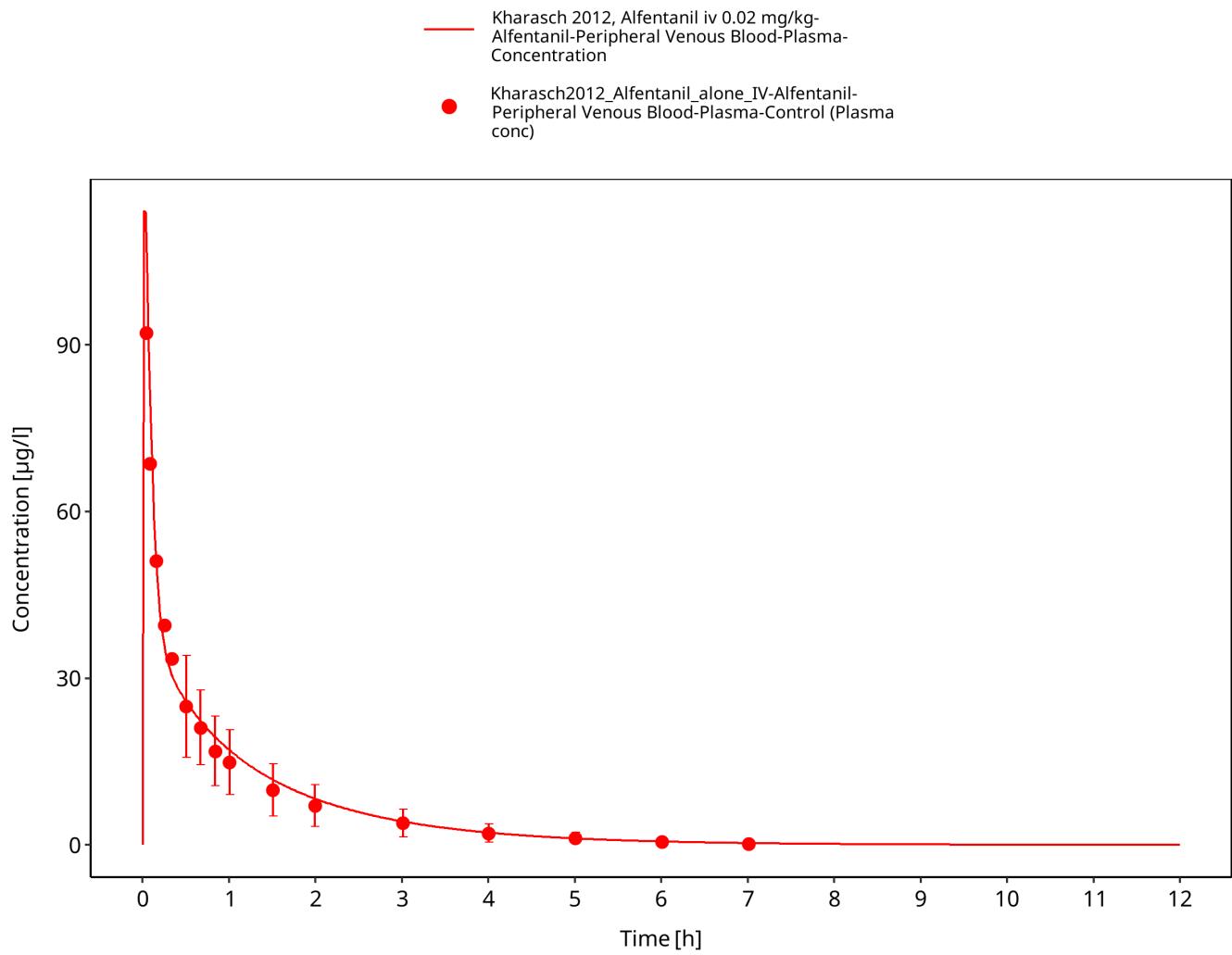


Figure 3-24: Kharasch 2012, Alfentanil iv 0.02 mg/kg - lin

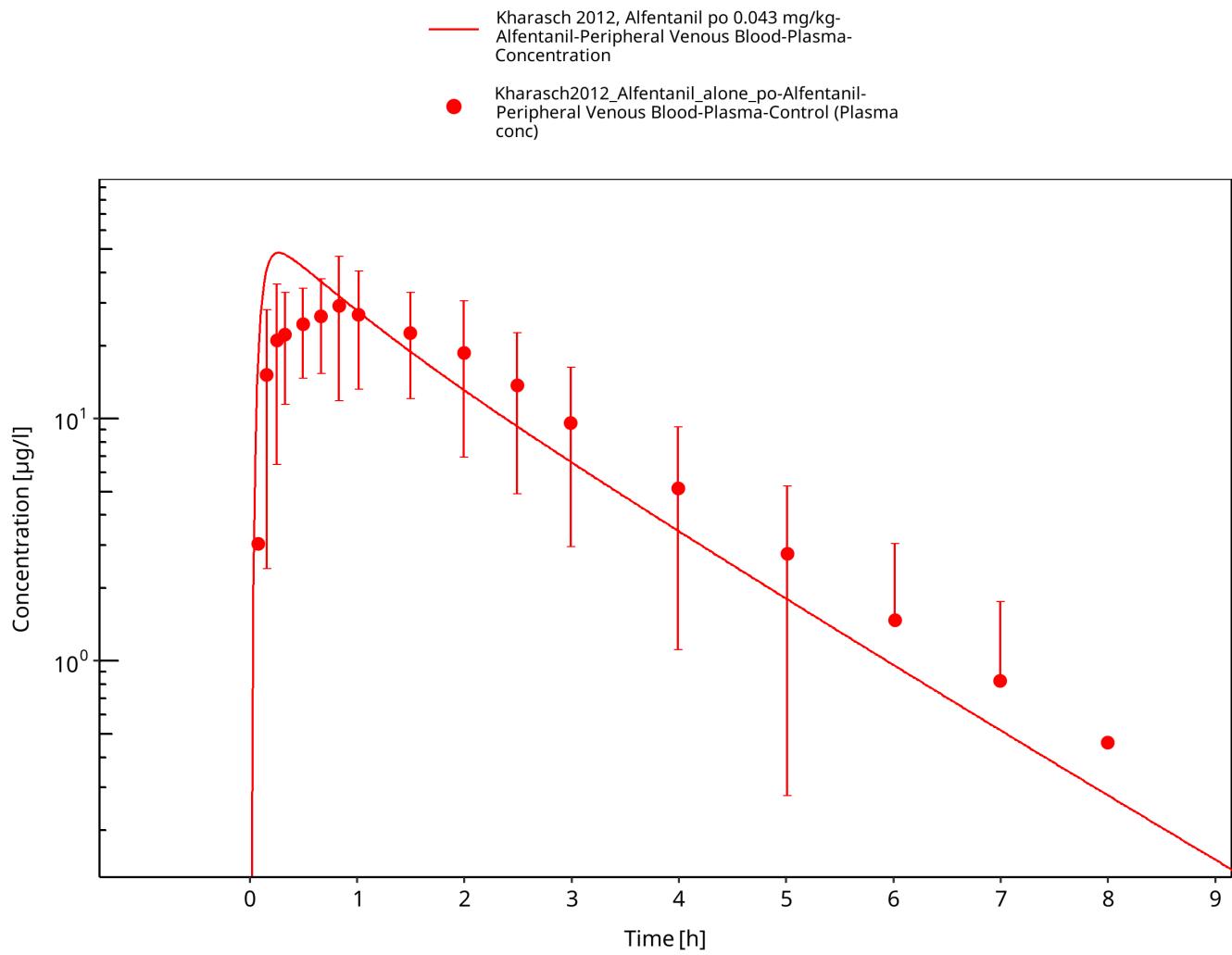


Figure 3-25: Kharasch 2012, Alfentanil po 0.043 mg/kg - log

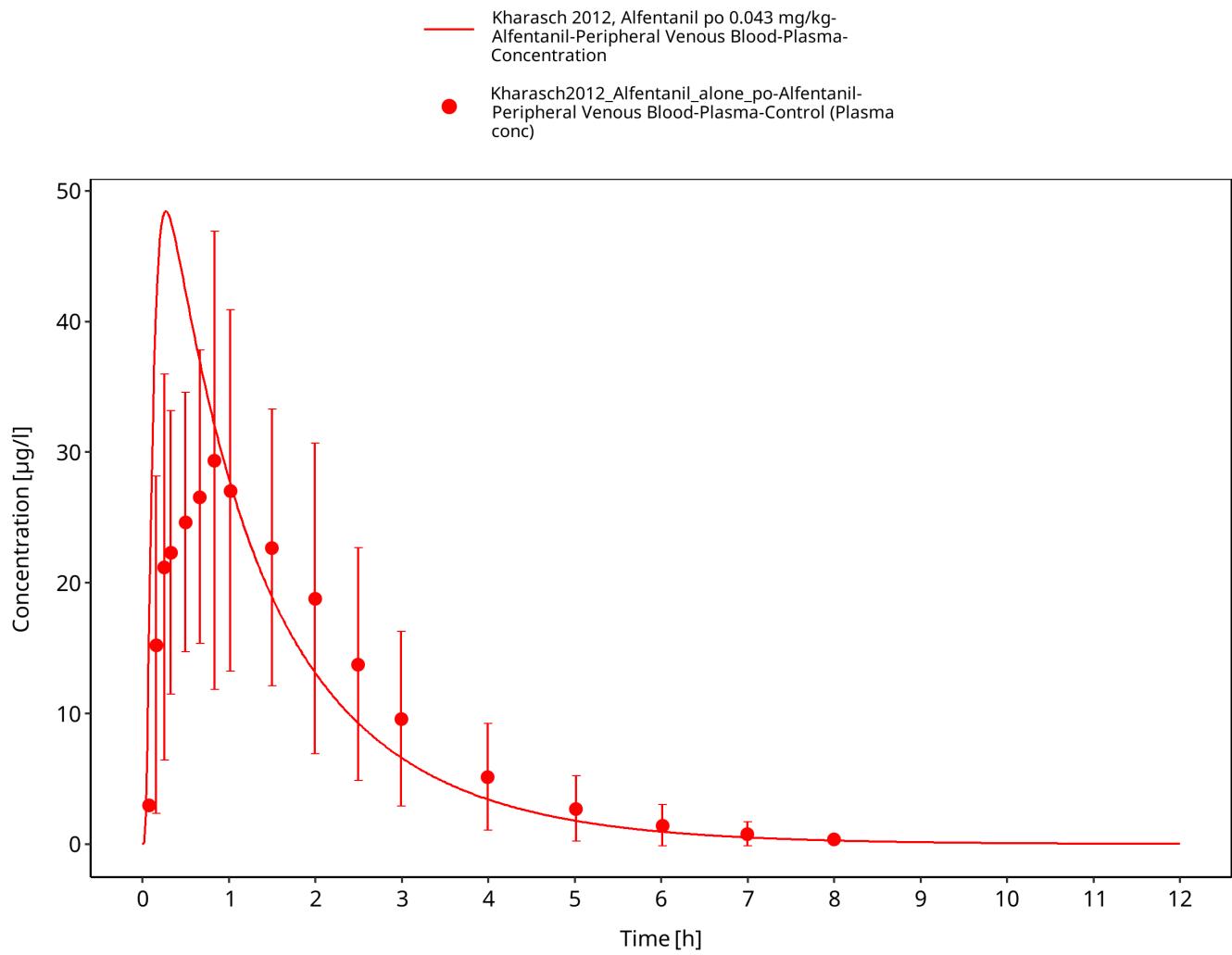


Figure 3-26: Kharasch 2012, Alfentanil po 0.043 mg/kg - lin

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of alfentanil after iv and oral administration of a variety of doses to healthy adults. Parameters that were optimized during parameter identification are in a close range to the measured or calculated values and, consistent with literature, no additional active processes were needed to describe the PK of alfentanil.

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

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PK-Sim Ontogeny Database Version 7.3 (<https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384cf25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf>)

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