Dextromethorphan qualification report

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> **ⓘ Note**
>
> This report has been created with simulation results loaded from results folder 2023-07-21 12-59 .

1 Introduction

This document describes the qualification of a published dextromethorphan physiologically-based pharmacokinetics (PBPK) model for the use with the Open Systems Pharmacology Software (OSPS) Version 11.2.

The PBPK model has been developed with OSPS version 9.1 and published by (Rüdesheim et al. 2022). Model snapshots have been downloaded on 16.06.2023 from the Open Systems Pharmacology (OSP) repository. As of 16.06.2023, no model version qualified for OSP version 11.2 is publicly available.

2 Methods

2.1 Software

For recreating the original results from the publication, OSPS version 9.1 was used. The qualification is done with OSPS version 11.2.142.

2.2 Drug-gene-interaction

The model is intended to be used in drug-drug interactions (DDI) simulations with dextromethorphan as a CYP2D6 victim. Drug-gene interactions (DGI) to describe variabilities of CYP2D6 activity are modeled as variations of the catalytic rate constant k_{cat}. Following values are used in the project:
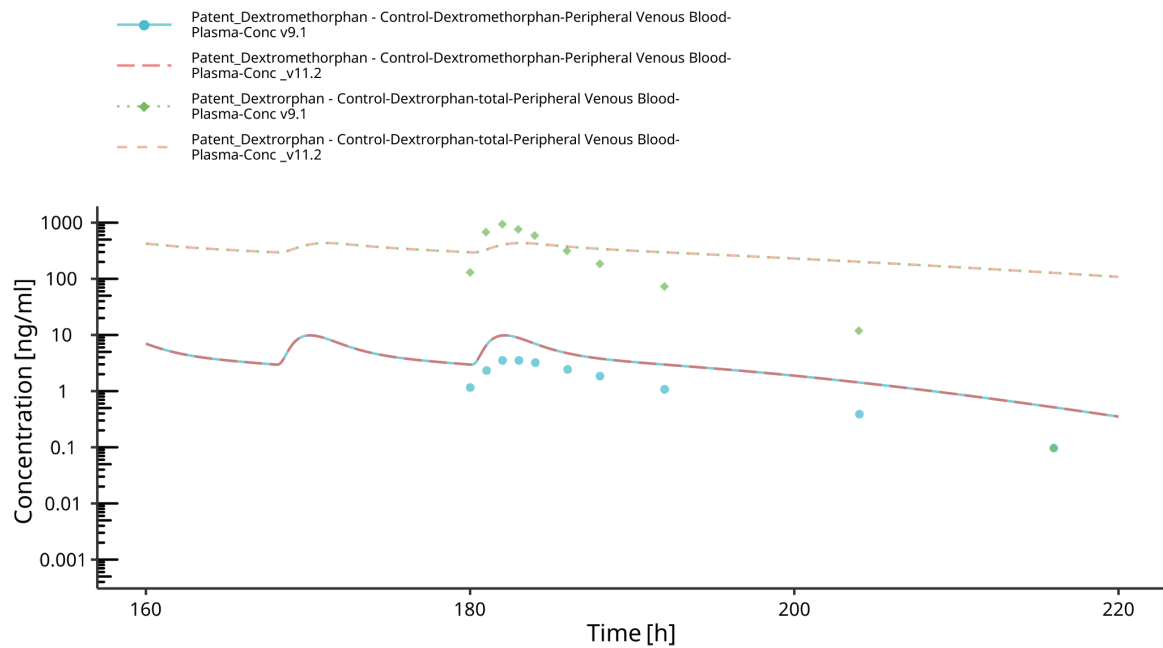
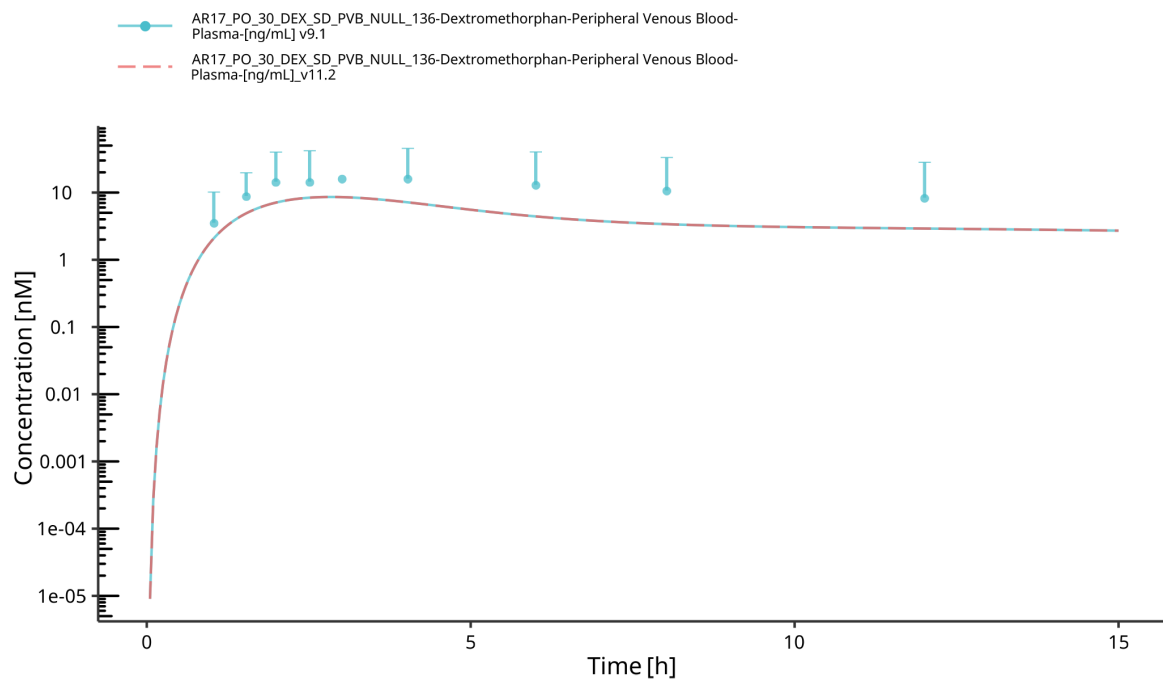## 2.3 Qualification process

2.4 Consolidation of expression profiles

3 Results

Comparison of time-concentration profiles generated with the different software versions are presented in the following:
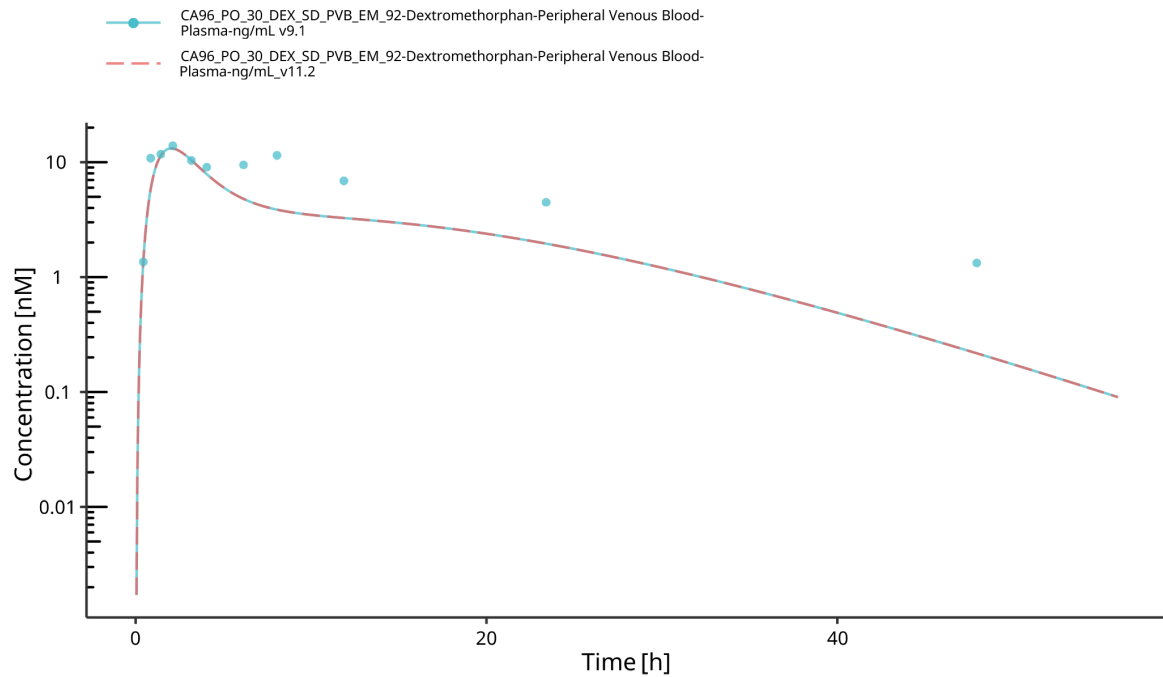
Antecip Bioventures EM, 60 mg dextromethorphan hydrobromide multiple dose (capsule/solution), n=10 - time profile

Legend:
- Patent_Dextromethorphan - Control-Dextromethorphan-Peripheral Venous Blood-Plasma-Conc v9.1
- Patent_Dextromethorphan - Control-Dextromethorphan-Peripheral Venous Blood-Plasma-Conc _v11.2
- Patent_Dextrorphan - Control-Dextrorphan-total-Peripheral Venous Blood-Plasma-Conc v9.1
- Patent_Dextrorphan - Control-Dextrorphan-total-Peripheral Venous Blood-Plasma-Conc _v11.2

Armani 2017 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=20 - time profile

Legend:
- AR17_PO_30_DEX_SD_PVB_NULL_136-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- AR17_PO_30_DEX_SD_PVB_NULL_136-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

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Capon 1996 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=6 - time profile

Legend:
- CA96_PO_30_DEX_SD_PVB_EM_92-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL v9.1
- CA96_PO_30_DEX_SD_PVB_EM_92-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL_v11.2

Y-axis: Concentration [nM]
X-axis: Time [h]

Capon 1996 PM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=6 - time profile

Legend:
- CA96_PO_30_DEX_SD_PVB_PM_93-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL v9.1
- CA96_PO_30_DEX_SD_PVB_PM_93-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL_v11.2

Y-axis: Concentration [ng/ml]
X-axis: Time [h]
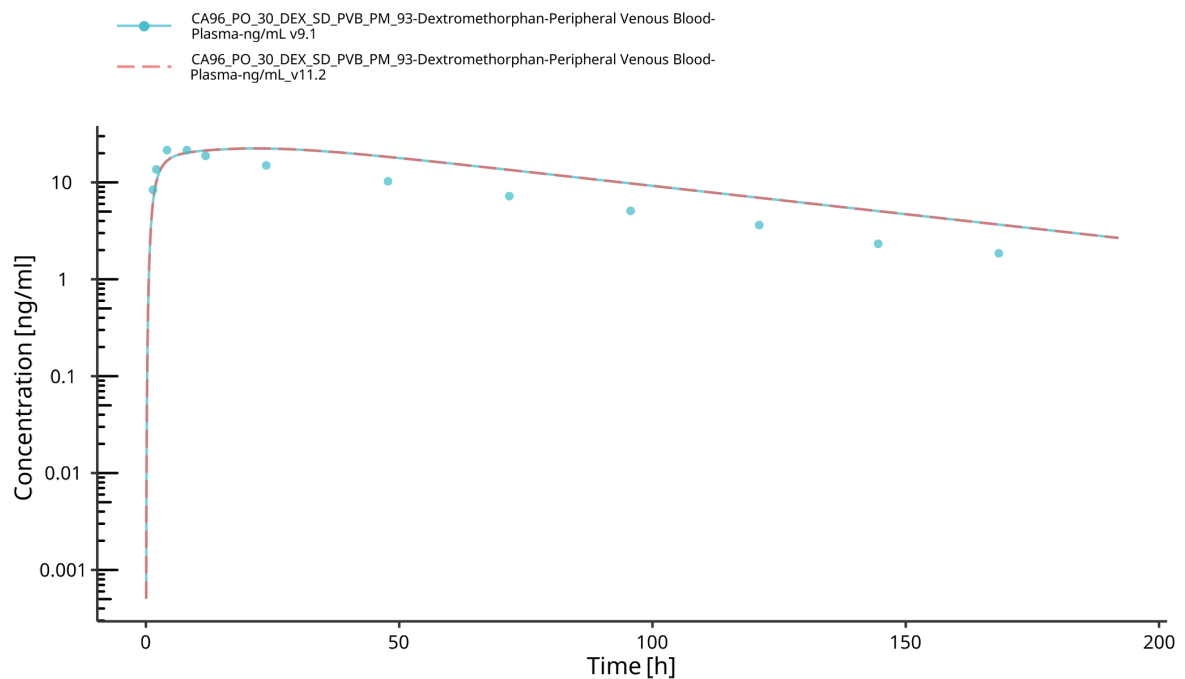
Duedahl 2005 EM, 0.5 mg/kg dextromethorphan base (infusion), n=24 - time profile

DU05_IV_0.5_DEX_SD_PVB_NULL_89-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL v9.1

DU05_IV_0.5_DEX_SD_PVB_NULL_89-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL_v11.2
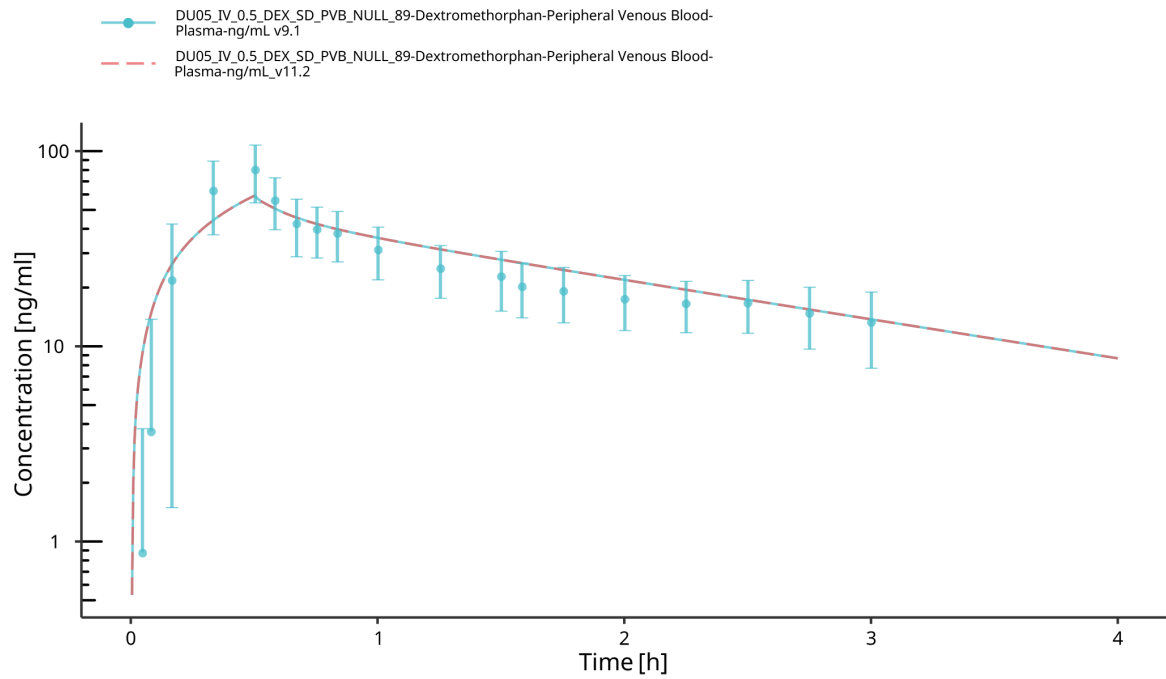
Dumond 2010 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=23 - time profile

DU10_PO_30_DEX__CVI_NULL_138_DDI-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

DU10_PO_30_DEX__CVI_NULL_138_DDI-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
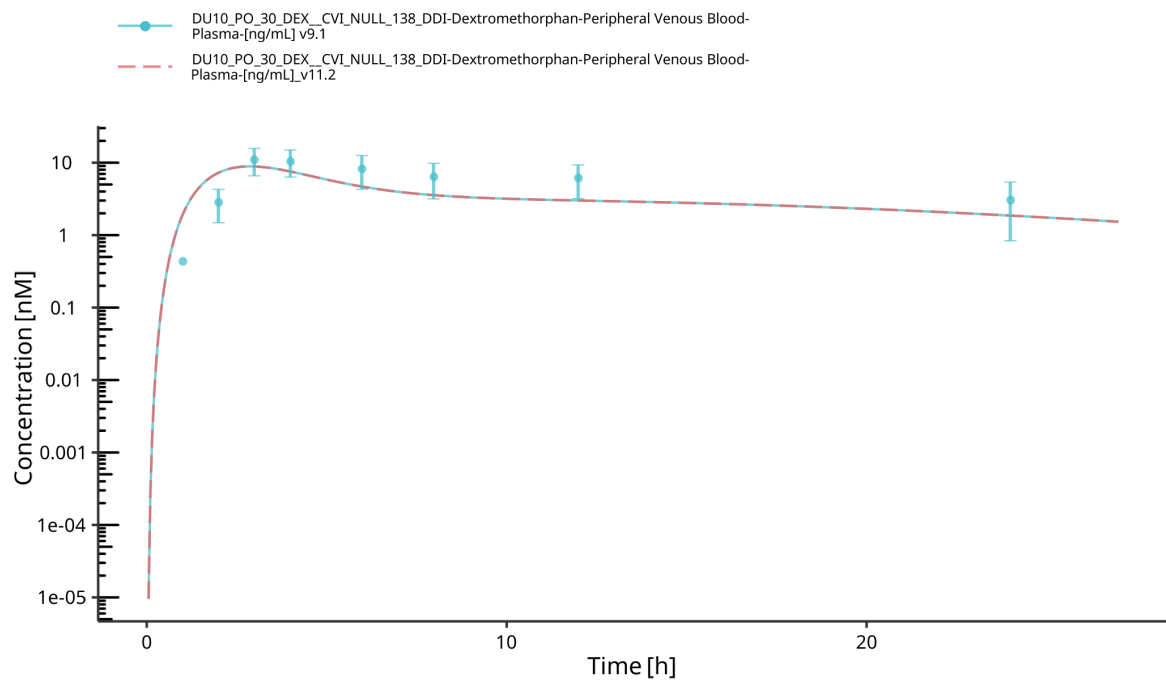
Edwards 2017 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=48 - time profile

Legend:
- ED17_PO_30_DEX_SD_PVB_NULL_118-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- ED17_PO_30_DEX_SD_PVB_NULL_118-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
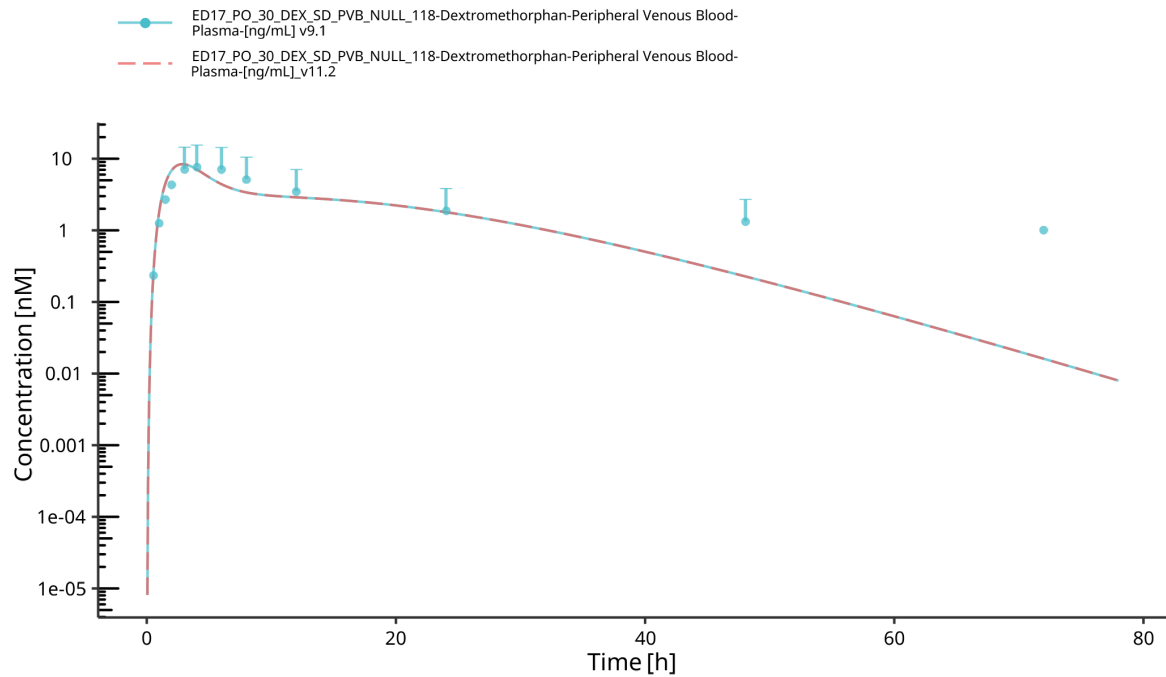
Ermer 2015 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=30 - time profile

Legend:
- ER15_PO_30_DEX_SD_PVB_NULL_186-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- ER15_PO_30_DEX_SD_PVB_NULL_186-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
- ER15_PO_30_DXT_SD_PVB_NULL_186-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- ER15_PO_30_DXT_SD_PVB_NULL_186-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

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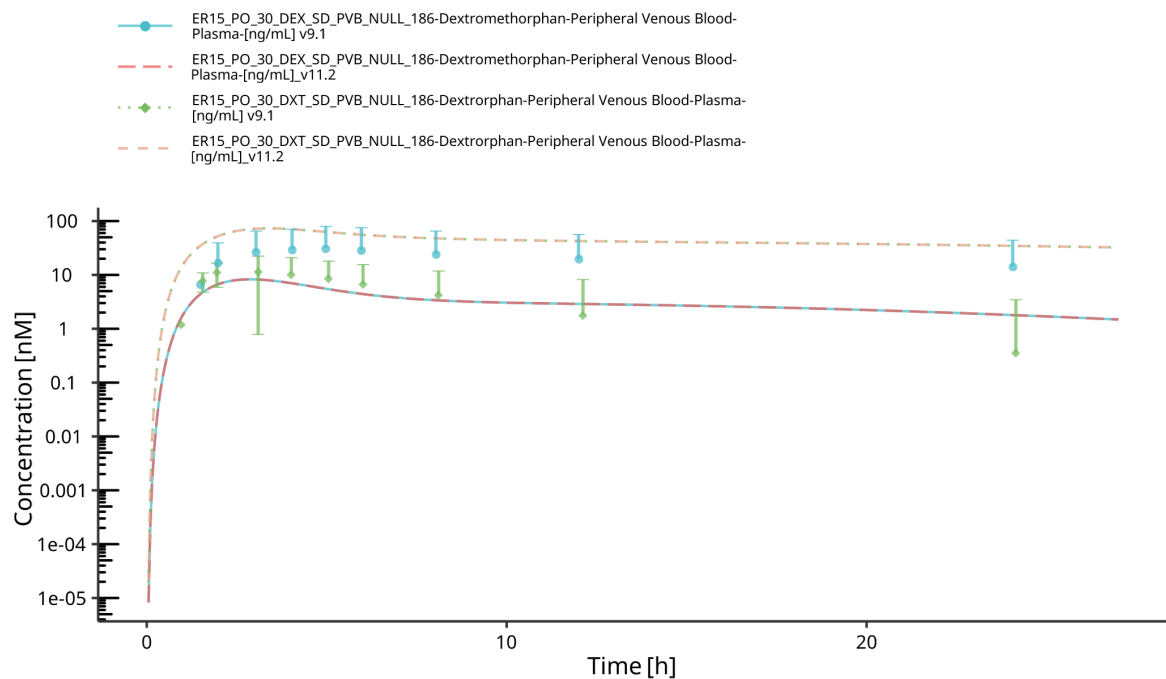
Feld 2013 EM, 60 mg dextromethorphan hydrobromide (capsule/solution), n=17 - time profile

Legend:
- Dextromethorpharm v11.2
- Dextromethorpharm v9.1
- Dextrorphan total v11.2
- Dextrorphan total v9.1
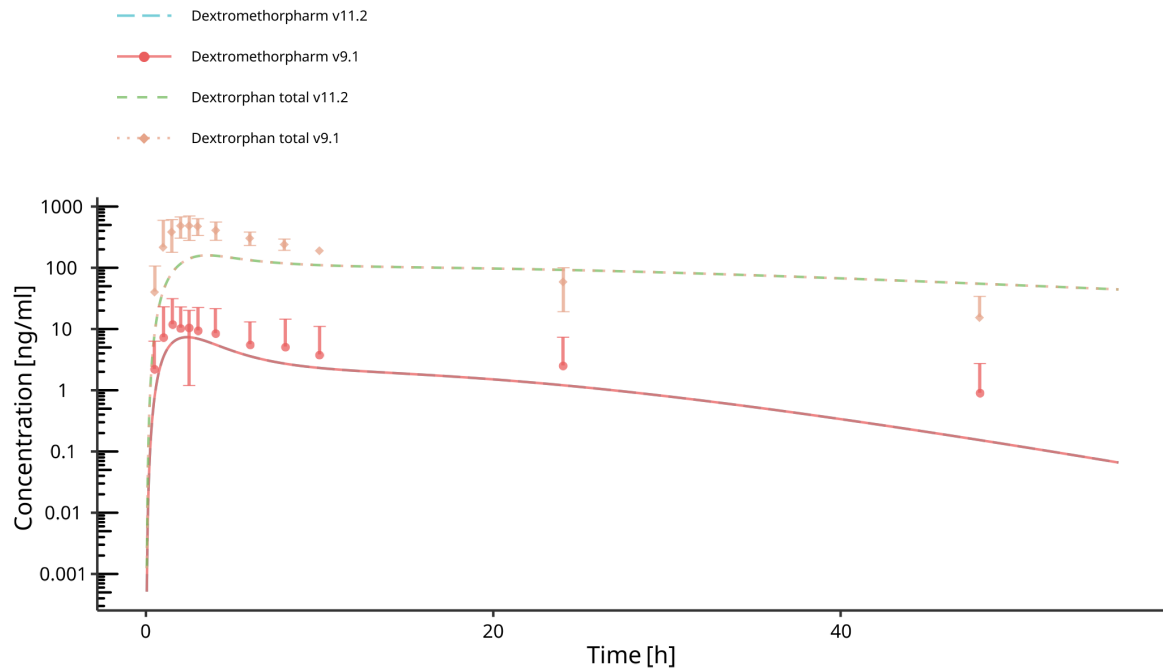
Gazzaz 2018 NM, 30 mg dextromethorphan hydrobromide (cocktail), n=30, AS=1.25 - time profile

Legend:
- GA18_PO_30_DEX_SD_PVB_NM_192-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- GA18_PO_30_DEX_SD_PVB_NM_192-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
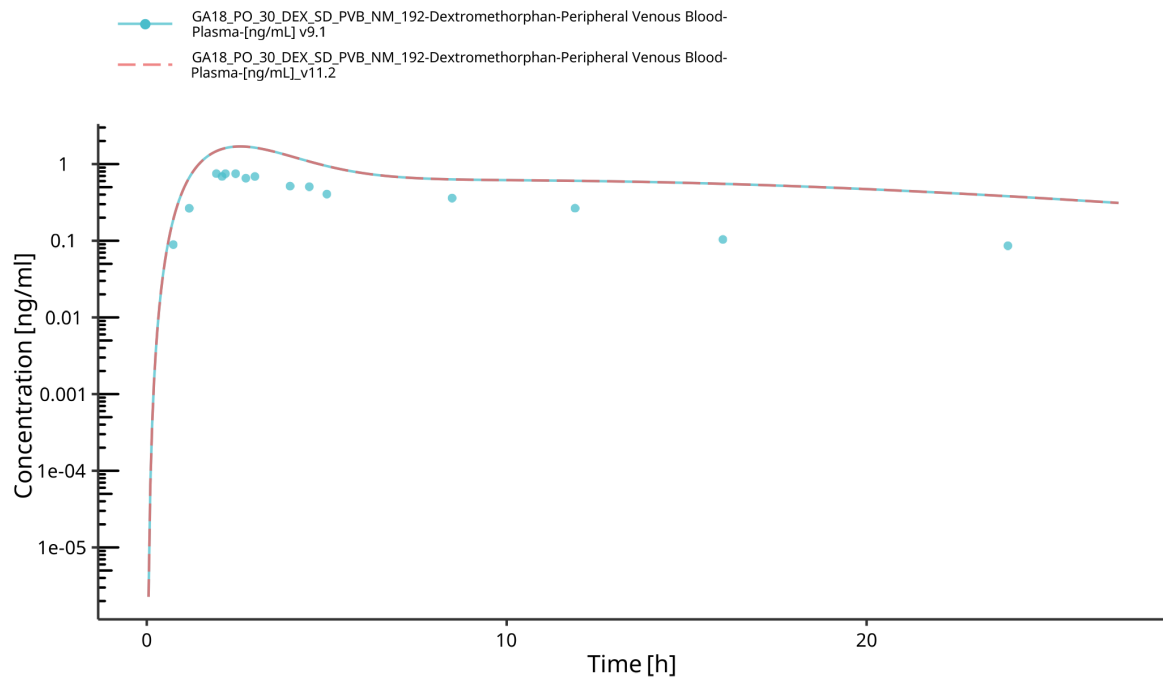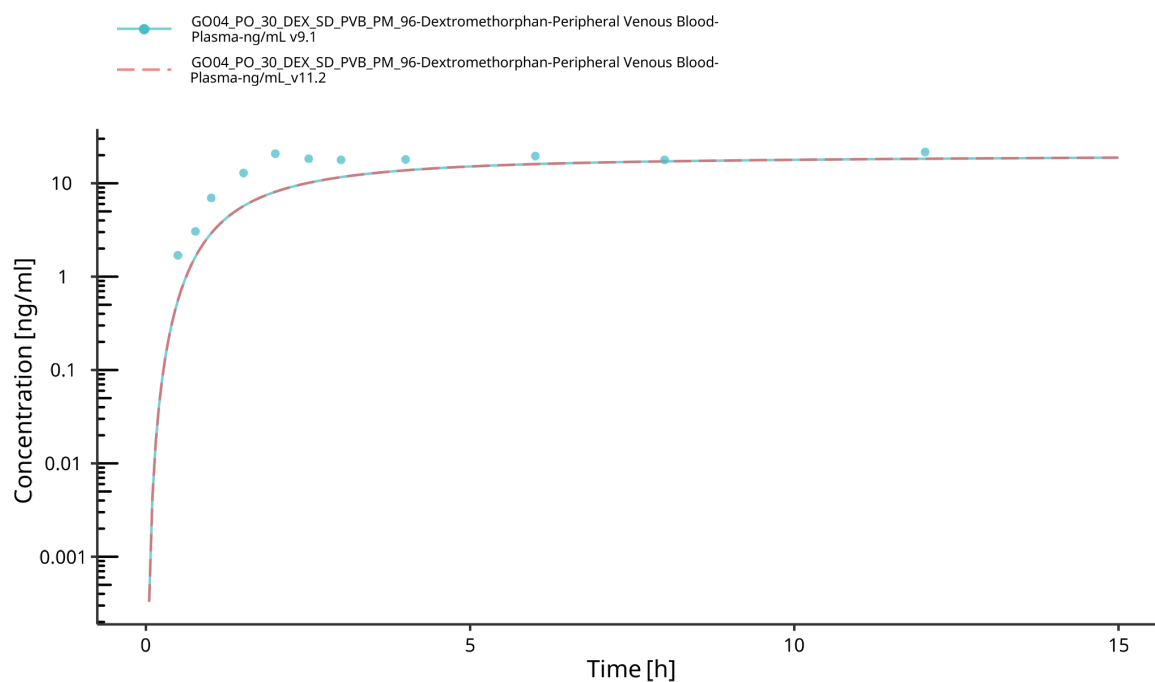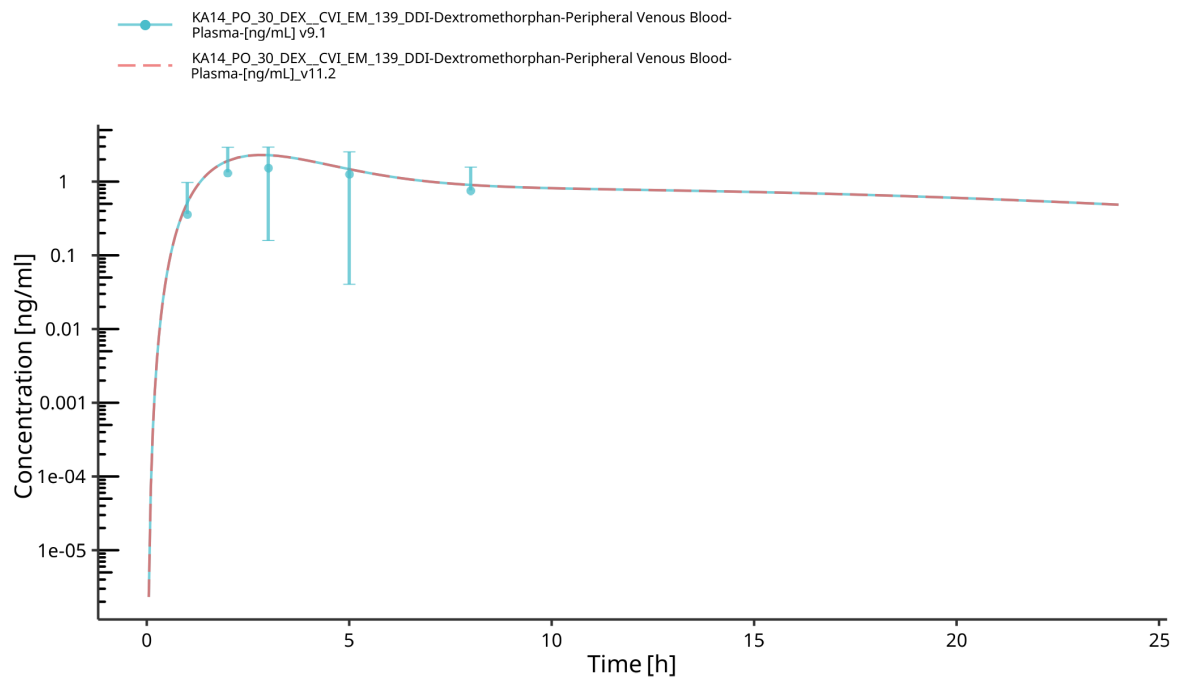
Gorski 2004 EM, 30 mg dextromethorphan hydromide (capsule/solution), n=11 - time profile
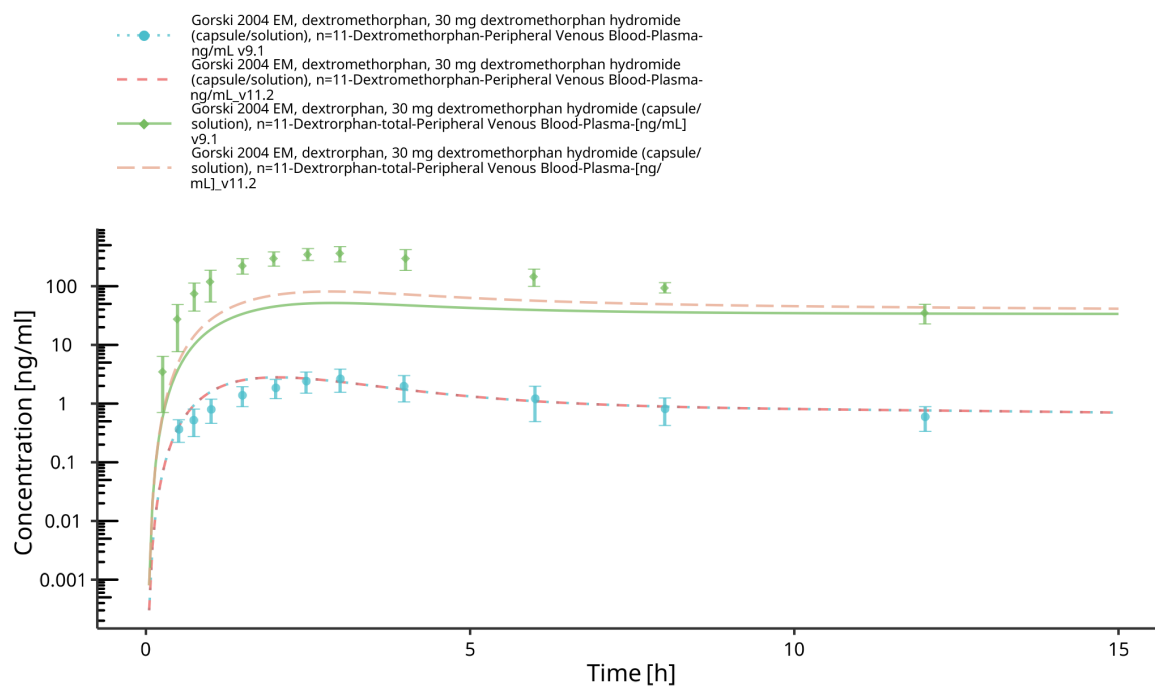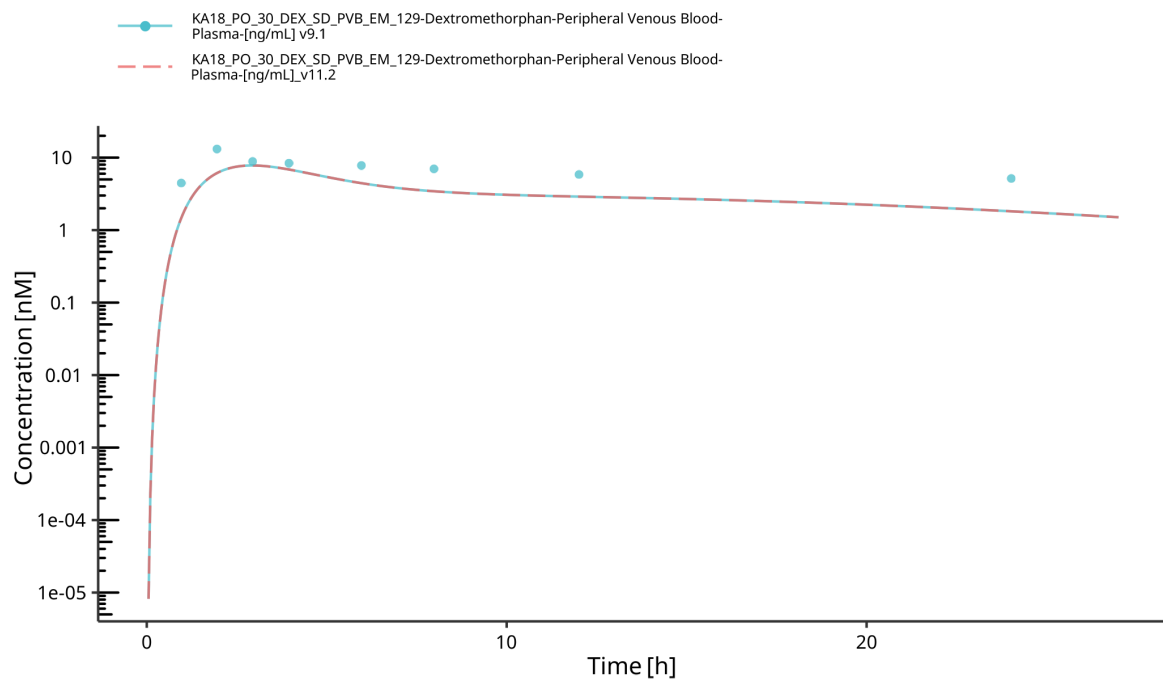
Gorski 2004 PM, 30 mg dextromethorphan hydromide (capsule/solution), n=1 - time profile
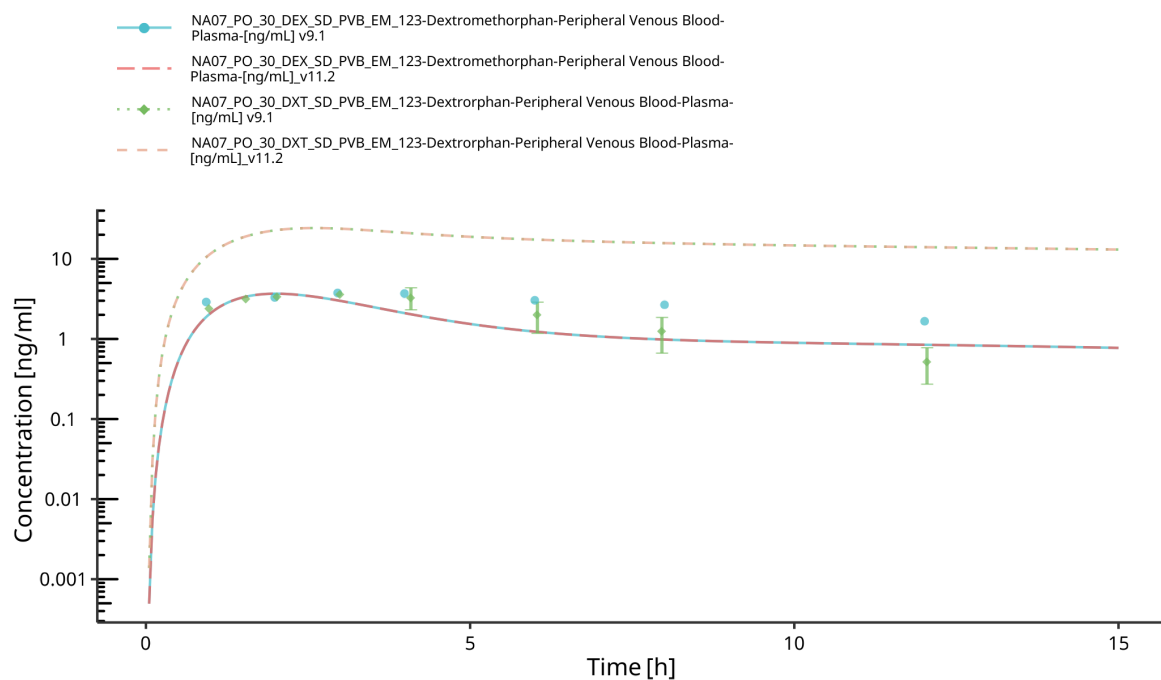
Kakuda 2014 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=14 - time profile

KA14_PO_30_DEX__CVI_EM_139_DDI-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

KA14_PO_30_DEX__CVI_EM_139_DDI-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

Khalilieh 2018 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=20 - time profile

KA18_PO_30_DEX_SD_PVB_EM_129-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

KA18_PO_30_DEX_SD_PVB_EM_129-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

Nakashima 2007 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=24 - time profile

Nyunt 2008 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=12 - time profile
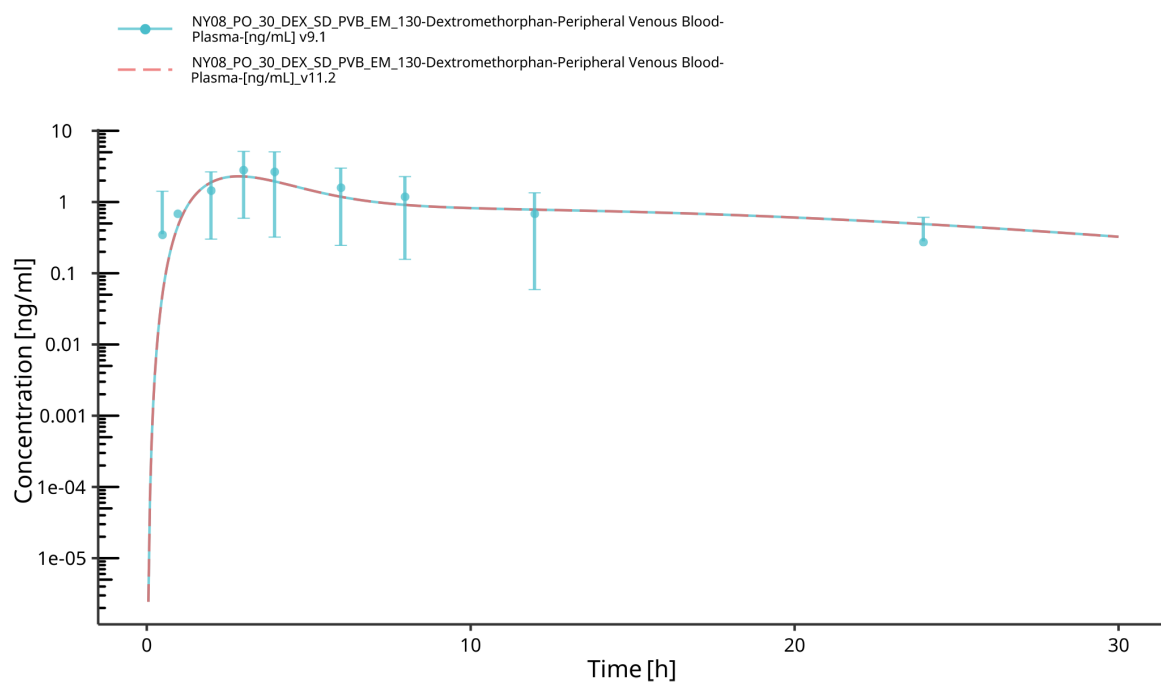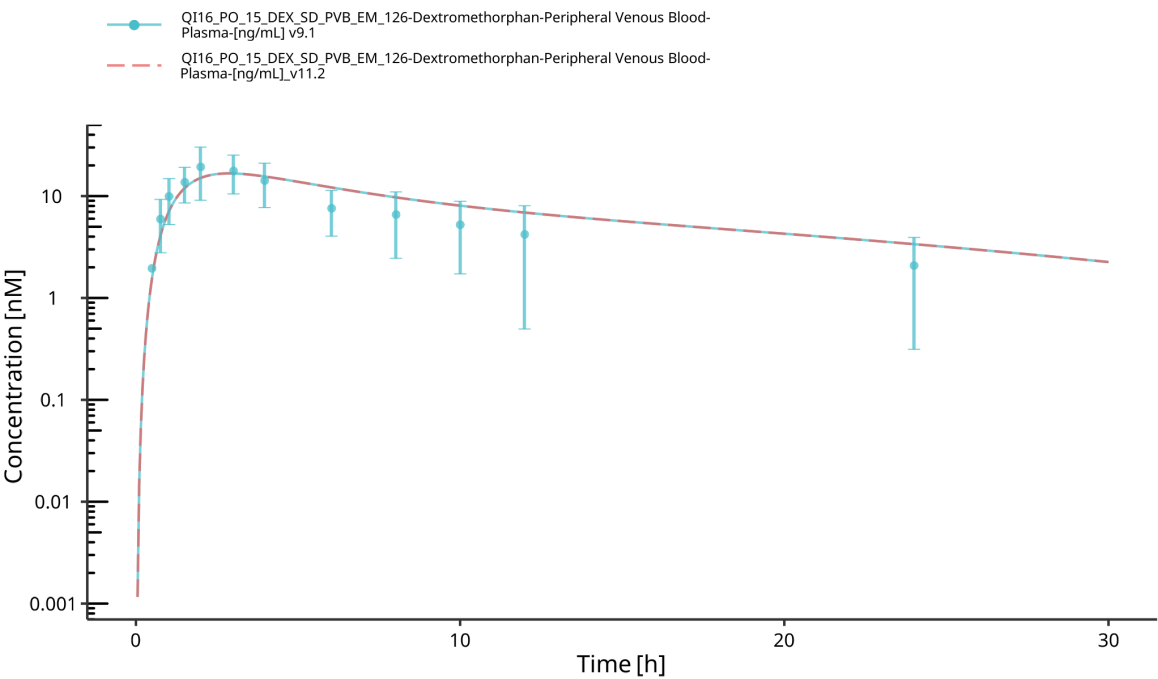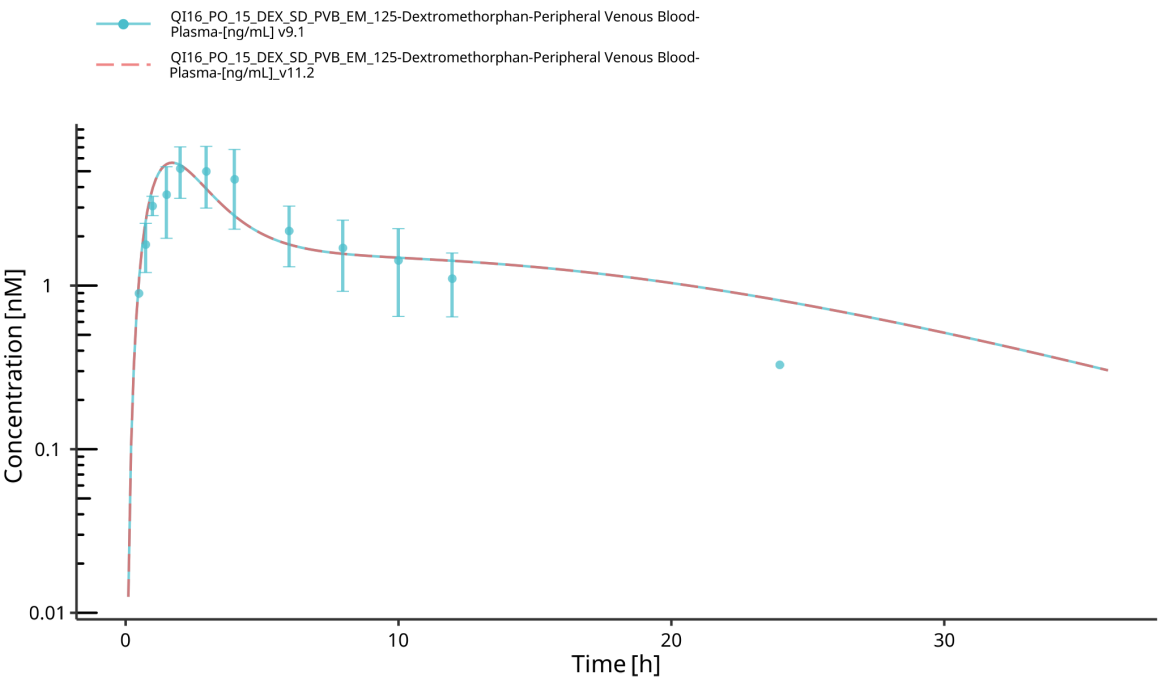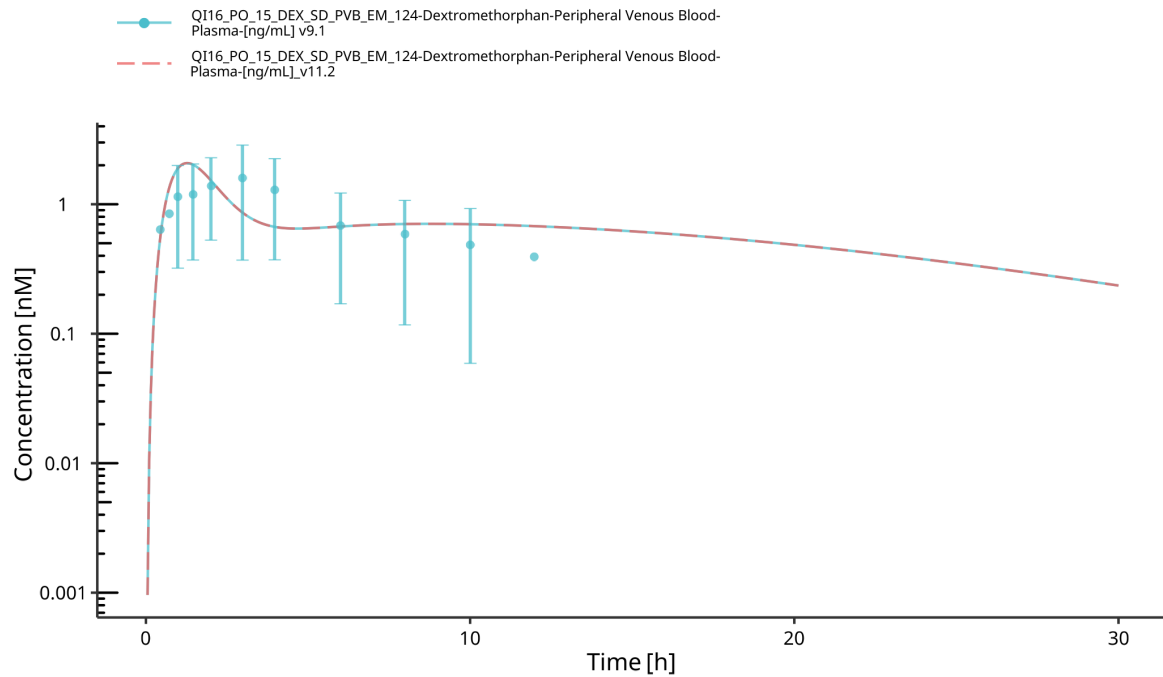
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Qiu 2016 IM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=0.5 - time profile

Qiu 2016 NM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=1.25 - time profile

Qiu 2016 NM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=2 - time profile

QI16_PO_15_DEX_SD_PVB_EM_124-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

QI16_PO_15_DEX_SD_PVB_EM_124-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

Sager 2014 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=10 - time profile

SA14_PO_30_DEX_SD_PVB_NM_135-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

SA14_PO_30_DEX_SD_PVB_NM_135-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

SA14_PO_30_DXT_SD_PVB_NM_135-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

SA14_PO_30_DXT_SD_PVB_NM_135-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

Schadel 1995 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=5 - time profile

Legend:
- SC95_PO_30_DXG_SD_PVB_EM_90-Dextrorphan-O-glucuronide-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- SC95_PO_30_DXG_SD_PVB_EM_90-Dextrorphan-O-glucuronide-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
- SC95_PO_30_DXT_SD_PVB_EM_90-Dextrorphan-Peripheral Venous Blood-Plasma-ng/mL v9.1
- SC95_PO_30_DXT_SD_PVB_EM_90-Dextrorphan-Peripheral Venous Blood-Plasma-ng/mL_v11.2
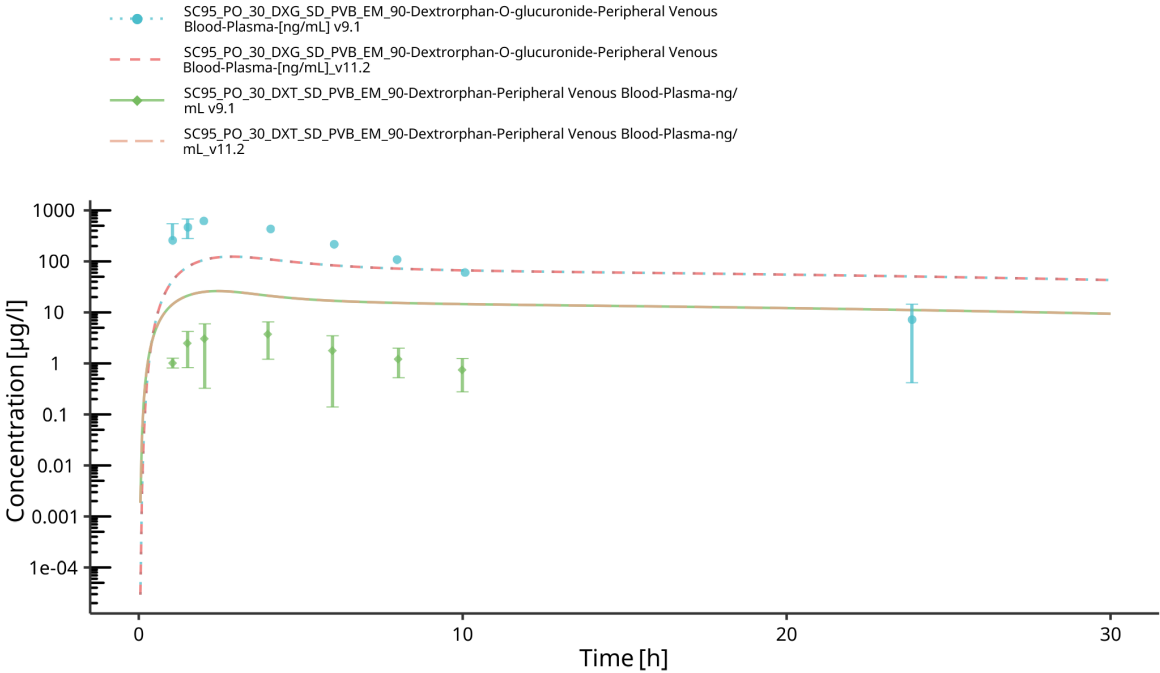
Schadel 1995 PM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=4 - time profile
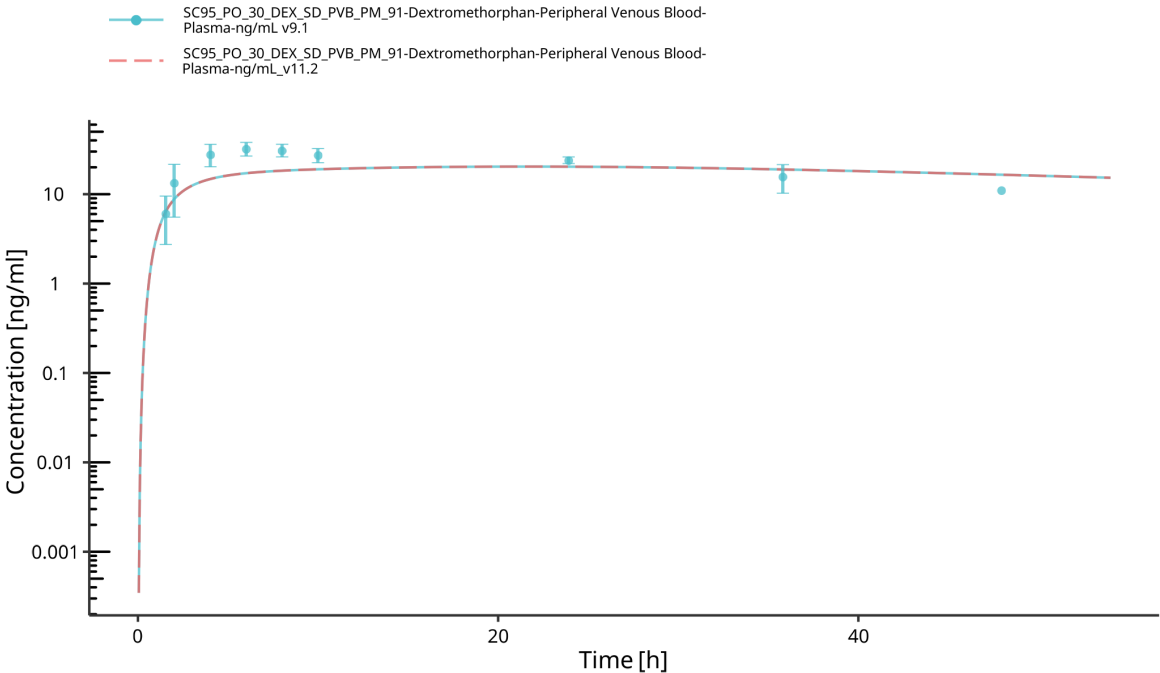
Legend:
- SC95_PO_30_DEX_SD_PVB_PM_91-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL v9.1
- SC95_PO_30_DEX_SD_PVB_PM_91-Dextromethorphan-Peripheral Venous Blood-Plasma-ng/mL_v11.2

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Stage 2018 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=12 - time profile

Legend:
- SA18_PO_30_DEX__PCO_NULL_137_DDI-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- SA18_PO_30_DEX__PCO_NULL_137_DDI-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
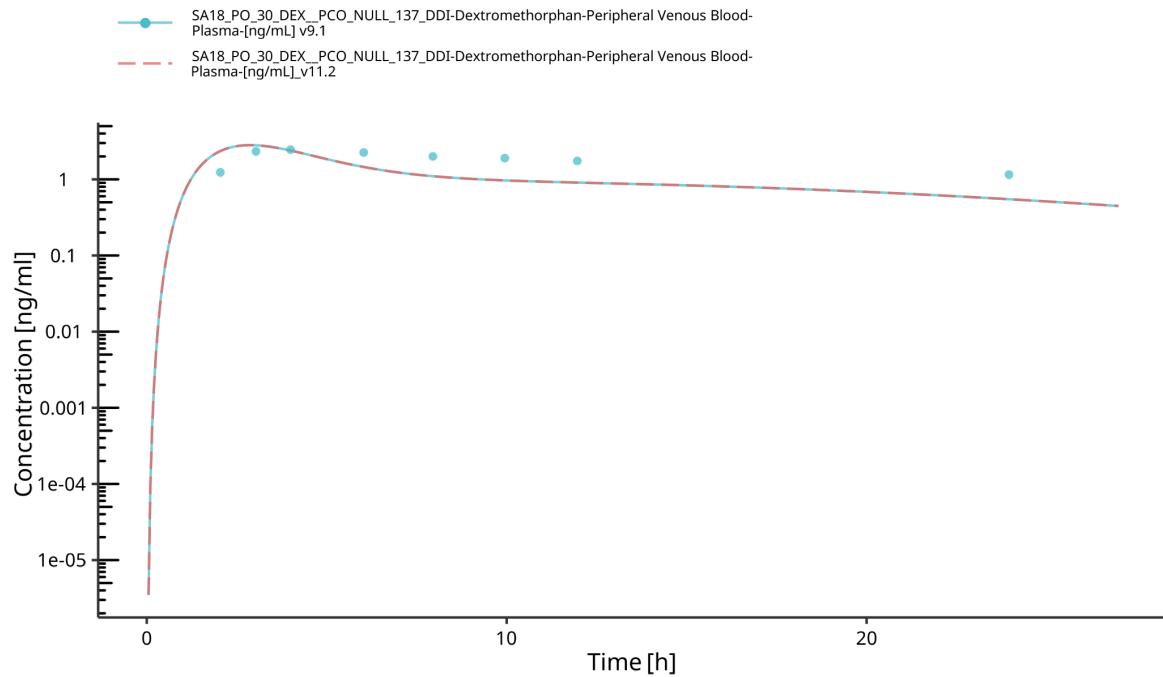
Storelli 2018 IM, 5 mg dextromethorphan base (capsule/solution), n=16 - time profile

Legend:
- ST18_PO_5_DEX_SD_PVB_IM_121-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- ST18_PO_5_DEX_SD_PVB_IM_121-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
- ST18_PO_5_DXT_SD_PVB_EM_121-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- ST18_PO_5_DXT_SD_PVB_EM_121-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

15
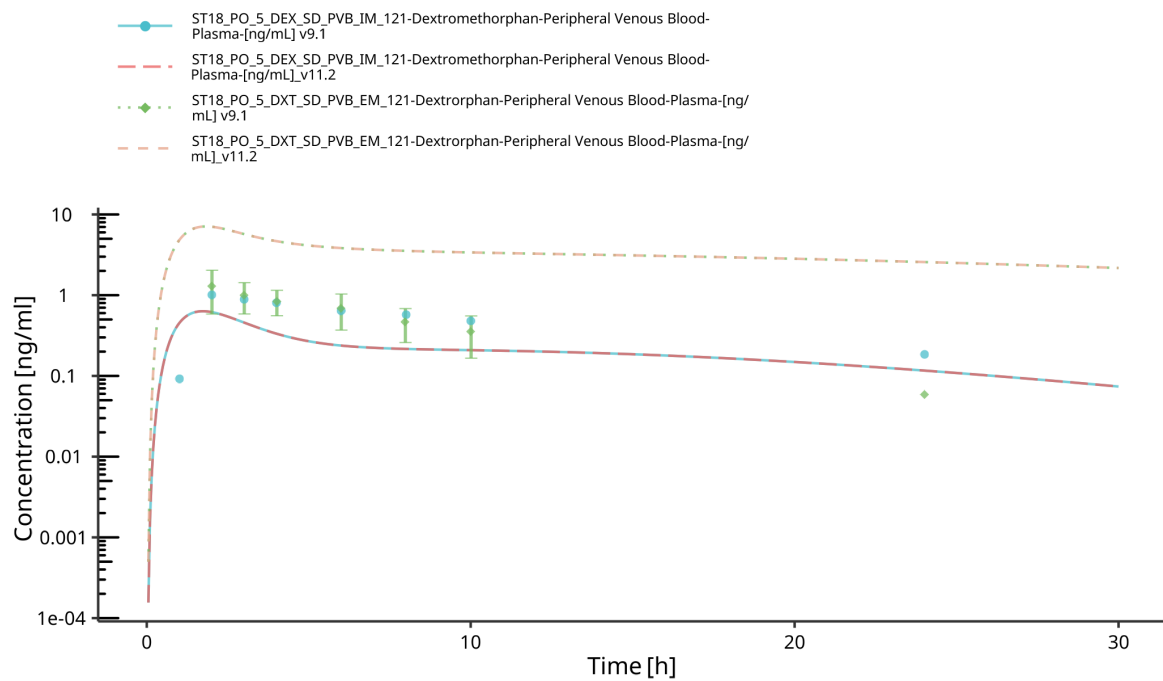
Storelli 2018 NM, 5 mg dextromethorphan base (capsule/solution), n=17, AS=2 - time profile

ST18_PO_5_DEX_SD_PVB_NM_120-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

ST18_PO_5_DEX_SD_PVB_NM_120-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

ST18_PO_5_DXT_SD_PVB_EM_120-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

ST18_PO_5_DXT_SD_PVB_EM_120-Dextrorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
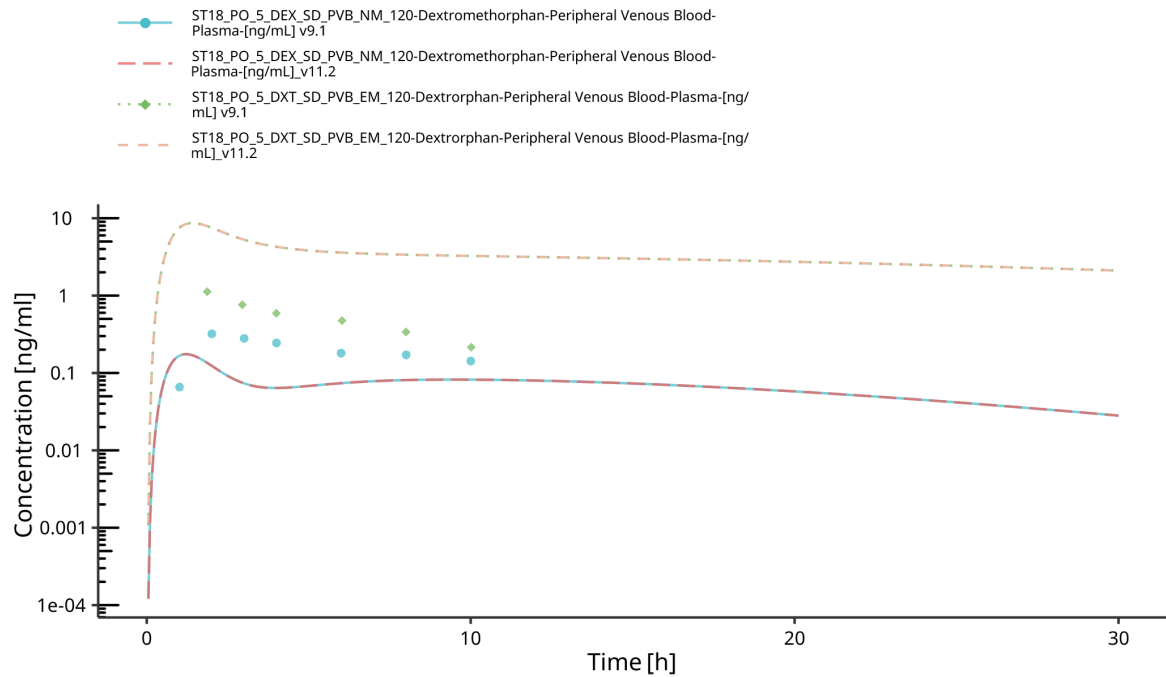
Tennezé 1999 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=36 - time profile

TE99_PO_80_DEX_SD_PVB_EM_122-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

TE99_PO_80_DEX_SD_PVB_EM_122-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

TE99_PO_80_DXT_SD_PVB_EM_122-Dextrorphan-total-Peripheral Venous Blood-Plasma-[ng/mL] v9.1

TE99_PO_80_DXT_SD_PVB_EM_122-Dextrorphan-total-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2

16
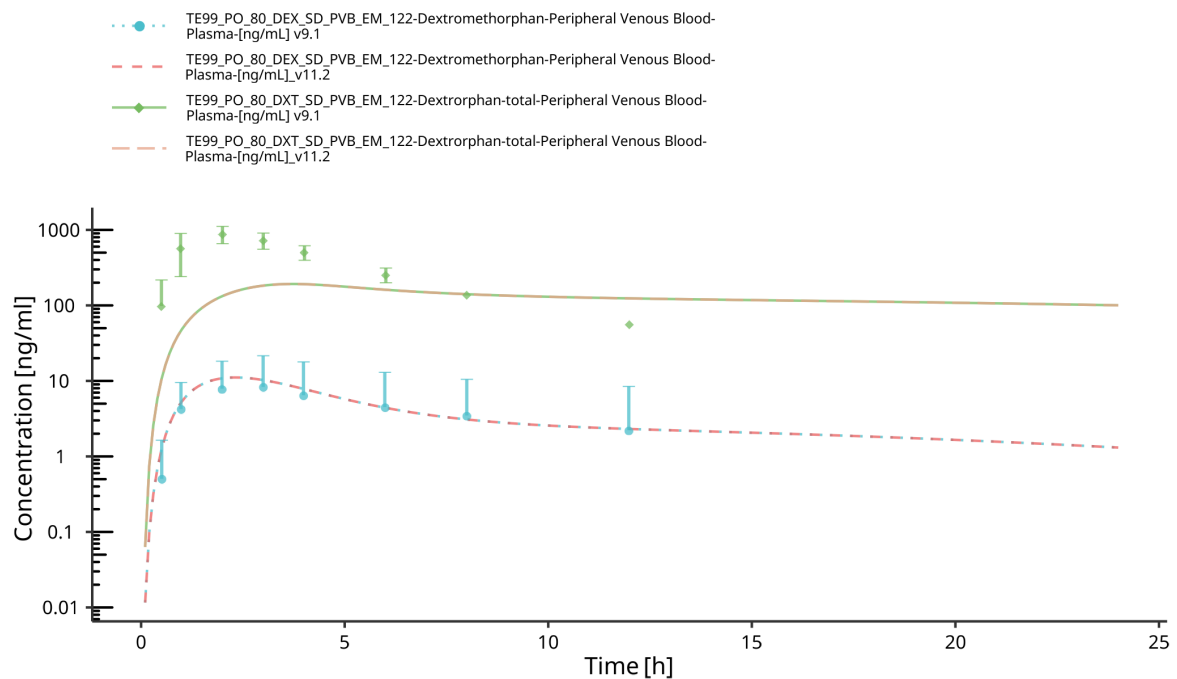
Yamazaki 2017 IM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=12, AS=0.5 - time profile

Legend:
- YA17_PO_30_DEX_SD_PVB_EM_128-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- YA17_PO_30_DEX_SD_PVB_EM_128-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
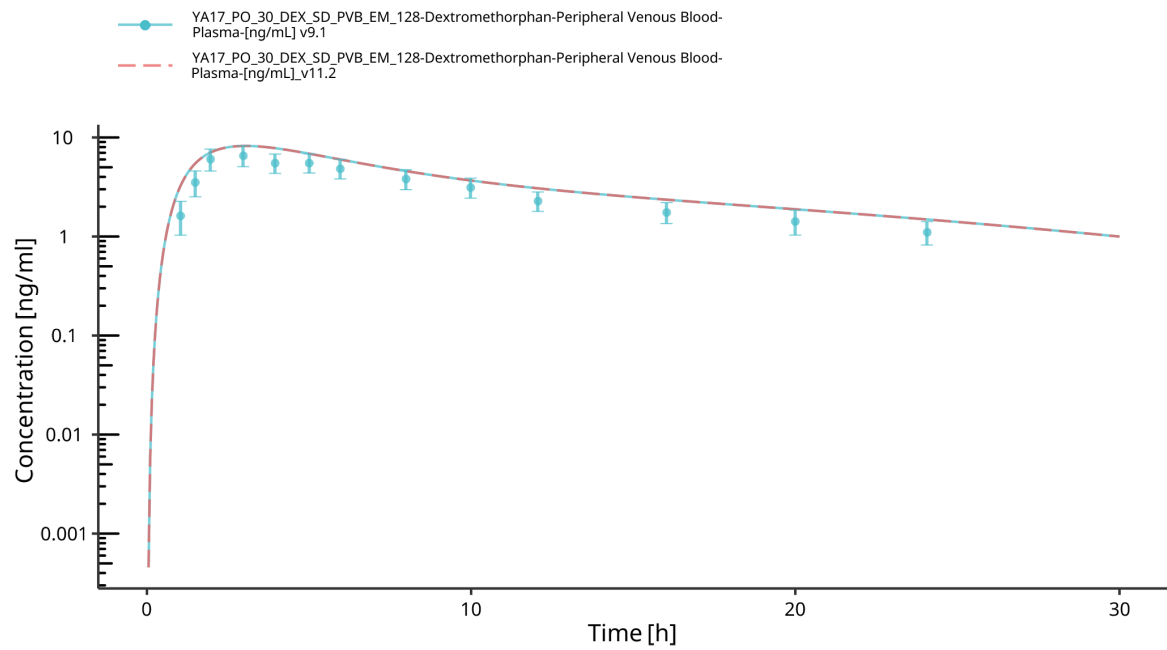
Yamazaki 2017 NM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=11, AS=2 - time profile

Legend:
- YA17_PO_30_DEX_SD_PVB_EM_127-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL] v9.1
- YA17_PO_30_DEX_SD_PVB_EM_127-Dextromethorphan-Peripheral Venous Blood-Plasma-[ng/mL]_v11.2
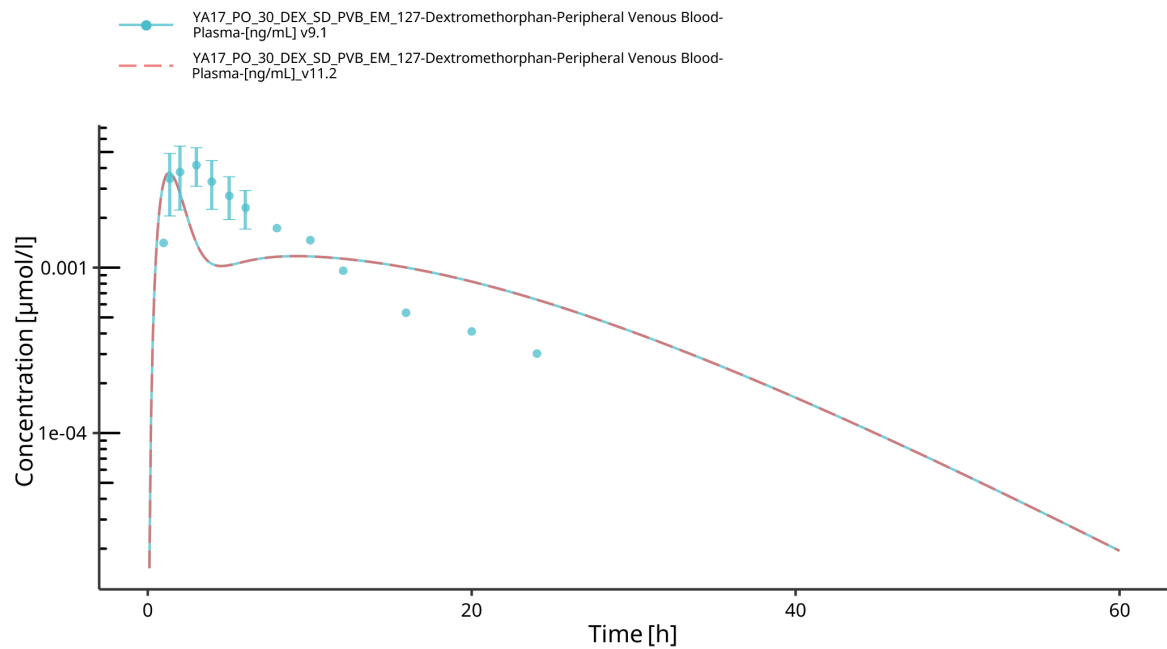
Zawertailo 2009 NM, 3 mg/kg dextromethorphan hydrobromide (capsule/solution), n=6, AS=2 - time profile
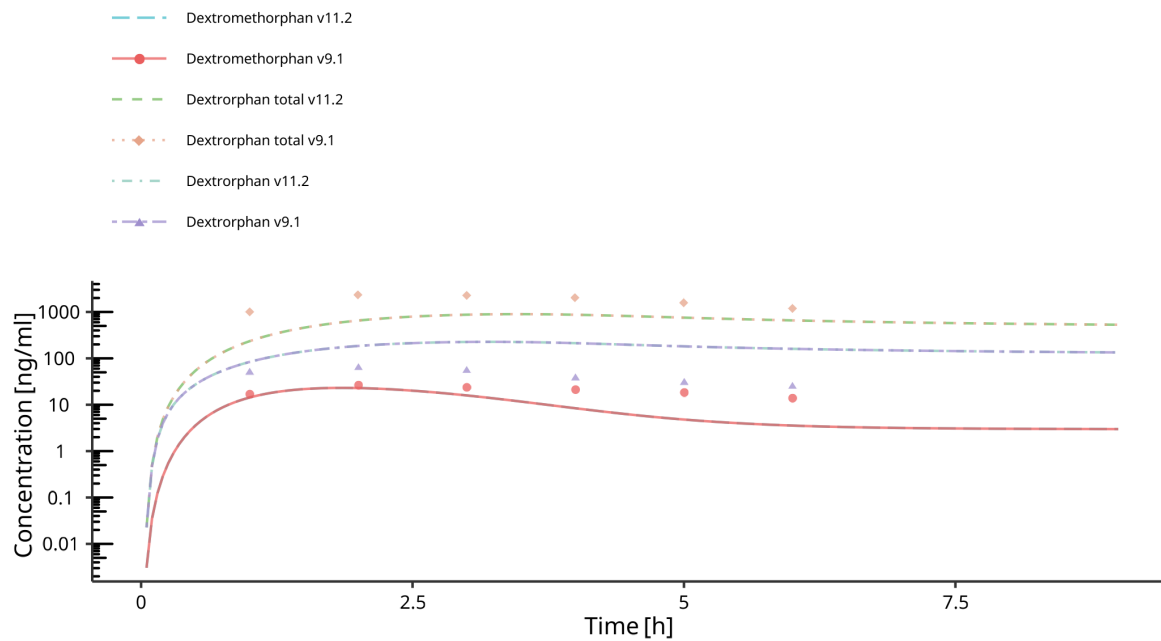
4 Conclusion

References

Rüdesheim, Simeon, Dominik Selzer, Uwe Fuhr, Matthias Schwab, and Thorsten Lehr. 2022. "Physiologically-Based Pharmacokinetic Modeling of Dextromethorphan to Investigate Interindividual Variability Within CYP2D6 Activity Score Groups." *CPT: Pharmacometrics & Systems Pharmacology* 11 (4): 494–511. https://doi.org/10.1002/psp4.12776.