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:

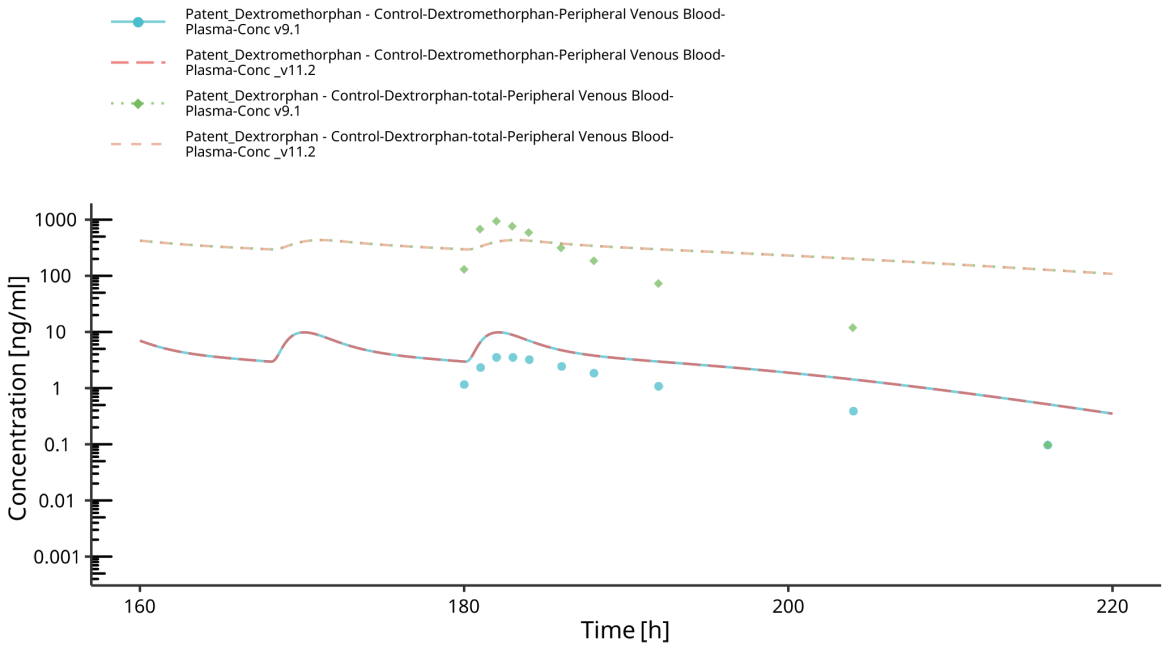
2.3 Qualification process

2.4 Consolidation of expression profiles

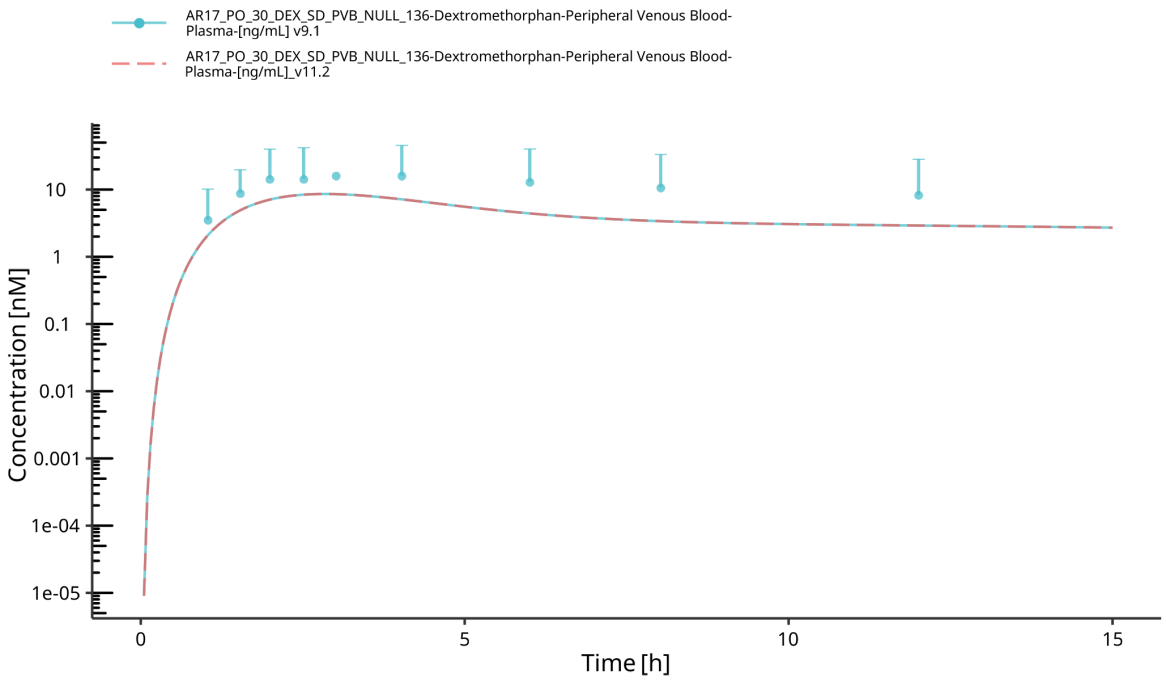
3 Results

Comparison of time-concentration profiles generated with the different software versions are presented in the following:

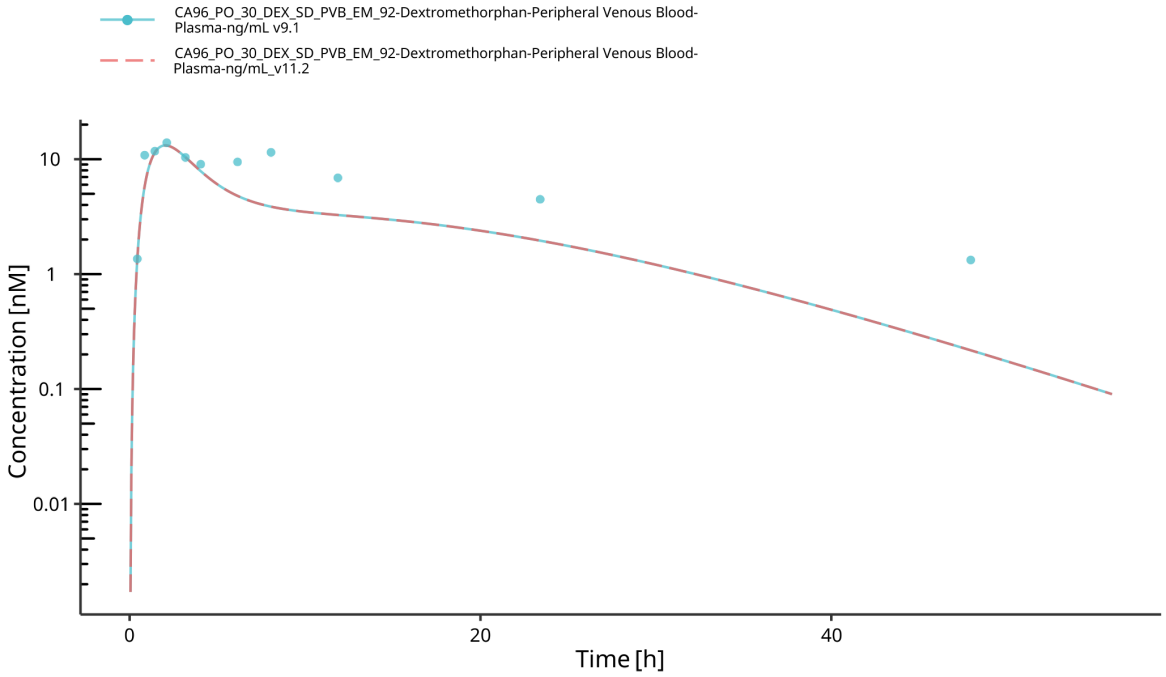
Antecip Bioventures EM, 60 mg dextromethorphan hydrobromide multiple dose (capsule/solution), n=10 - time profile



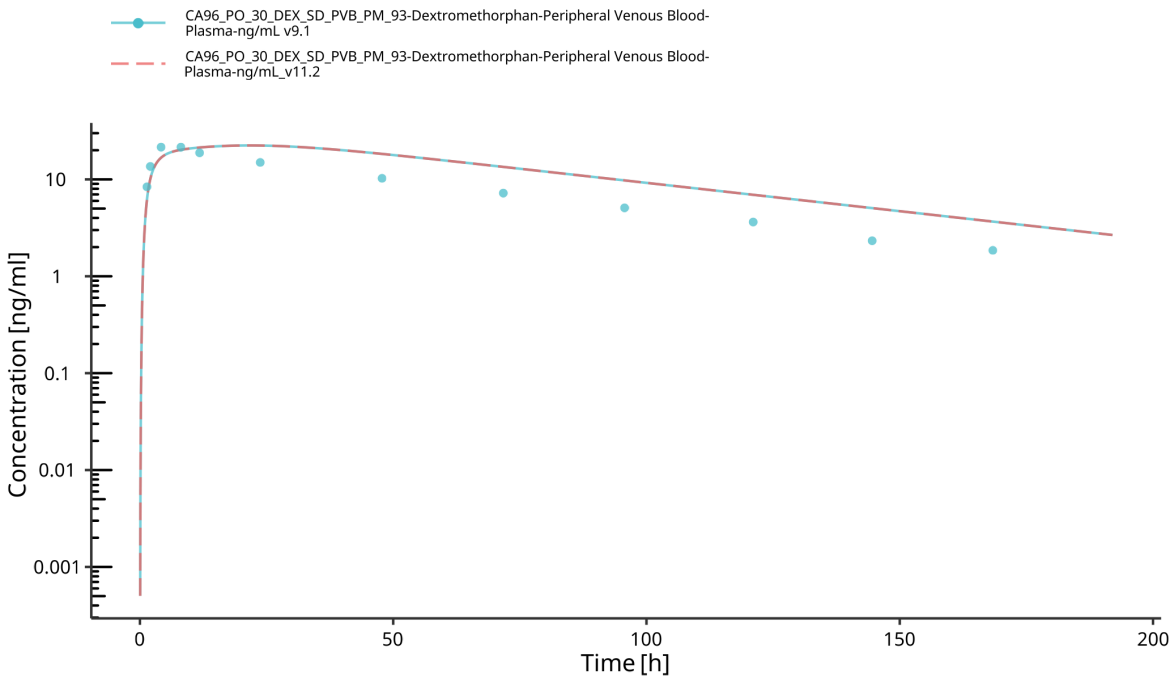
Armani 2017 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=20 - time profile



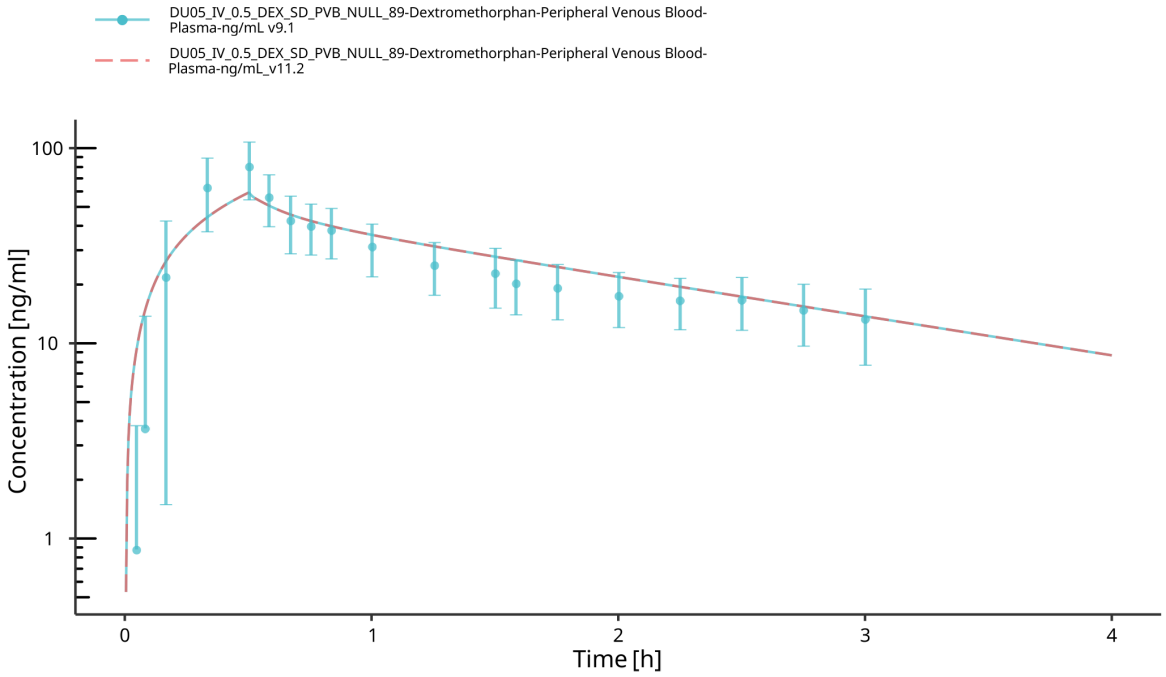
Capon 1996 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=6 - time profile



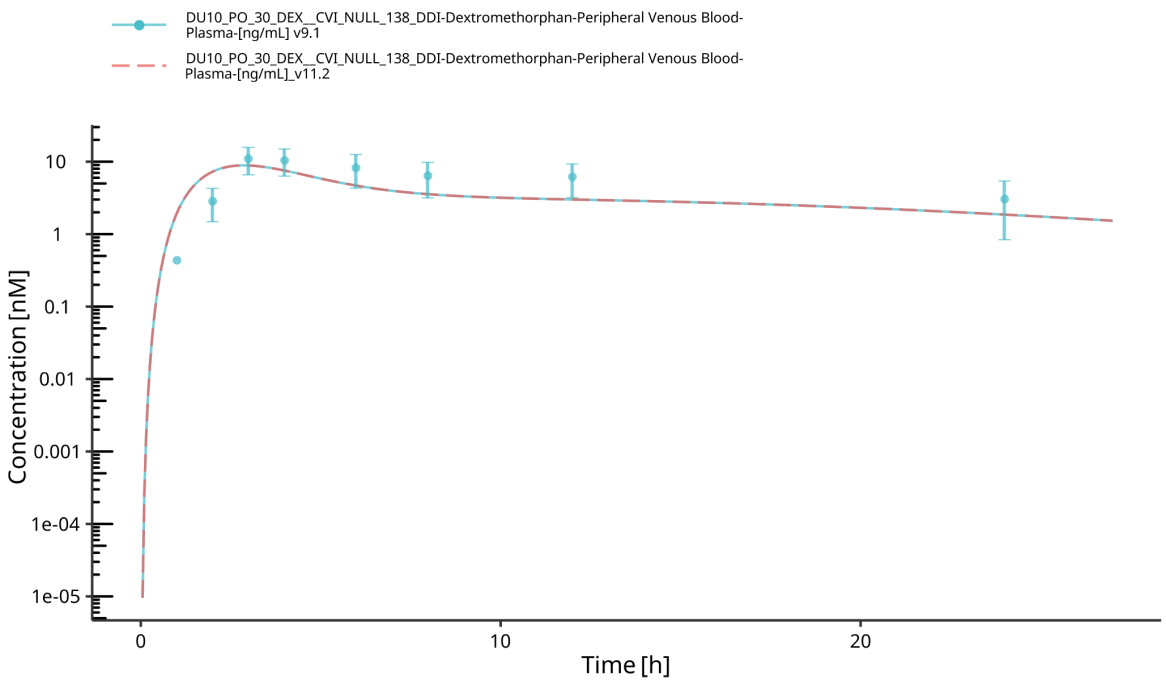
Capon 1996 PM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=6 - time profile



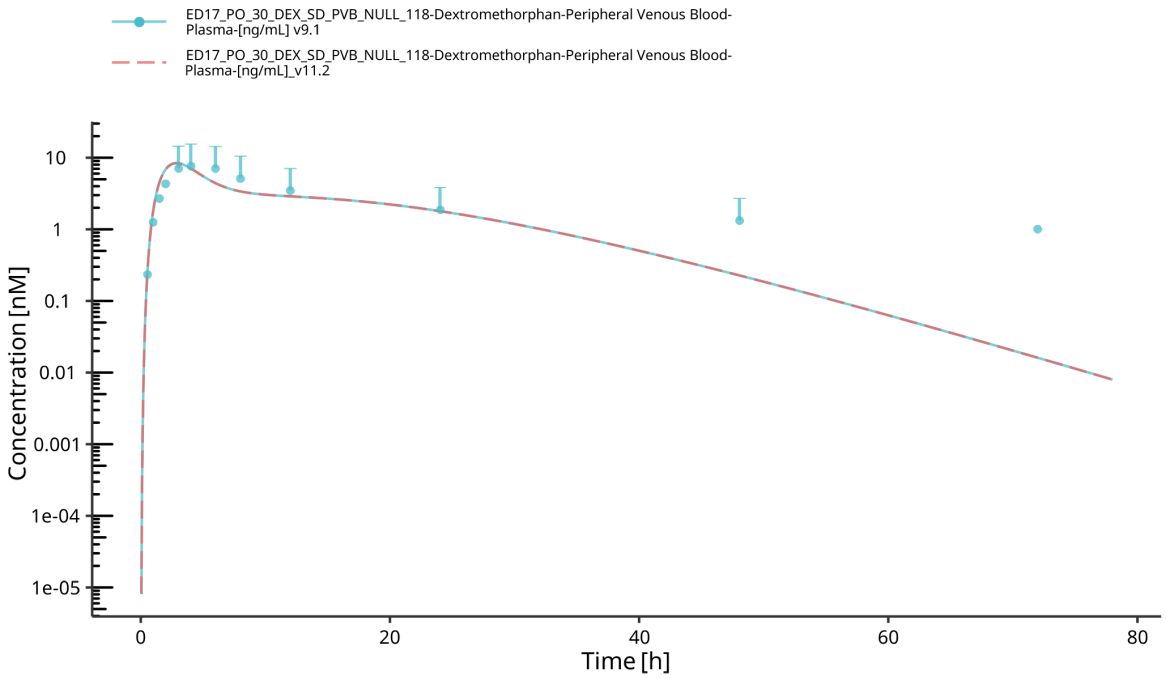
Duedahl 2005 EM, 0.5 mg/kg dextromethorphan base (infusion), n=24 - time profile



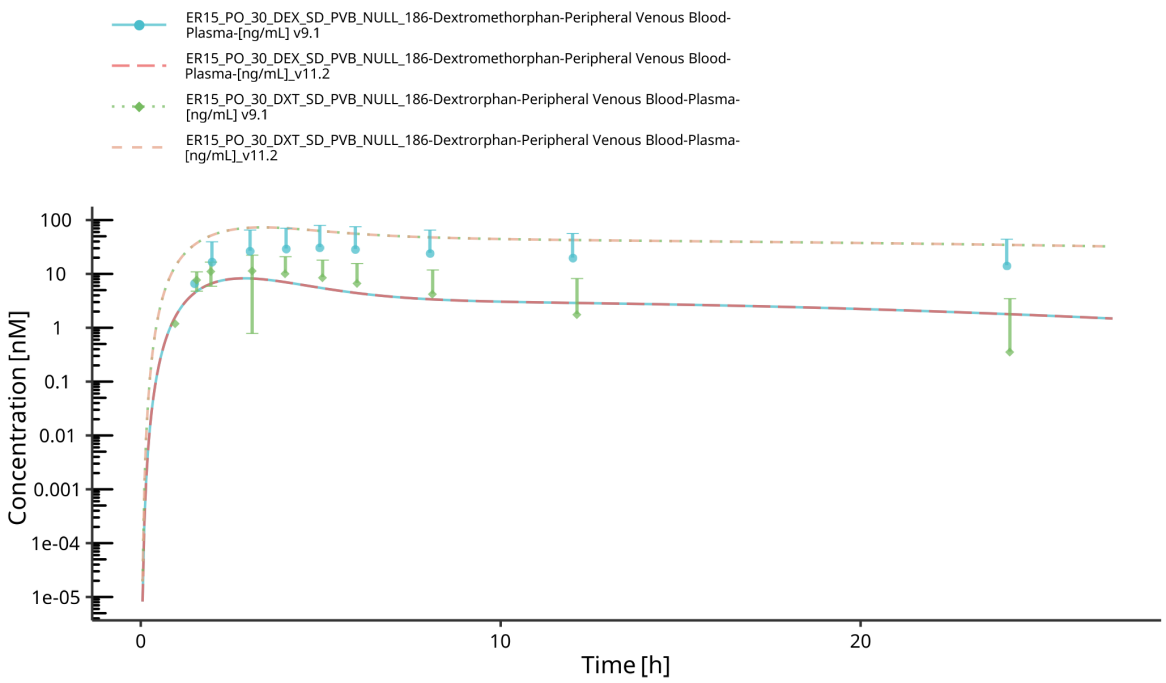
Dumond 2010 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=23 - time profile



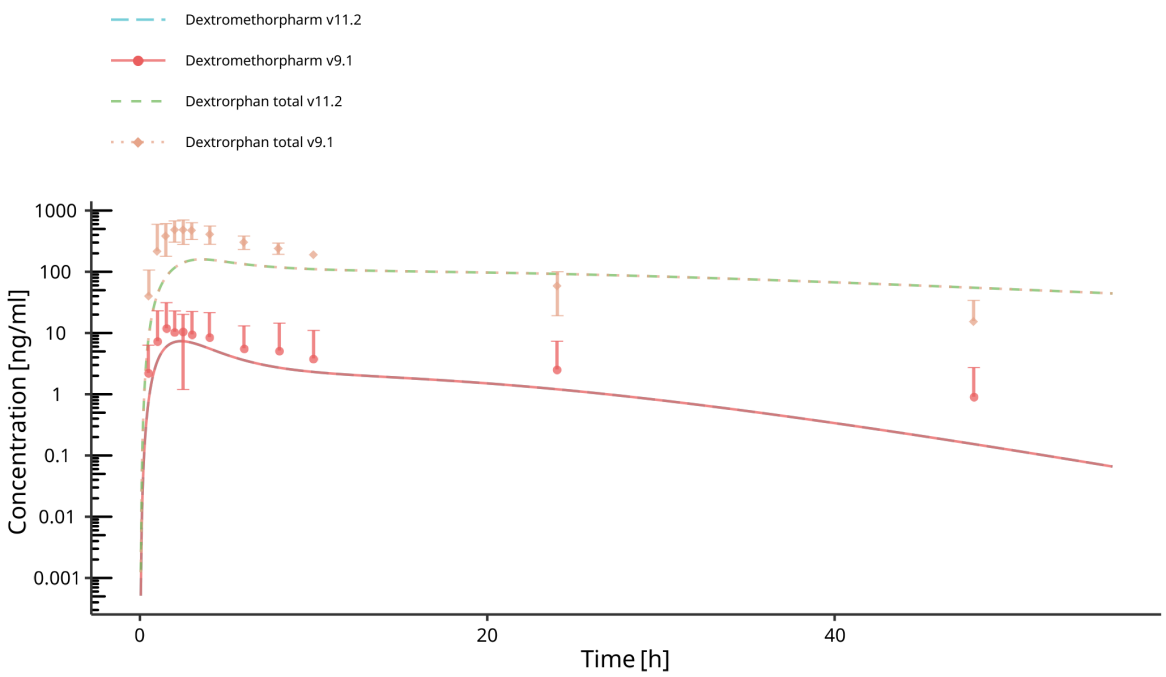
Edwards 2017 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=48 - time profile



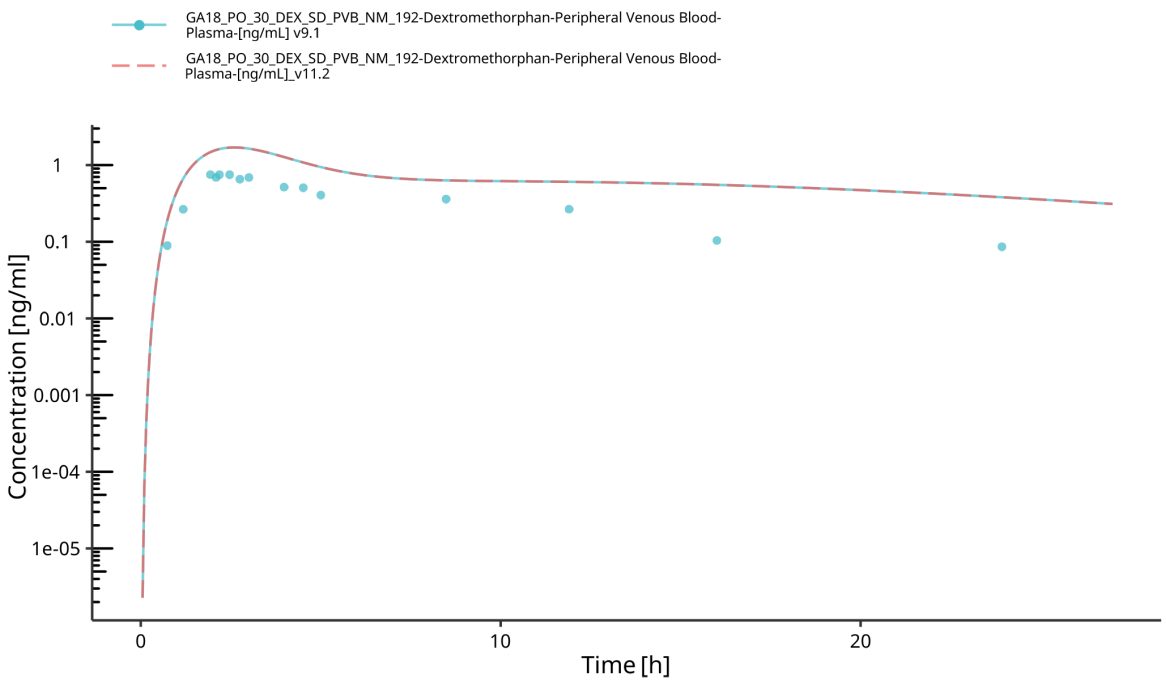
Ermer 2015 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=30 - time profile



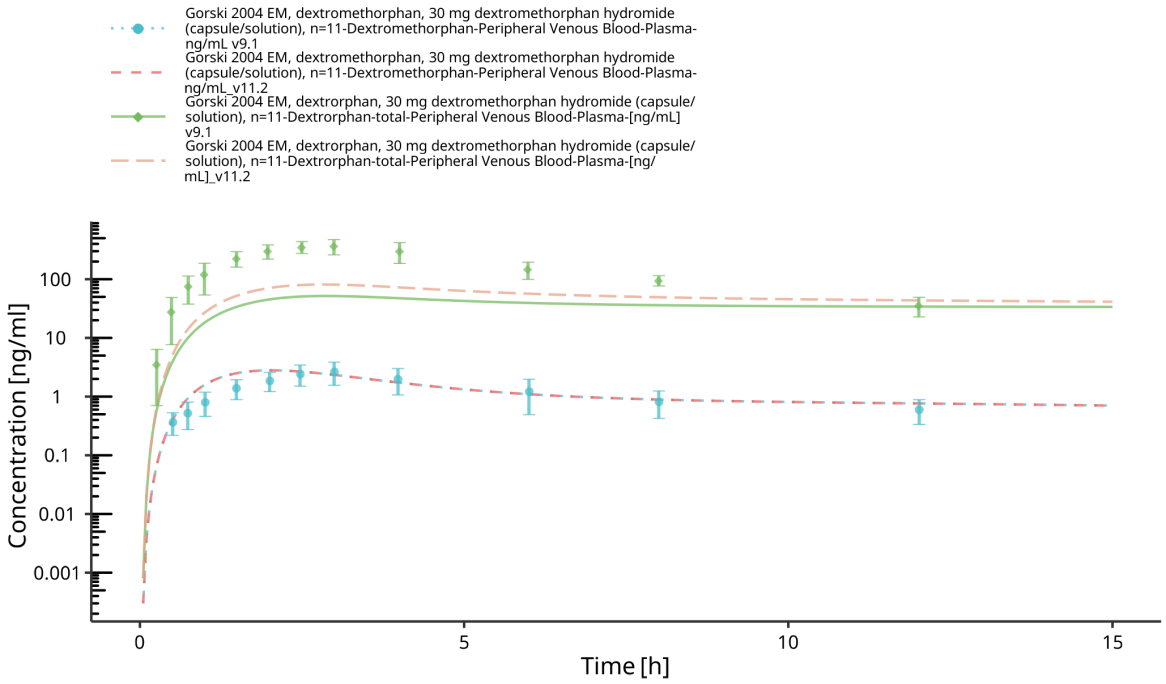
Feld 2013 EM, 60 mg dextromethorphan hydrobromide (capsule/solution), n=17 - time profile



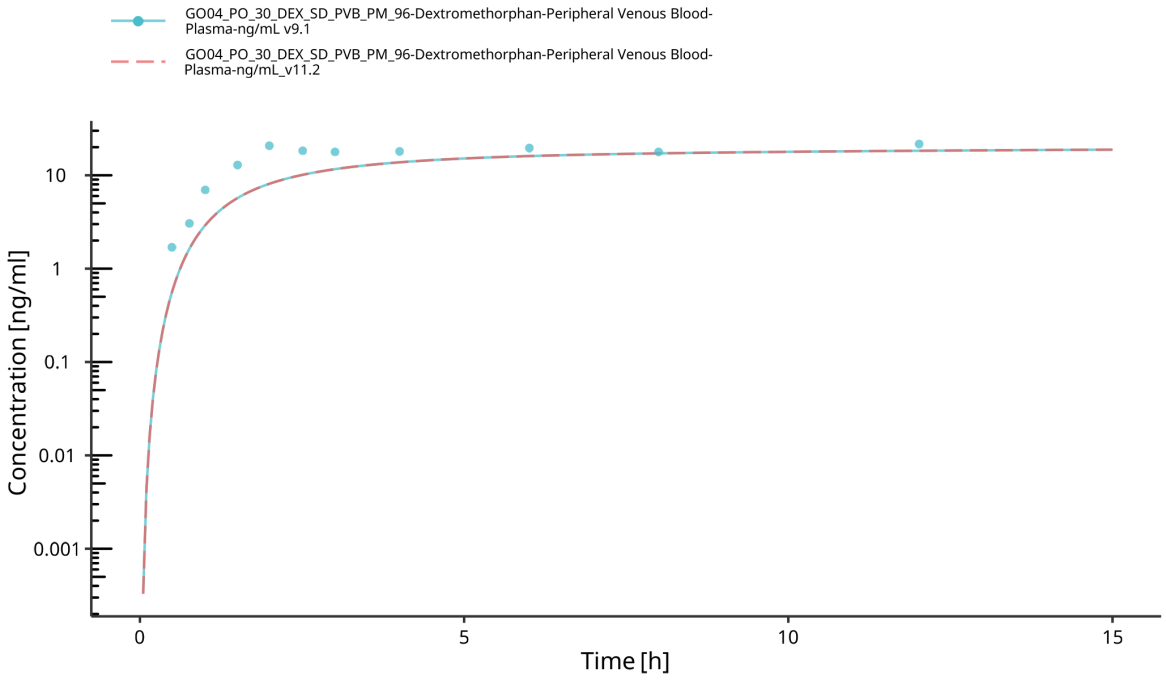
Gazzaz 2018 NM, 30 mg dextromethorphan hydrobromide (cocktail), n=30, AS=1.25 - time profile



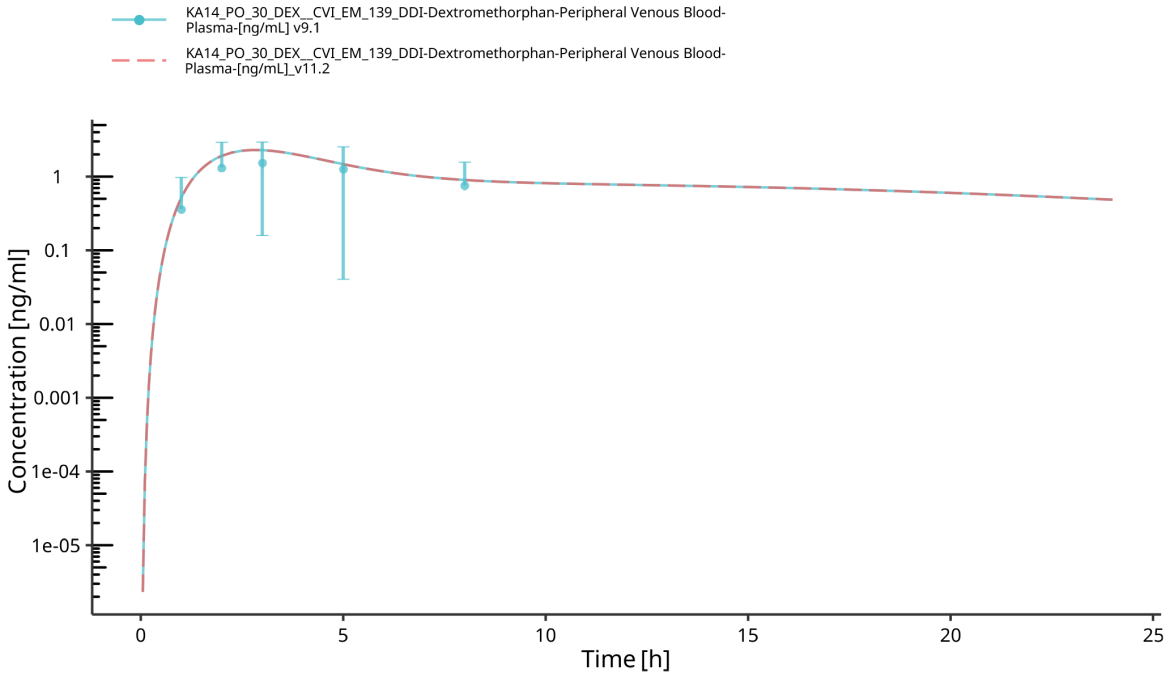
Gorski 2004 EM, 30 mg dextromethorphan hydromide (capsule/solution), n=11 - time profile



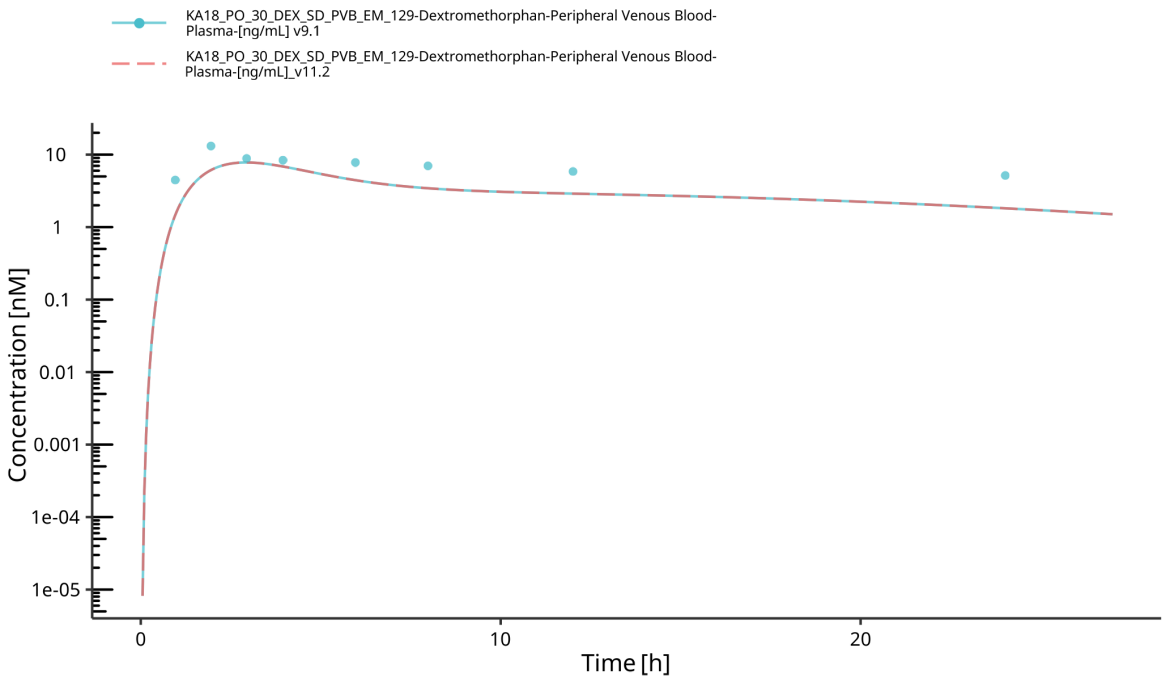
Gorski 2004 PM, 30 mg dextromethorphan hydromide (capsule/solution), n=1 - time profile



Kakuda 2014 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=14 - time profile



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



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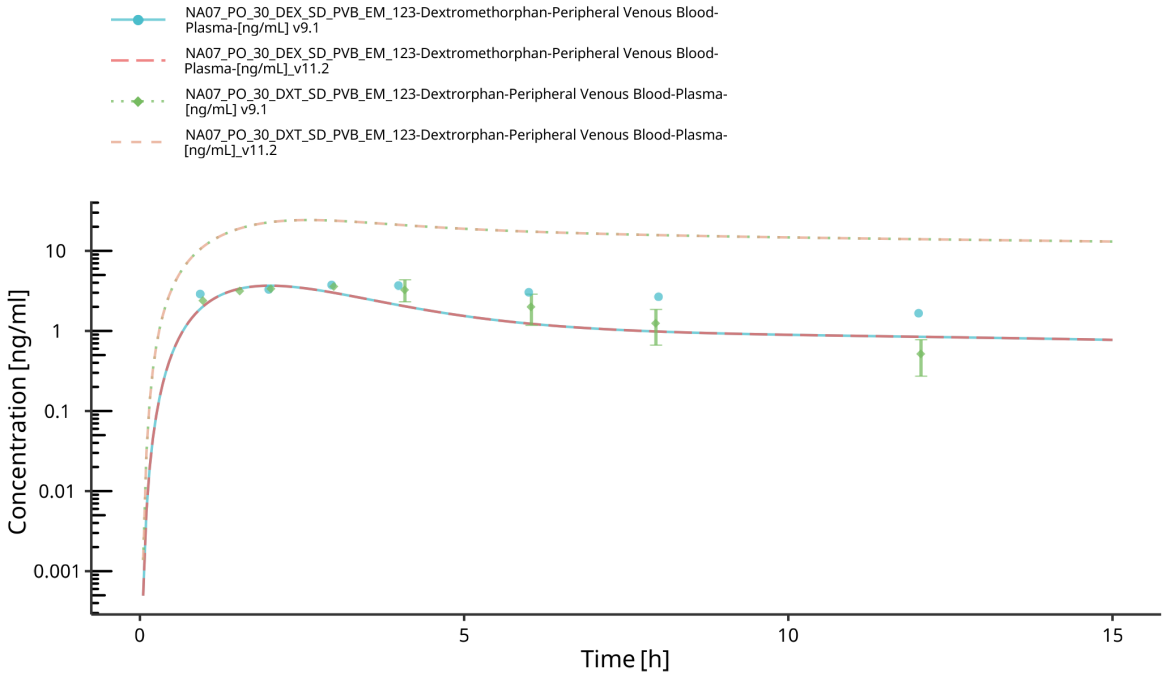
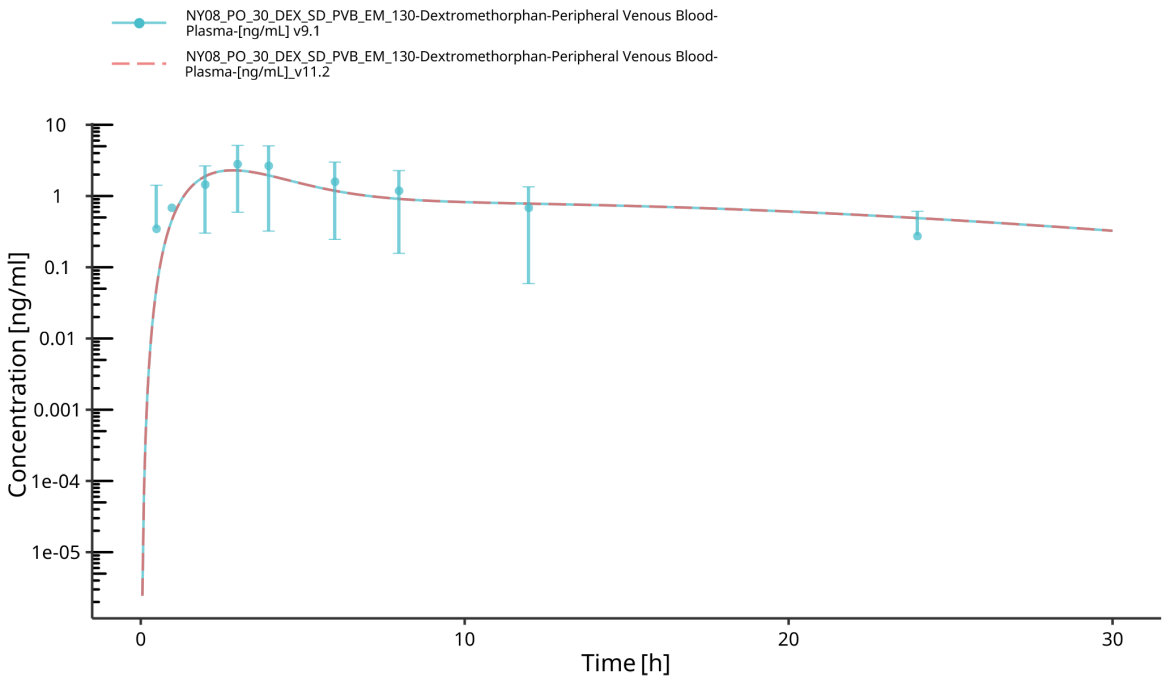
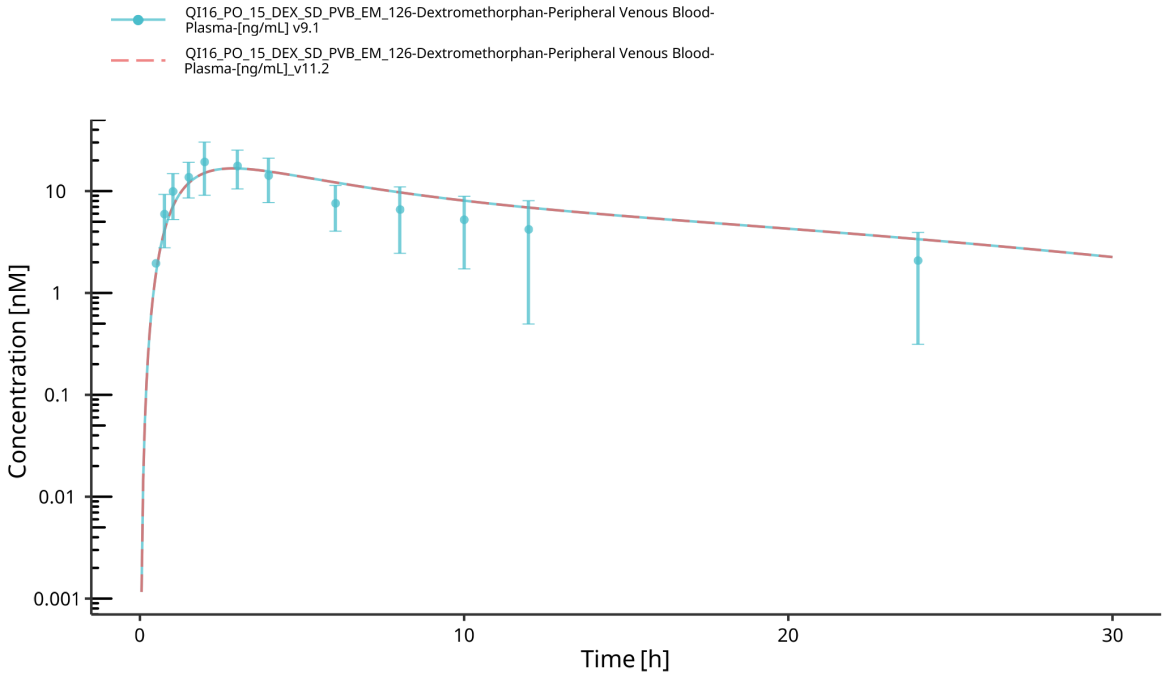


Nyunt 2008 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=12 - time profile



Qiu 2016 IM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=0.5 - time profile



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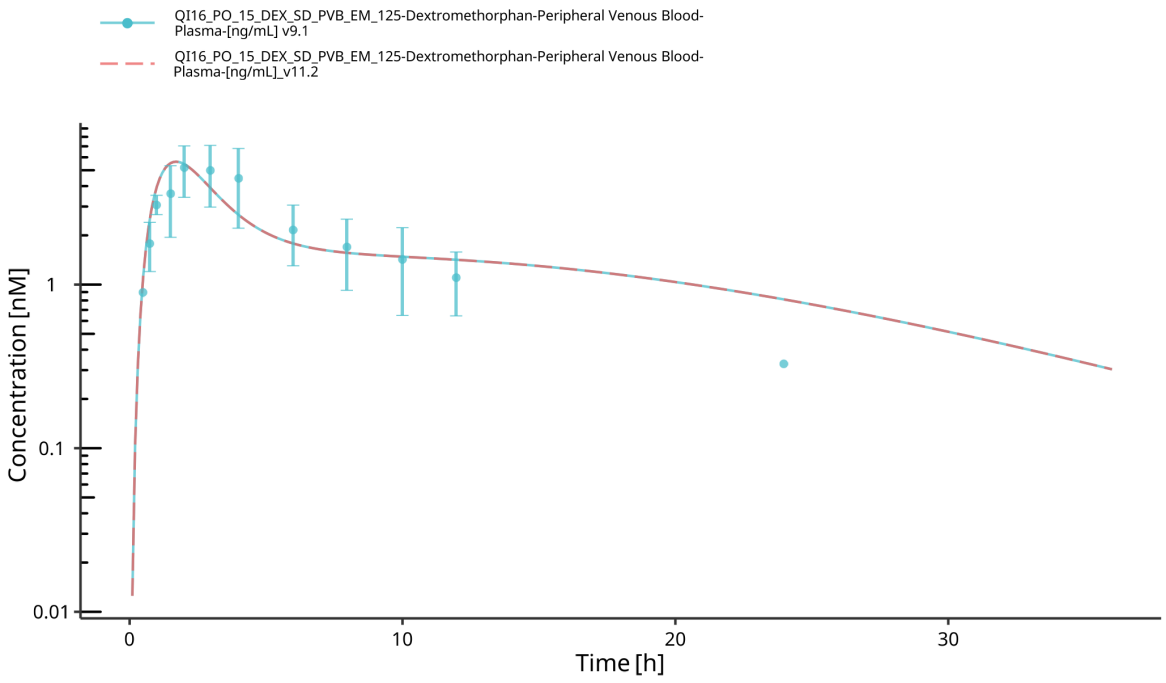
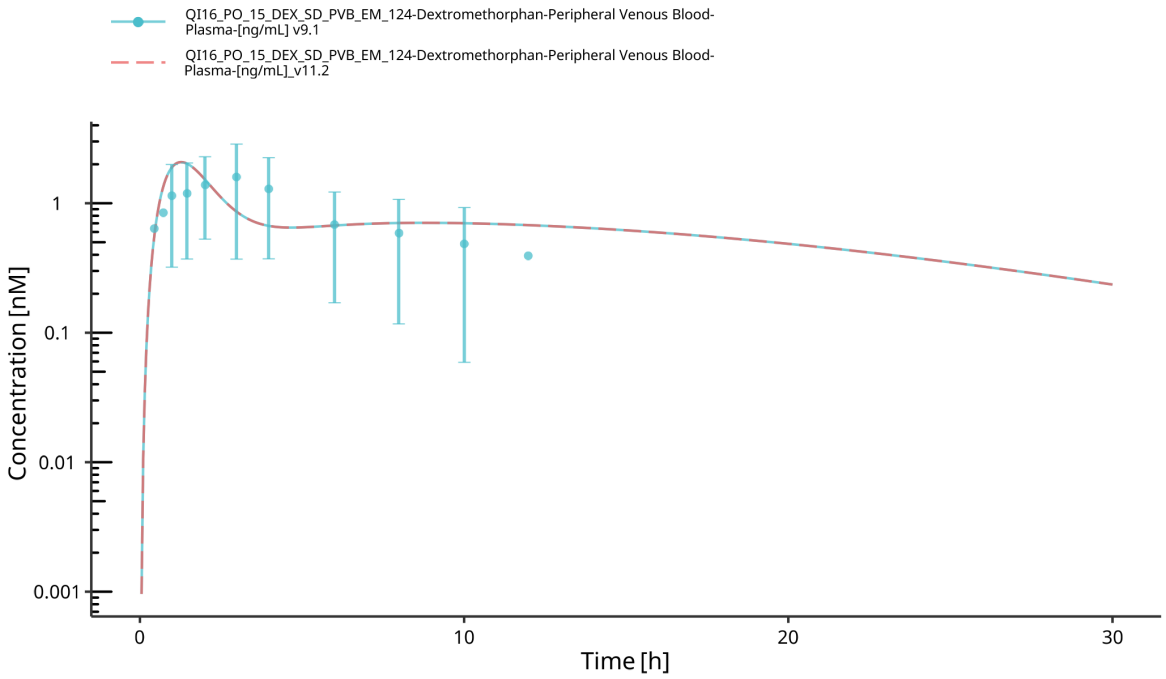
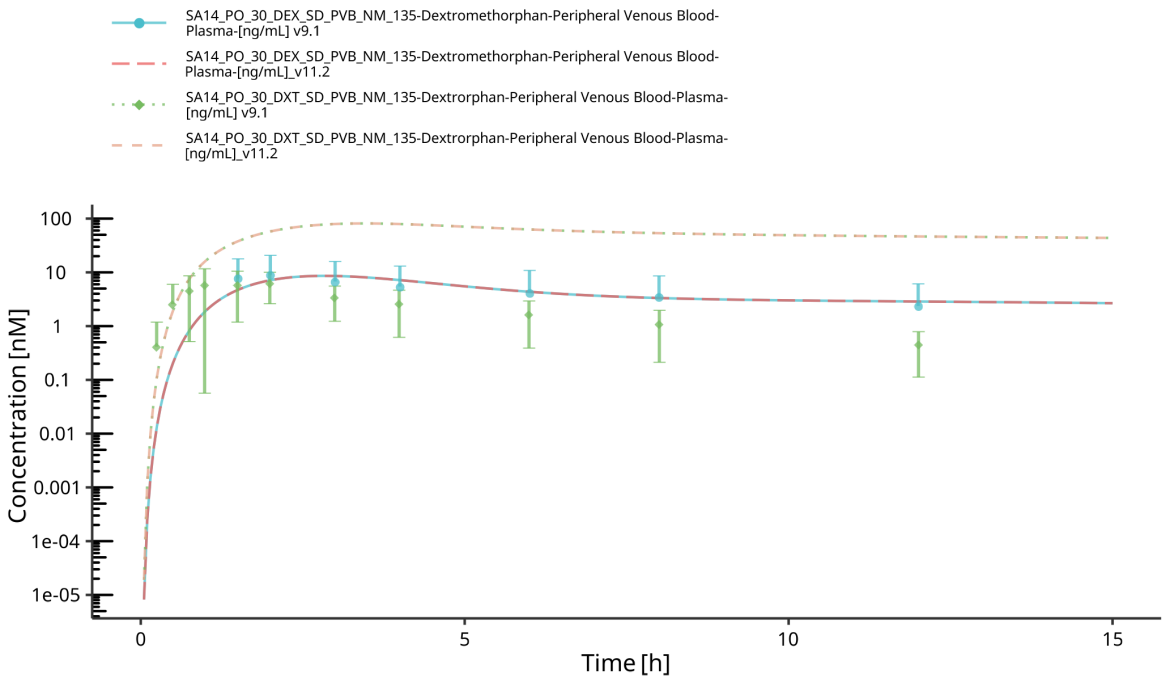


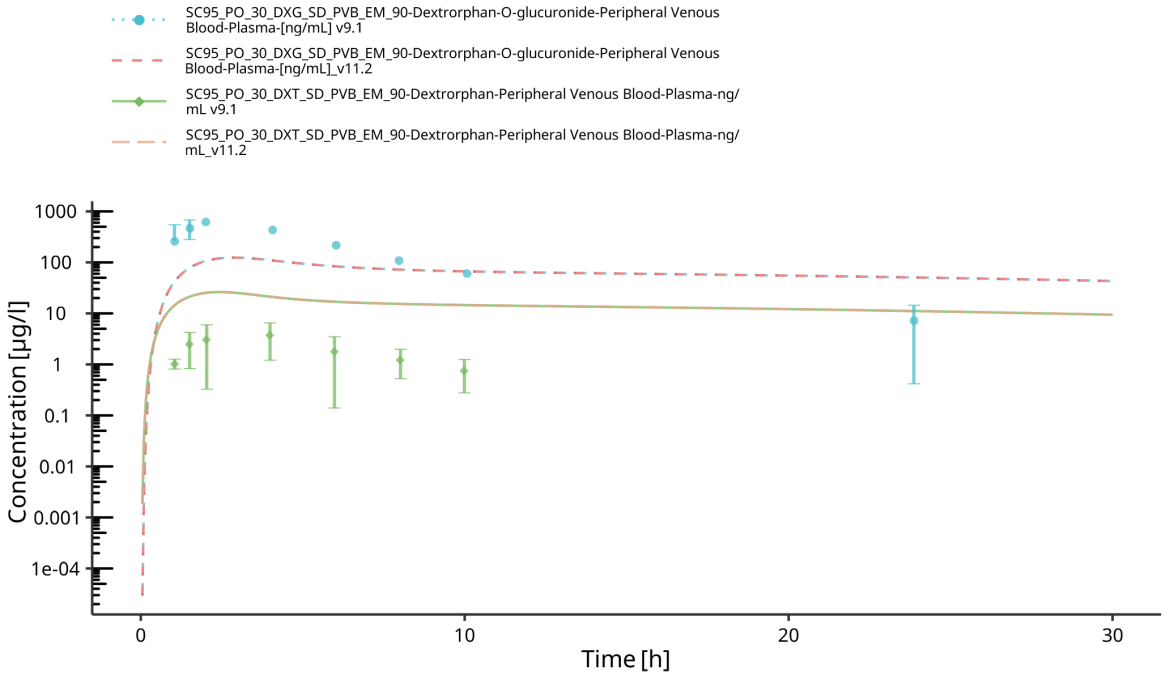
Qiu 2016 NM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=2 - time profile



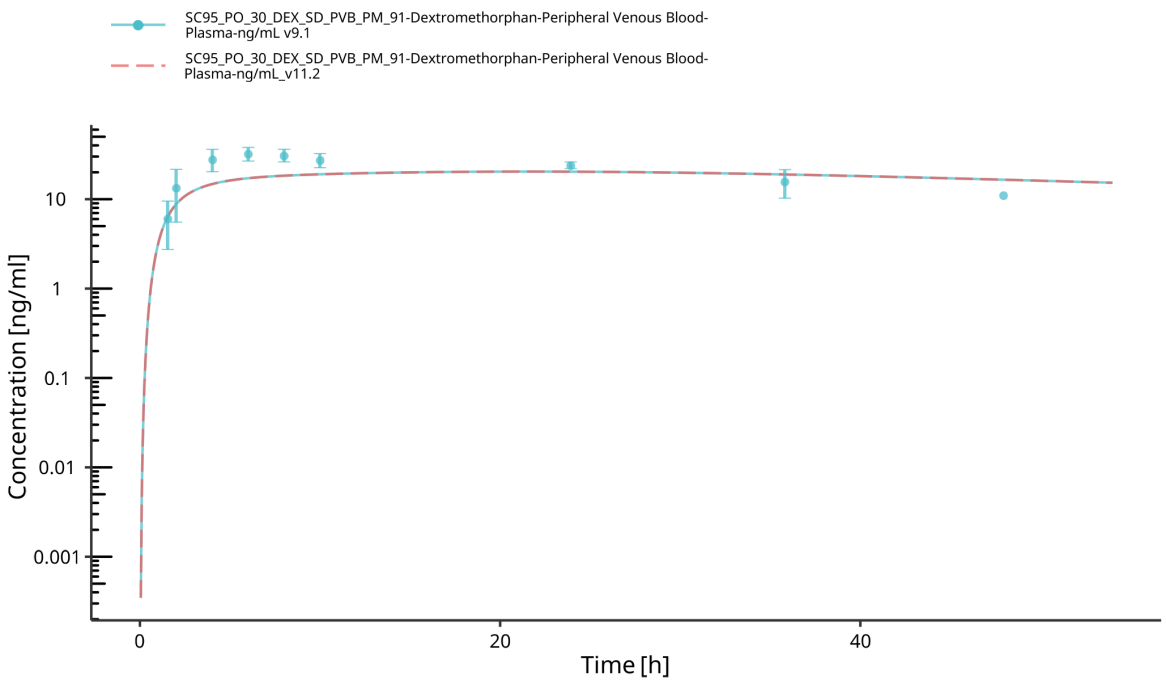
Sager 2014 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=10 - time profile



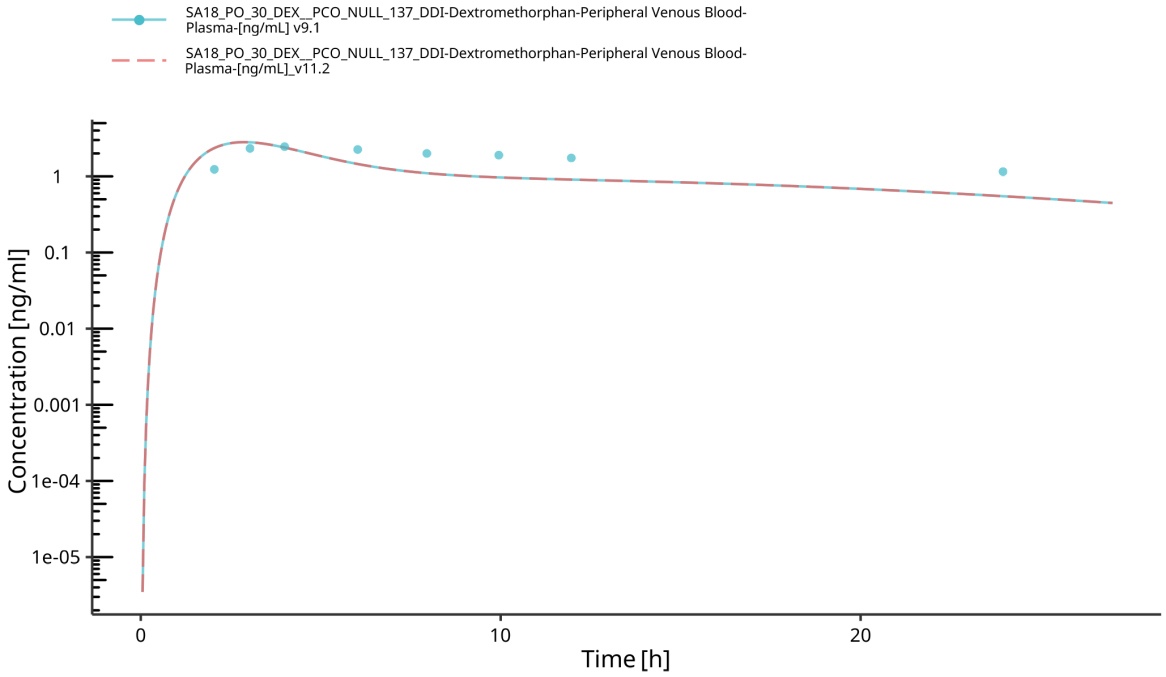
Schadel 1995 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=5 - time profile



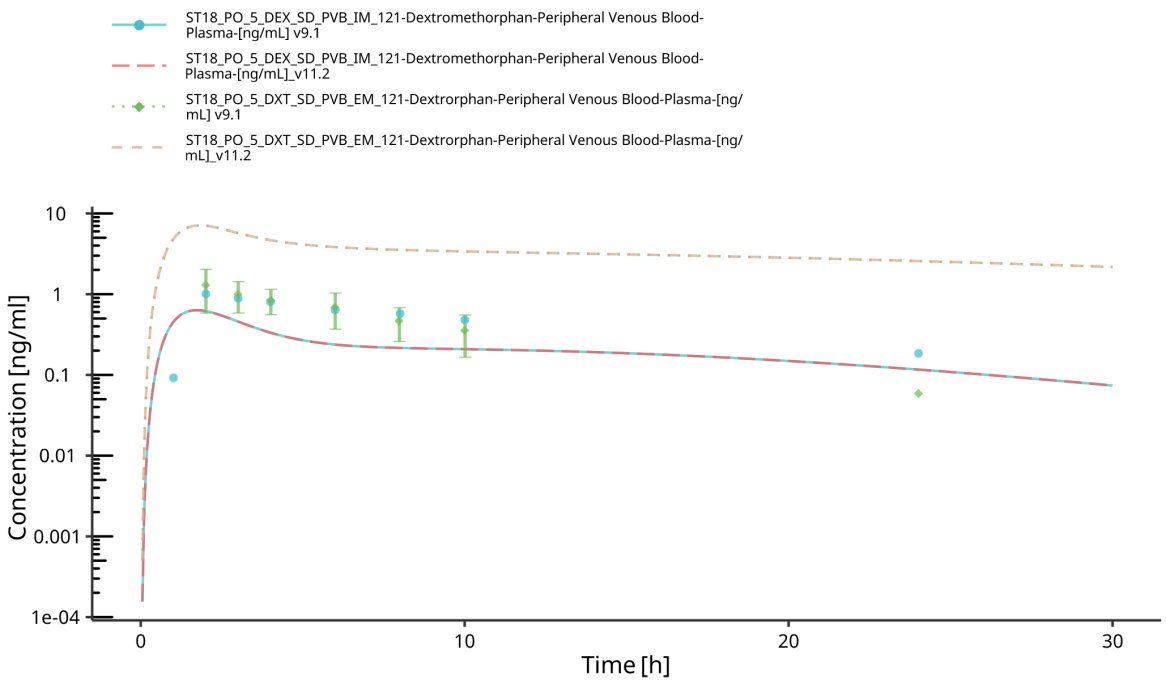
Schadel 1995 PM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=4 - time profile



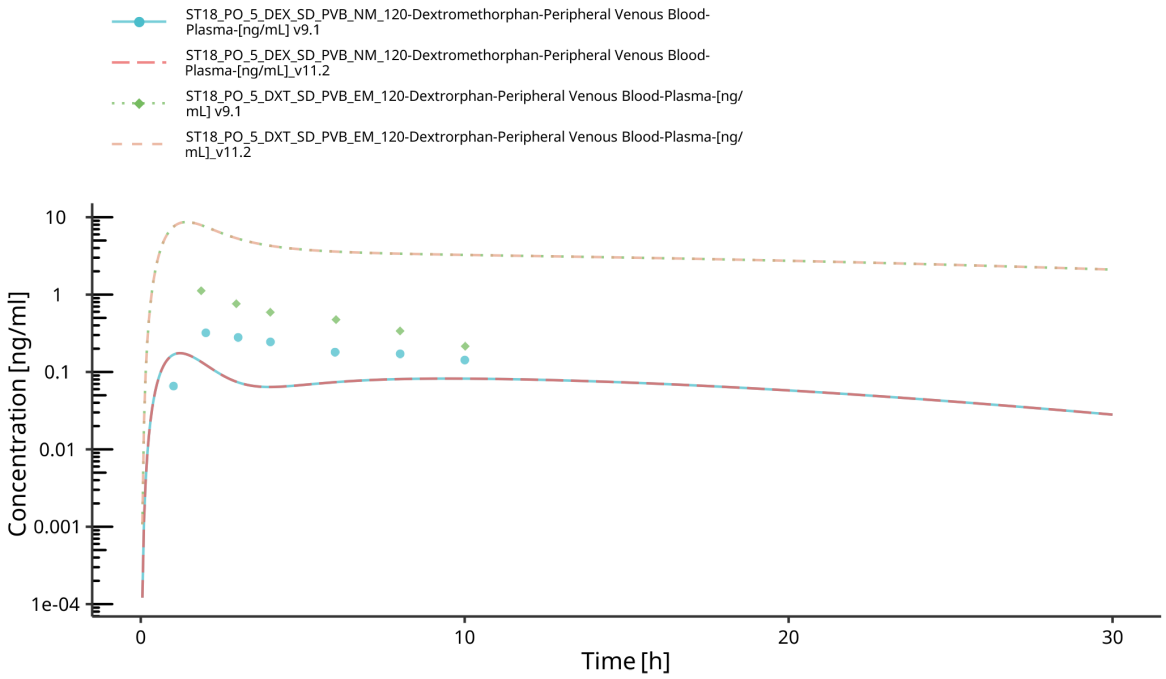
Stage 2018 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=12 - time profile



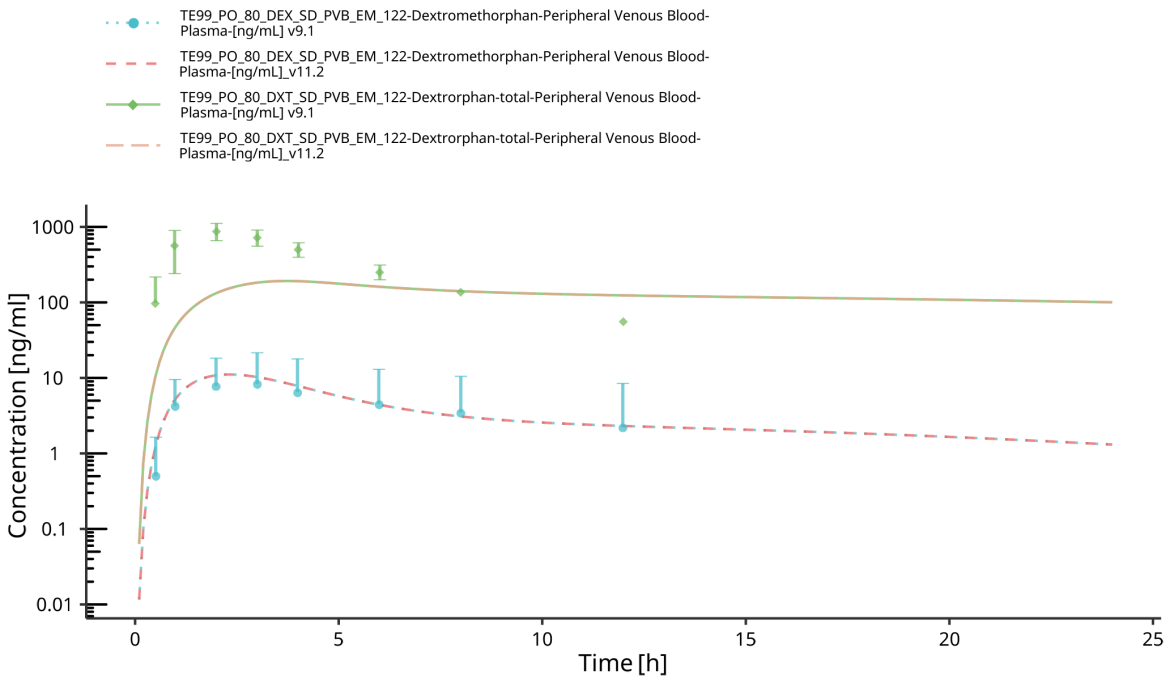
Storelli 2018 IM, 5 mg dextromethorphan base (capsule/solution), n=16 - time profile



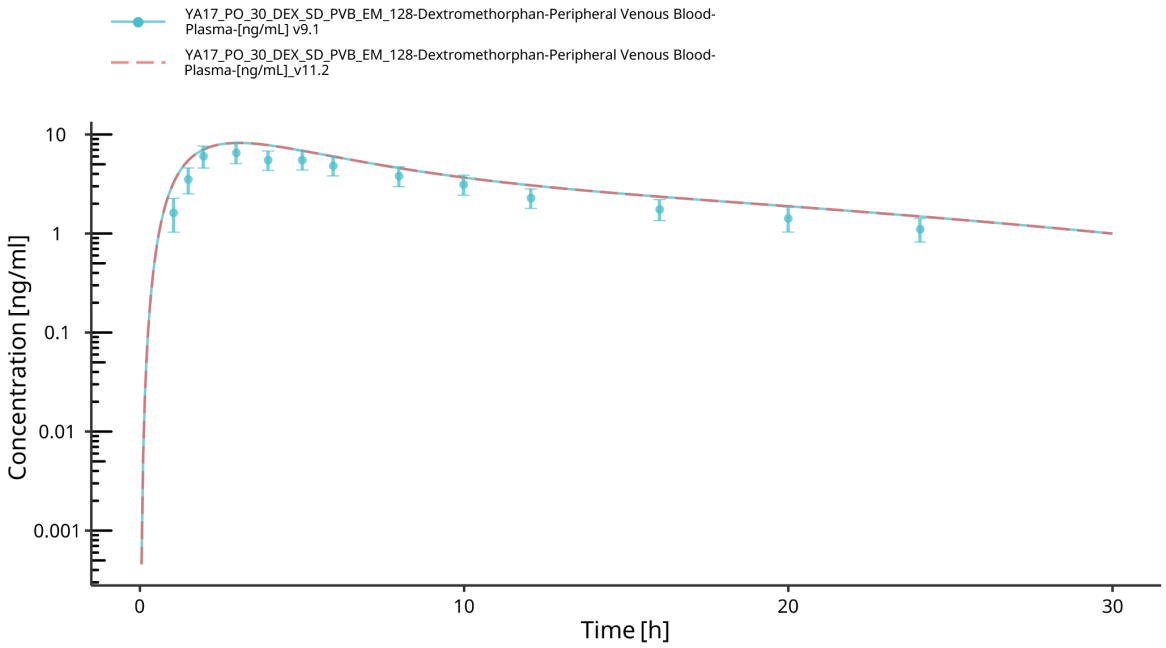
Storelli 2018 NM, 5 mg dextromethorphan base (capsule/solution), n=17, AS=2 - time profile



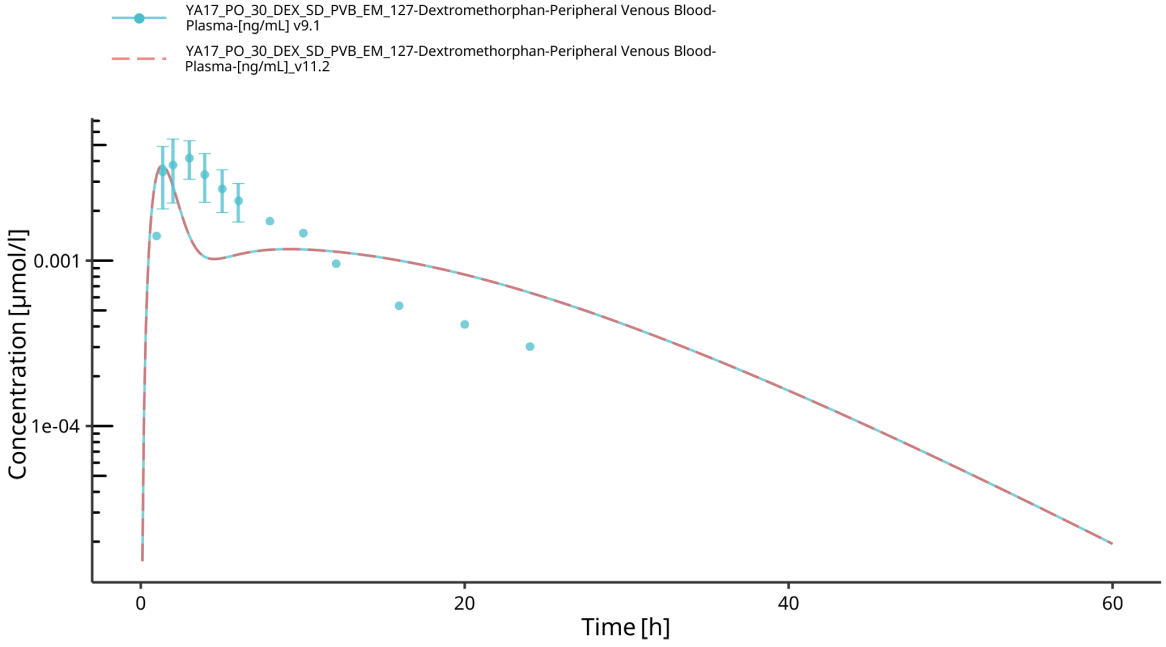
Tennezé 1999 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=36 - time profile



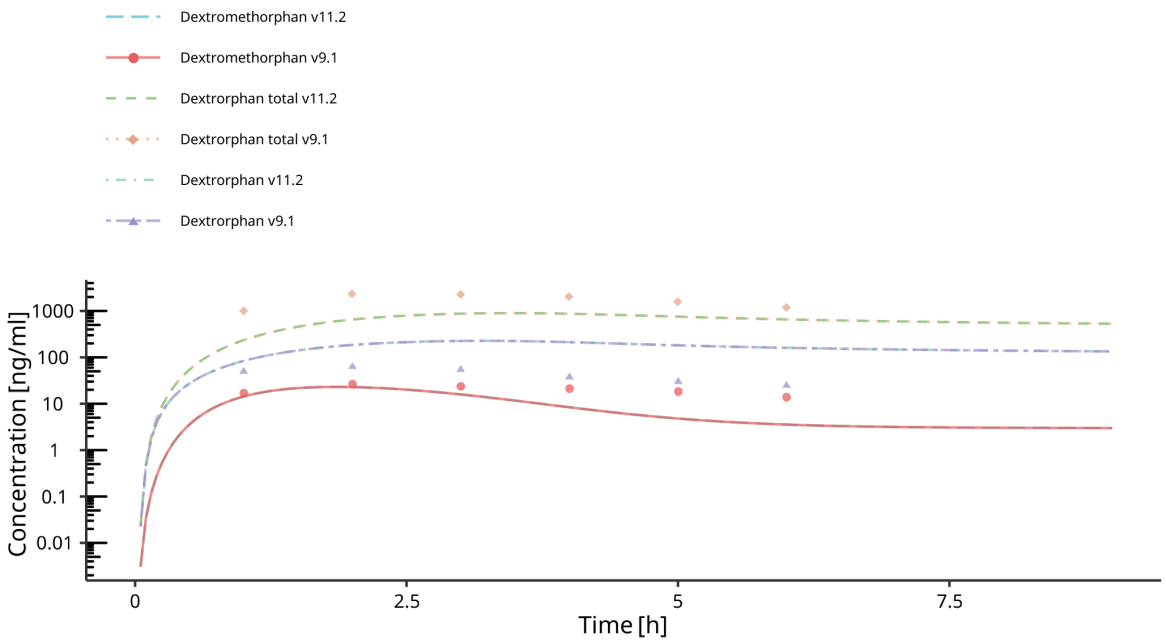
Yamazaki 2017 IM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=12, AS=0.5 - time profile



Yamazaki 2017 NM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=11, AS=2 - time profile



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.