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 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 @rüdesheim2022. 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}.

2.3 Qualification process

1. Import project snapshot "dextromethorphan_aggregated_simulations.json" in PK-Sim v9.1. During the import processes, the following error is thrown:

   ```
   Information: Loading Project from snapshot file 'xxx.json'

   Warning: Snapshot is outdated and cannot be loaded for the following
   reason:

   Individual 'Gorski 2004 (96) PM, n=1 not found in the project.

   Error: Cannot load Simulation 'Gorski 2004 PM, 30 mg dextromethorphan
   hydromide (capsule/solution), n=1'

   Information: Project loaded from snapshot
   ```

   Investigation of the project snapshot showed that an Individual "Gorski 2004 PM, n=1" is present in the project and is not used in any simulation. It was concluded that the missing individual "Gorski 2004 (96) PM, n=1" referenced in the simulation should be "Gorski 2004 PM, n=1". The snapshot was modified to reference the present individual. After the modification, the snapshot was successfully loaded.

2. The snapshot contains 29 simulations. All simulations were exported to `*.pkml` for simulation in R.

3. Import project snapshot "dextromethorphan_aggregated_simulations.json" in PK-Sim v11.2. During import, the following warning for each loaded simulation is shown:
`Warning: Snapshot parameter 'Ontogeny factor GI' was not found in 'CYP3A4'.`
All simulations were exported to `*.pkml` for simulation in R.
4. All observed data from the project created with version 11.2 were exported '*.pkml' for loading in R.
5. Simulations created with versions 9.1 and 11.2 were simulated and the results visually compared.

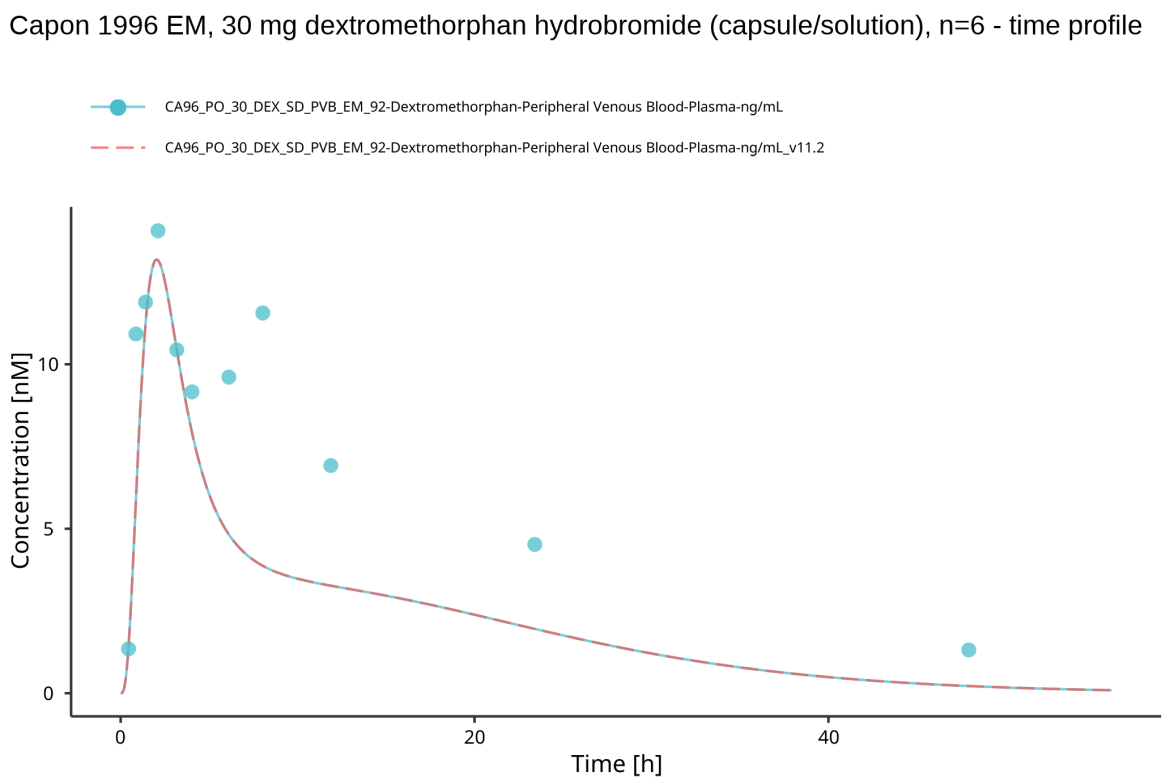
2.4 Model consolidation

During conversion of projects created with versions before 11, a separate expression profile is created for each individual. To ensure that all individuals are using the same expression, expression profiles of the same protein were compared. All expression profiles for the same protein were equal. Therefore, the same expression profile was set in every individual, and the remaining profiles were removed.

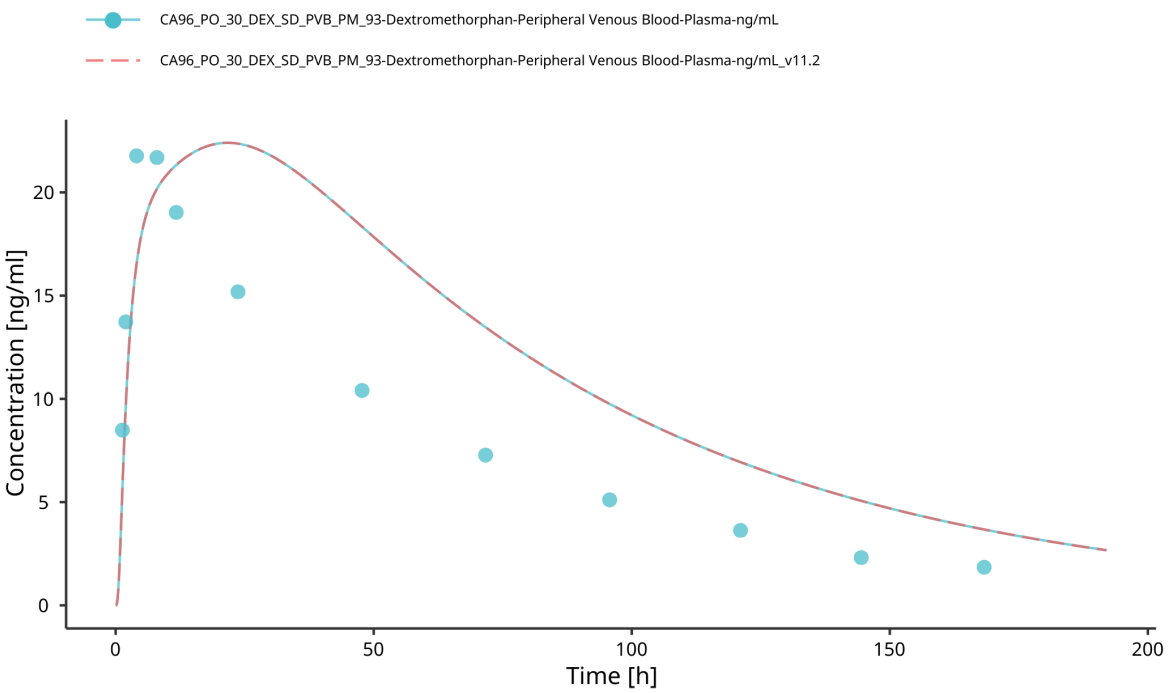
3 Results

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

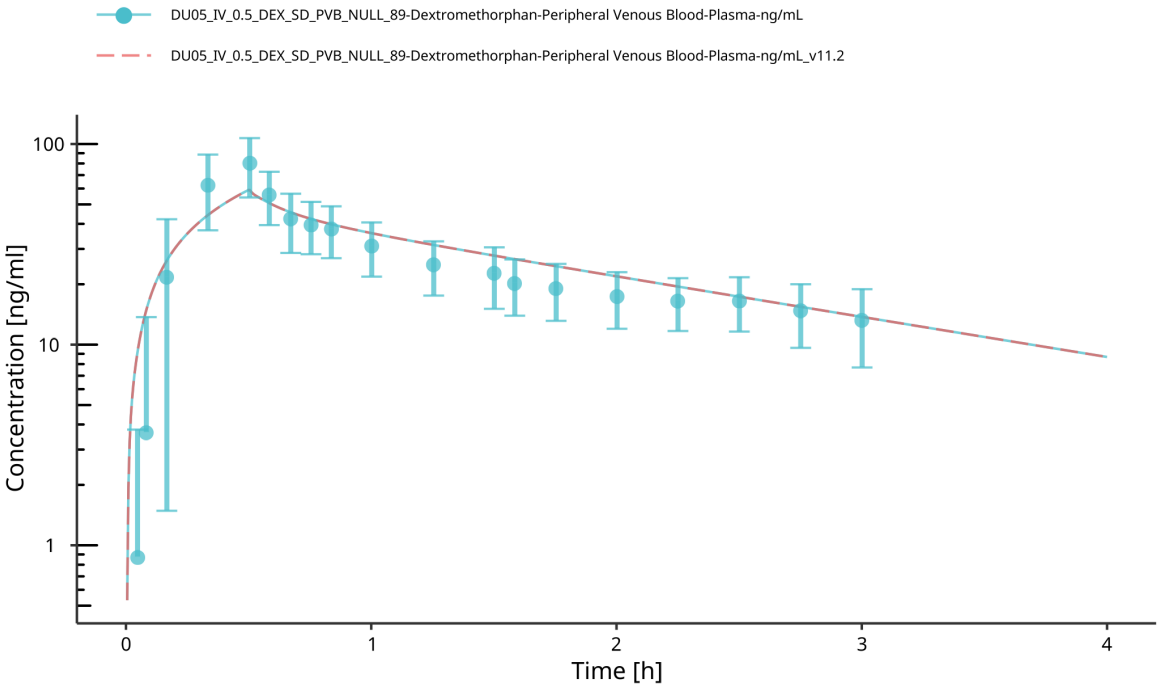
!!! When doing it in the loop, no caption is created (Figure xxx: blablabl). Why?



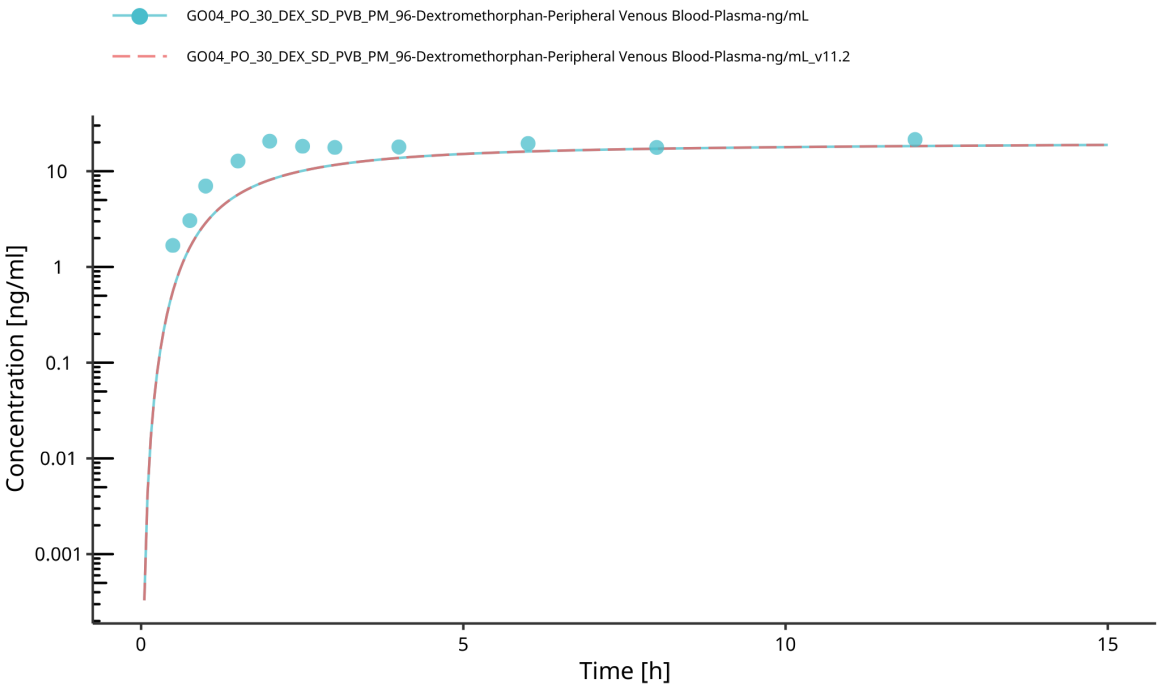
Capon 1996 PM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=6 - time profile



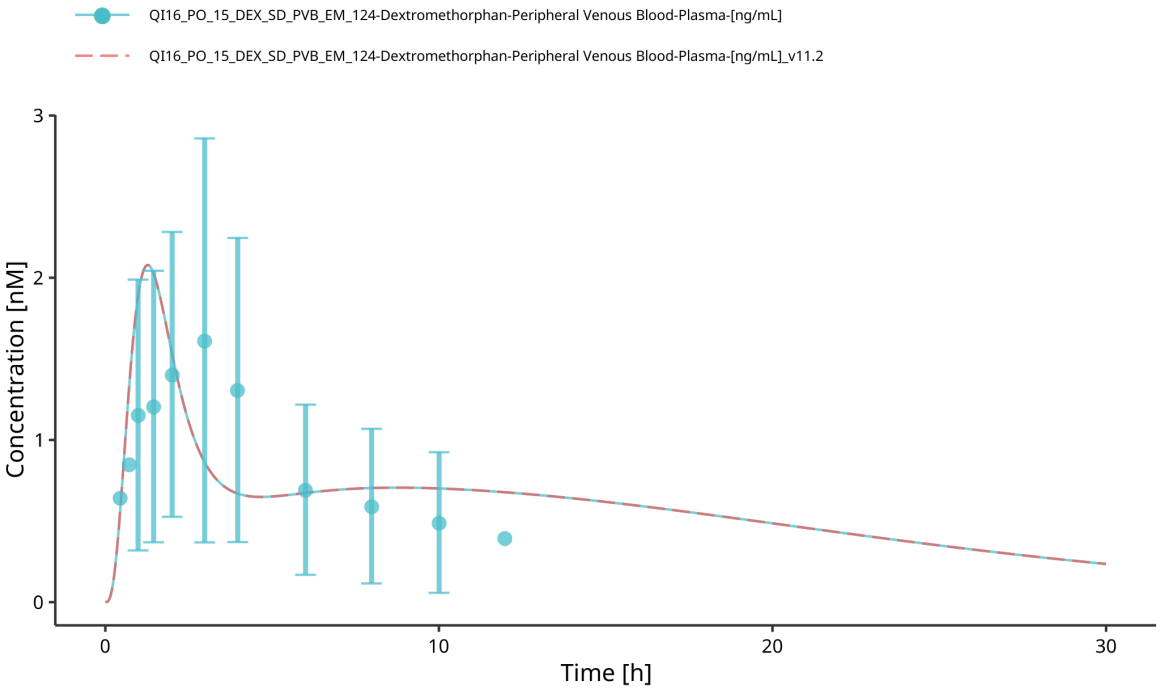
Duedahl 2005 EM, 0.5 mg/kg dextromethorphan base (infusion), n=24 - time profile



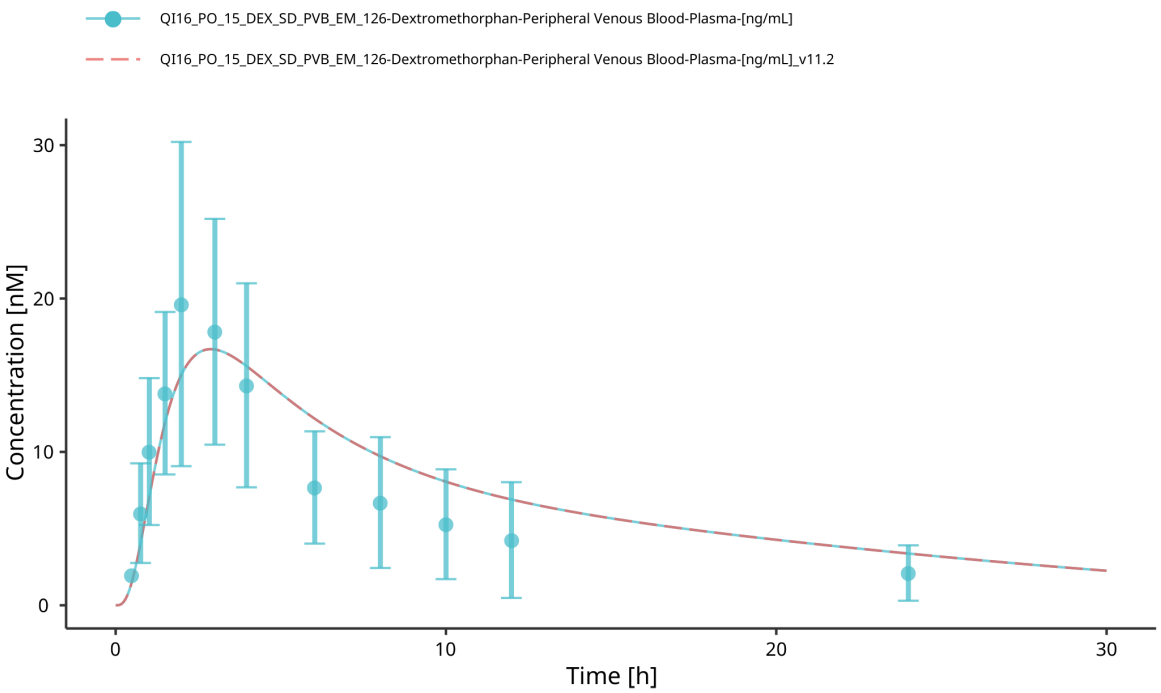
Gorski 2004 PM, 30 mg dextromethorphan hydromide (capsule/solution), n=1 - time profile



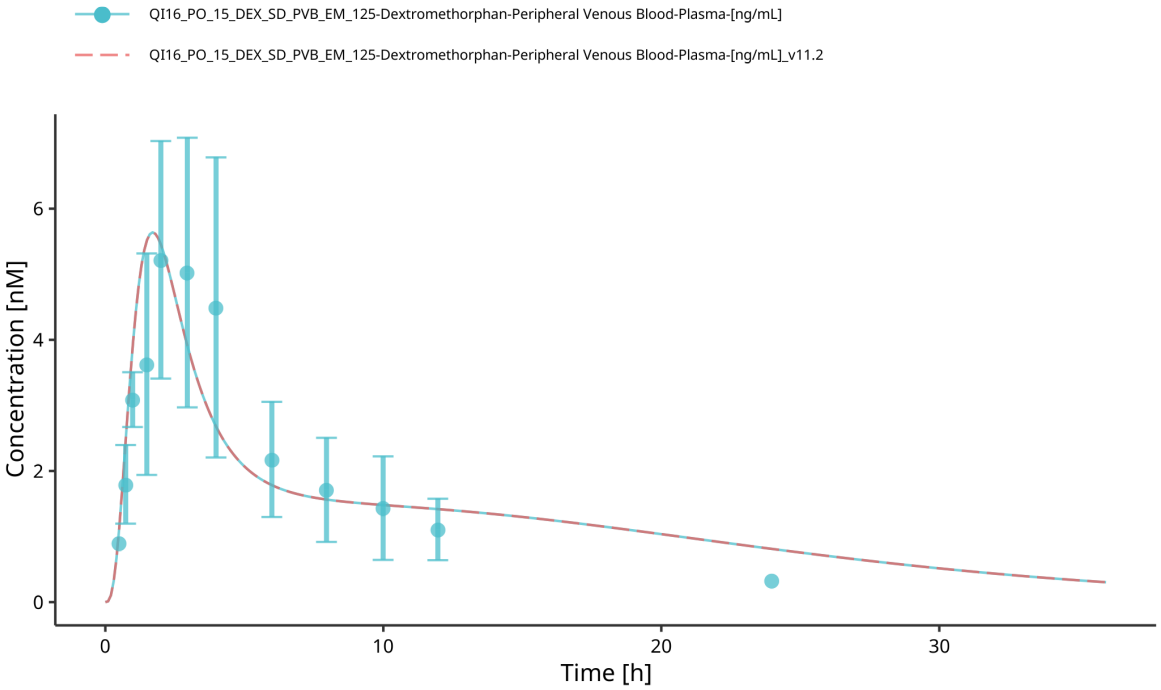
Qiu 2016 NM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=2 - time profile



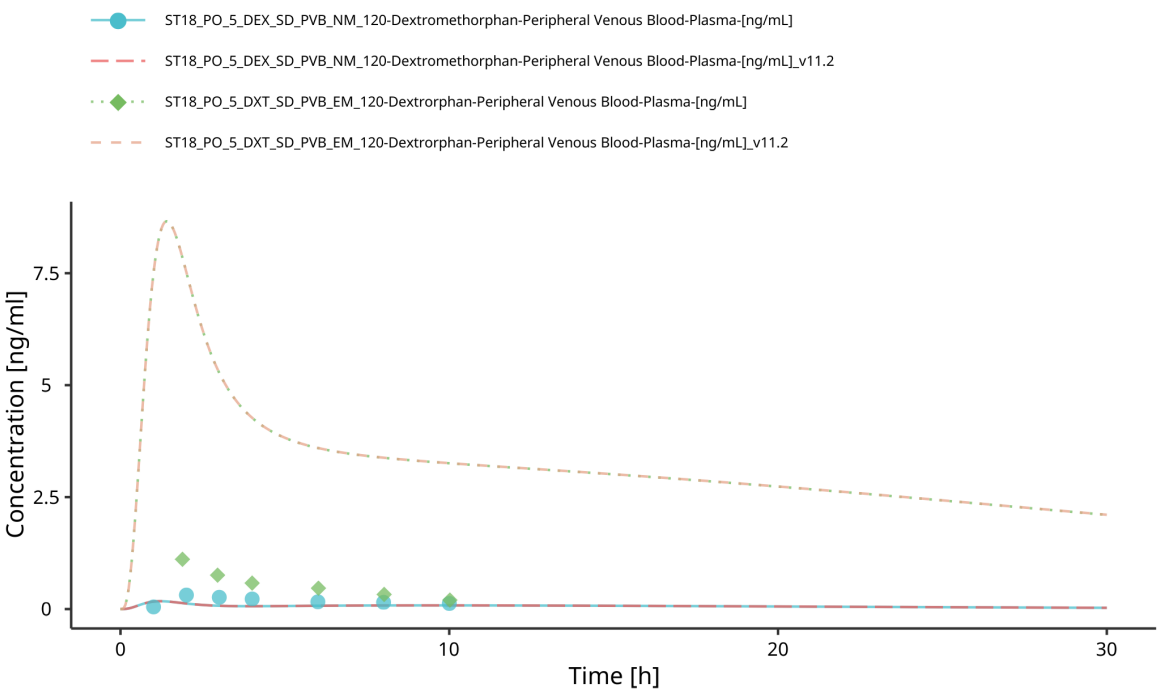
Qiu 2016 IM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=0.5 - time profile



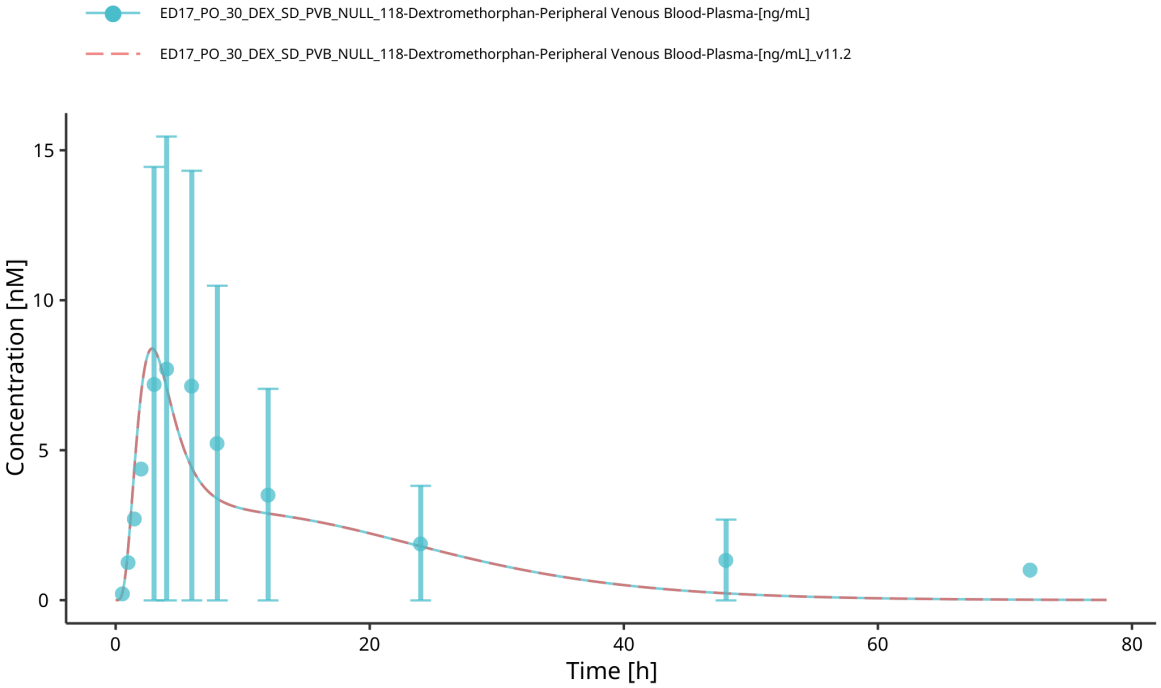
Qiu 2016 NM, 15 mg dextromethorphan hydrobromide (capsule/solution), n=6, AS=1.25 - time profile



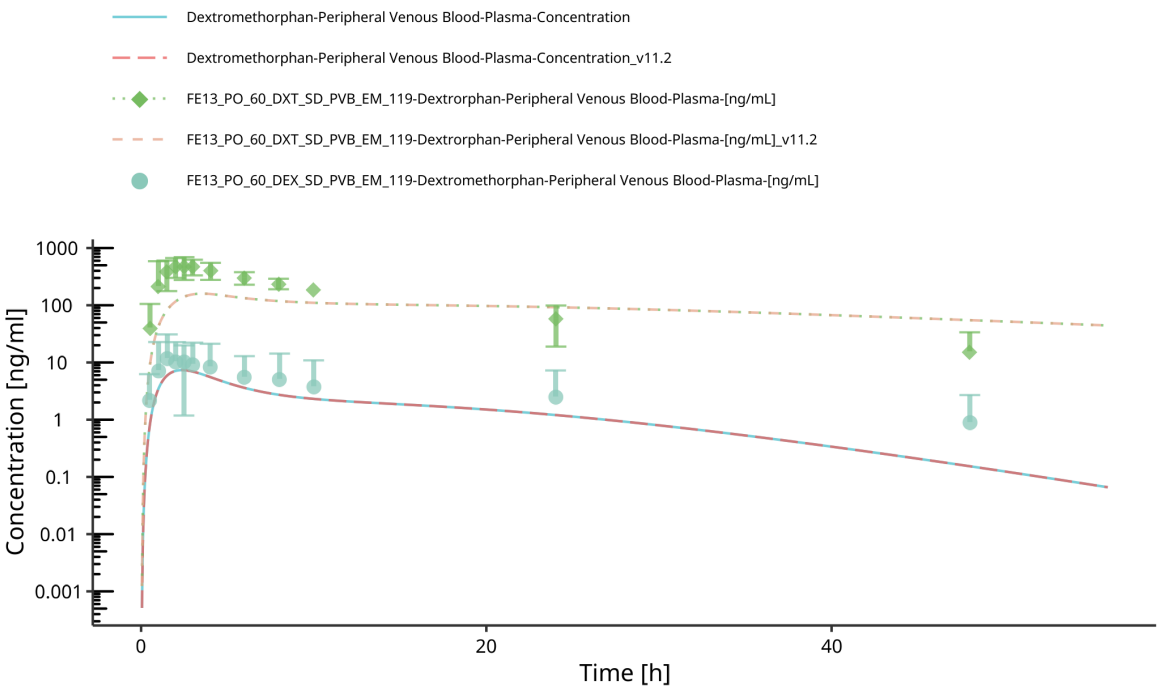
Storelli 2018 NM, 5 mg dextromethorphan base (capsule/solution), n=17, AS=2 - time profile



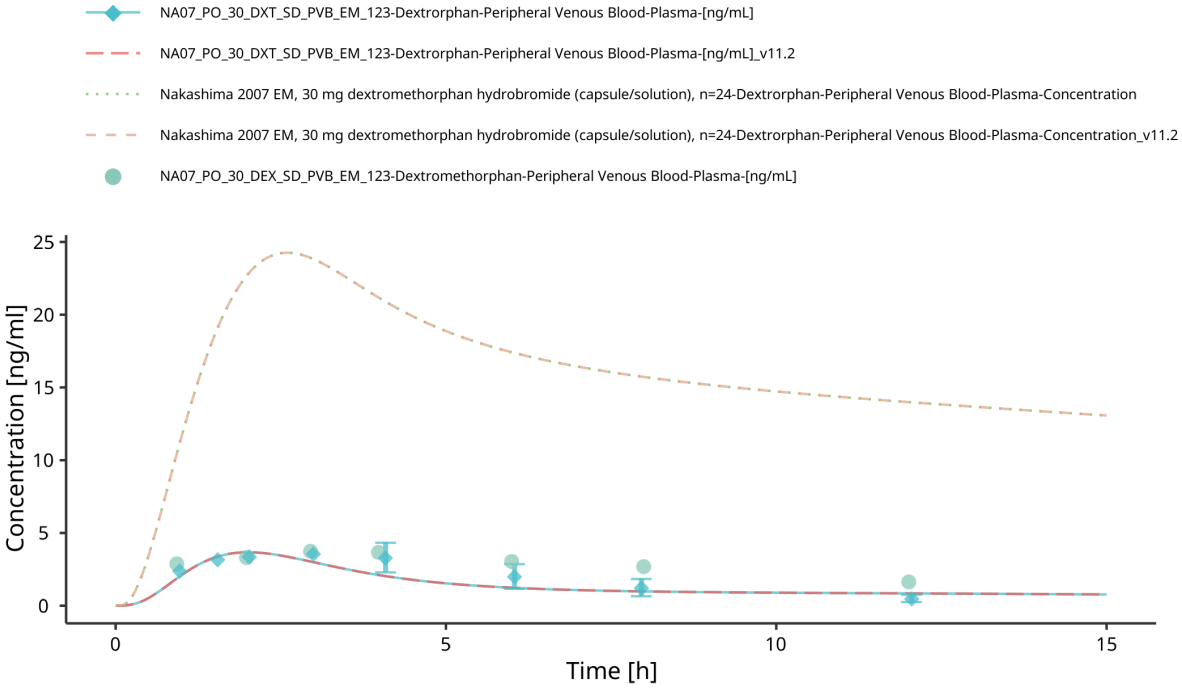
Edwards 2017 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=48 - time profile



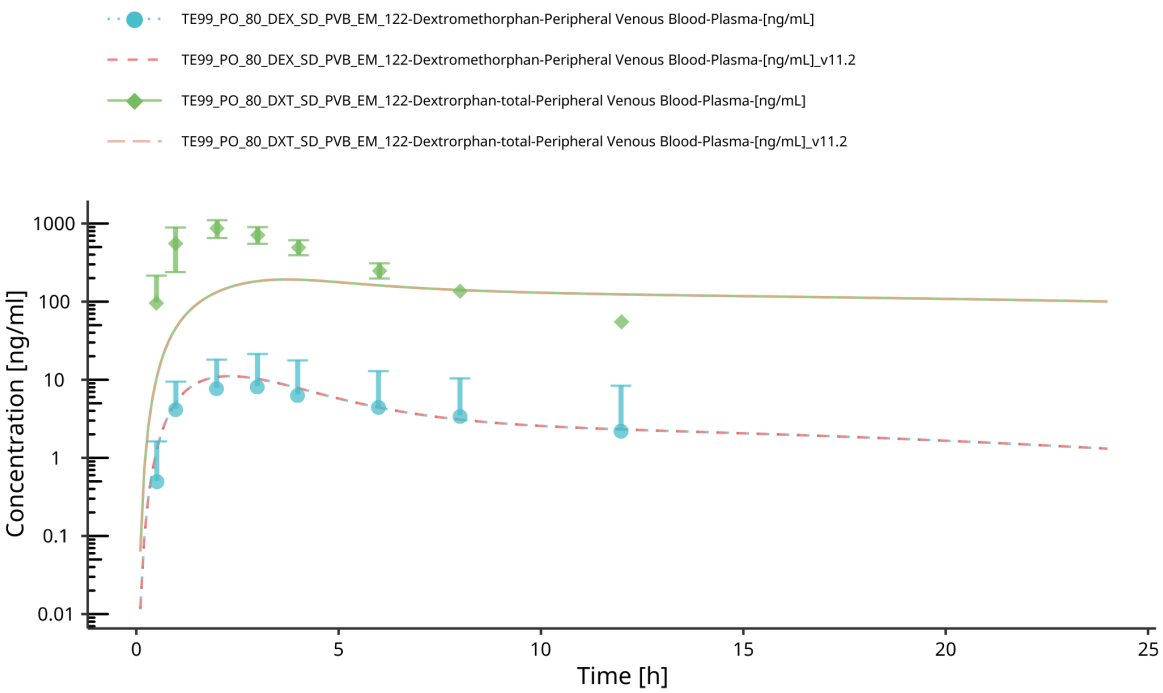
Feld 2013 EM, 60 mg dextromethorphan hydrobromide (capsule/solution), n=17 - time profile



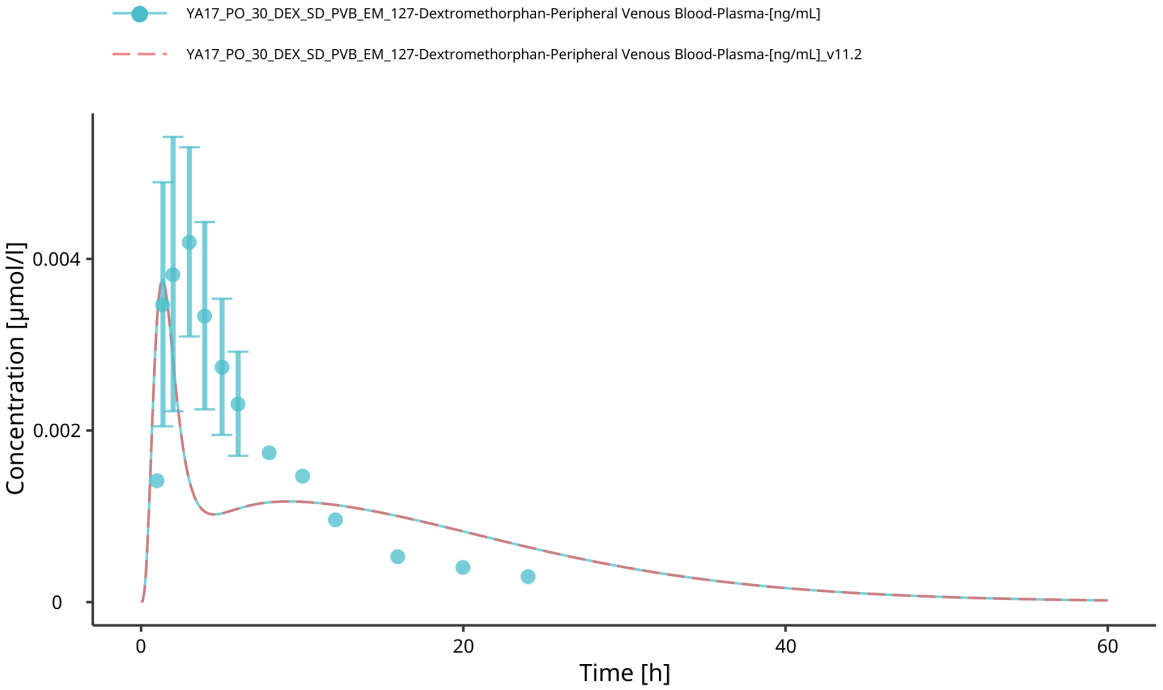
Nakashima 2007 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=24 - time profile



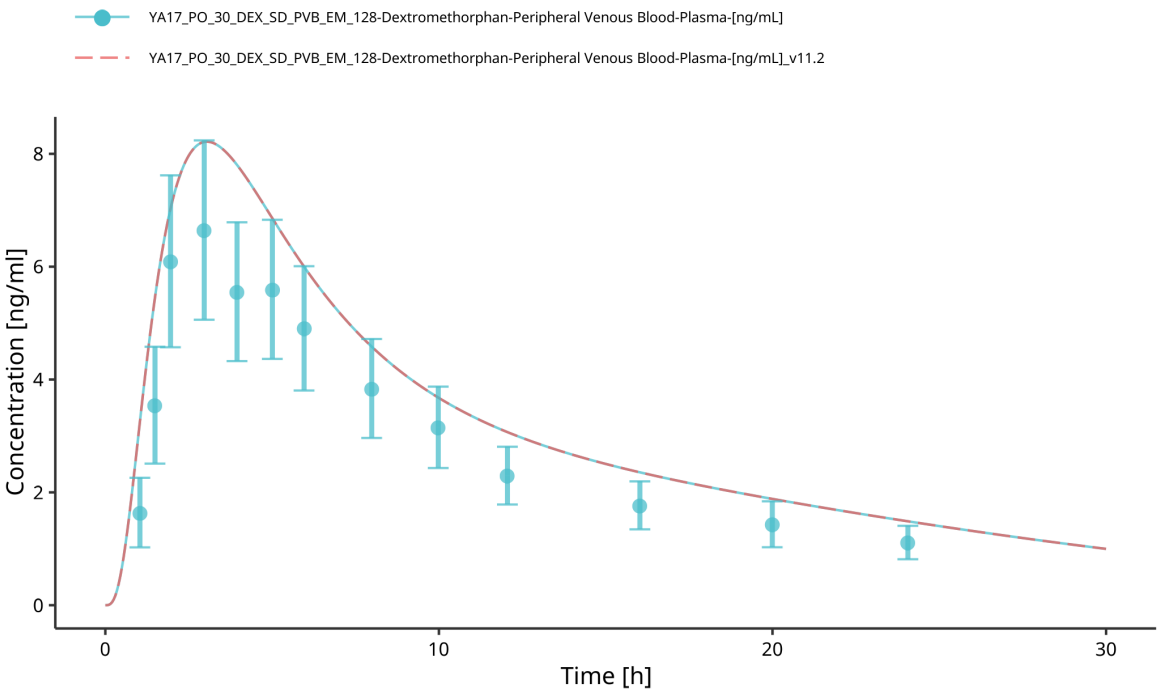
Tennezé 1999 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=36 - time profile



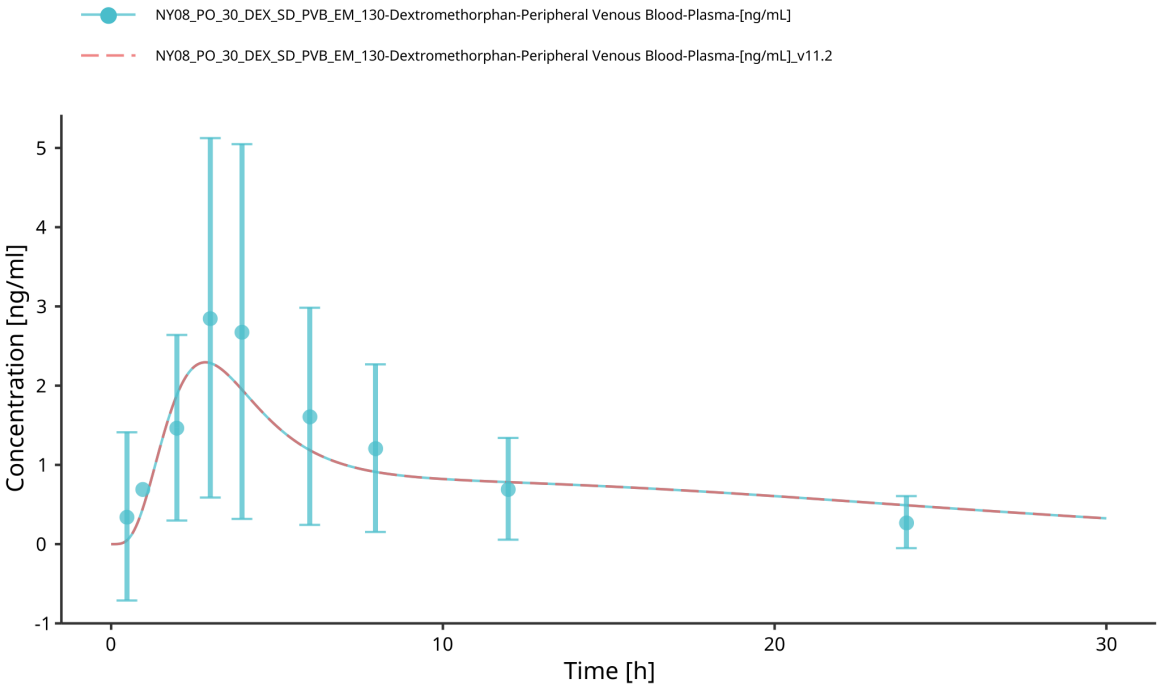
Yamazaki 2017 NM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=11, AS=2 - time profile



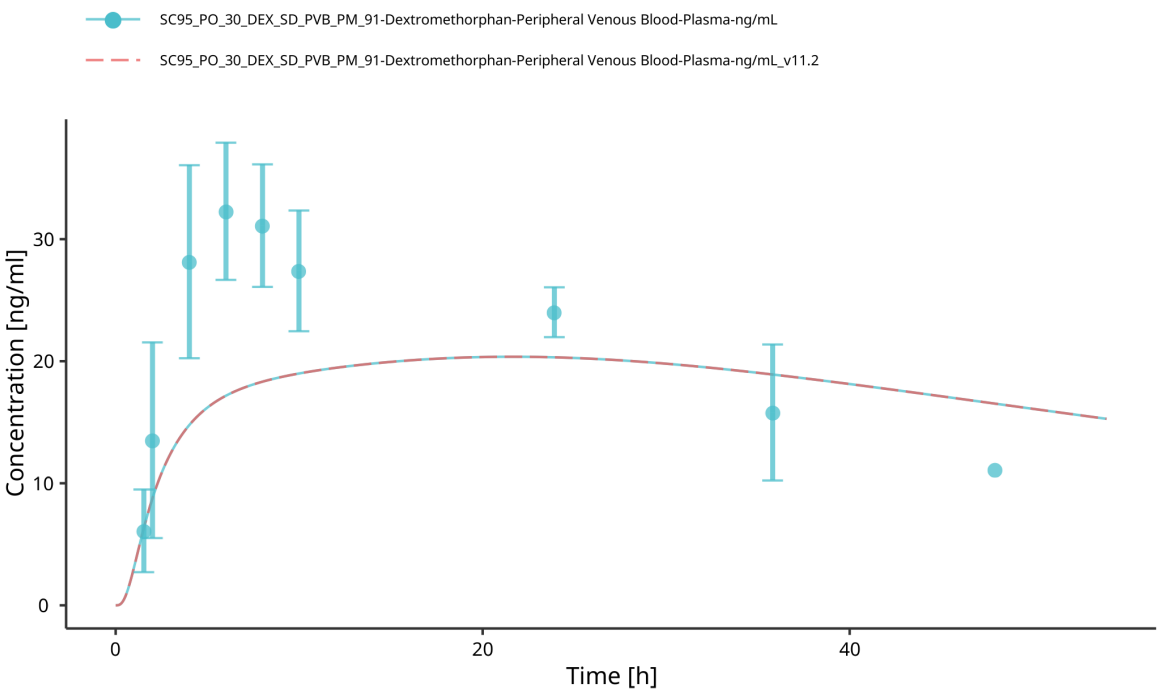
Yamazaki 2017 IM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=12, AS=0.5 - time profile



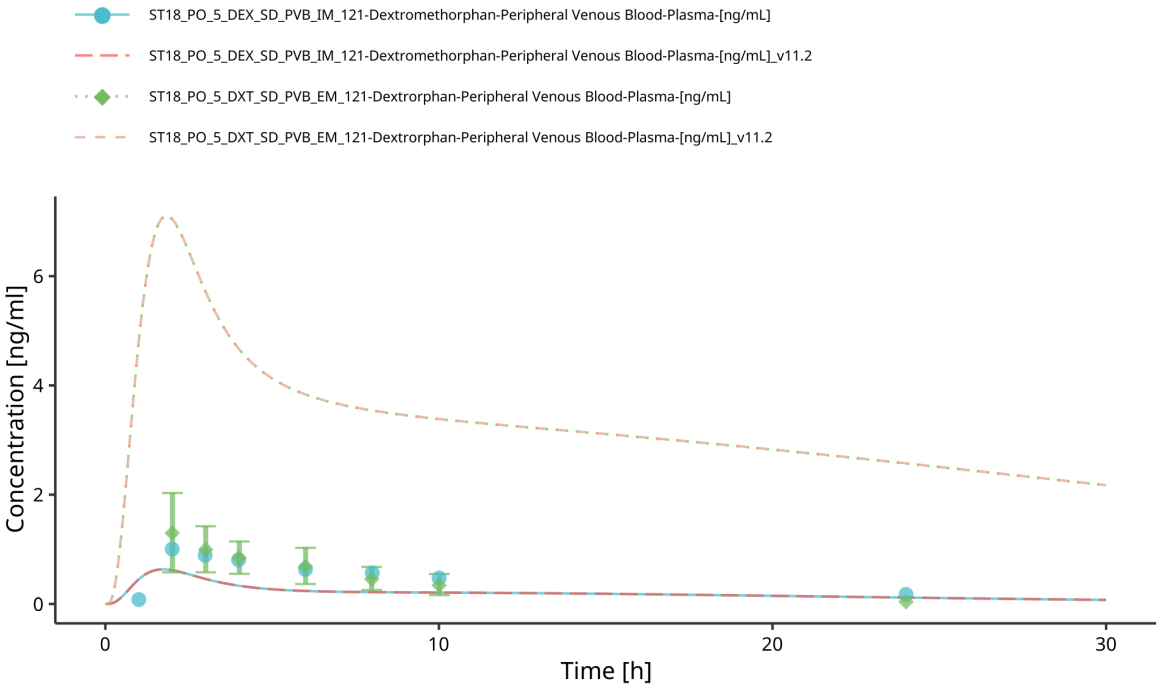
Nyunt 2008 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=12 - time profile



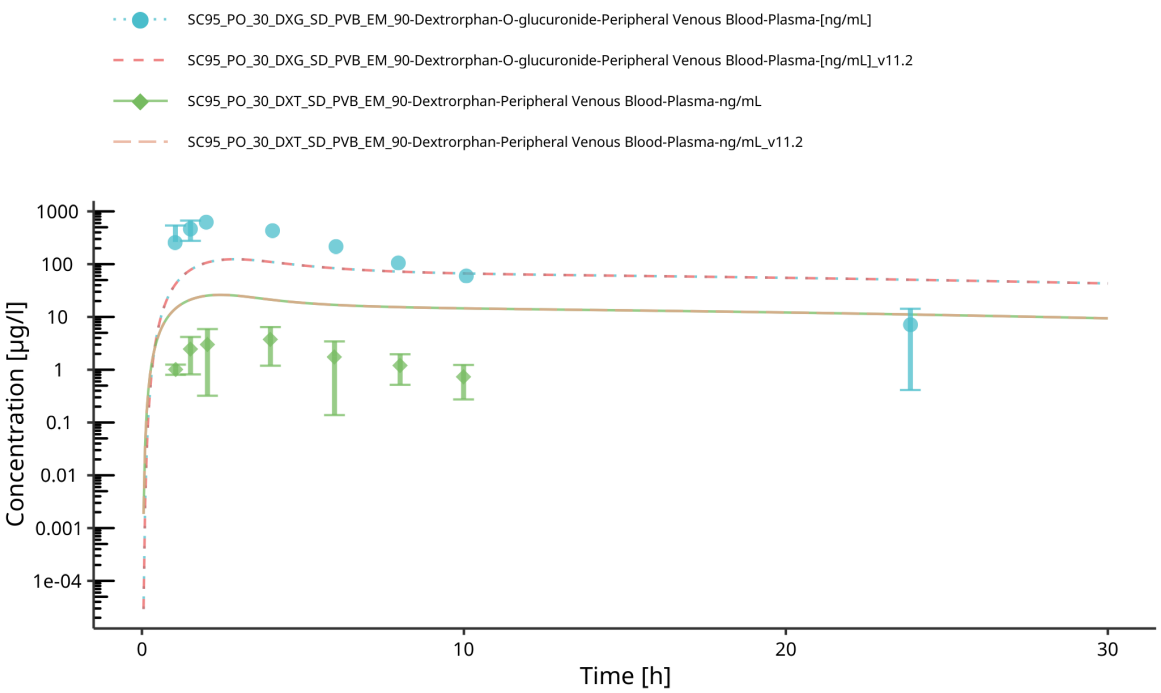
Schadel 1995 PM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=4 - time profile



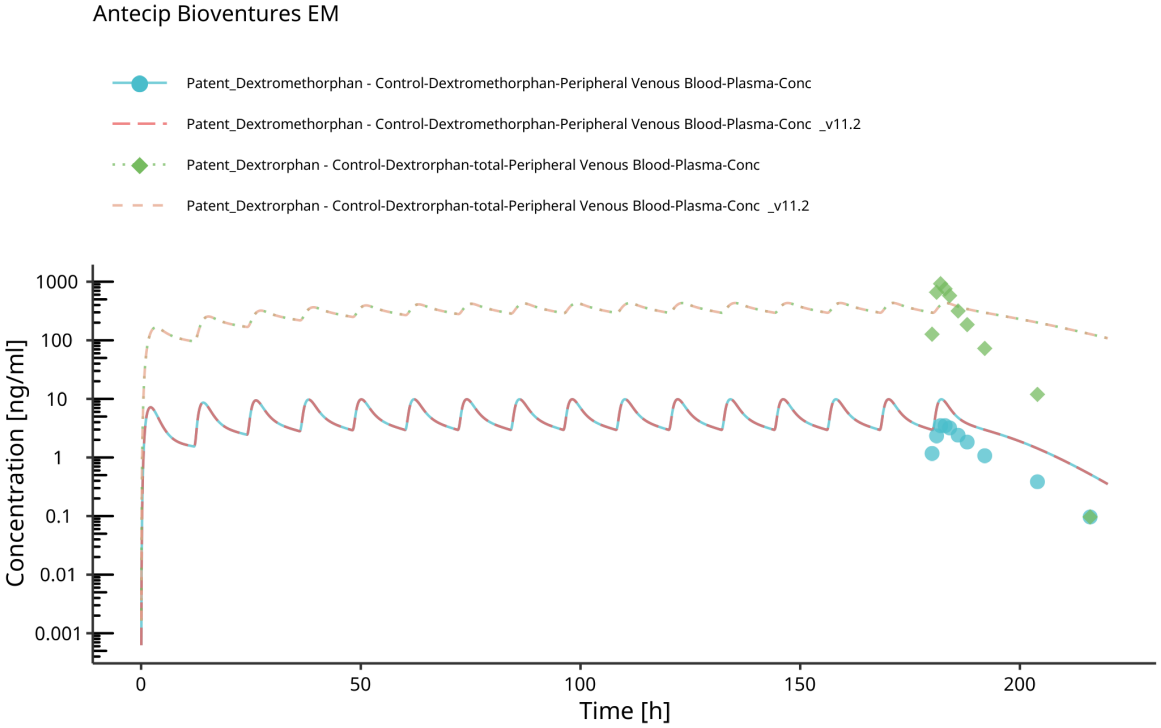
Storelli 2018 IM, 5 mg dextromethorphan base (capsule/solution), n=16 - time profile



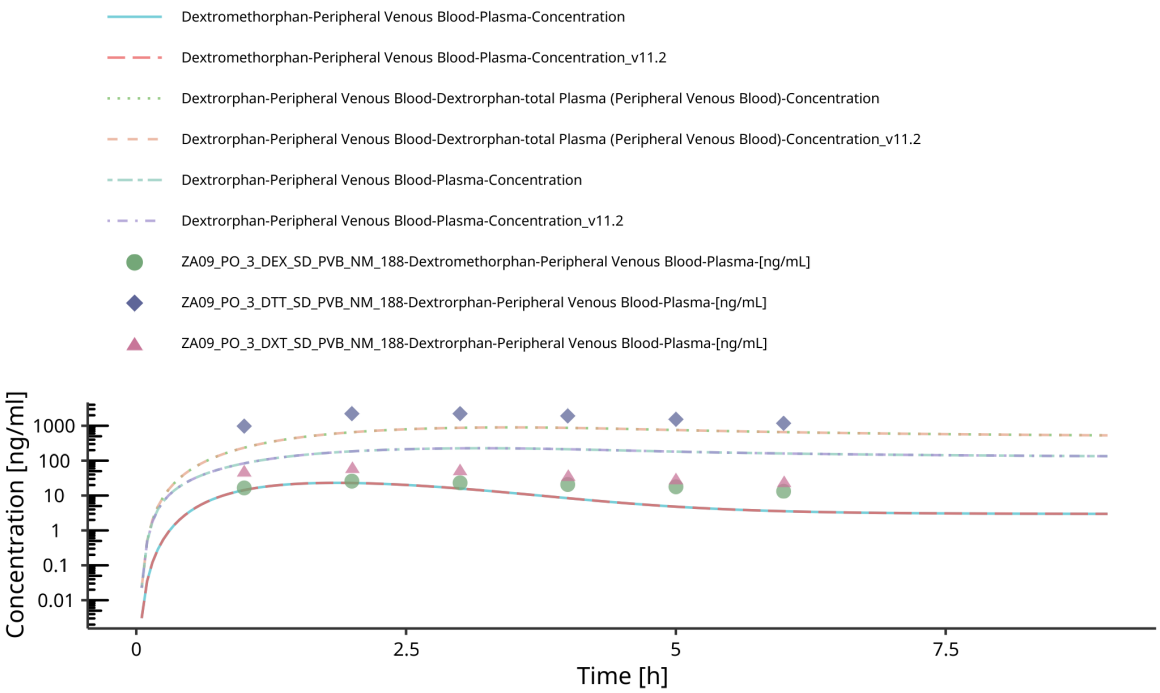
Schadel 1995 EM, 30 mg dextromethorphan hydrobromide (capsule/solution), n=5 - time profile



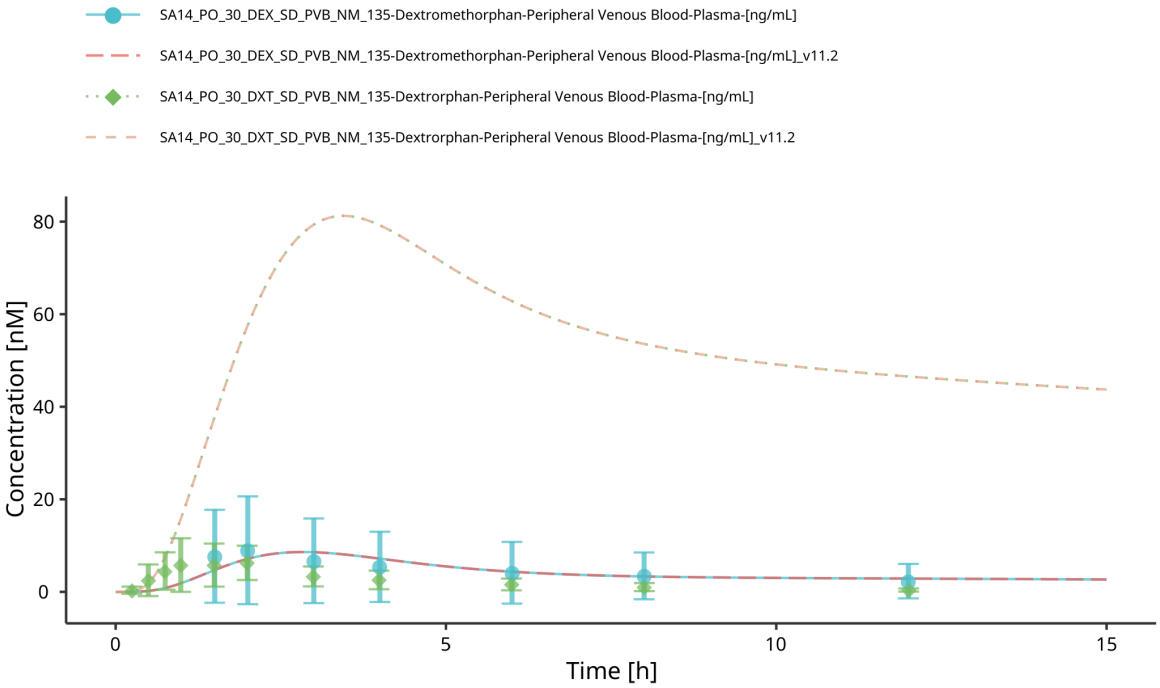
Antecip Bioventures EM, 60 mg dextromethorphan hydrobromide multiple dose (capsule/solution), n=10 - time profile



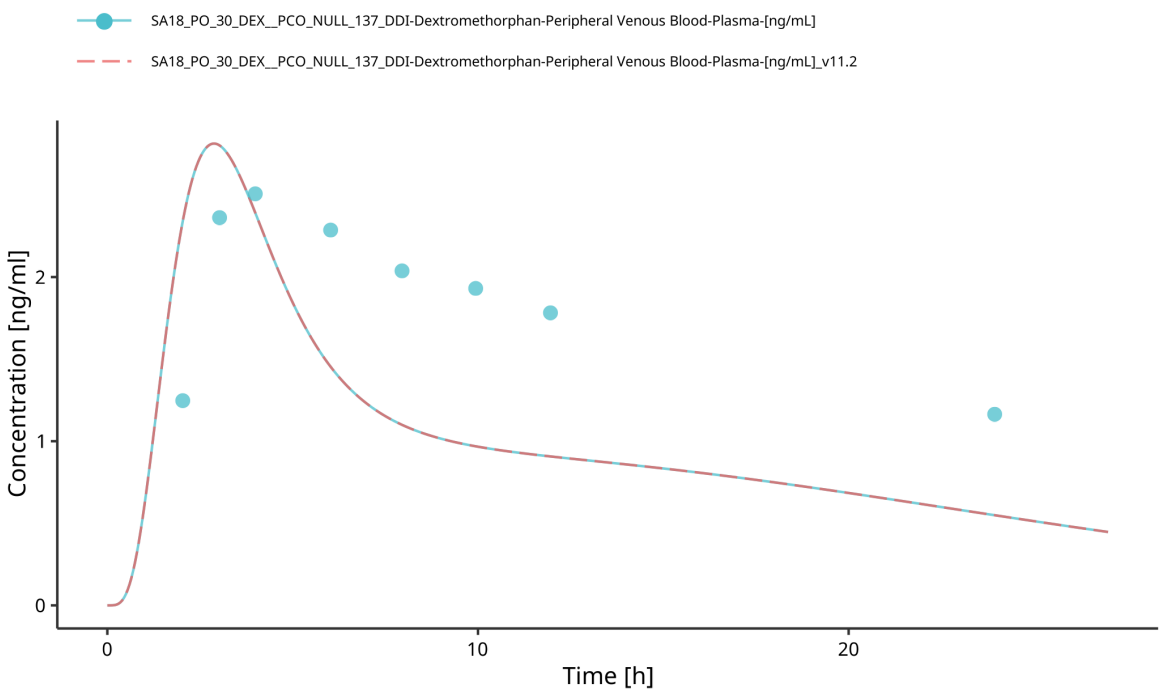
Zawertailo 2009 NM, 3 mg/kg dextromethorphan hydrobromide (capsule/solution), n=6, AS=2 - time profile



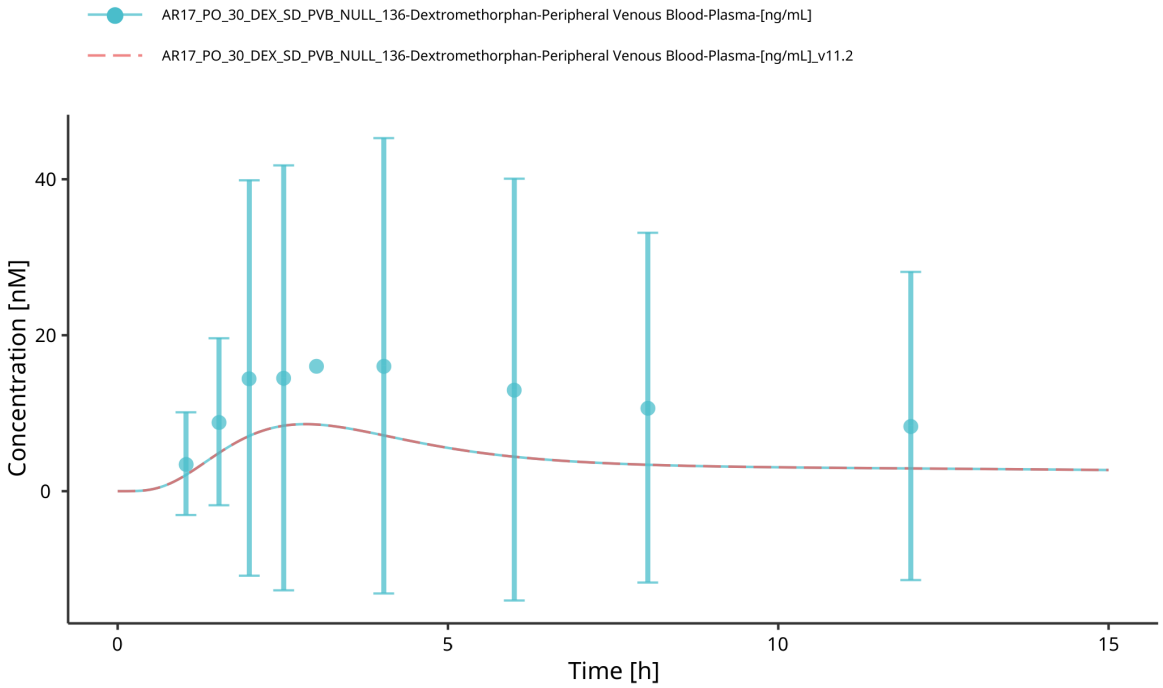
Sager 2014 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=10 - time profile



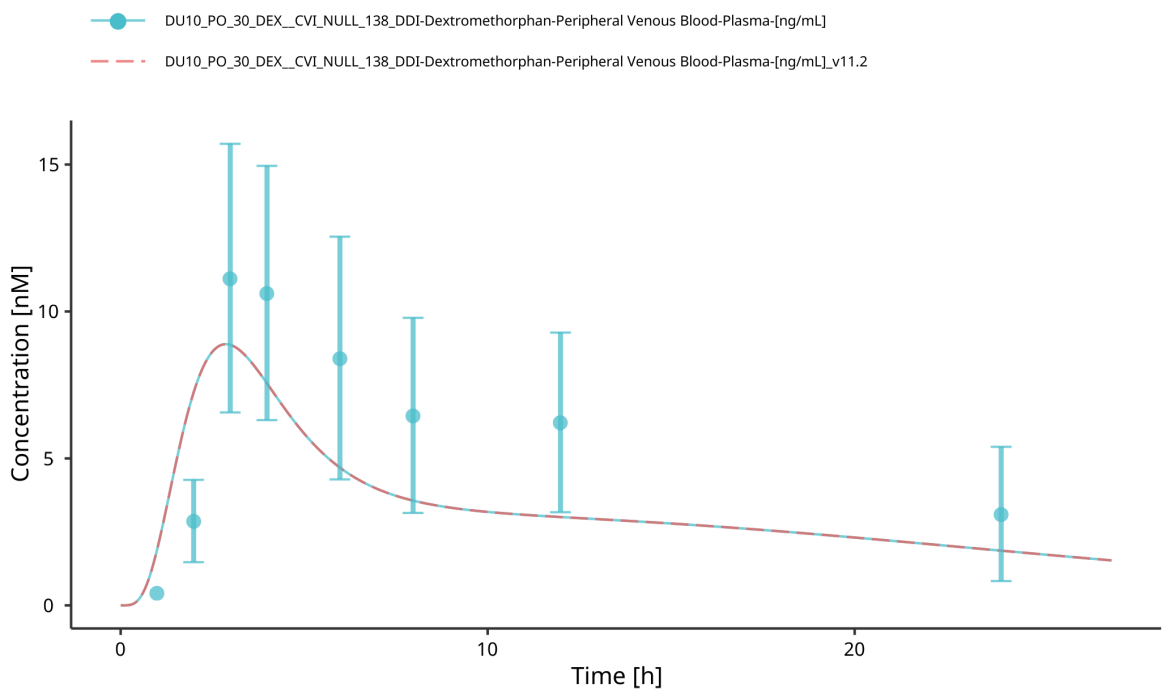
Stage 2018 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=12 - time profile



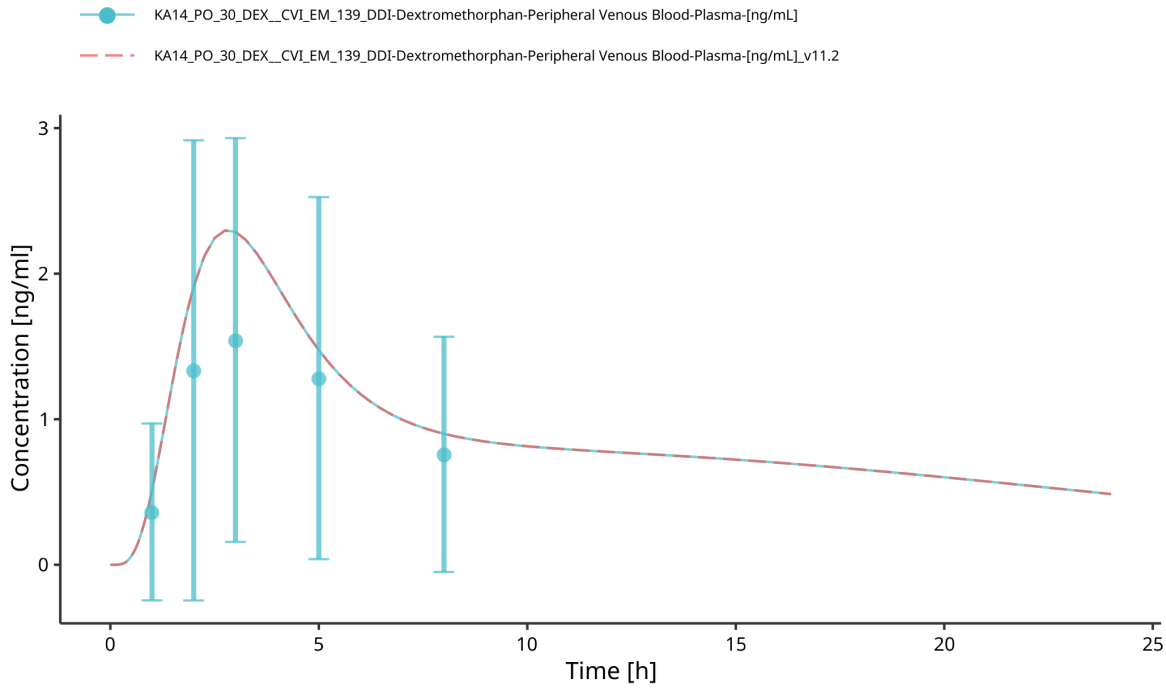
Armani 2017 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=20 - time profile



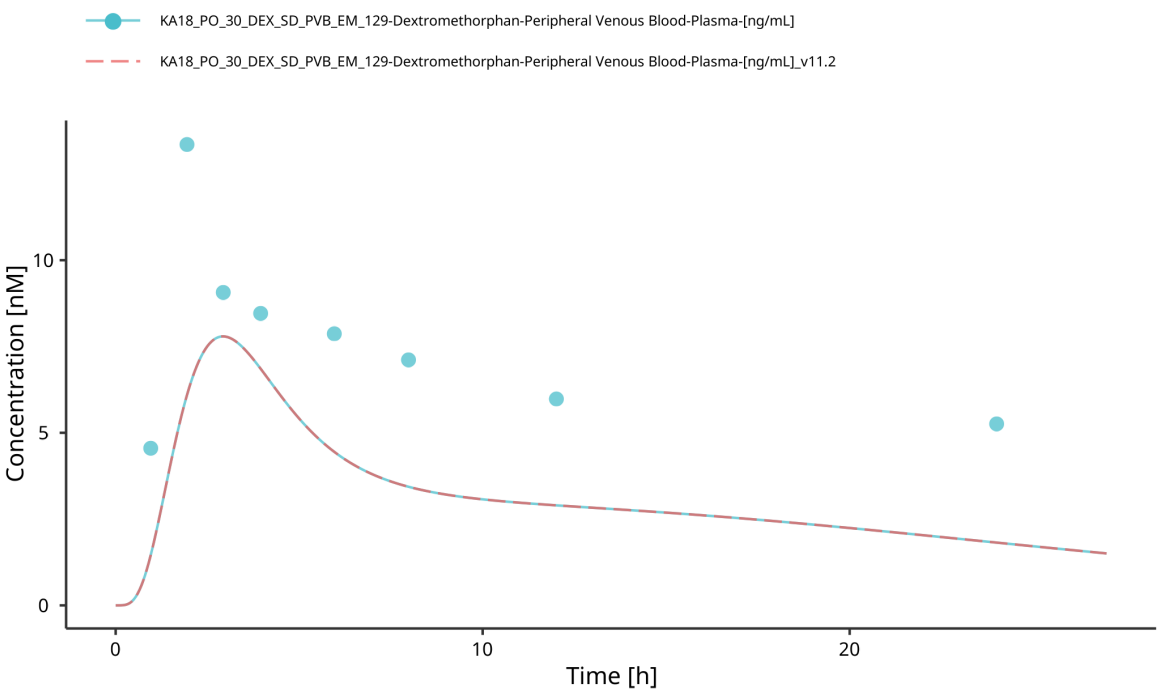
Dumond 2010 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=23 - time profile



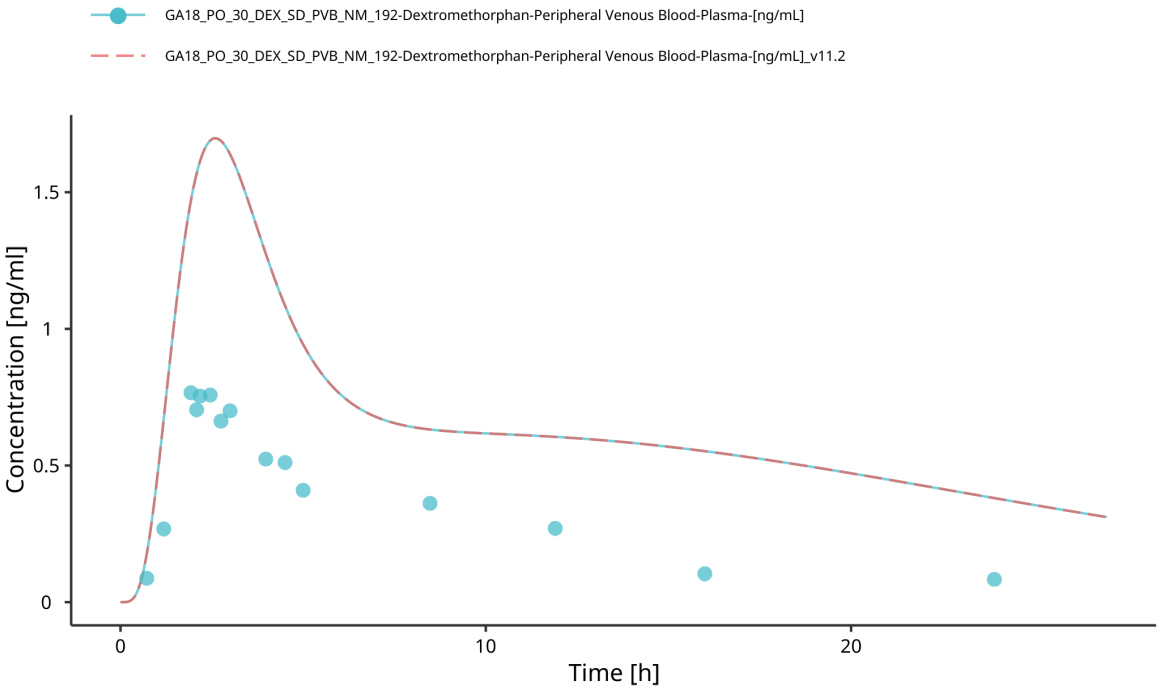
Kakuda 2014 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=14 - time profile



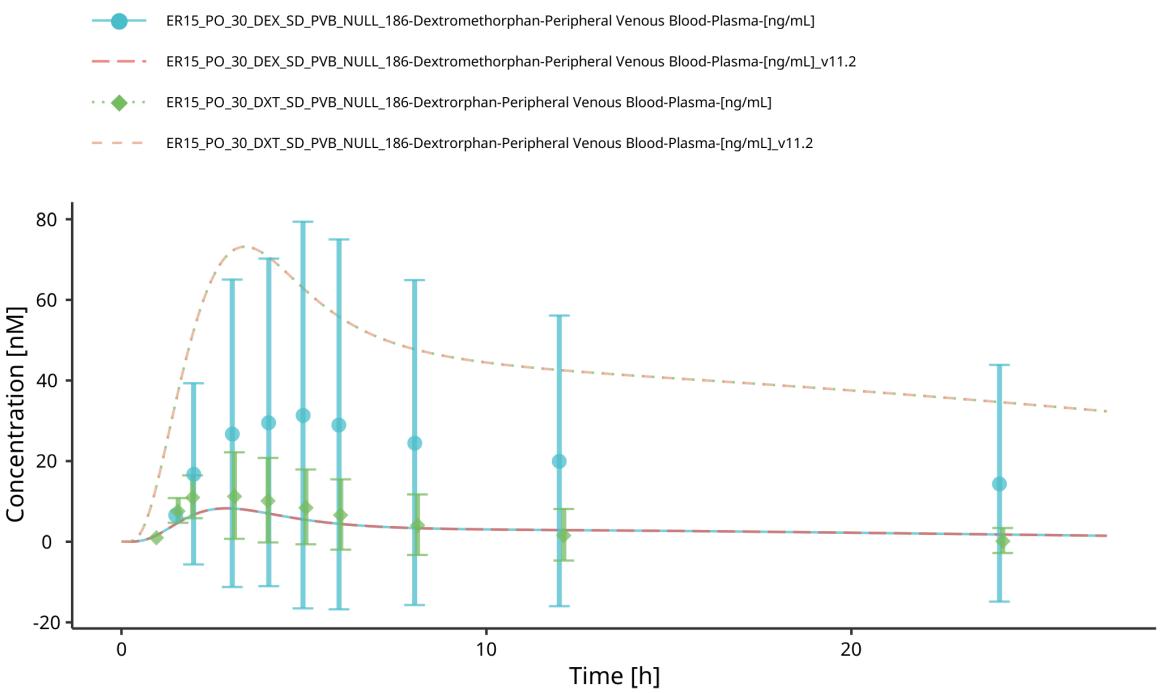
Khalilieh 2018 EM, 30 mg dextromethorphan hydrobromide (cocktail), n=20 - time profile



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



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



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