LISBON ADDICTIONS 2019

Session: The challenges of monitoring new drugs

Lisbon, 23 October 2019

Use of physiologically based pharmacokinetic modelling of new psychoactive substances

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NPS euronet

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In relation to this presentation, the lead author has not conflit of interest that need to be diclosed

Problem Statement

- **Increased number of detections of New Psychoactive Substances in Europe (nearly two NPS are detected every week)**

- **It stands as a major challenge to drug policy and practice regarding the implementation of European legislation on NPS, and to develop a best practice protocol on prevention.**

ESTIMATE NPS USE IN EUROPEAN POPULATIONS

Wastewater plants and sampling

+

Urine samples from patients admitted in emergence rooms in central hospitals

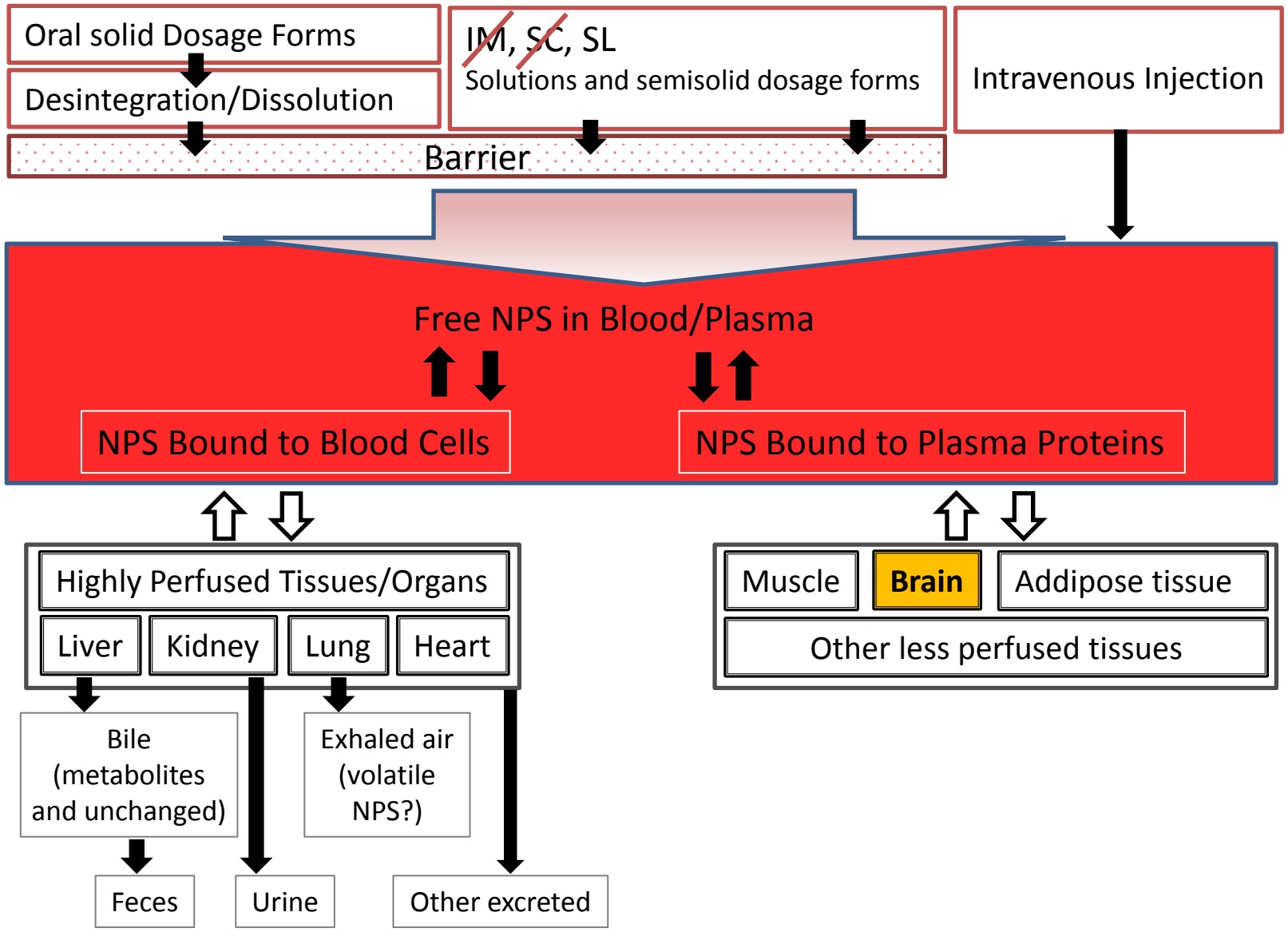
NPS Quantification

NPS pharmacokinetic properties (metabolism and excretion patterns)

- From literature for specific compounds
- Predicted *in silico for* undescribed NPS

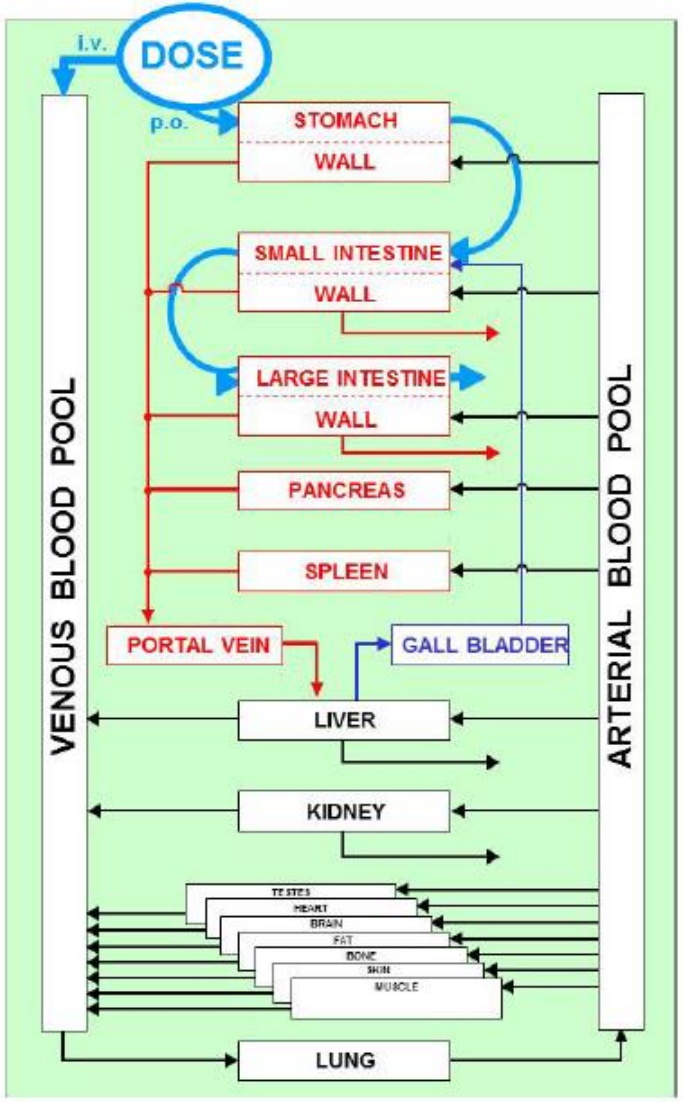
Estimates of NPS population consumption patterns

PHARMACOKINETICS OF SMALL MOLECULES



What body does to a drug/drug product?

PREDICTION OF HUMAN ABSORPTION, DISTRIBUTION AND ELIMINATION THROUGH *IN SILICO* MODELS



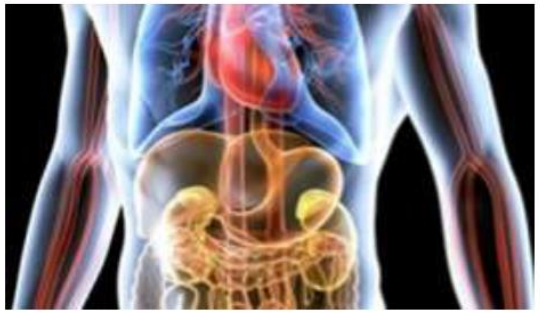
PK-Sim® (Open Systems Pharmacology)

http://www.open-systems-pharmacology.org/

- ✓ PK-Sim® is a reliable, powerful and easy-to-use modelling & simulation tools for pharmaceutical and other life-sciences applications.
- ✓ PK-Sim® is qualified and accepted by the scientific community including academia, regulatory agencies and industry.

PK-Sim® is a comprehensive software tool for whole-body physiologically based pharmacokinetic modelling

Organism properties



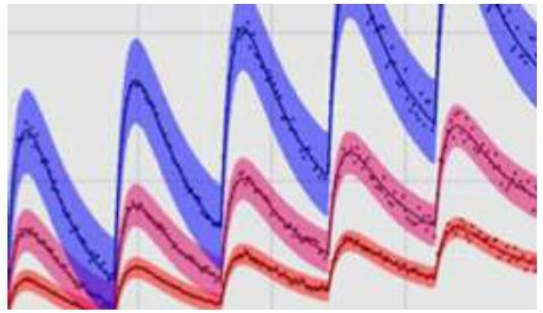
Anatomy and physiology
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

Drug properties

Physico-chemical properties
- Lipophilicity (LogD/P/MA)
- **Molecular Weight**
- pKa/pKb
- Solubility @ reference pH

Anatomy and physiology
- **fu** (plasma protein binding / fraction unbound in plasma)
- (Partition coefficients)
- ((Intestinal) permeability)
- Active processes (K_m, V_{max}, K_d) / Mass Balance

Study protocol and formulation properties



Formulation
(empirical or mechanistic dissolution function)

Administration protocol
(dose and dosing regimen)

Special events
(food intake, exercise, EHC)

Image from OSPS Workshop PAGE 2018

OBJECTIVES

- **To develop NPS PBPK model for healthy teenage (15-18 years old) and adult (18-64 years old) populations**
- **To compare PBPK model predictions for pharmacokinetic exposure with published data for cathinone and mephedrone**
- **To simulate virtual populations and estimate pharmacokinetic profiles and derived pharmacokinetic parameters for other NPS for different age groups, in the simulated population**

PK-Sim® (Open Systems Pharmacology)

✓ Information regarding the compound (basic physical-chemistry properties)

Basic Physico-chemistry | ADME | Advanced Parameters

☑ Is small molecule

Lipophilicity:

	Experiment	Lipophilicity	Default
	Measurement	-0.20 Log Units	☐
	DrugBank	-0.07 Log Units	☑

Fraction unbound (plasma, reference value):

Binds to: ◉ Albumin ○ α1-acid glycoprotein ○ Unknown

	Experiment	Fraction Unbound	Species
	Lelo et al. 1986	0.70	Human

Molweight:

Molecular weight	194.20 g/mol
Has halogens	No
Effective molecular weight	194.20 g/mol

Compound type / pka:

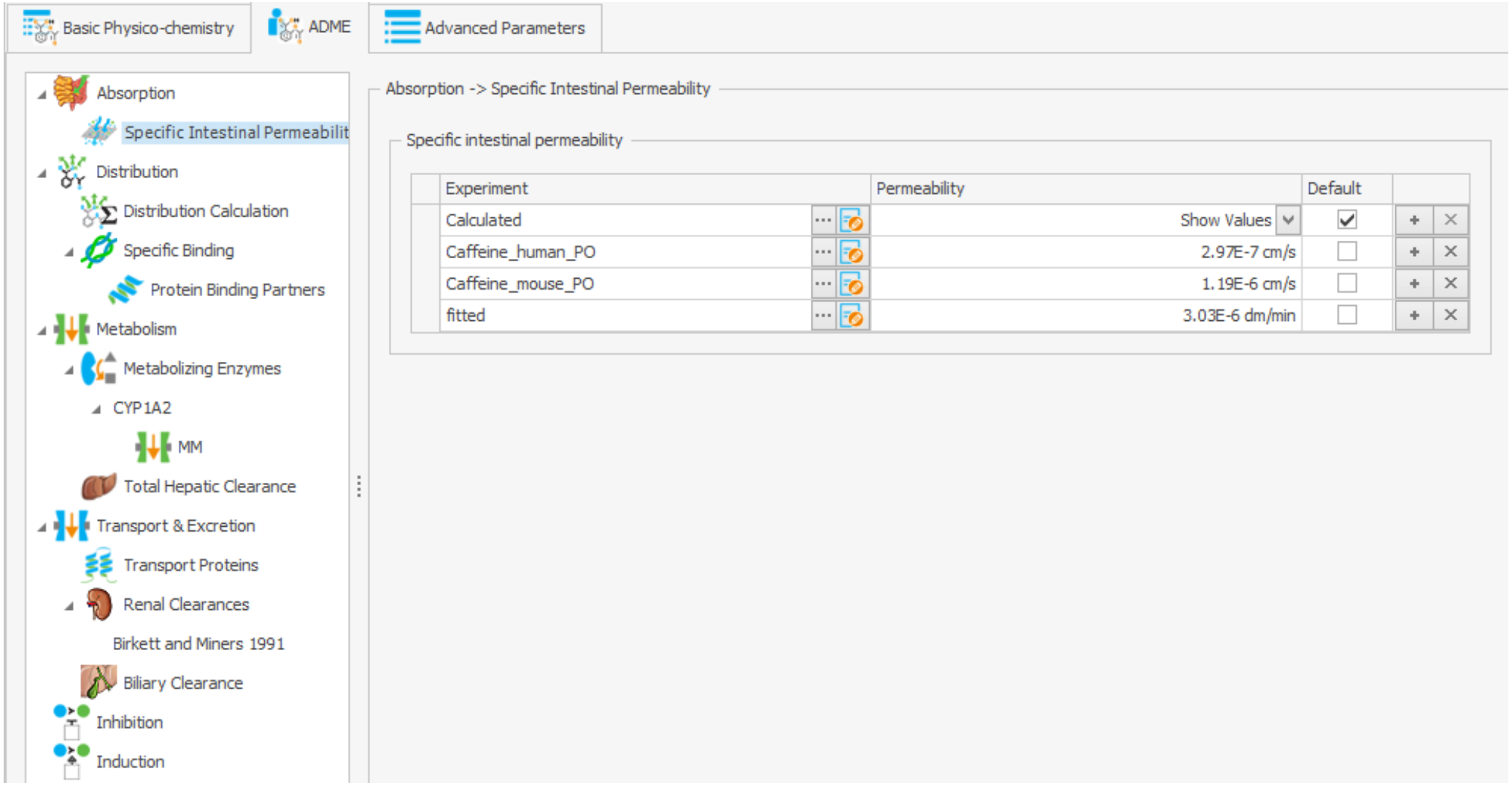
Base	0.80
Neutral	<None>
Neutral	<None>

Solubility:

	Experiment	Solubility at Ref-pH	Ref-pH	Solubility gain per charge	pH-dependent Solubility
	Water solubility	21600.00 mg/l	7.00	1000.00	Show Graph

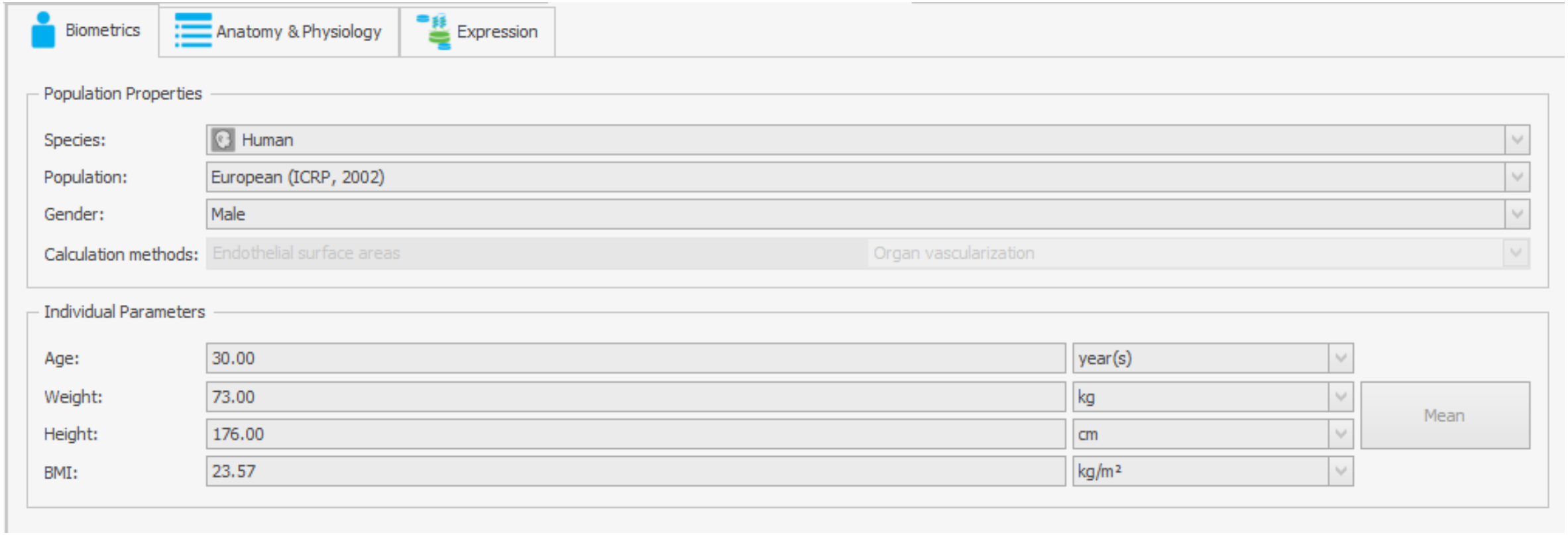
PK-Sim® (Open Systems Pharmacology)

✓ **Information regarding the compound (ADME properties)**



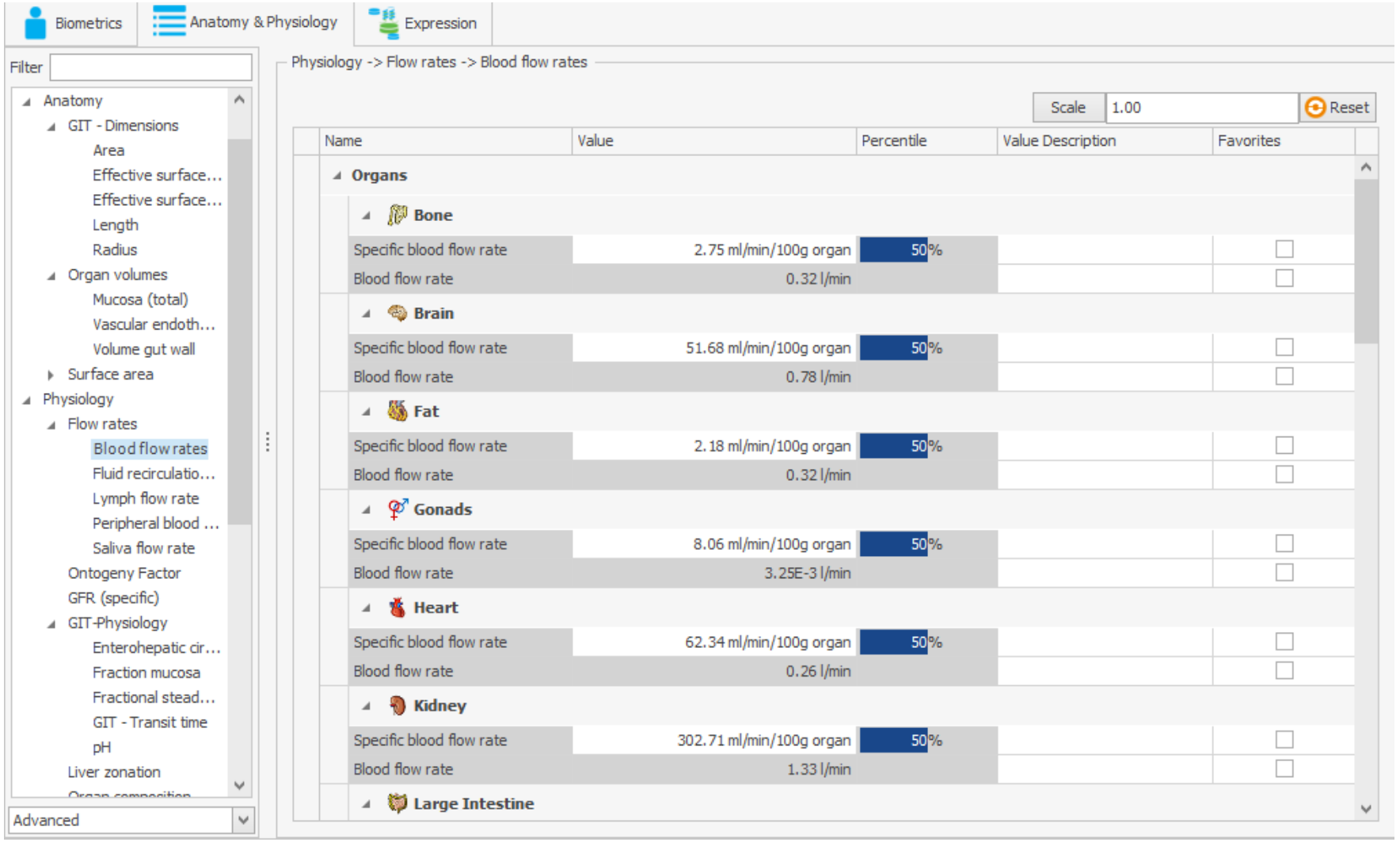
PK-Sim® (Open Systems Pharmacology)

- ✓ **Information regarding the population selected for biosimulation (biometrics)**



PK-Sim® (Open Systems Pharmacology)

✓ **Information regarding the population selected for biosimulation (anatomy and physiology)**



PK-Sim® (Open Systems Pharmacology)

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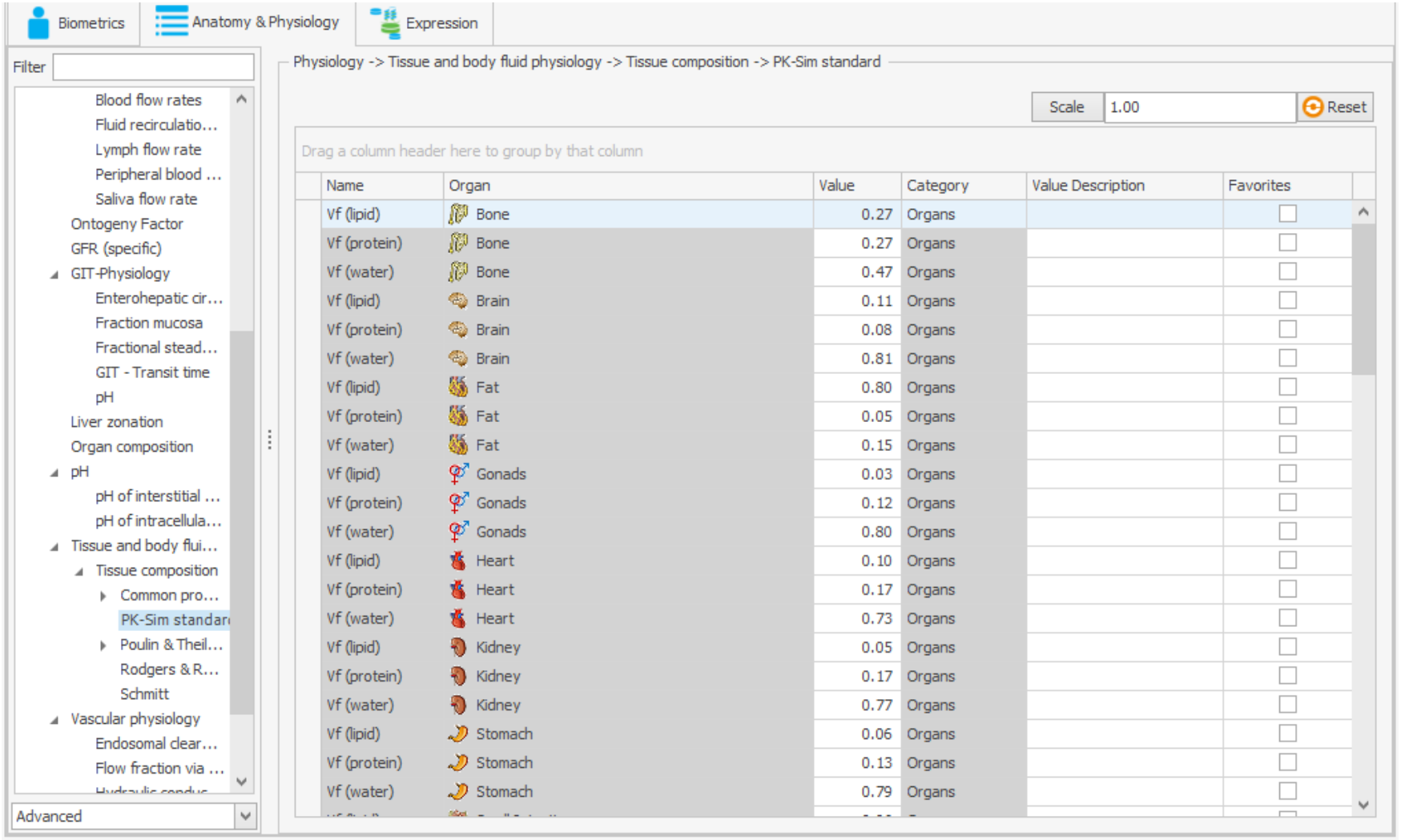
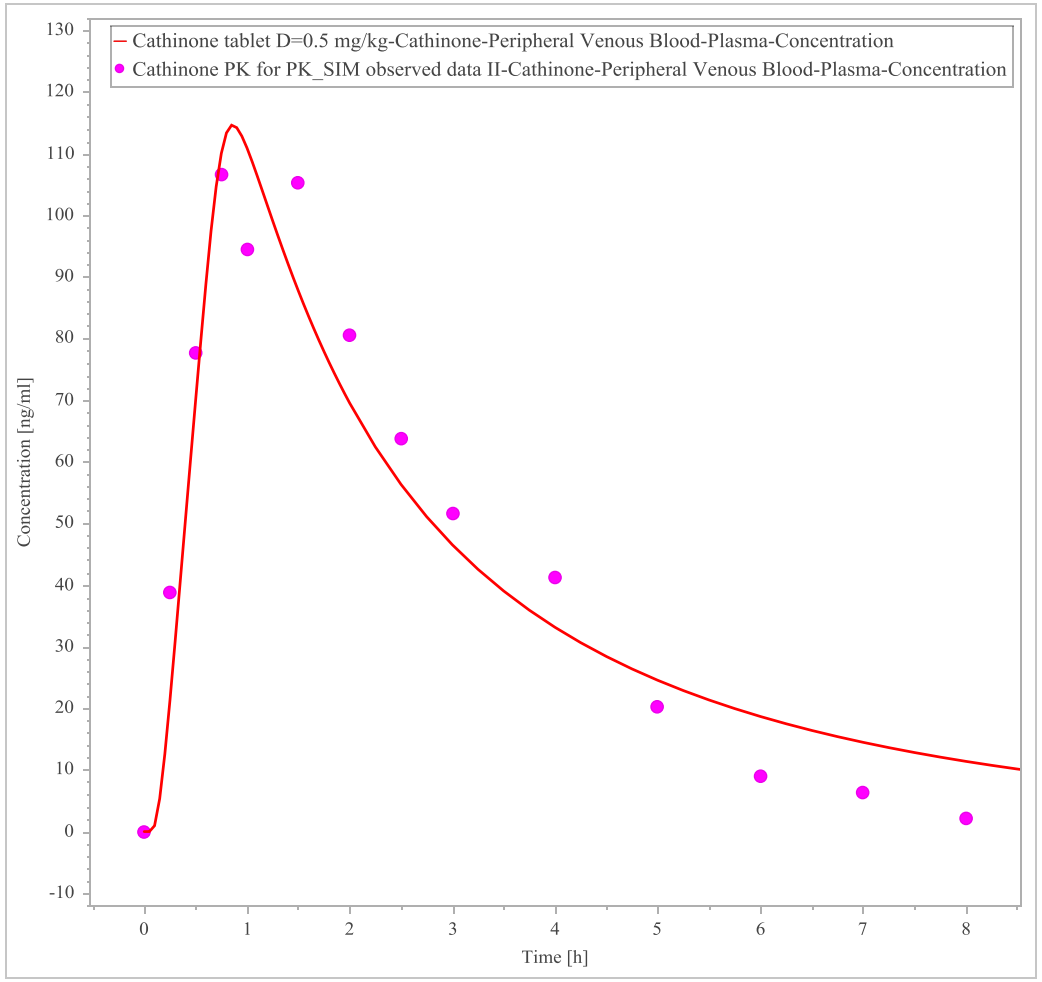
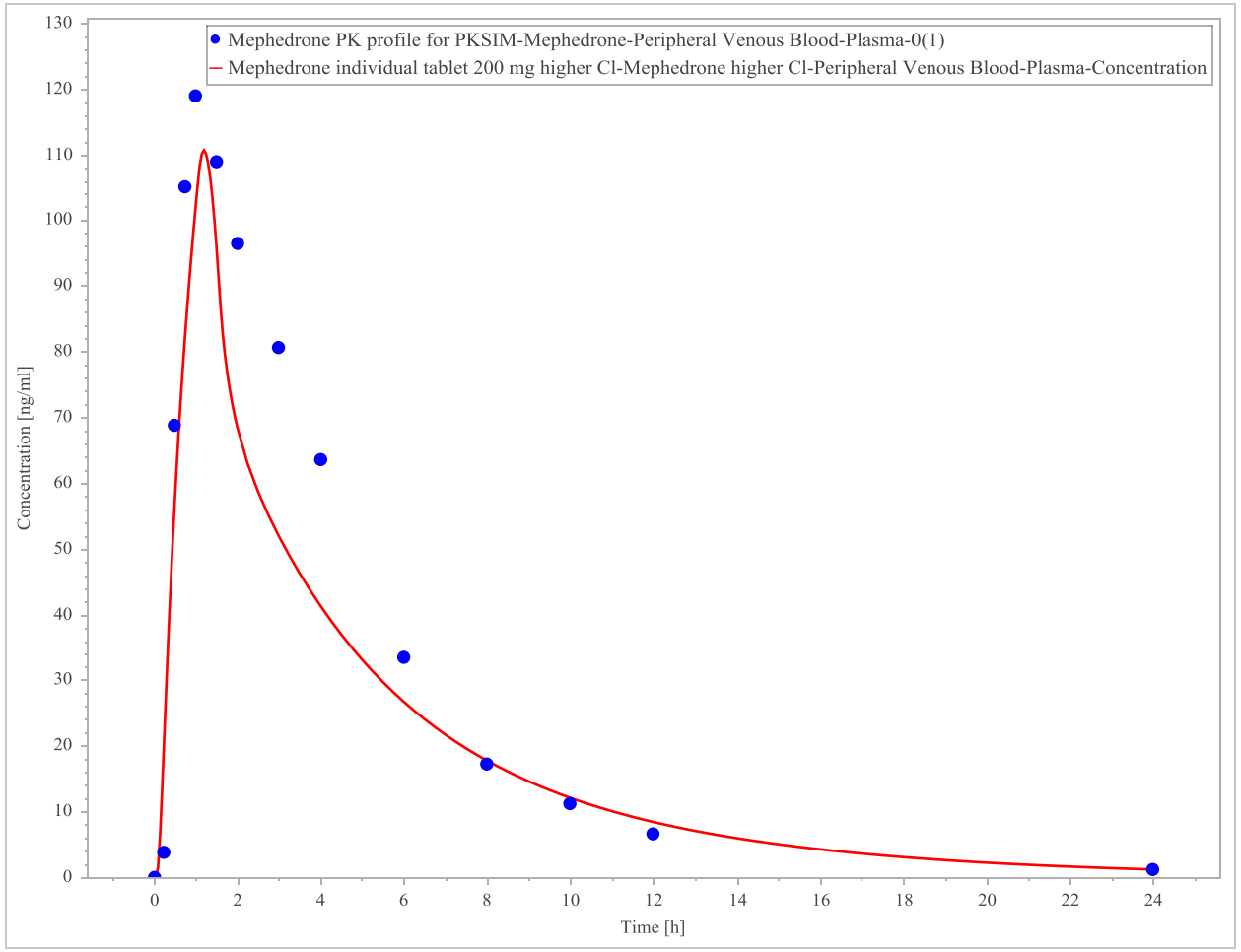


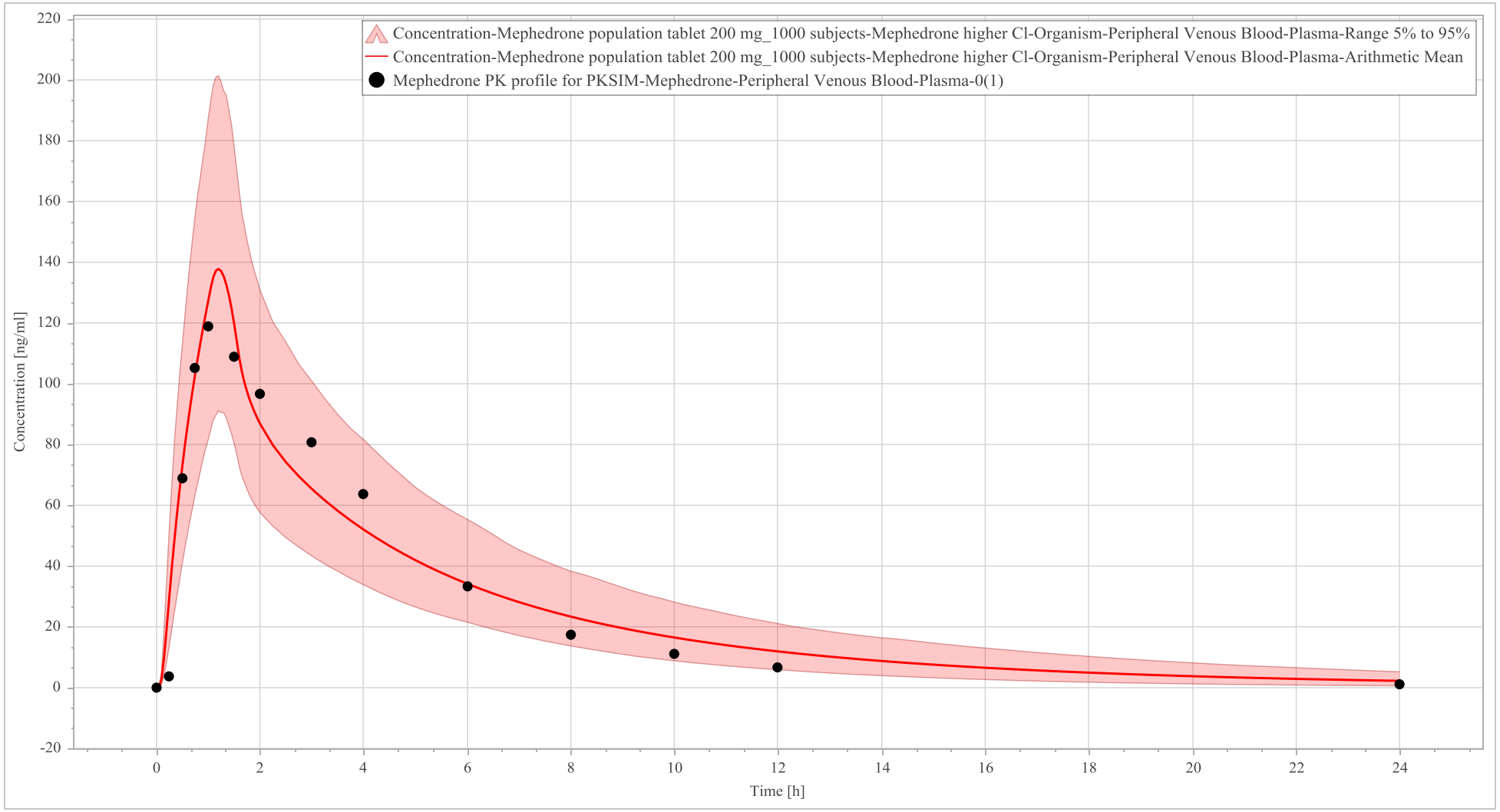
PK-Sim® (Open Systems Pharmacology)

✓ Biosimulation in the selected population (validation of the model – example for cathinone and mephedrone)

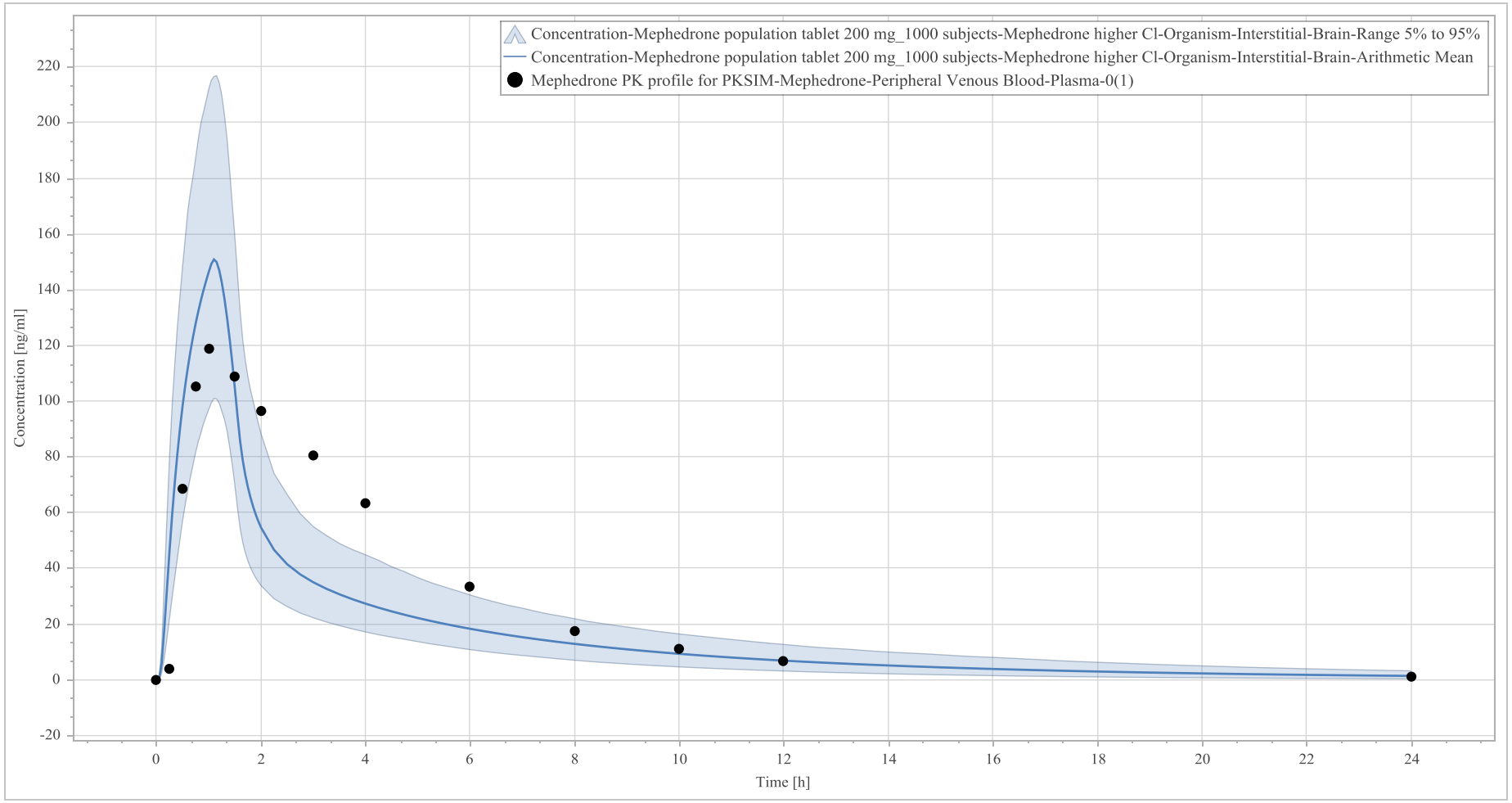




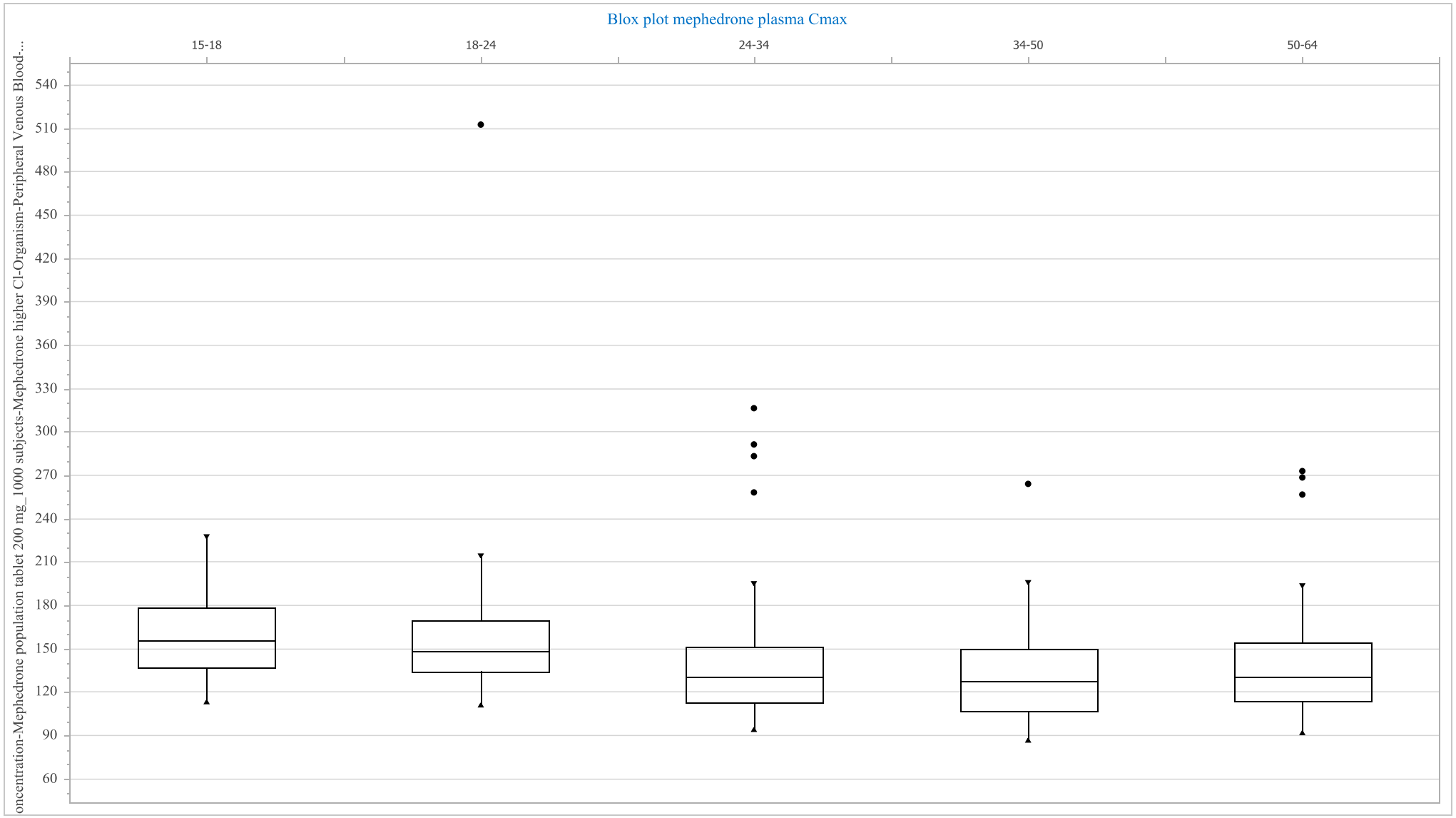
- ✓ **Biosimulation in the selected population (prediction for mephedrone pharmacokinetic profiles in the population)**
- ✓ **Simulation of 1000 subjects**



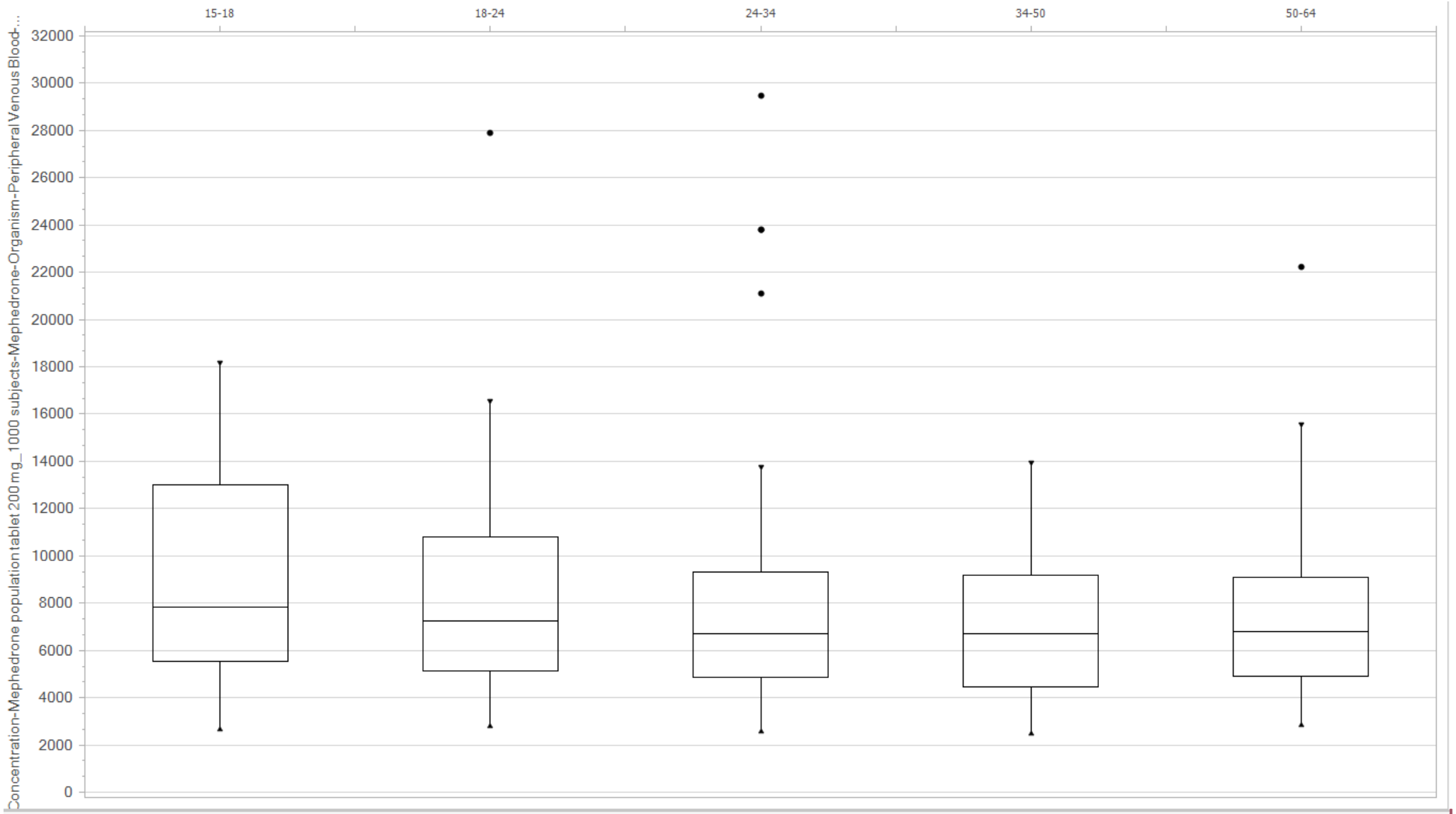
- ✓ **Biosimulation in the selected population (prediction for mephedrone pharmacokinetic profiles in the population)**
- ✓ **Simulation of 1000 subjects**



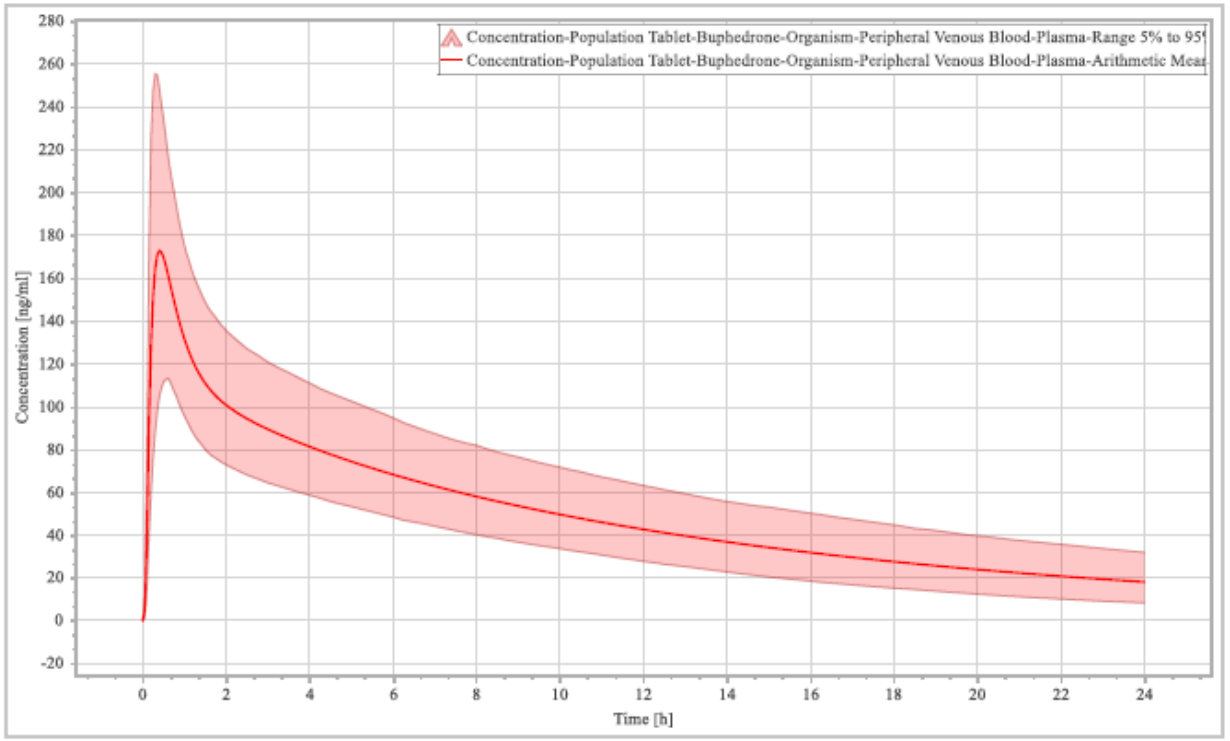
Simulation of 1000 subjects (*Box-Whisker of maximum plasma concentration (C_{max}) by age groups) for mephedrone*

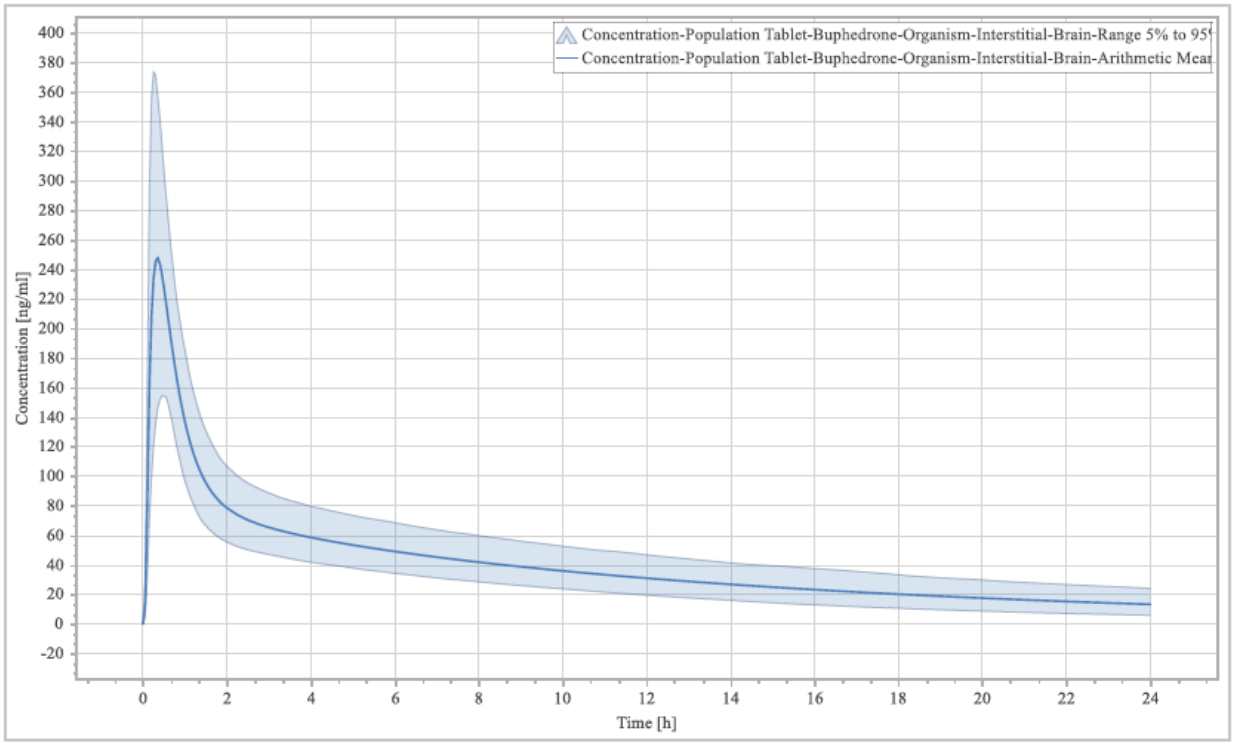


Simulation of 1000 subjects (*Box-Whisker of exposition (AUC_{0-inf}) by age groups) for mephedrone*

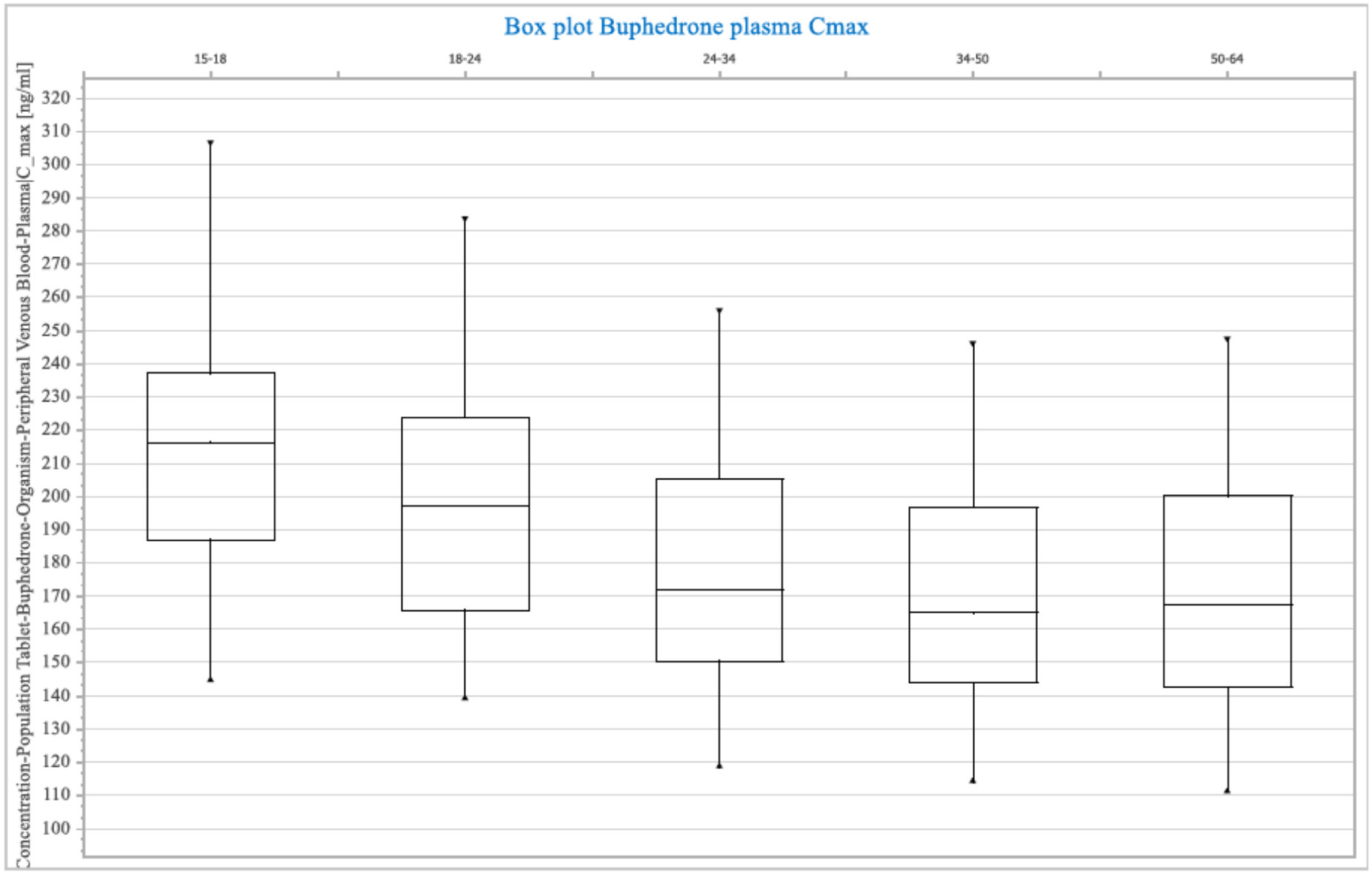


- ✓ **Biosimulation in the selected population (prediction for buphedrone pharmacokinetic profiles in the population)**
- ✓ **Simulation of 1000 subjects**





Simulation of 1000 subjects (*Box-Whisker of maximum plasma concentration (C_{max}) by age groups) for buphedrone*



Simulation of 1000 subjects (*mean results for tested NPS)*

	Cathinone Dose 200 mg		Mephedrone Dose 200 mg		Buphedrone Dose 100 mg	
PK Parameters	*Interstitial Brain*	*Plasma*	*Interstitial Brain*	*Plasma*	*Interstitial Brain*	*Plasma*
C_{max} *(ng/mL)*	154.60	125.01	150.84	137.66	247.82	173.02
C_{max} *(µM)*	1.04	0.84	0.85	0.78	1.40	0.98
$AUC_{0\text{-}inf}$ *(ng.h/mL)*	361.20	450.10	426.90	605.25	1202.86	1509.64
$AUC_{0\text{-}inf}$ *(µmol.h/mL)*	2.42×10^{-3}	3.02×10^{-3}	2.41×10^{-3}	3.41×10^{-3}	0.00679	0.00852
T_{max} *(h)*		0.85		1.20		0.40
Elimination half-life ($t_{1/2}$) *(h)*	5.32	4.74	5.54	5.22	10.23	10.07

Simulation of 1000 subjects (*mean results for tested NPS)*

	4-FMC Dose 100 mg		N-ethylhexedrone Dose 100 mg		4-MEC Dose 100 mg	
PK Parameters	*Interstitial Brain*	*Plasma*	*Interstitial Brain*	*Plasma*	*Interstitial Brain*	*Plasma*
C_{max} *(ng/mL)*	492.55	617.47	33.36	38.55	178.65	169.05
C_{max} *(µM)*	2.72	3.41	0.15	0.18	0.93	0.88
$AUC_{0\text{-}inf}$ *(ng.h/mL)*	2173.05	27012.69	1926.68	3587.92	2588.34	4133.70
$AUC_{0\text{-}inf}$ *(µmol.h/mL)*	0.01	0.01	8.78×10^{-3}	0.02	0.01	0.02
T_{max} *(h)*		0.30		0.40		0.45
Elimination half-life ($t_{1/2}$) *(h)*	9.52	9.44	111.62	120.46	27.50	27.24

CONCLUSIONS

- **PK-Sim® is a powerful tool for developing PBPK models for prediction of *in vivo* NPS exposure and pharmacokinetic properties**
- **PBPK models enable predictions for different population cohorts (ex. teenage (15-18 years old) populations)**
- **PBPK models may help on the assessment of public health risks on the use of NPS and challenging drug policy**
- **PBPK models may help on the assessment of public health risks caused by the use of NPS and in the challenging drug policy and consumption prevention of these substances**

Use of physiologically based pharmacokinetic modelling of new psychoactive substances

Thank you for your attention

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