

MECHANISTIC PREDICTION OF ACETAMINOPHEN METABOLISM AND PHARMACOKINETICS IN CHILDREN USING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING APPROACH

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INTRODUCTION

Tylenol® (Acetaminophen, APAP) is generally considered safe. However, APAP can cause in part severe liver toxicity in adults and children when given at a high dose or even at the recommended dose in certain situations (e.g. chronic alcohol use). This toxicity has been associated with the saturation of major elimination pathways (glucuronidation, sulfation and glutathione conjugation) and subsequent accumulation of NAPQI, a reactive metabolite generated by cytochrome P450 enzymes (e.g. CYP2E1, CYP3A4 and CYP1A2) [1].

Prediction of APAP pharmacokinetics (PK) in children is challenging, because multiple biological components (e.g. body size, blood flow and the expression levels of enzymes participating in APAP elimination and bioactivation) that are involved in *in vivo* drug disposition undergo developmental changes.

Physiologically-based pharmacokinetic (PBPK) models incorporate information on drug-specific (e.g. physicochemical properties, enzyme kinetics) and system-specific parameters (e.g. organ size, blood flows, tissue composition and enzymes abundance). They further allow to account for maturational changes of the biological system over time [2], which enables the prediction of drug metabolism and disposition in children.

The aim of this project was to develop a PBPK model for APAP that uses available information on APAP's biotransformation, adult PK data and developmental changes of the human body to predict APAP metabolism and PK in children.

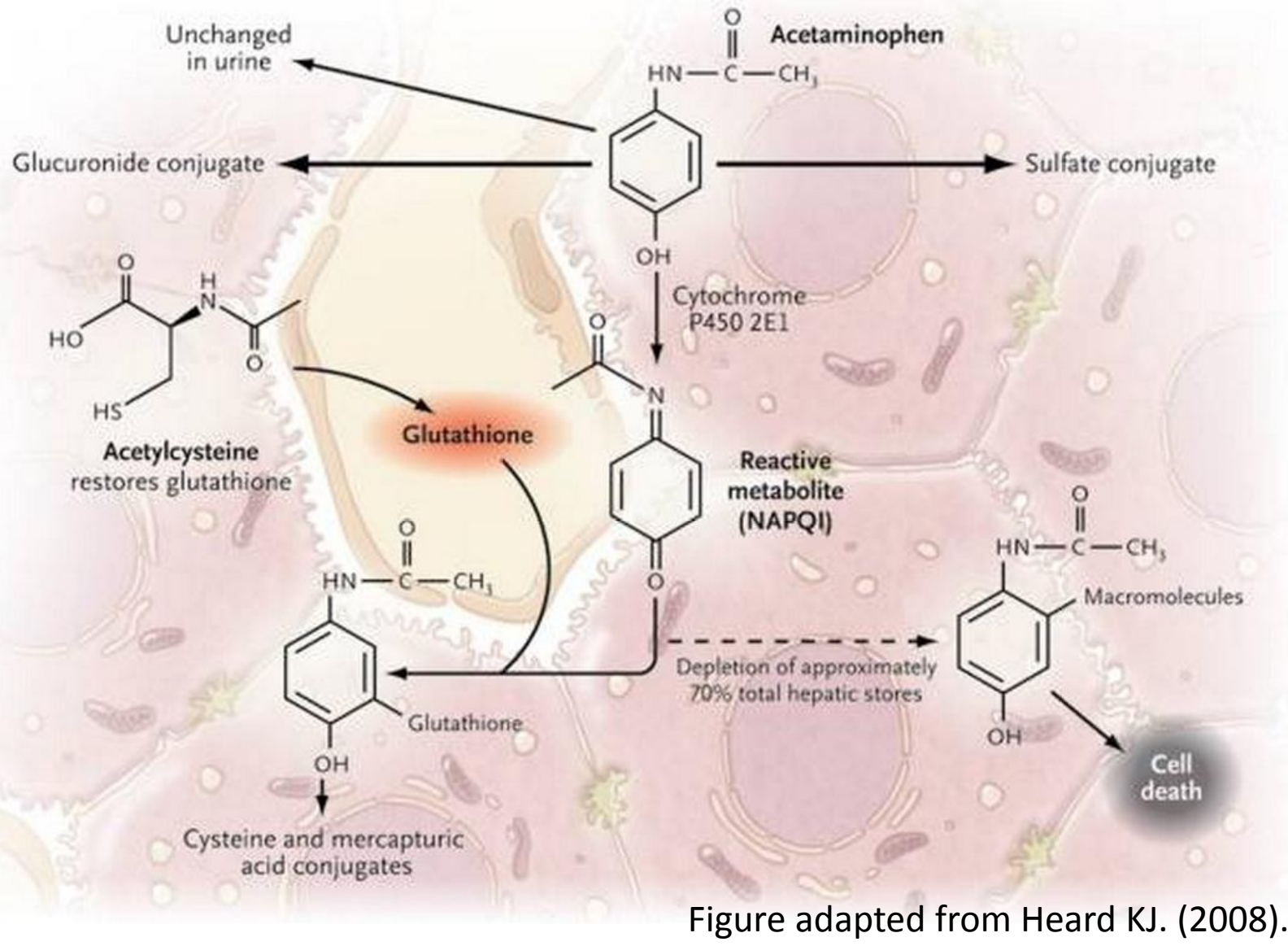


Figure adapted from Heard KJ. (2008).

METHODS

- A PBPK model was developed for APAP using SimCYP 12.1 (SimCYP, Sheffield, UK).
- Information on APAP's physicochemical properties and plasma protein binding was obtained from the literature [3]. Distribution kinetics (V_{ss} and organ partition coefficients) was predicted by SimCYP [4]. Blood to plasma (B/P) ratio and tissue : plasma partition coefficients (K_p) scalar value were estimated by parameter estimation (PE) function using adult intravenous (i.v.) dosing information from different studies [5, 6].
- Total *in vivo* clearance was estimated by NONMEM 7.2 (Icon Development Solutions, Ellicott City, MD) using adult i.v. dose data from different studies [5, 6]. Then the clearance of each individual metabolic pathway was calculated using urinary recovery data following 5 mg/kg i.v. infusion [5] and intrinsic clearance value was calculated by multiplying the clearance value of each pathway with a scaling factor of 1.5 to correct for human liver blood flow.
- The contribution of each UDP-glucuronosyltransferase (UGT) to the overall APAP glucuronidation (intrinsic clearance) was derived based on clinical pharmacogenetic studies and *in vitro* kinetic model using human liver microsomes (HLMs) [6-8]. The Michaelis-Menten constant (K_m) values were obtained from *in vitro* study using baculovirus-insect cell-expressed recombinant UGTs [9]. The maximum metabolic rate (V_{max}) was calculated by multiplying K_m value with intrinsic clearance.
- The K_m value of sulfotransferase (SULT) was obtained from *in vitro* study with cryopreserved human hepatocytes [10]. V_{max} was calculated by multiplying K_m value with intrinsic clearance.
- The formation intrinsic clearance of NAPQI pathway was derived from urinary recovery study with cysteine and mercapturic acid conjugate data. K_m values were obtained from *in vitro* study using baculovirus-insect cell-expressed recombinant human CYPs [11]. V_{max} of each CYP enzyme was converted from relative activity by incorporating enzyme abundance, microsomal protein expression level, liver weight, intersystem extrapolation factor and intrinsic clearance derived from *in vivo* study.
- Apparent first-order absorption rate constant (k_a) and lag time (T_{lag}) values for different APAP oral formulations (solution, tablet or syrup/elixir) were estimated using PE function by fitting the PBPK model to mean PK profiles of orally dosed APAP from different literature [12-18].
- The model was qualified throughout the model building process by comparing simulated APAP plasma concentration-time profiles and observations from various independent clinical study settings and dosages in both adults and children [19-32]. Simulation of APAP PK after i.v. or oral doses was conducted using 10 trials, each containing 10 virtual fasted volunteers (age, sex may vary depending on the default setting of SimCYP population) of a standard healthy or cirrhosis adult or pediatric population.

RESULTS

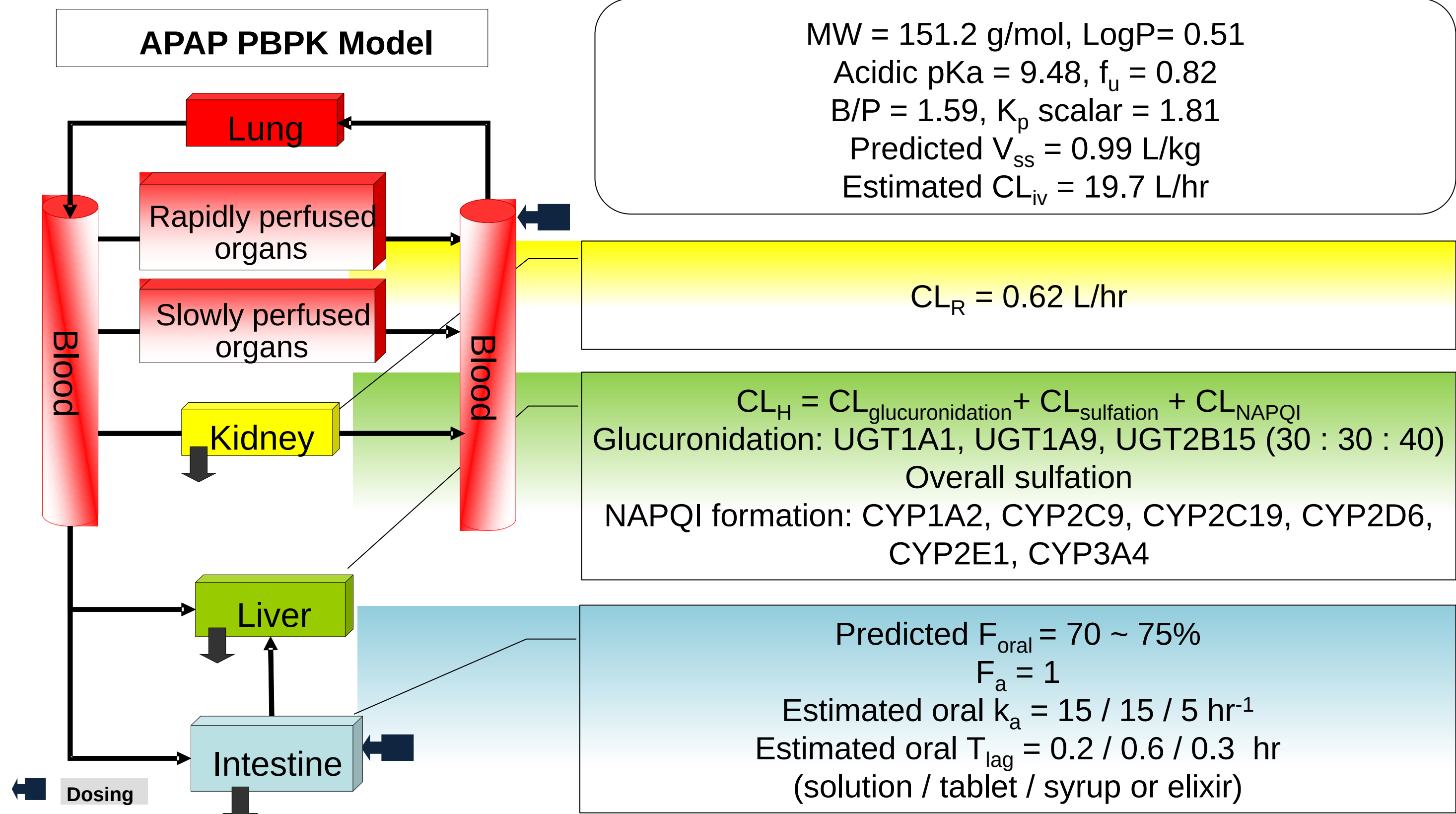


Figure 1. APAP Full PBPK Model with input parameters

Table 1. Observed [6] vs. predicted APAP systemic clearance in healthy adults and Gilbert's syndrome patients (UGT1A1 activity decreased 75%).

APAP clearance (mL/min/kg)	Healthy Control	Gilbert's Syndrome Patients
Observation	4.70 ± 0.16	4.19 ± 0.34
Prediction	4.66 ± 0.13	4.20 ± 0.12

Table 2. Observed [7] vs. predicted urinary recovered APAP-glucuronide (APAP-G) percentage in subjects carrying different UGT2B15 alleles.

APAP-G (%)	UGT2B15 (*1/*1)	UGT2B15 (*1/*2)	UGT2B15 (*2/*2)
Observation	40.2 ± 1.6	35.1 ± 1.1	29.3 ± 1.5
Prediction	42.8 ± 1.3	37.8 ± 1.2	31.5 ± 1.0

RESULTS

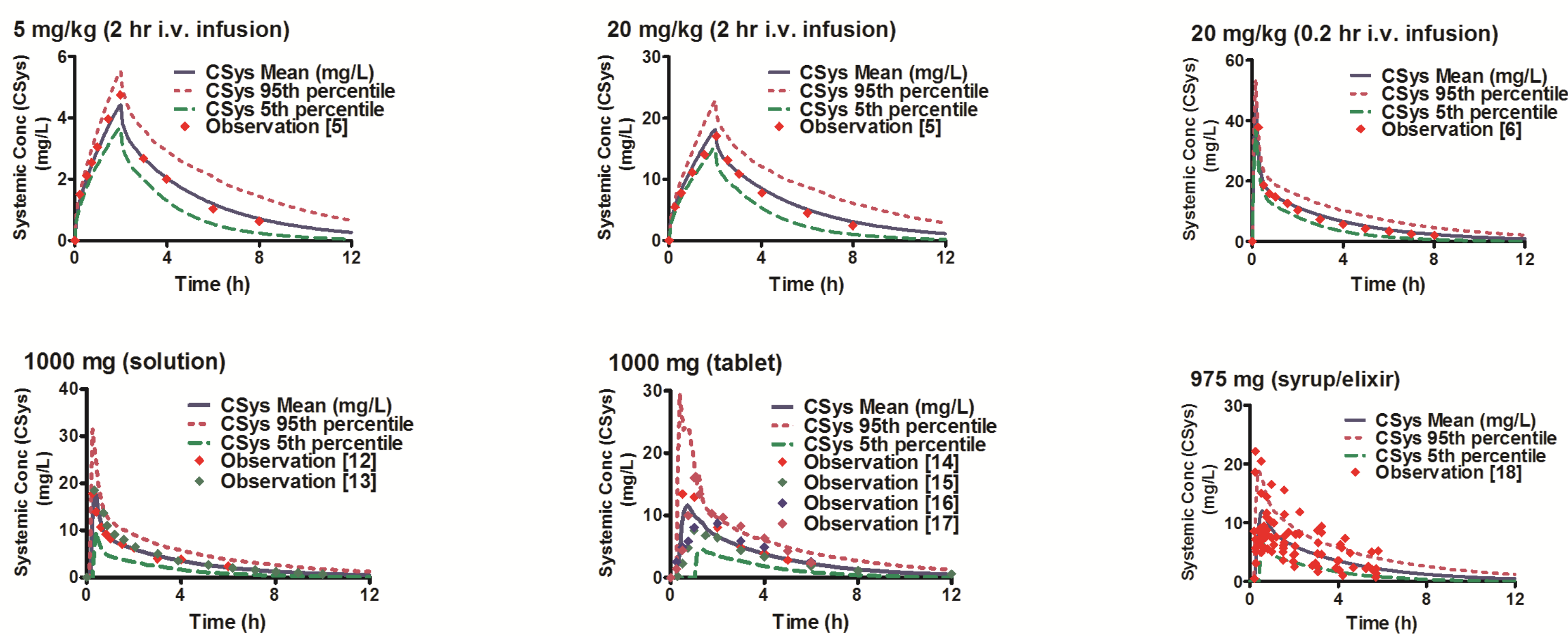


Figure 2. Observed vs. predicted APAP plasma concentration profiles in model development.

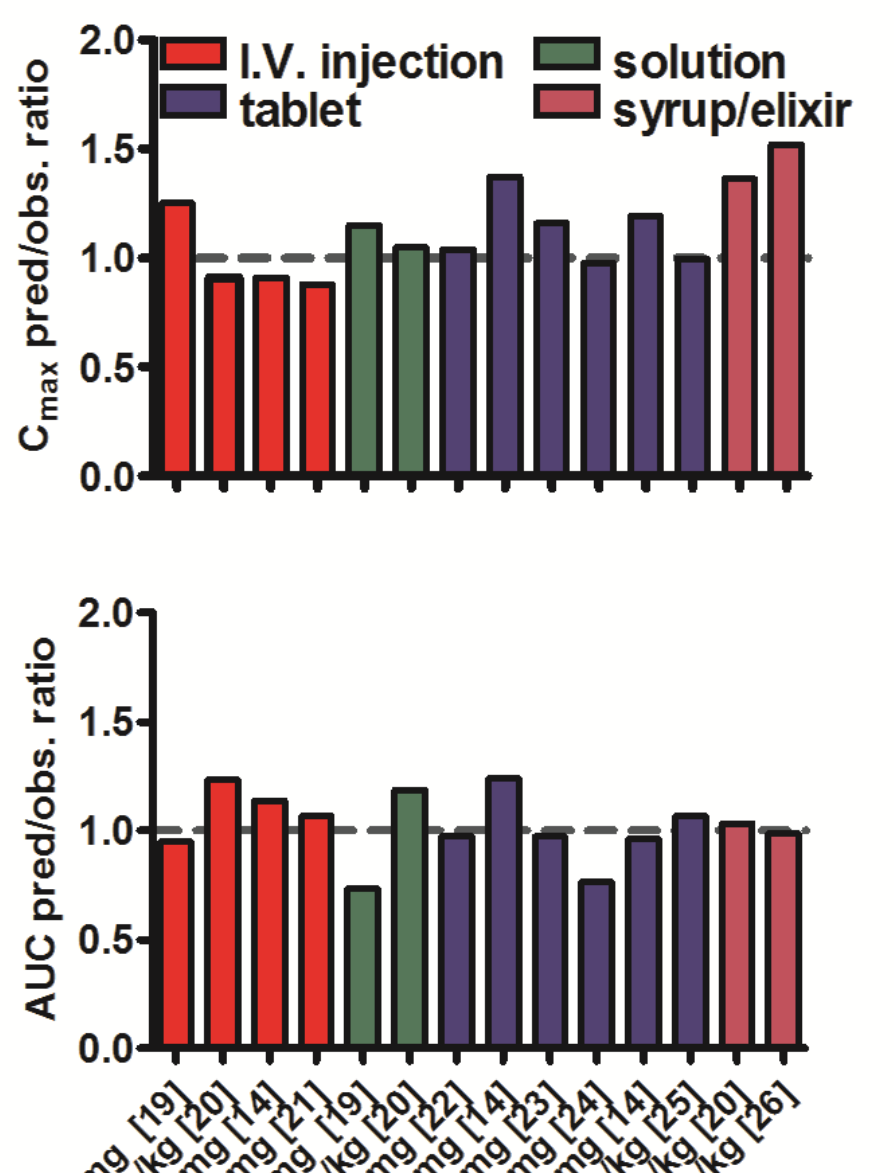


Figure 3. Verification of PBPK model performance in prediction of independent APAP PK in healthy adult subjects.

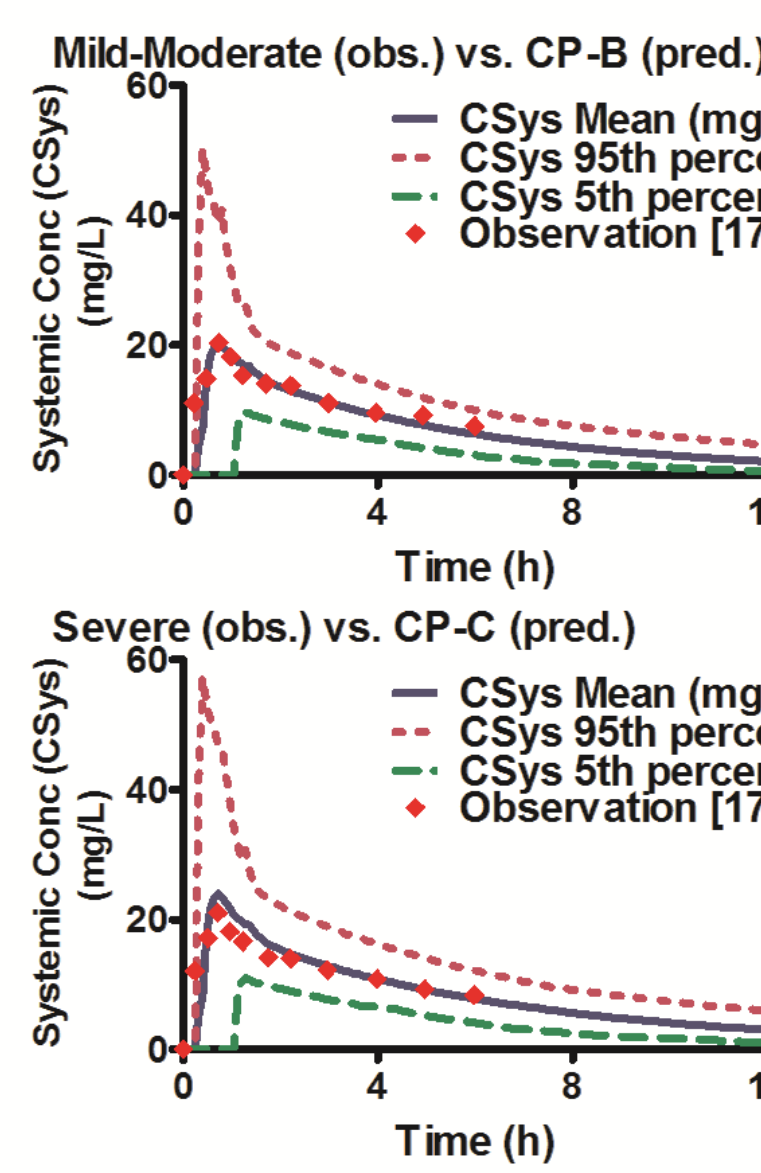


Figure 4. Verification of PBPK model performance in prediction of independent APAP PK in cirrhosis patients.

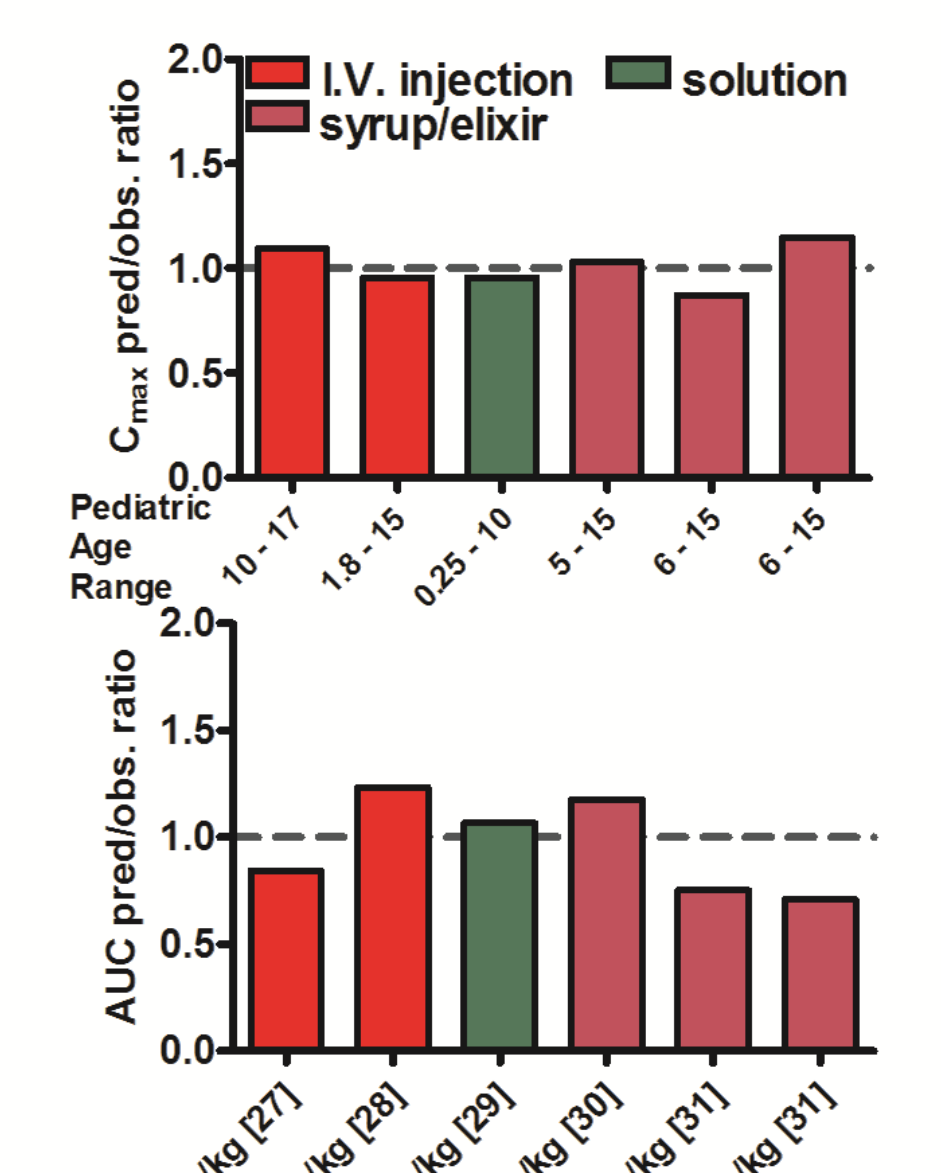


Figure 5. Verification of PBPK model performance in prediction of APAP PK in pediatric subjects.

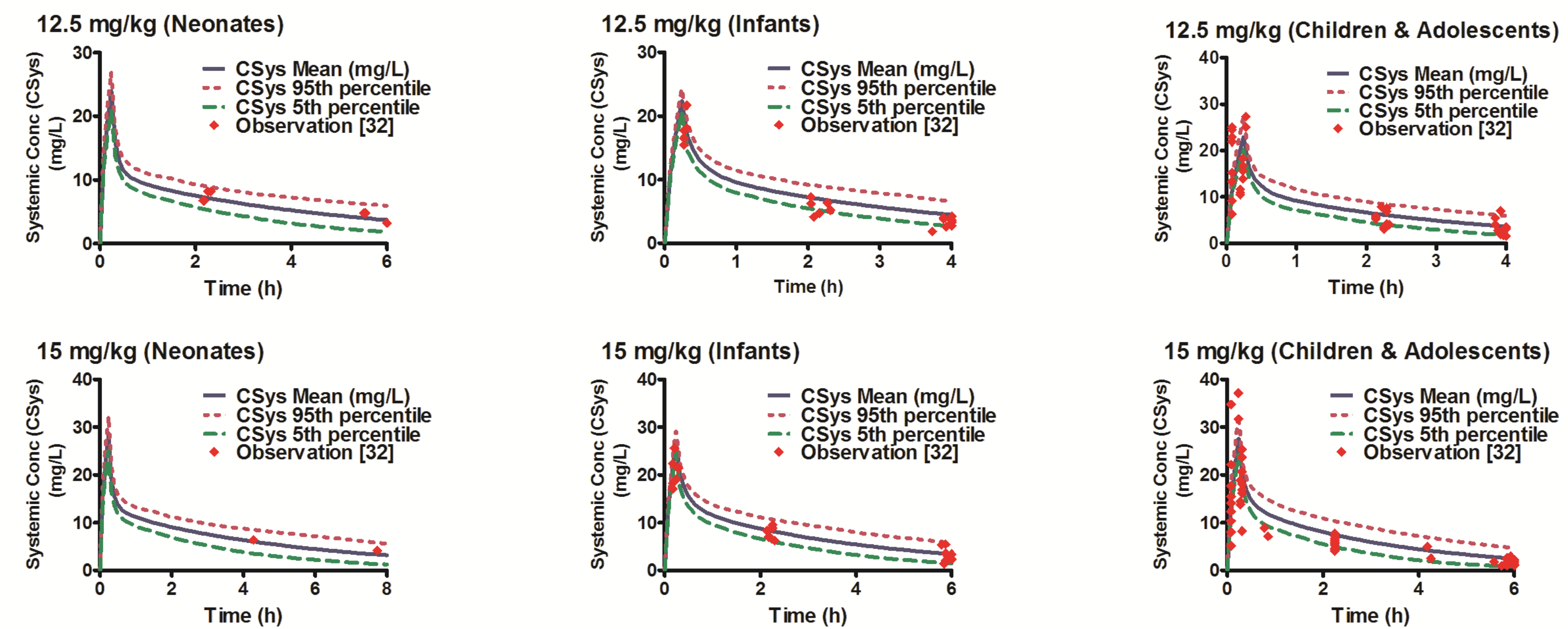


Figure 6. Observed vs. predicted APAP plasma concentration profiles in different pediatric age groups.

Table 3. Comparison of the steady state APAP-G/APAP-sulfate (APAP-S) ratio values from model predictions and that from literature in different pediatric age groups .

Age Groups	Urinary APAP-G/APAP-S Ratio (Steady State)		
	(12.5 and 15 mg/kg) [32]	Model Prediction (12.5 mg/kg)	Model Prediction (15 mg/kg)
Neonates (0 – 0.08 year)	0.603 (N = 2)	0.566 (N = 100)	0.570 (N = 100)
Infants (0.08 – 2 years)	0.970 (N = 13)	1.12 (N = 100)	1.11 (N = 100)
Children (2 – 12 years)	1.38 (N = 15)	1.44 (N = 100)	1.44 (N = 100)
Adolescents (12 – 16 years)	1.24 (N = 13)	1.45 (N = 100)	1.45 (N = 100)

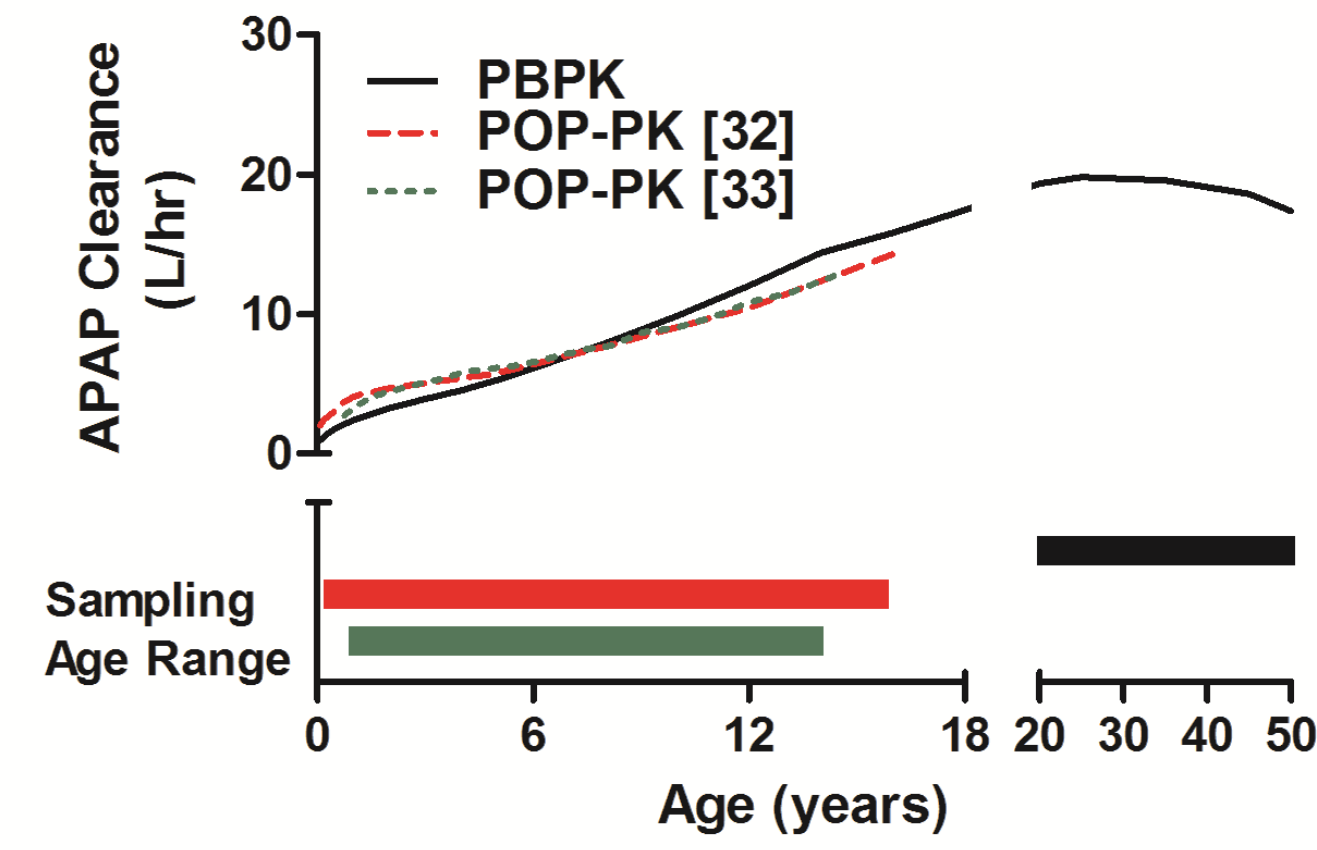


Figure 7. Systemic clearance of APAP in different pediatric age groups predicted from the present PBPK model were similar to that estimated from two independent pediatric population PK analyses [32, 33].

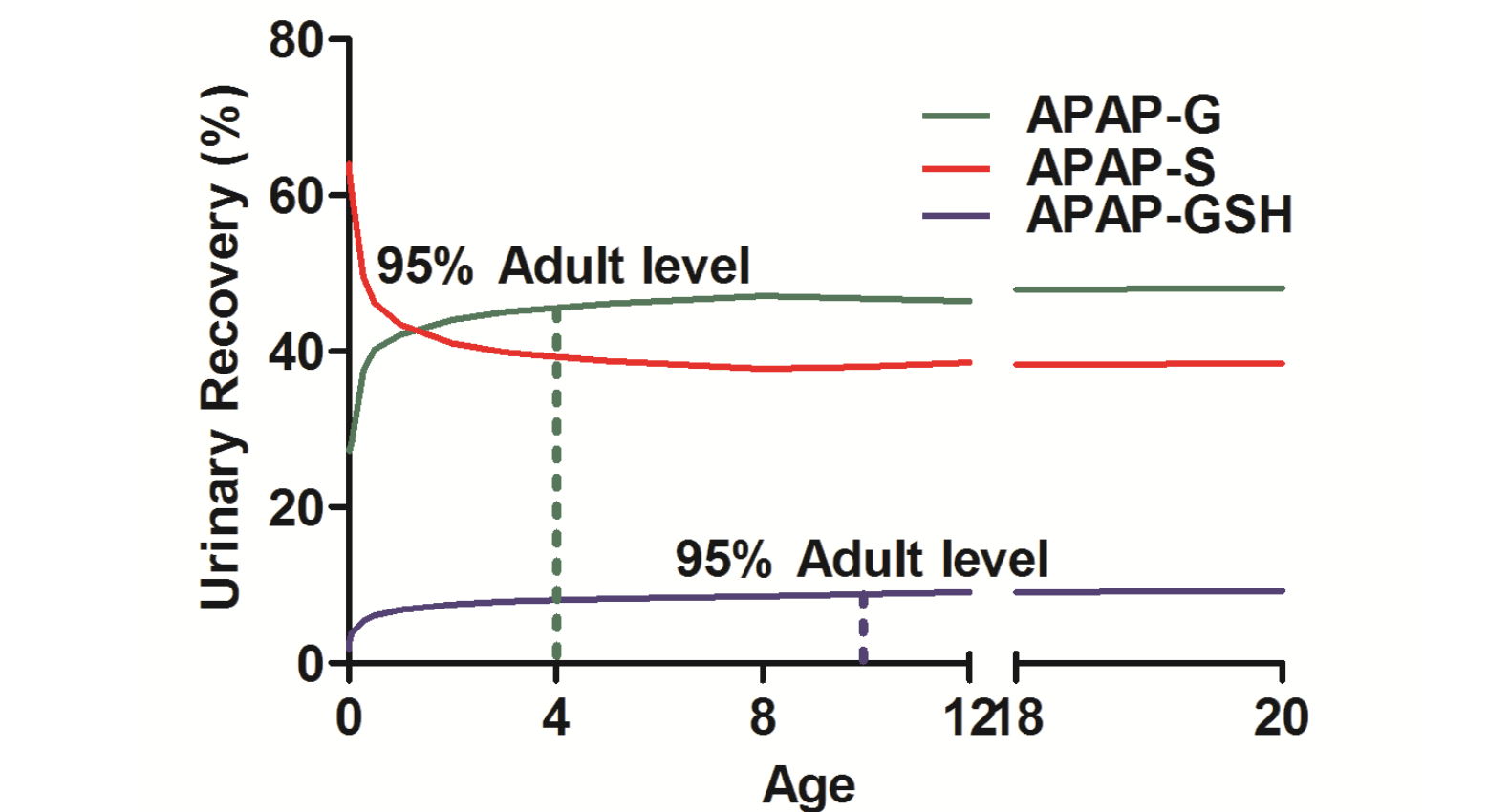


Figure 8. Simulation from the present PBPK model showed that 24 hr urinary recovered APAP-G and APAP-GSH (reflecting NAPQI generation) reached 95% adult levels at 4 and 10 years old, respectively.

CONCLUSIONS

- The developed PBPK model containing detailed information on each drug metabolizing enzyme thought to contribute to APAP metabolism successfully predicted PK and metabolic pathways of APAP in children.
- This study demonstrated the clinical utility of PBPK models for predicting PK in understudied populations, such as children, using *in vitro* data and PK data from adults.
- This APAP PBPK model may be further developed to identify subgroups which are most susceptible to APAP-induced liver injury.

ACKNOWLEDGEMENTS

- X.-L. J.* was supported in part by an appointment to the Research Participation Program at the Center for Drug Evaluation and Research administered by Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the US Food and Drug Administration and by FDA Critical Path Initiative Project "Investigation of the relative contribution of phase II drug metabolizing enzymes to acetaminophen clearance and their implications to the acetaminophen induced liver toxicity in humans with the aid of physiologically-based pharmacokinetic (PBPK) modeling".

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