

# Modelling of the Age Related Changes of Human CYP Enzymes for Predicting Drug Disposition in Neonates, Infants and Children



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## INTRODUCTION

Scaling *in vitro* data on drug metabolism to predict *in vivo* exposure to drugs in neonates, infants and children requires a detailed knowledge of developmental physiology and the ontogeny of relevant enzyme systems. The paediatric version of Simcyp® software ([www.simcyp.com](http://www.simcyp.com)) incorporates a mechanistic PBPK model for *in vitro* - *in vivo* extrapolation (IVIVE) of ADME properties (see Figure 1). The software has already been used successfully to predict drug clearance (CL) and its associated variability in neonates, infants and children<sup>1</sup>.

The aim of this study was to review the available information on hepatic CYP ontogeny and to identify the 'best models' to describe the developmental changes of the enzymes in neonates, infants and children. The sensitivity of predictions of age-related changes in CL to the models was also assessed using CYP3A-mediated CL of midazolam as an example.

## METHODS

A data base was compiled from studies of human CYP ontogeny in which either Western blotting had been used to measure CYP abundances or selective probe substrates had been used to assess CYP specific activity per mg of microsomal protein. All values were expressed as a proportion of mean adult values. Median age was used if the age range had been reported, and the data were weighted by study size. Different models were fitted to the data (using the Solver function within Microsoft Excel), including hyperbolic (HYP), sigmoidal (SIG) and logarithmic (LN) functions. The most parsimonious models were identified using the Akaike Information Criteria and visual inspection for systematic disparity with observed data. As an example, the sensitivity of predictions of midazolam clearance after intravenous administration (CL) to the different models (for CYP3A4/5 development) was assessed with regard to precision and bias.

## RESULTS

The results are summarised in Table 1. In general, the data were best described by HYP or SIG models:

$$\text{Fractional Expression} = \frac{(1 - F_{\text{birth}}) \times \text{Age}^n}{A_{50\%}^n \times \text{Age}^n} + F_{\text{birth}}$$

where  $A_{50\%}$  indicates the age at which abundance or activity reaches half of the adult value,  $F_{\text{birth}}$  is the fractional activity or abundance at birth, Age is the actual age of the children, and n reflects the steepness of the sigmoidal relationship. CYPs 1A2, 2E1 and 3A4/5 showed better fits with SIG (i.e. n = 1.41, 0.56 and 0.83, respectively) while the HYP model (n = 1) was adequate for other CYP enzymes. The data and best model fits for each CYP are shown in Figure 2. The ranking of the models with regard to the prediction of midazolam CL (Figure 3) was SIG = HYP > LN and for bias it was LN < SIG = HYP. At lower ages, the SIG model appeared superior to the LN model.

## REFERENCES

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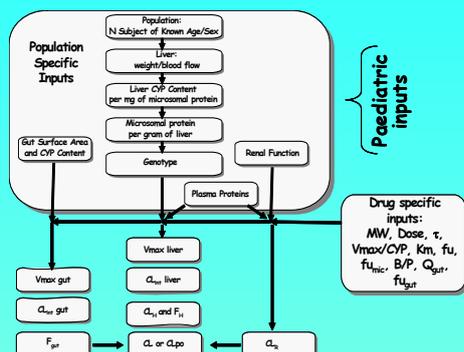


Figure 1. Schematic representation of the basic Simcyp algorithm indicating the input of data specific to paediatrics

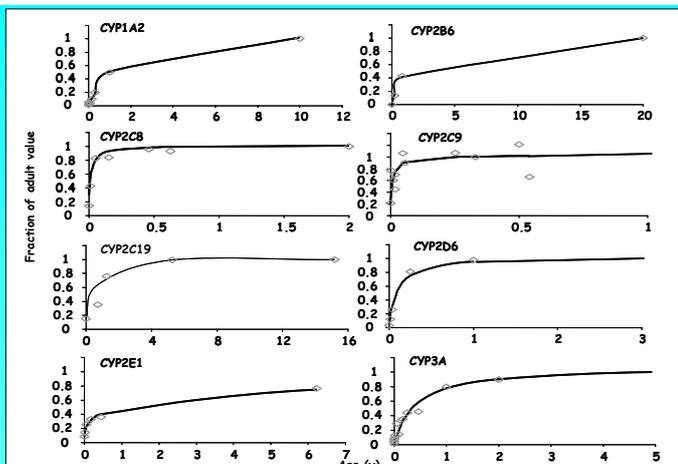


Figure 2. Age-related changes in CYP expression/activity as a fraction of adult values. Grey diamonds indicate *in vitro* data; lines are 'best' model fits (Table 1) to the experimental data.

Table 1. Summary of model fits to data on CYP ontogeny ('Best' models and associated statistics are indicated in *italics* and by *underlining*; the data in the right-hand panel refer to the 'best' models).

CYP	Model	AIC	r <sup>2</sup>	N	F <sub>birth</sub>	A <sub>50%</sub>	References
CYP1A2	HYP	-52.1	0.98	8	Negligible	0.9	2 - 4
	<u>SIG</u>	<u>-58.6</u>	<u>0.99</u>				
	LN	-7.4	0.67				
CYP2B6	HYP	-22	0.99	4	Negligible	1.31	2
	<u>SIG</u>	<u>-23</u>	<u>0.99</u>				
	LN	-23	0.99				
CYP2C8	HYP	-17.6	0.93	9	0.28	0.02	2, 5, 6
	<u>SIG</u>	<u>-16.5</u>	<u>0.90</u>				
	LN	-15.4	0.90				
CYP2C9	HYP	-7.1	0.61	14	0.18	0.01	2, 5, 6
	<u>SIG</u>	<u>-6.9</u>	<u>0.49</u>				
	LN	-6.5	0.38				
CYP2C18/19	HYP	-22.8	0.88	8	0.14	0.99	2, 5, 6
	<u>SIG</u>	<u>-21.7</u>	<u>0.87</u>				
	LN	-13.1	0.69				
CYP2D6	HYP	-24.3	0.99	6	0.036	0.101	7
	<u>SIG</u>	<u>-24</u>	<u>0.99</u>				
	LN	-5.77	0.84				
CYP2E1	HYP	-7.9	0.84	6	Negligible	0.6	8, 9
	<u>SIG</u>	<u>-22.5</u>	<u>0.98</u>				
	LN	-14.9	0.89				
CYP3A4/5	HYP	-29.2	0.96	14	Negligible	0.31	10 - 12
	<u>SIG</u>	<u>-32.9</u>	<u>0.96</u>				
	LN	-19.6	0.89				
CYP3A (Gut)	HYP	-3.4	0.99	6	0.42	2.36	13
	<u>SIG</u>	<u>-33</u>	<u>0.99</u>				
	LN	-14	0.78				

r<sup>2</sup> = Correlation Coefficient for obs vs pred values, N = number of age groups, F<sub>birth</sub> = fractional activity or abundance at birth compared to adults, A<sub>50%</sub> = age (yr) at which 50% of adult activity or expression is reached.

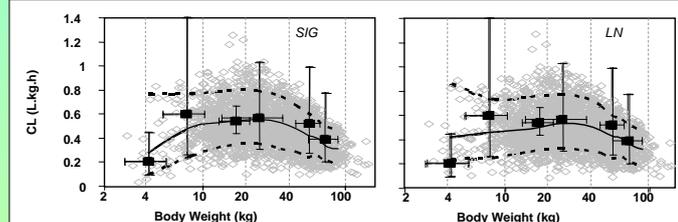


Figure 3. Changes in weight normalised midazolam clearance versus body weight predicted by SIG and LN models. The grey data points indicate data for 2000 virtual subjects; the solid and dashed lines are median predicted clearance and its 95% CL, respectively; the data points and error bars represent mean and 95% CL values from *in vivo* studies.

## DISCUSSION

Based on the limited data that are currently available, we have defined models that described the development of major human CYPs from birth to adulthood. These models may not be optimal pending the availability of extended data from larger numbers of livers, particularly with respect to CYPs 2B6, 2C8 and 2C18. Also, further studies are needed with additional substrates to clarify the influence of different CYP ontogeny models on the outcome of IVIVE.