

Changes in the Relative Contribution of Hepatic Metabolism and Glomerular Filtration to Total Plasma Clearance in Children Younger than Four Years of Age; When is Scaling for the Dominant Elimination Route in Adults Appropriate?

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Background and Objective

Common pediatric clearance (CL) scaling approaches rely on maturation functions for the dominant elimination route (e.g., route with >50% elimination) in adults. This study explores whether hepatic metabolism can be assumed to remain dominant (>50%) in children younger than 4 years for drugs that are predominantly cleared in adults through hepatic metabolism with glomerular filtration being the minor CL pathway in adults.

Methods

A PBPK-based simulation framework was adapted from Calvier *et al.* [1] in R (v4.4.3) to predict absolute and relative CL through hepatic metabolism (CL_h) and CL through glomerular filtration (CL_{GFR})

- Hypothetical drugs:
 - Exclusive binding to human serum albumin (HSA) or α1-acid glycoprotein (AGP)
 - f_u in adults of 1%, 25%, 50%, 75%, or 99%
 - Intrinsic microsomal clearance (CL_{int,mic}) selected to yield CL_h in adults of 90% (scenario 1) or 70% (scenario 2)
 - Partition coefficient for red blood cells of 1
- System models for CL predictions:
 - CL_h calculated based on unbound drug fraction (f_u), whole-liver intrinsic clearance (CL_{int}), blood-to-plasma ratio (B:P), and hepatic blood flow (Q_h) using the dispersion model
 - CL_{GFR} calculated as product of glomerular filtration rate (GFR) and f_u
- Virtual population:
 - A typical adult of 25 years and typical pediatric individuals of 1 day, 2 weeks, 1 month, 6 months, 1 year, 2 years, and 4 years of age, all assumed to be born at term, for which:
 - average weights and heights from males and females were obtained from CDC growth charts [2]
 - body Surface Area (BSA) was calculated according to Haycock [3] for children ≤15 kg and according to Du Bois and Du Bois [4] for the heavier children and the adult.
 - age-related changes in f_u were calculated based on changes in expression of HSA and AGP, changes in B:P were calculated based on changes in f_u and hematocrit, and changes in Q_h were calculated based on changes in cardiac output, all according to Johnson *et al.* [5].
 - age-related changes in GFR were calculated according to Salem *et al.* [6].
 - age-related changes in CL_{int} were calculated based on changes in liver volume (LV) [5], changes in milligram protein per gram of liver (MPPGL) according the Simcyp V15.R1 library, and an age-specific enzyme maturation factor (MF)
 - The MF was 1 for the typical adult; for the pediatric individuals two scenarios were explored representing drugs that were substrates for:
 - Hypothetical isoenzymes with constant maturation in pediatric individuals at 100%, 75%, 50%, 25%, 10%, 5%, or 0.5% of adult values
 - CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, SULT1A1, UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 with maturation according to the Simcyp V15.R1 library or Hines [7].

Results

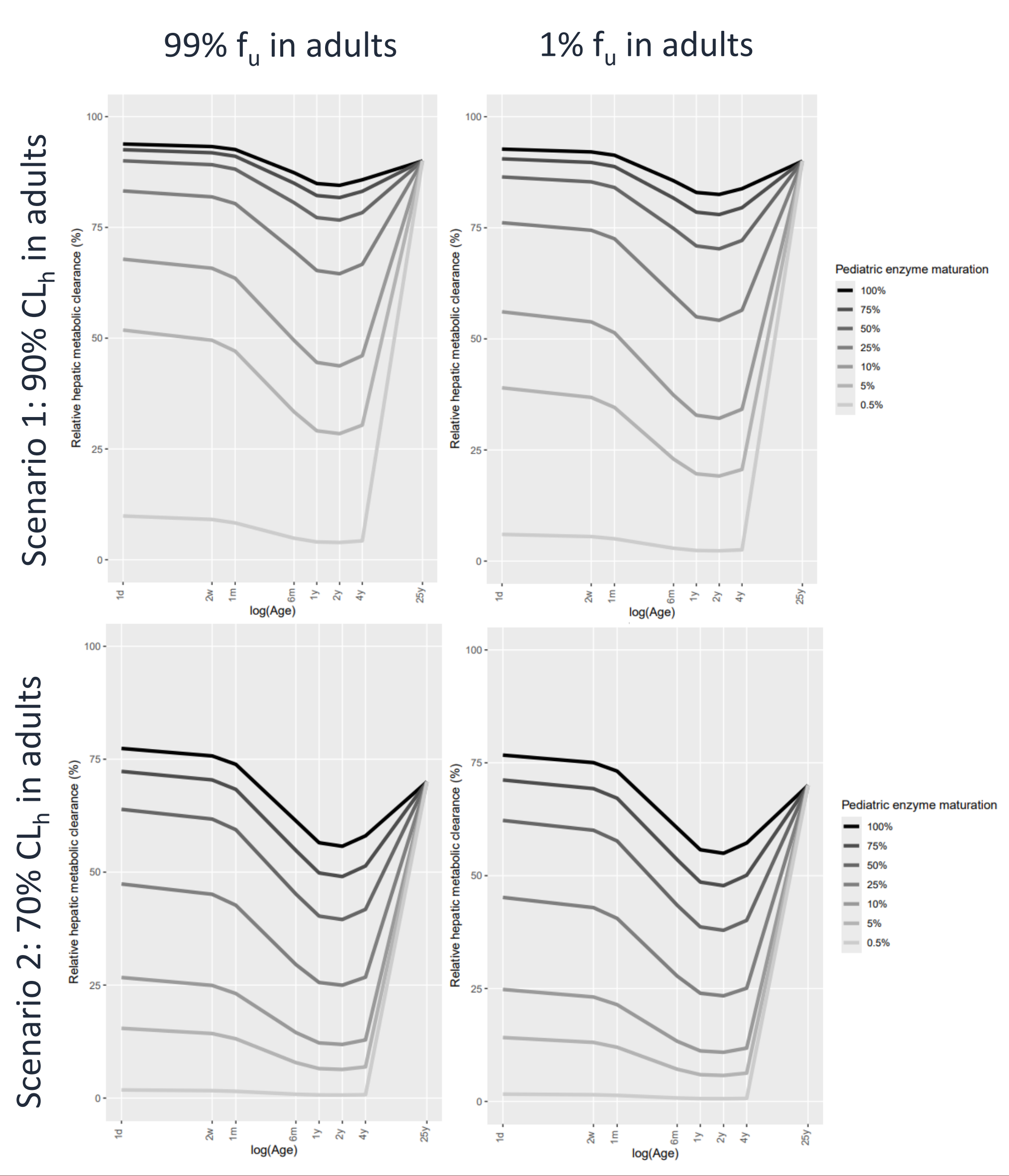


Figure 1: Relative contribution of CL_h to total CL for drugs that are substrates for hypothetical isoenzymes with constant pediatric enzyme maturation (MF) that bind 1% (left) or 99% (right) to HSA in adults.

- When CL_h in adults is 90% of total CL (scenario 1, top), CL_h remains dominant throughout childhood, when MF remains at or above 25%.
- When CL_h in adults is 70% of total CL (scenario 2, bottom), CL_h is not dominant between the ages of 1 – 4 years, when MF is at or below 75%, and it is not dominant at all ages below 4 years when MF is at or below 50%.
- Very similar results were obtained for drugs binding to AGP

Results (ctd)

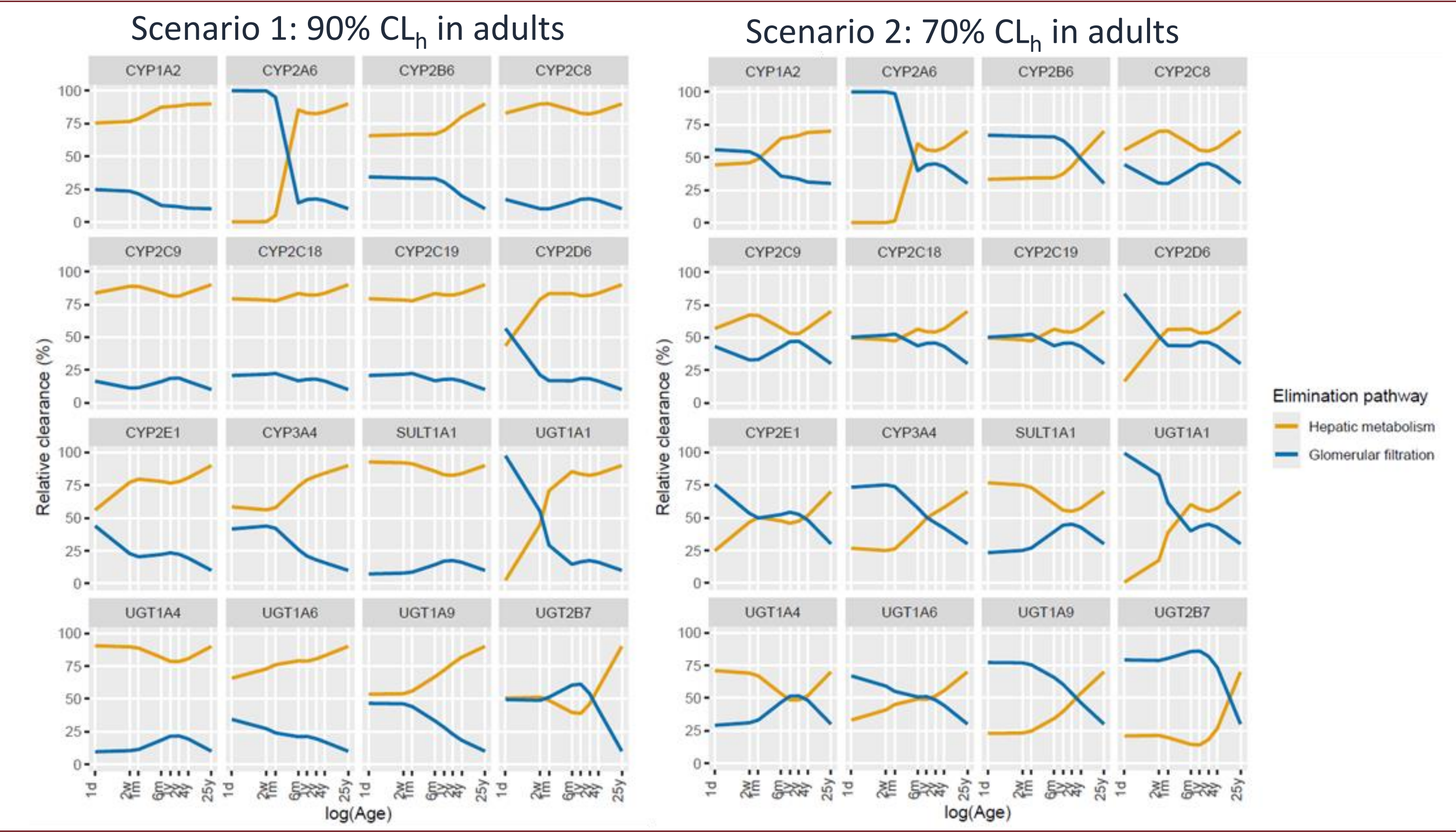


Figure 2: Relative contribution of CL_h and CL_{GFR} to total CL for drugs with 90% (left) or 70% (right) CL_h in adults, binding to HSA with an f_u in adults of 1%.

- when CL_h in adults is 90% (scenario 1), CL_h will remain dominant throughout childhood for substrates of most isoenzymes, except for substrates of CYP2A6, CYP2D6, UGT 1A1, and UGT2B7.
- when CL_h in adults is 70% (scenario 2), CL_h will remain dominant throughout childhood only for substrates of CYP2C8, CYP2C9, and SULT1A1

Scenario 1: 90% CL _h in adults	Isoenzymes	1 day	2 weeks	1 month	6 months	1 year	2 years	4 years
	CYP1A2	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2A6	GF	GF	GF	Hep	Hep	Hep	Hep
	CYP2B6	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2C8	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2C9	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2C18	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2C19	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2D6	GF / Hep*	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2E1	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP3A4	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	SULT1A1	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	UGT1A1	GF	GF	Hep	Hep	Hep	Hep	Hep
	UGT1A4	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	UGT1A6	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	UGT1A9	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	UGT2B7	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*
Scenario 2: 70% CL _h in adults	Isoenzymes	1 day	2 weeks	1 month	6 months	1 year	2 years	4 years
	CYP1A2	GF	GF	GF / Hep*	Hep	Hep	Hep	Hep
	CYP2A6	GF	GF	GF	Hep	Hep	Hep	Hep
	CYP2B6	GF	GF	GF	GF	GF	GF	GF / Hep*
	CYP2C8	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2C9	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	CYP2C18	GF / Hep*	GF / Hep*	GF / Hep*	Hep	Hep	Hep	Hep
	CYP2C19	GF / Hep*	GF / Hep*	GF / Hep*	Hep	Hep	Hep	Hep
	CYP2D6	GF	GF / Hep*	Hep	Hep	Hep	Hep	Hep
	CYP2E1	GF	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*
	CYP3A4	GF	GF	GF	GF	GF / Hep*	GF / Hep*	Hep
	SULT1A1	Hep	Hep	Hep	Hep	Hep	Hep	Hep
	UGT1A1	GF	GF	GF	Hep	Hep	Hep	Hep
	UGT1A4	Hep	Hep	Hep	Hep	GF / Hep*	GF / Hep*	Hep
	UGT1A6	GF	GF	GF / Hep*	GF / Hep*	GF / Hep*	GF / Hep*	Hep
	UGT1A9	GF	GF	GF	GF	GF	GF	Hep
	UGT2B7	GF	GF	GF	GF	GF	GF	GF

Table 1: Summary overview of whether hepatic metabolism (HEP) or glomerular filtration (GF) is the major elimination pathway in children for drugs metabolized by the indicated isoenzyme with CL_h in adults of 90% (top) or 70% (bottom), binding between 1 and 99% to either HSA or AGP.

* CL_h and CL_{GFR} fluctuate around 50% with CL_{GFR} becoming more dominant when the f_u in adults is lower.

Conclusions

- When CL_h is 90% of total CL in adults, CL_h remains dominant throughout childhood for substrates of most, but not all, isoenzymes.
- When CL_h is 70% of total CL in adults, CL_h will not remain dominant for at least part of the pediatric age-range for substrates of most, but not all, isoenzymes.
- When CL_h is not dominant in children, scaling for the CL route that is dominant (>50%) in adults will yield underprediction of CL unless the contribution of alternative routes are taken into account.

References

[1] Calvier *et al.* Clin Pharmacokinet. 2017 Mar;56(3):273-285; [2] <https://www.cdc.gov/growthcharts/cdc-growth-charts.htm>; [3] Haycock. J Pediatr. 1978 Jul;93(1):62-6.; [4] Du Bois and Du Bois, Archives of Internal Medicine, 17, 863-871. [5] Johnson *et al.*, Clin Pharmacokinet. 2006;45(9):931-56; [6] Salem *et al.*, Clin Pharmacokinet. 2014;53(7):625–36; [7] Hines, Pharmacol Ther. 2008 May;118(2):250-67.