“First dose in children”: comparing allometric scaling and PBPK

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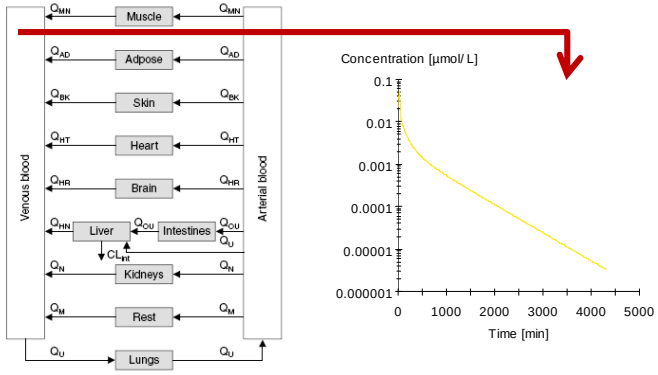
Introduction: “first dose in children”

- Estimation of first dose in children is dependent on scaling from adults of the:
  - Pharmacokinetics (almost always!)
  - Pharmacodynamics (when indication, disease process and outcome of the therapy are unlikely or unknown to be comparable between adults and children)

- For scaling of the pharmacokinetics, mainly two approaches can be applied:
  - PBPK
  - Allometric scaling *plus* maturation function

Introduction: scaling pharmacokinetics

PBPK



- Differences in PK between adults and children are explained by anatomical and physiological age related changes
- Predictions of concentration-time curves at different ages

Allometric scaling + maturation function

$$CL_{children} = CL_{adults} \cdot \left(\frac{Weight_{children}}{Weight_{adults}} \right)^{0.75} \cdot AS\ maturation$$

- Differences in clearance between adults and children are explained by size and maturation function that accounts for developmental changes during early life
- AS maturation functions have been established using paediatric clinical data
- Physiological understanding on the AS maturation functions is currently lacking

Objectives

- Provide insight into
  - the physiological meaning of the AS maturation functions of the clearance pathways
  - the interchangeability of PBPK and allometric scaling + maturation function

- This investigation focused on the AS maturation functions established using paediatric clinical data of paracetamol and morphine

Drug	Metabolic route	Lipophilicity	CL blood flow perc. (%)	CL liver diffusion perc. (%)	Free fraction	MW	Extraction ratio
Paracetamol	UGT1A6 (58%) Sulfation (29%) CYP2E1 (10%) Renal (3%)	0.46	21	0	0.82	151.2	0.27
Morphine	UGT2B7 (90.5%) CYP3A4 (5%) Renal (4.5%)	0.89	96	78	0.75	285.3	0.51

First step

Does AS maturation function fully represent enzyme activity?

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Methods

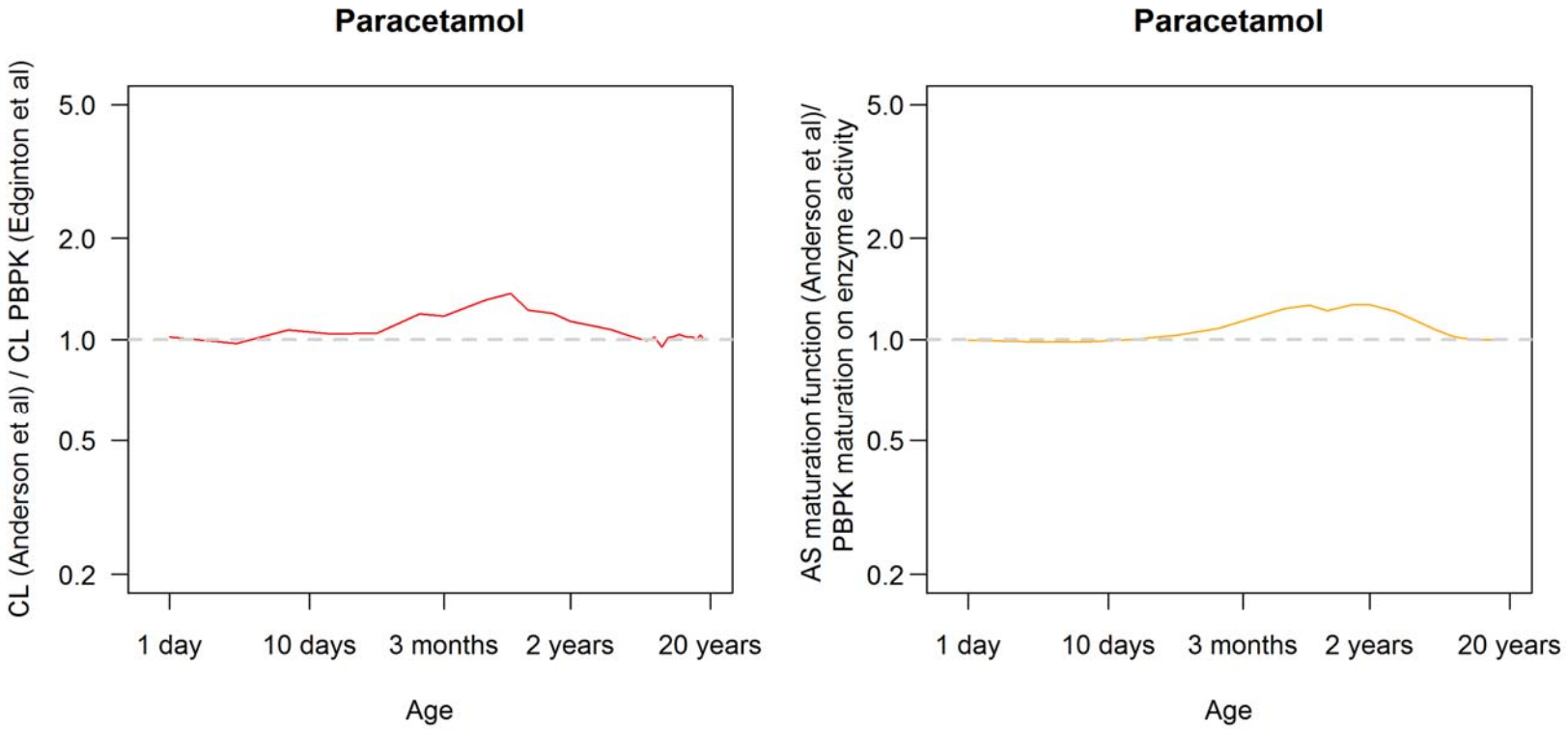
Paracetamol and morphine were used as case drugs

1. Comparison of clearance
   - predictions using PBPK models[1]
   - estimates from popPK models describing paediatric clinical data [2,3]

2. Comparison of maturation functions
   - of enzyme activity as described by PBPK models (PKSim®)
   - established using popPK models to describe the developmental changes in clearance during early life [2,3]

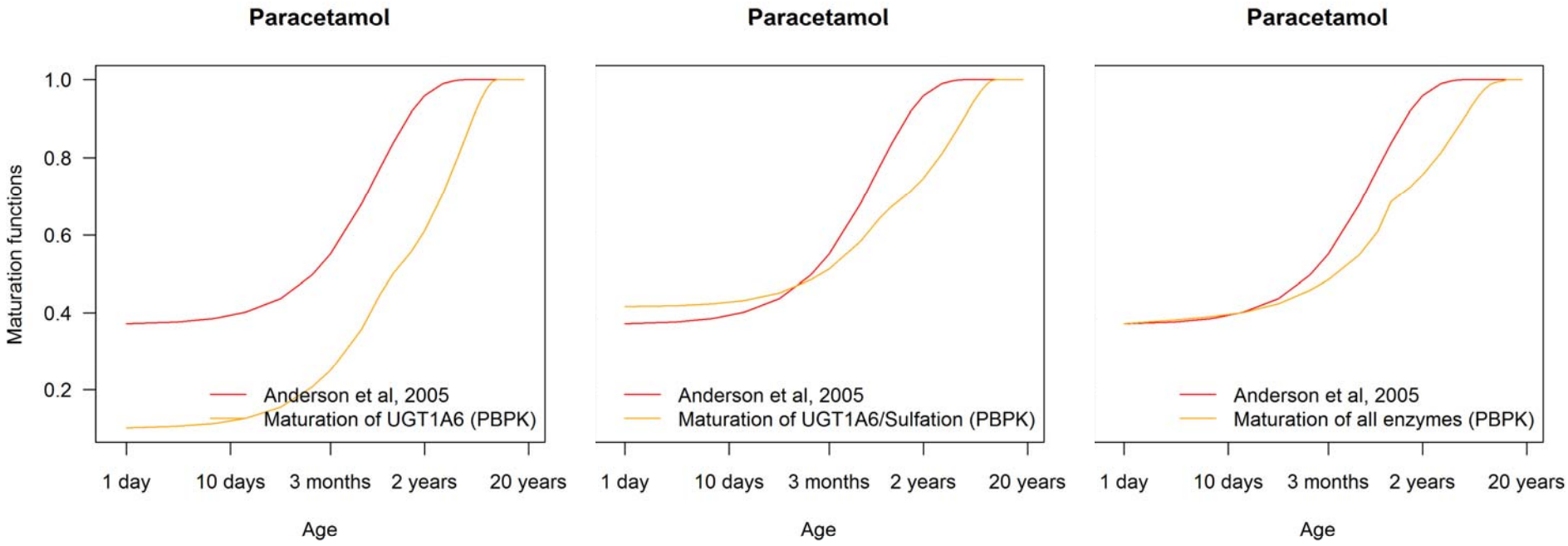
[1] Edginton *et al* Clin Pharmacokinet. 2006;45(10):1013-34
[2] Anderson *et al,* 2005 Pediatric Anesthesia 15:282-292
[3] Anand *et al*, 2008 British Journal of Anesthesia 101:680-689

Does maturation function fully represent enzyme activity?



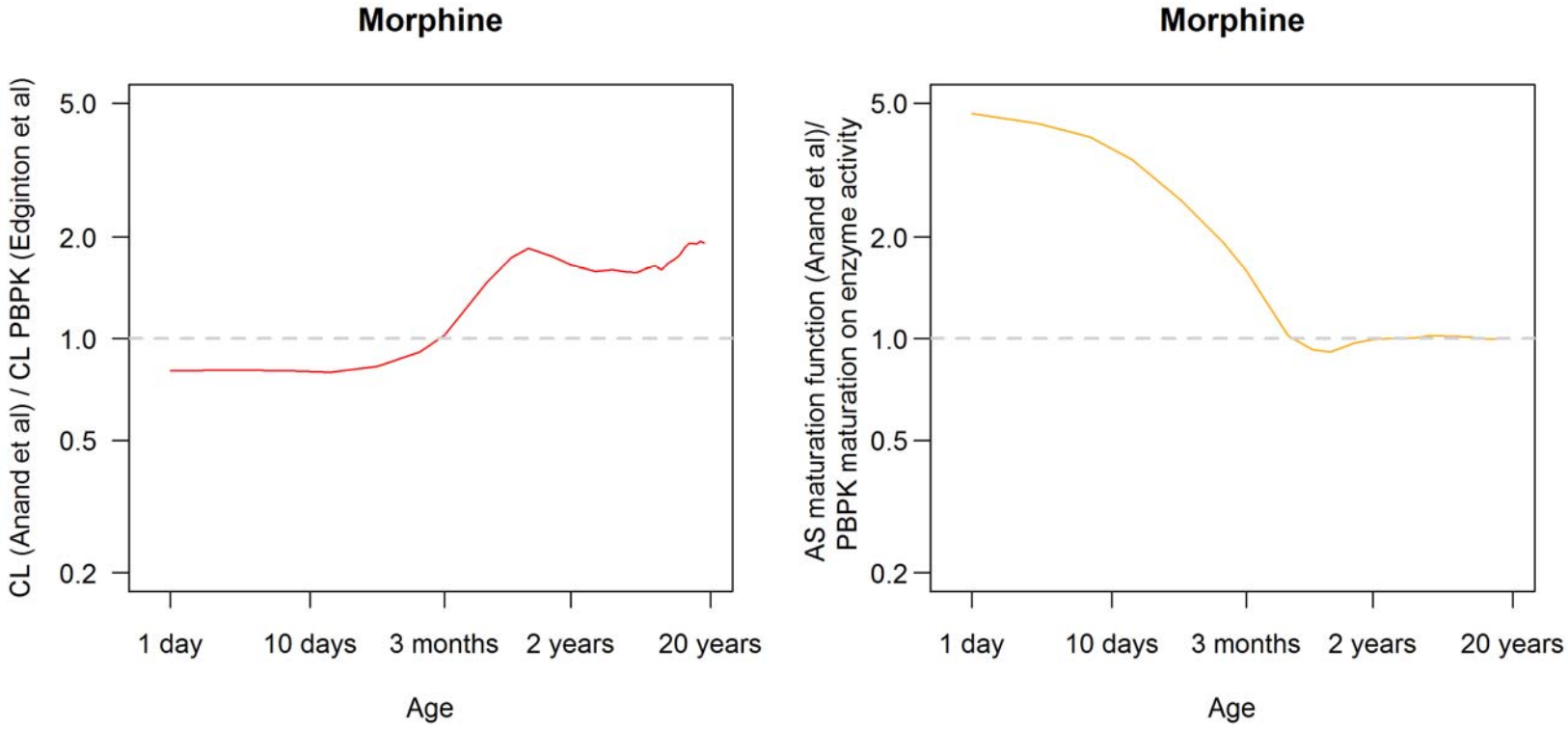
- The AS maturation function established using paracetamol paediatric data represents maturation of liver enzyme → in agreement with low extraction ratio

What are the main liver enzymes relevant for AS maturation function?



- The AS maturation function mainly represents UGT1A6/Sulfation (65/35)
- Role of sulfation cannot be neglected, whereas the role of CYP2E1 and renal clearance can be neglected when extrapolating AS maturation funtion to other drugs

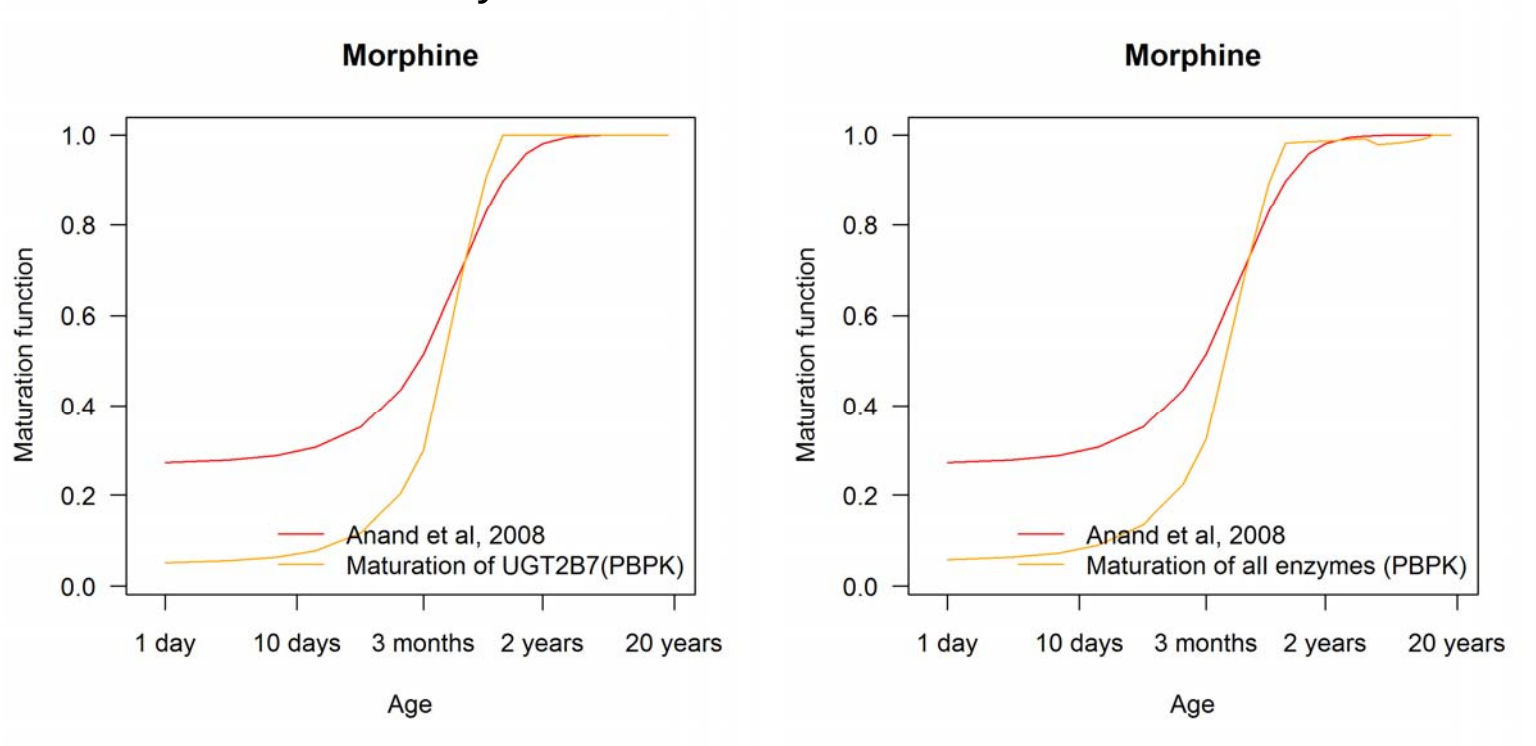
Does maturation function fully represent enzyme activity?



- The AS maturation function established using morphine paediatric data does not only represent maturation of liver enzyme → in agreement with intermediate extraction ratio

What are the main liver enzymes relevant for AS maturation function?

- Assumption: AS maturation function at least partially represented by maturation of the enzymes



- The AS maturation function mainly represents UGT2B7
- Role of CYP3A4 and renal clearance can be negleted when extrapolating the AS maturation function to other drugs

Second step

When does extrapolation of AS maturation function to other drugs lead to interchangeable predictions when compared to PBPK?

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Methods (1)

1. PKSim® was used to **create hypothetical drugs** with different PK properties and similar metabolic routes as the case drugs

Drug	Metabolic route	Lipophilicity	CL blood flow perc. (%)	CL liver diffusion perc. (%)	Free fraction	MW	Extraction ratio	N
Paracetamol	UGT1A6 (58%) Sulfation (29%) CYP2E1 (10%) Renal (3%)	0.46	21	0	0.82	151.2	0.27	
Hypotheticals	UGT1A6 (65%) Sulfation (35%)	0.46	10, 50, 90	10, 50, 90	0.05, 0.50, 0.95	96 - 865	0.0056 – 0.91	17
Hypotheticals	UGT1A6 (65%) Sulfation (35%)	1	10, 50, 90	10, 50, 90	0.05, 0.50, 0.95	185 - 600	0.017 - 0.89	14
Hypotheticals	UGT1A6 (65%) Sulfation (35%)	2	50, 90	10	0.05, 0.50, 0.95	370 - 667	0.074 – 0.72	6
Morphine	UGT2B7 (90.5%) CYP3A4 (5%) Renal (4.5%)	0.89	96	78	0.75	285.3	0.51	
Hypotheticals	UGT2B7	0.89	10, 50, 90	10, 50, 90	0.05, 0.50, 0.95	144 - 446	0.055 – 0.90	15

Hypothetical drugs with unrealistic MW (<90 and >1000) were excluded from the analysis

Methods (2)

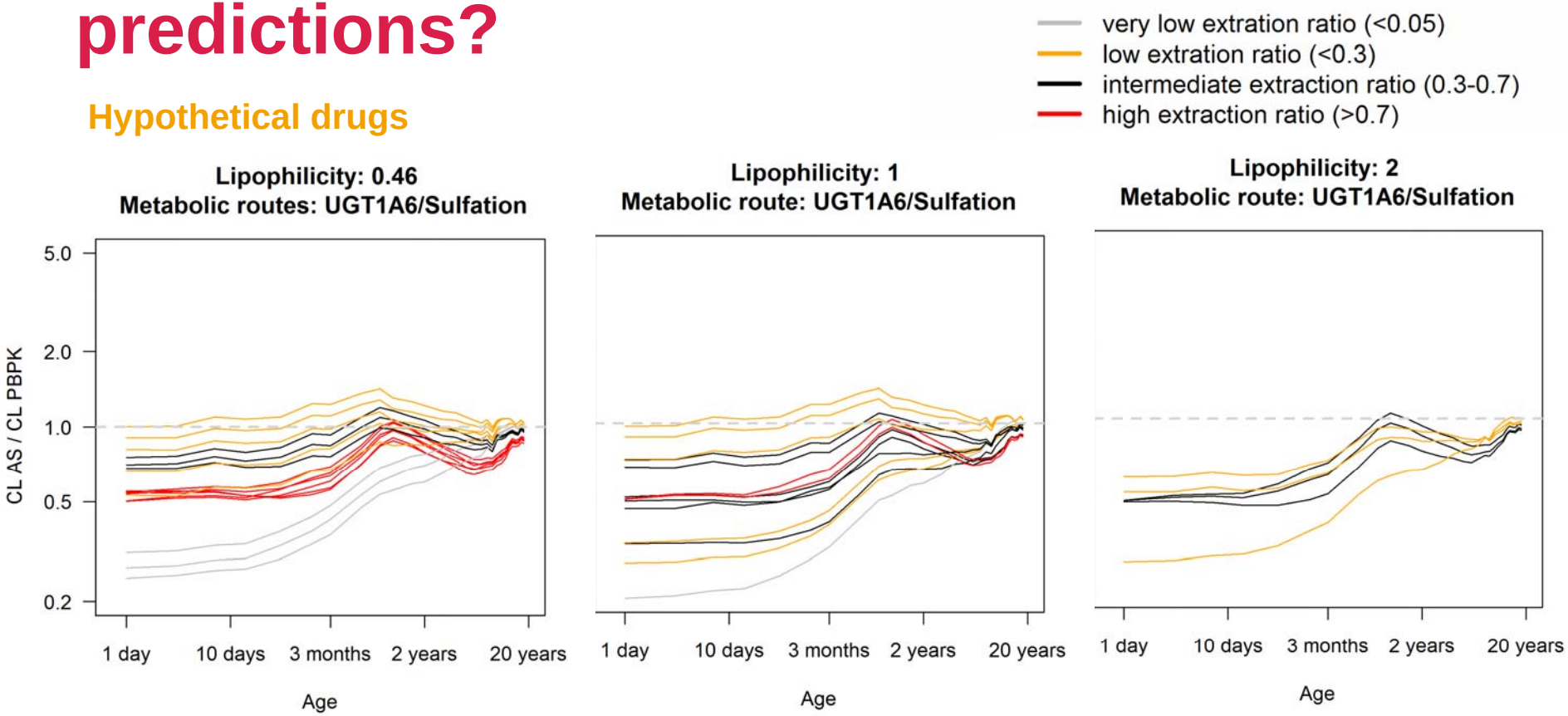
2. **PBPK** model (PKSim®) was used to predict the PK of the hypothetical drugs in children
   - by considering anatomical and physiological age related changes
   - the clearance was derived from the predicted PK curves

3. **Allometric scaling + maturation function** was used to predict the clearance of the hypothetical drugs in children
   - by considering weight and maturation as observed for the case-drugs
   - the clearance was predicted based on the clearance in adults for each hypothetical drug

$$CL_{children} = CL_{adults} \cdot \left(\frac{Weight_{children}}{Weight_{adults}} \right)^{0.75} \cdot AS\ maturation$$

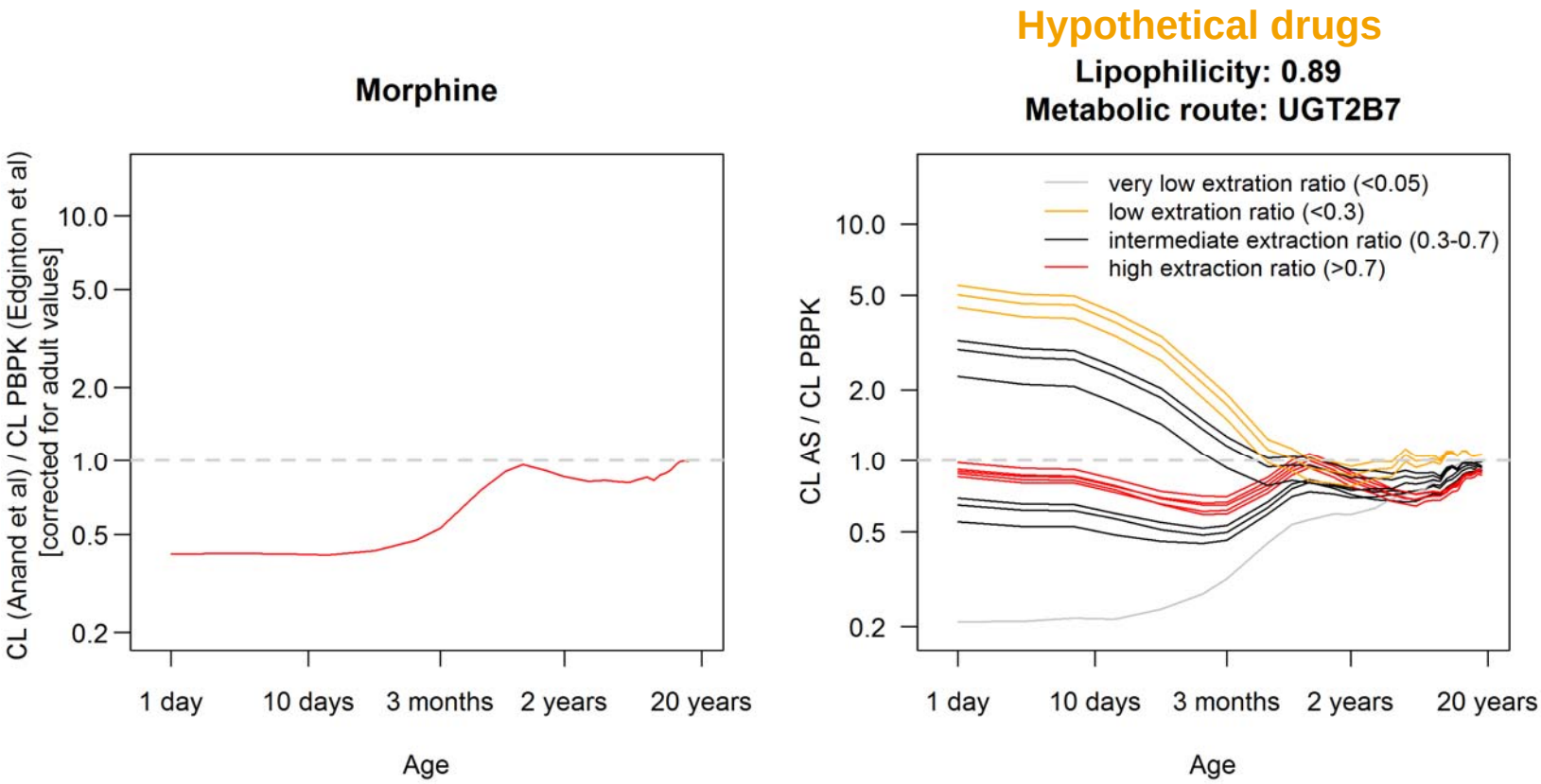
When does extrapolation of AS maturation function lead to interchangeable predictions?

Hypothetical drugs



- Extrapolation of AS maturation function to drugs with similar metabolic routes, but different PK properties does not always lead to interchangeable clearance predictions when compared to PBPK. Major differences were observed in children < 3 mo
- Interchangeability was only observed for drugs with similar metabolic route, extraction ratio and lipophilicity as paracetamol

When does extrapolation of AS maturation function lead to interchangeable predictions?



- On the contrary of paracetamol, interchangeability was only observed for some of the drugs with similar metabolic route, extraction ratio and lipophilicity as morphine

Discussion

- This investigation provides insights into the physiological meaning of the AS maturation functions
  - AS maturation functions not solely represent maturation of enzyme activity, but also aggregate multiple specific drug-related PK properties
  - Allometric scaling + maturation function and PBPK are not always interchangeable probably due to over-simplification of the physiological meaning of the AS maturation function when used for extrapolation of other drugs
- Implications for the “first dose in children”
  - Methodological uncertainty should be addressed in the risk-benefit assessment of the first dose in children
  - Extensive validation of both approaches with paediatric clinical data is required to allow improvement of the predictability and enhanced assessment of the uncertainties