DEVELOPMENTAL PK/PD: WHAT HAVE WE LEARNT?

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SIMCYP

UNDERSTANDING AND PREDICTING PK/PD IN JUVENILES

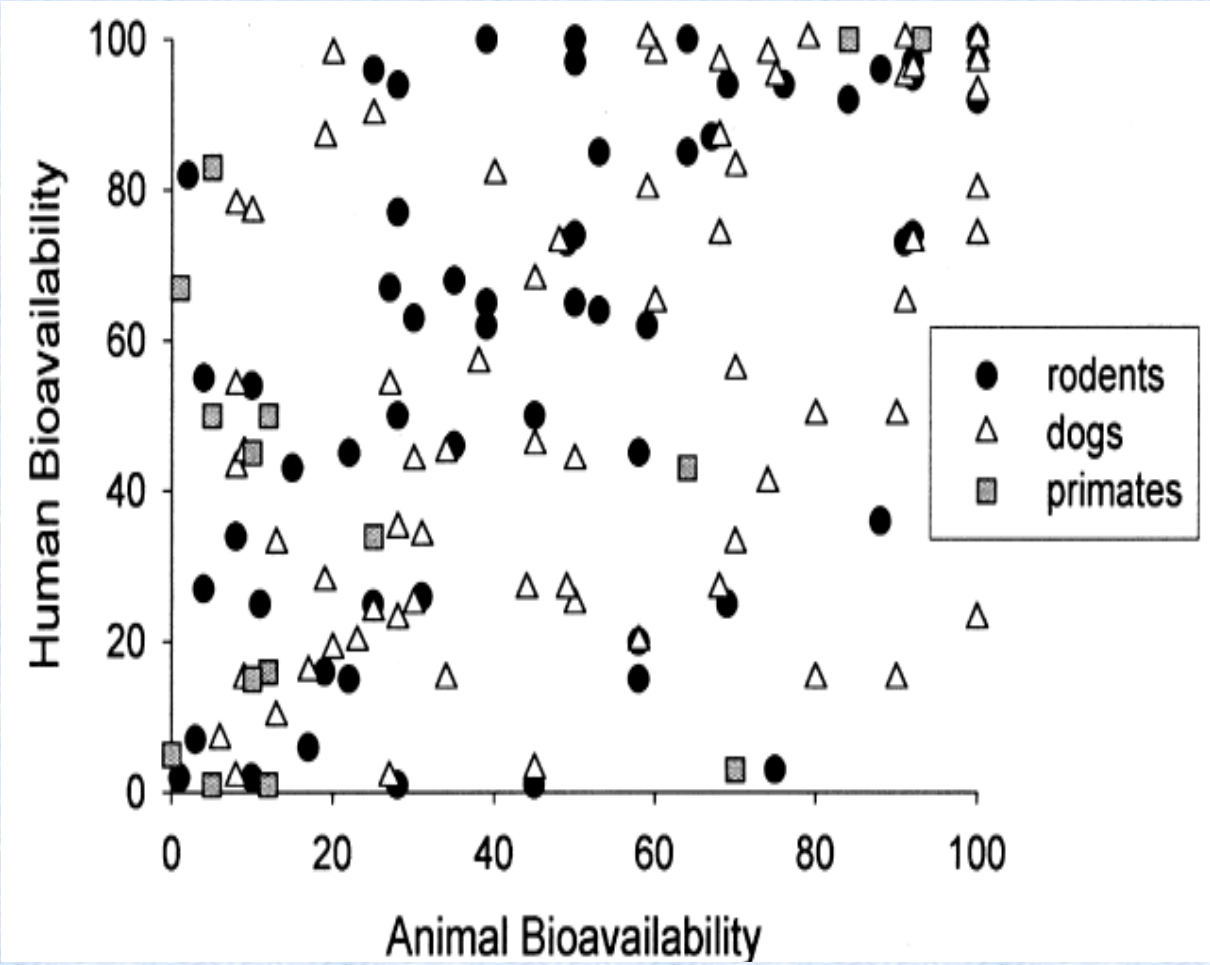
PHARMACOKINETICS

Can we scale from juvenile animals?

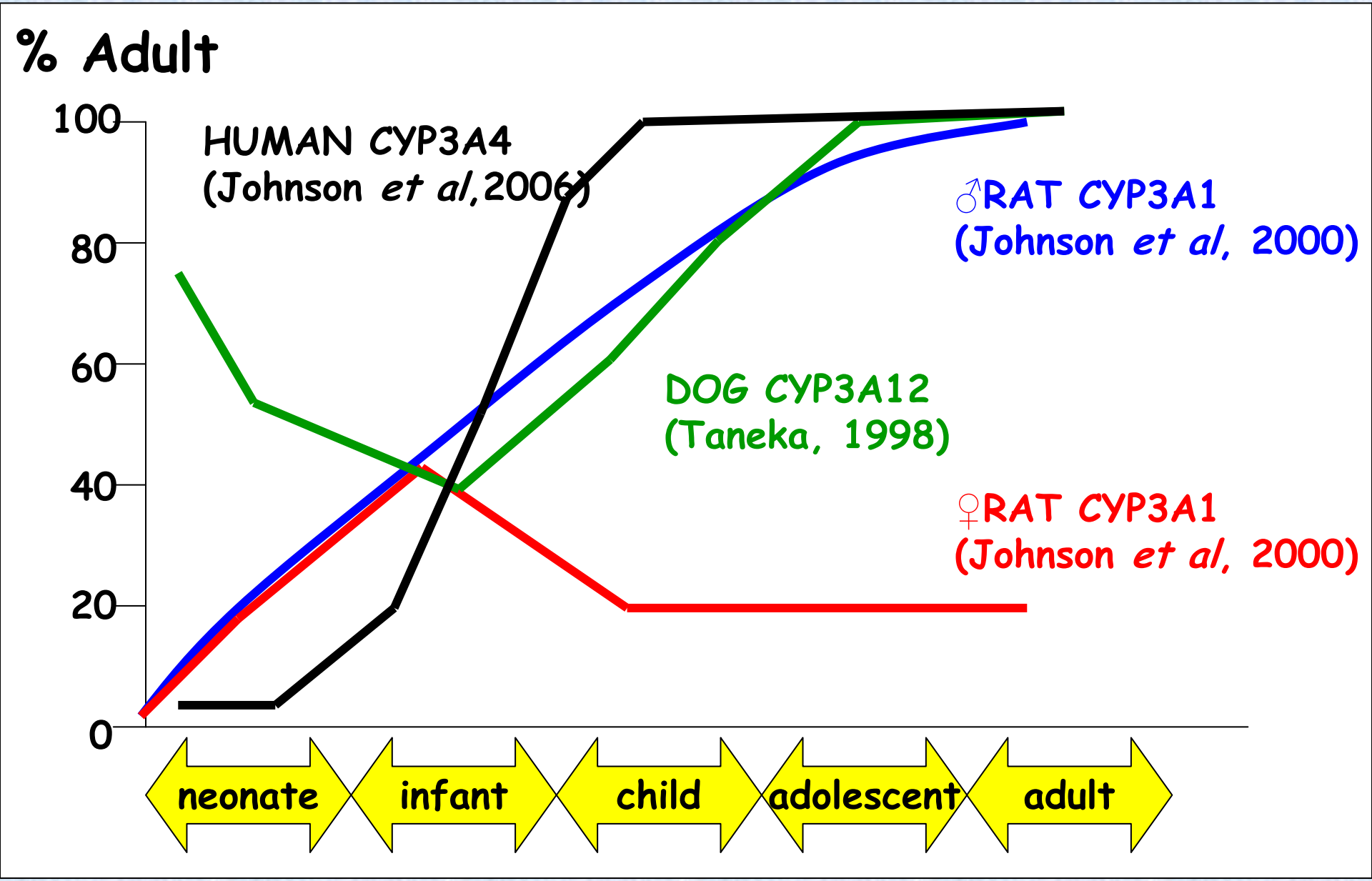
Can we scale from allometry?

Can we scale from *in vitro*?

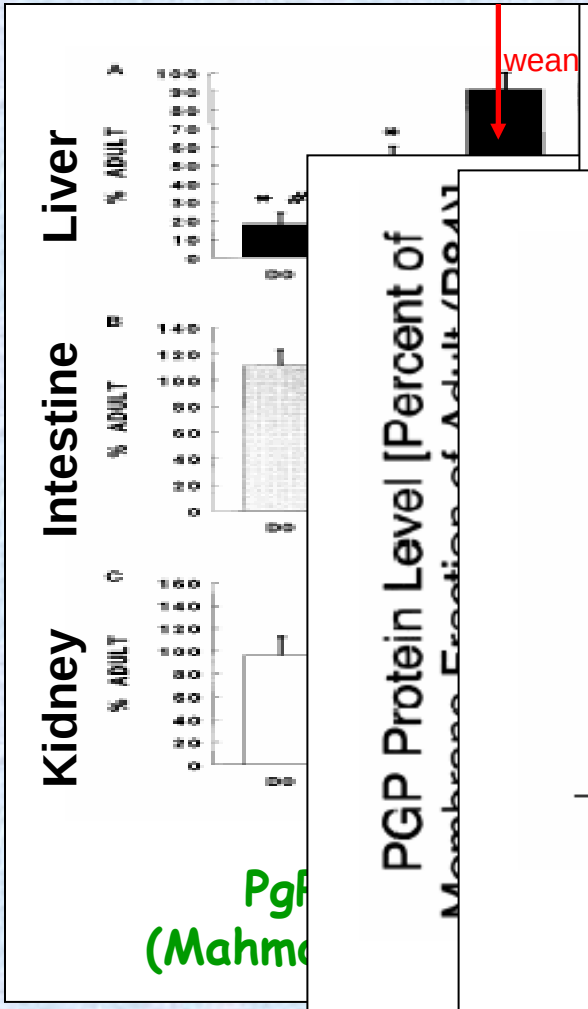
ORAL BIOAVAILABILITY



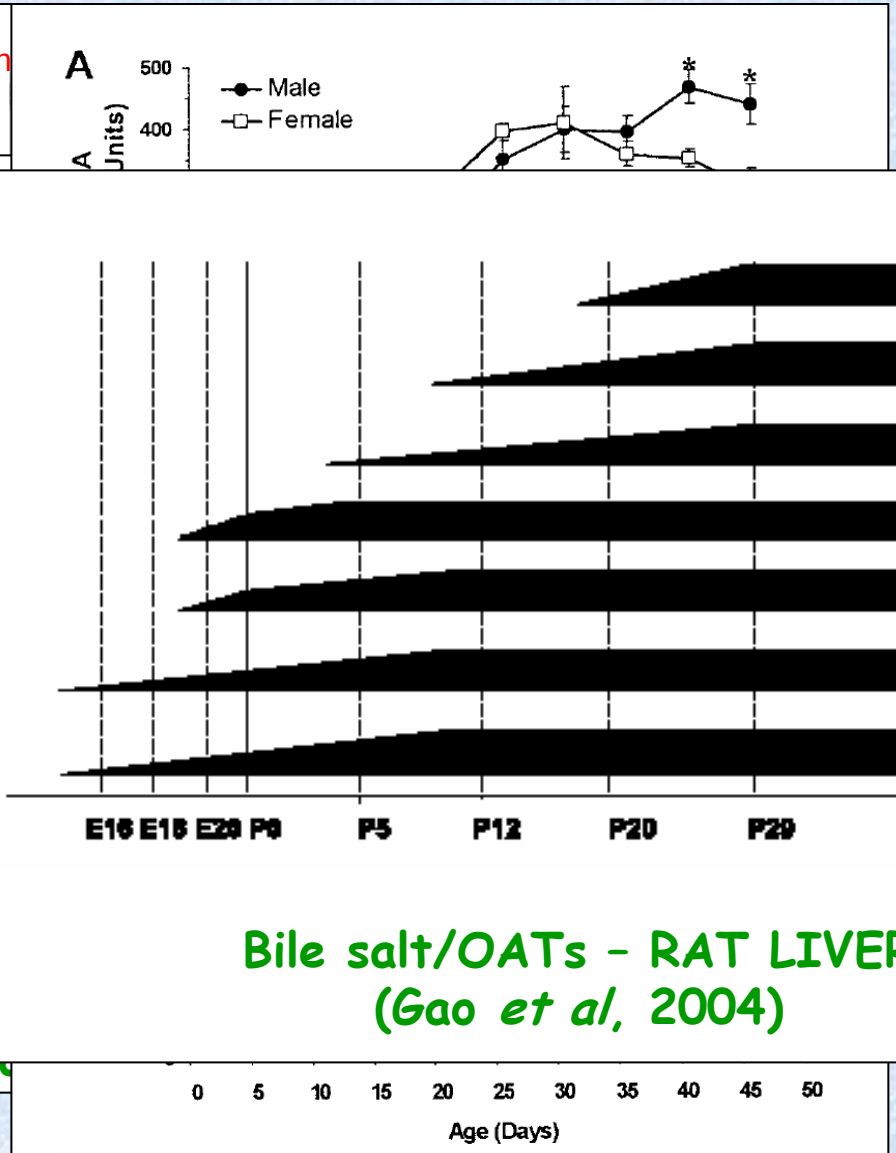
From Grass & Sinko (*Adv Drug Deliv Rev, 2002*) from Sietsema (*Int J Clin Pharmacol Ther Toxicol, 1989*)


% Adult
100
80
60
40
20
0
HUMAN CYP3A4
(Johnson et al,2006)
♂RAT CYP3A1
(Johnson et al, 2000)
DOG CYP3A12
(Taneka, 1998)
♀RAT CYP3A1
(Johnson et al, 2000)
neonate
infant
child
adolescent
adult

ONTOGENY OF TRANSPORTERS (ANIMALS)



PgP
(Mahm



OATs – RAT KIDNEY
(Buist *et al*, 2002)

Bile salt/OATs – RAT LIVER
(Gao *et al*, 2004)

PHARMACOKINETICS

Can we scale from juvenile animals?

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"THE 3/4 (Klieber's) LAW"

From allometric principles:

$$\text{Metabolic Rate} \propto BW^{0.75}$$

$$\text{Clearance} \propto BW^{0.75}$$

Holford – "A size standard for pharmacokinetics"
Clin Pharmacokin 30: 392-32, 1996

"THE 3/4 (Klieber's) LAW"

From measurements in 5036 N.Europeans, N.Americans and Japanese:

$$\text{Liver Volume} = 0.722 \times \text{BSA}^{1.176}$$

$$\text{BSA} \propto \text{BW}^{0.67}$$

$$\text{Liver Volume} \propto \text{BW}^{0.78}$$

$$\text{Clearance} \propto \text{BW}^{0.78}$$

Johnson *et al* – "Changes in liver volume from birth to adulthood: a meta-analysis"
Liver Transpl 11: 1481-93, 2005

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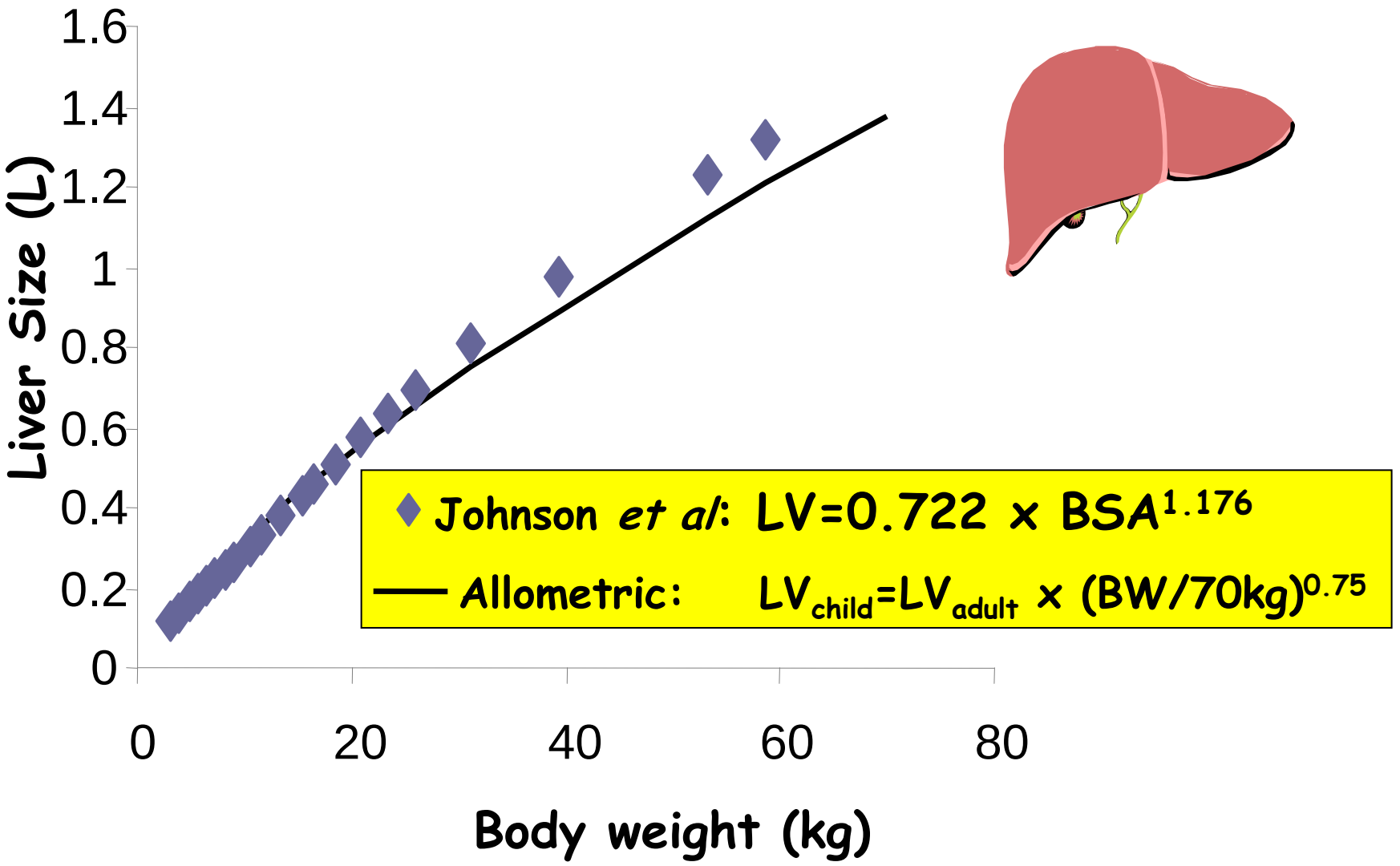
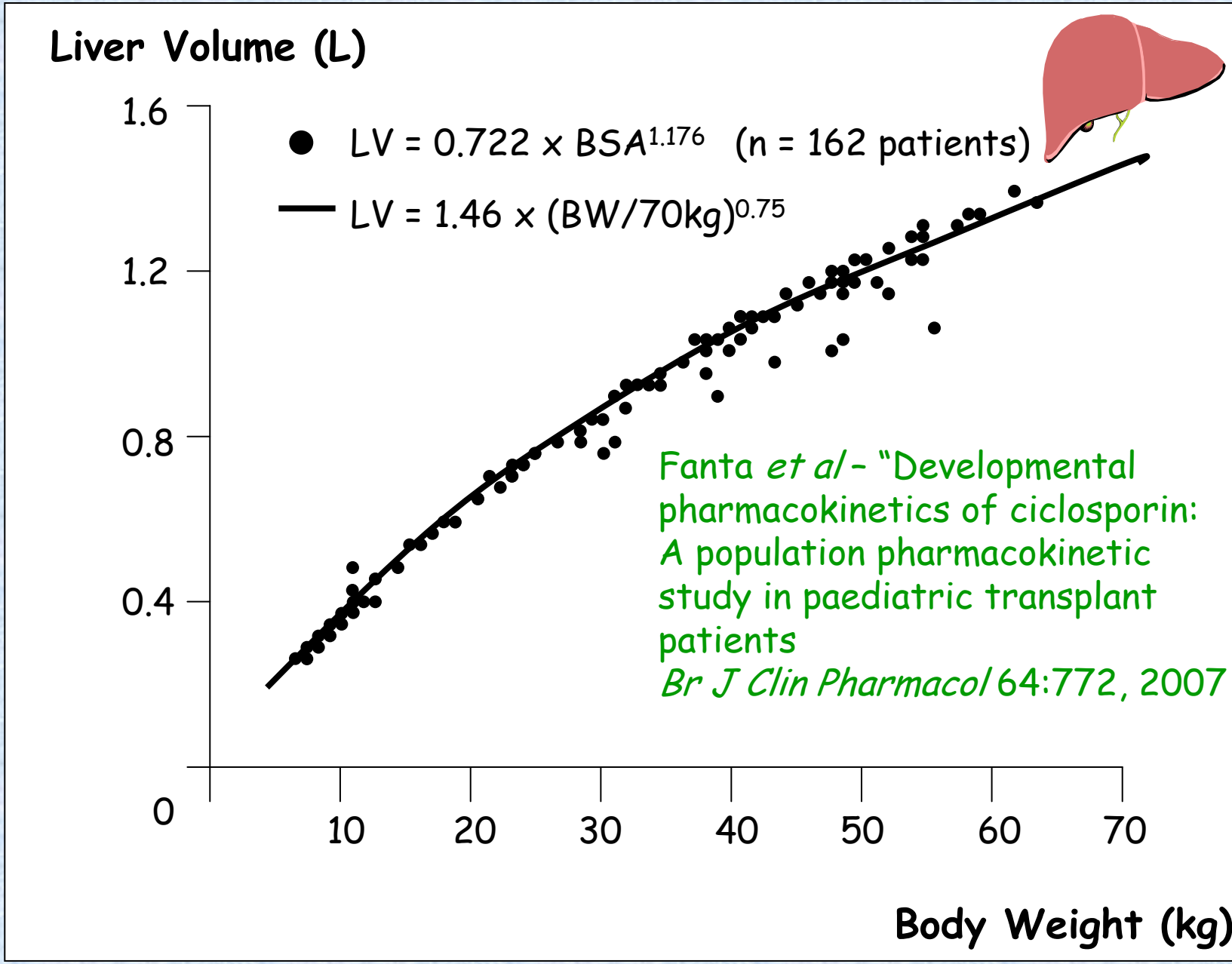

Liver Size (L)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
20
40
60
80
Body weight (kg)
Johnson et al: LV=0.722 x BSA1.176
Allometric: LVchild=LVadult x (BW/70kg)0.75


Liver Volume (L)
1.6
1.2
0.8
0.4
0
LV = 0.722 x BSA^1.176 (n = 162 patients)
LV = 1.46 x (BW/70kg)^0.75
Fanta et al – "Developmental pharmacokinetics of ciclosporin: A population pharmacokinetic study in paediatric transplant patients
Br J Clin Pharmacol 64:772, 2007
10
20
30
40
50
60
70
Body Weight (kg)

- The '3/4 Rule' holds for predicting the clearance of several drugs (e.g.CYP3A substrates– ciclosporine, midazolam, alfentanil etc)

- But it does not account for the ontogeny of drug metabolising enzymes in neonates and infants.

- Use '3/4 Rule' to normalise clearance only > 2 years.

PHARMACOKINETICS

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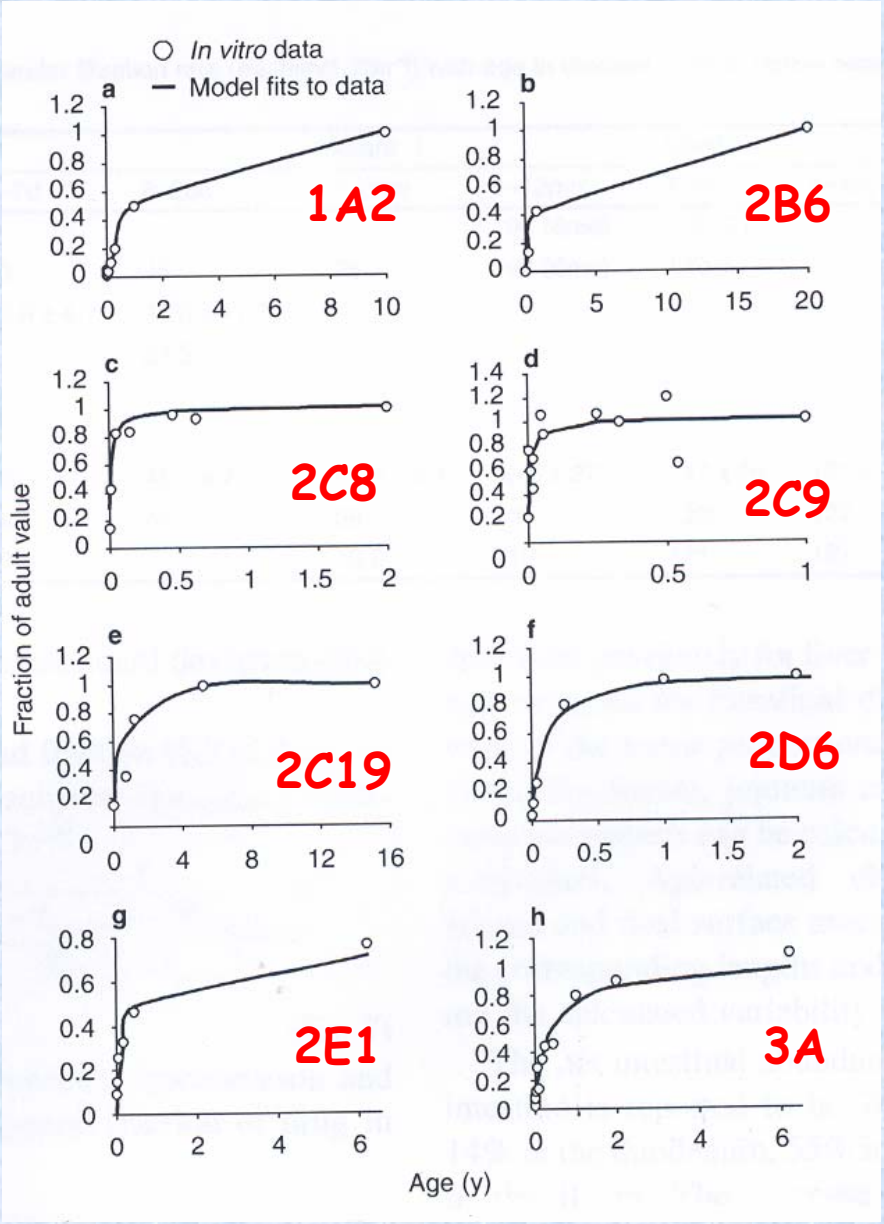
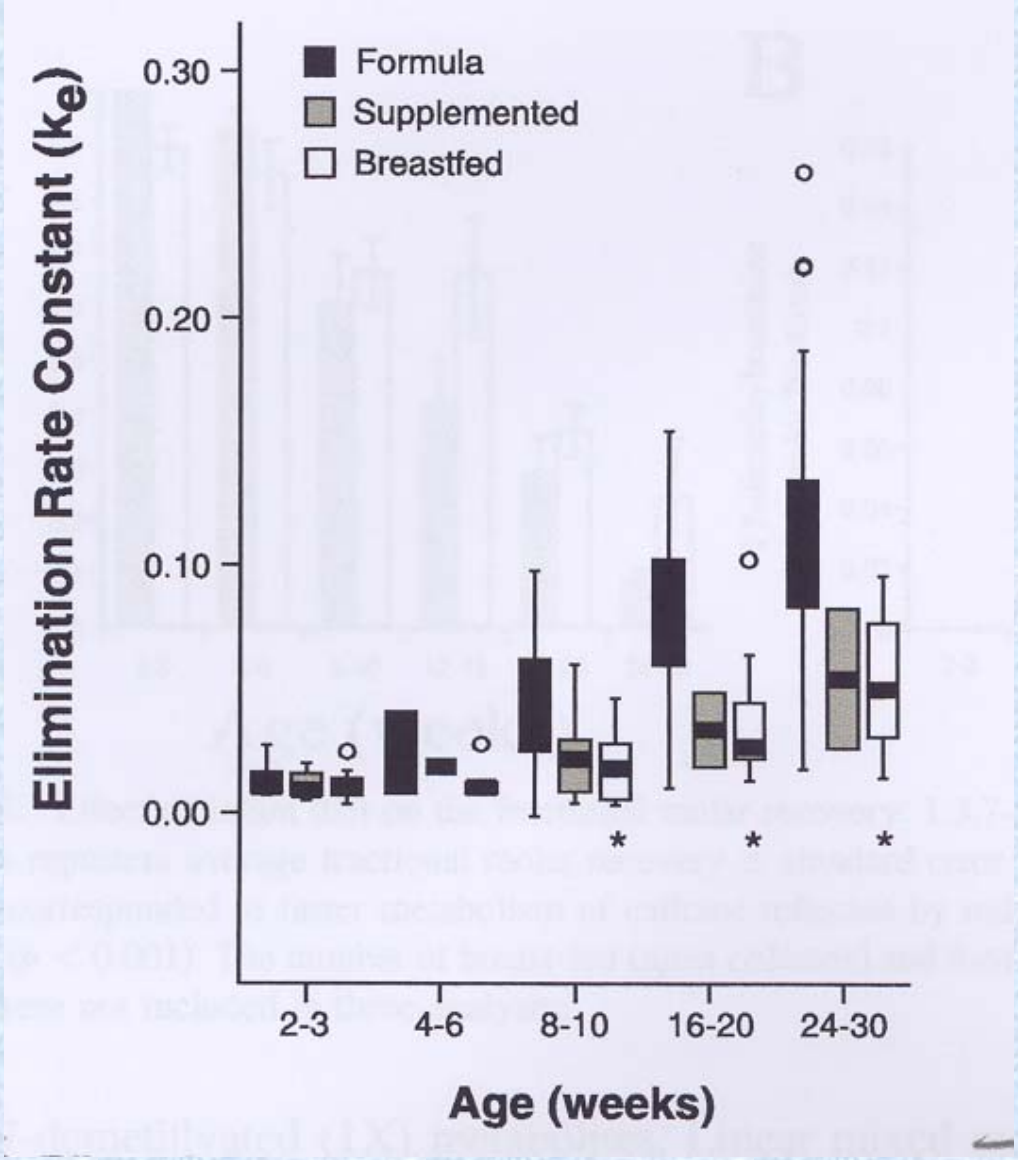
AGE-RELATED CHANGES IN CYP EXPRESSION/ACTIVITY



Johnson *et al* (2006)

EFFECT OF DIET ON CAFFEINE ELIMINATION RATE CONSTANT (CYP1A2)



Blake *et al* (2006)

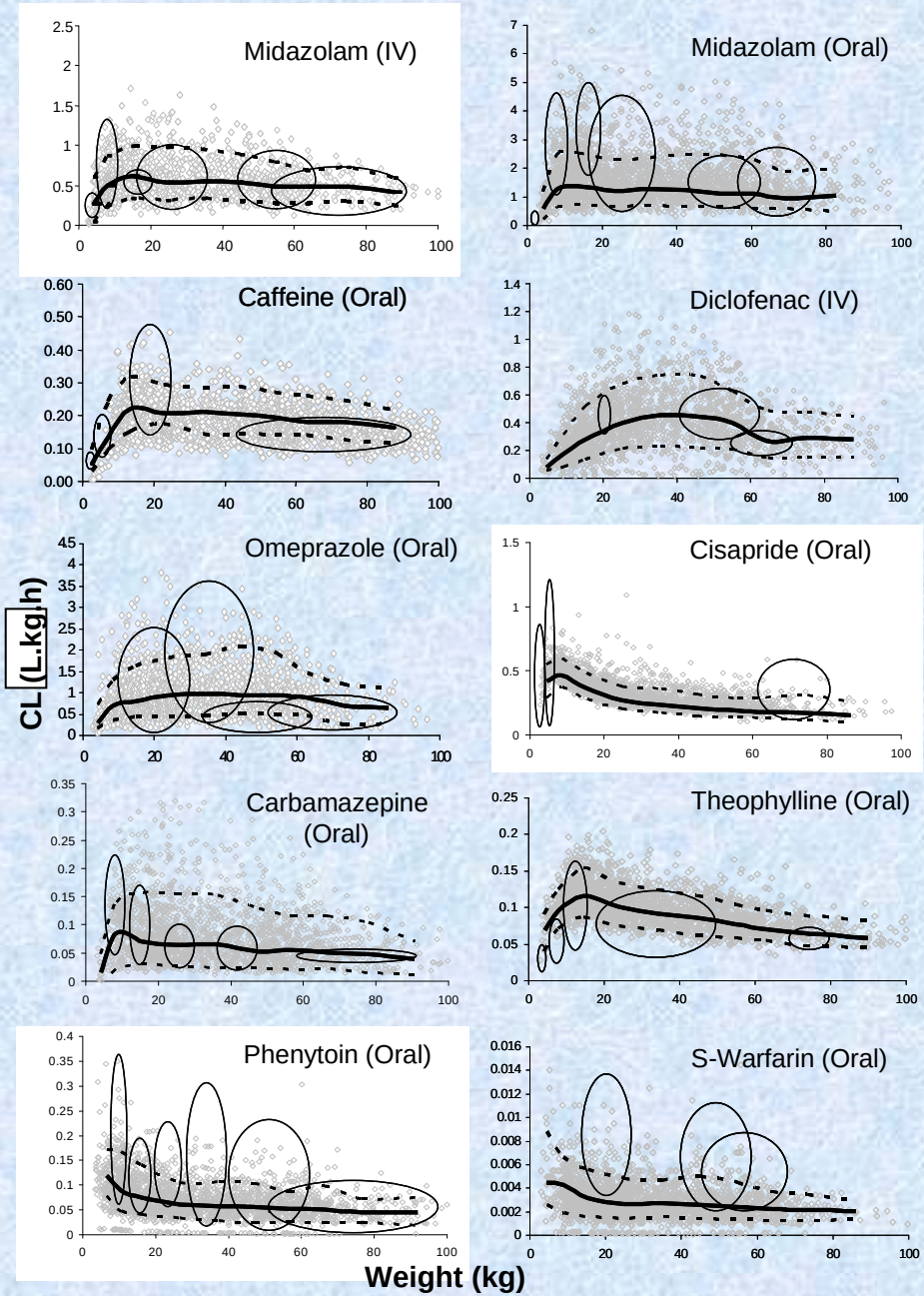
GLUCURONIDATION

Time to maturity?

UGT1A1	(*e.g.* ethinylestradiol	< 6 months
UGT1A4	(*e.g.* imipramine)	< 2 years
UGT1A9	(*e.g.* propofol)	> 2 years
UGT2B4		> 2 years
UGT2B7	(e.g. morphine)	< 6 months

Strassburg *et al*, 2002; Miyagi & Collier, 2007

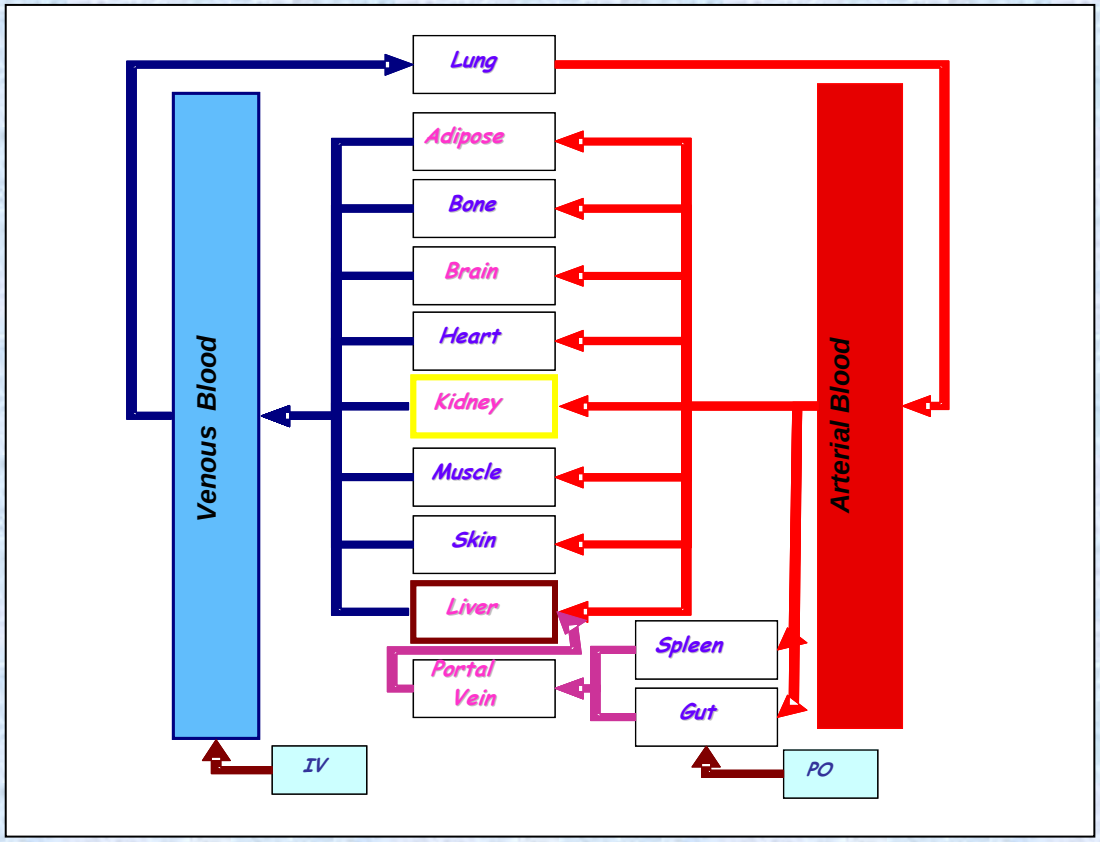
Predicting Paediatric Clearance



Johnson *et al.*
Clin Pharmacokin 2006

- Below ~ 2years – prediction of clearance is drug specific due to differential development of its determinants.

Full Paediatric PBPK Model



- Incorporating information on organ size, tissue composition and blood flow
- Allows for prediction of full PK profile (V, MRT, C_{max}, C_{min})

ORGAN SIZE

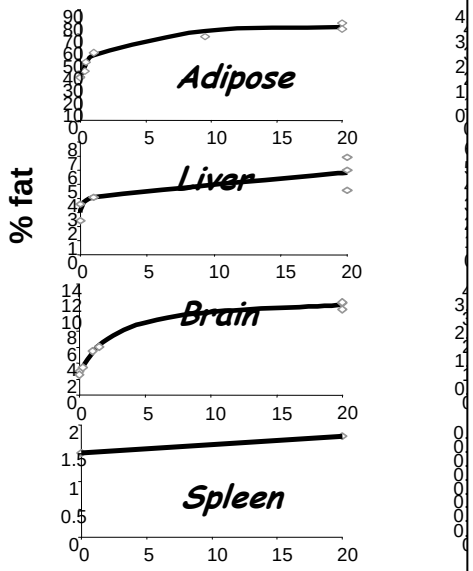
ORGAN BLOOD F

RENAL FUNCTION

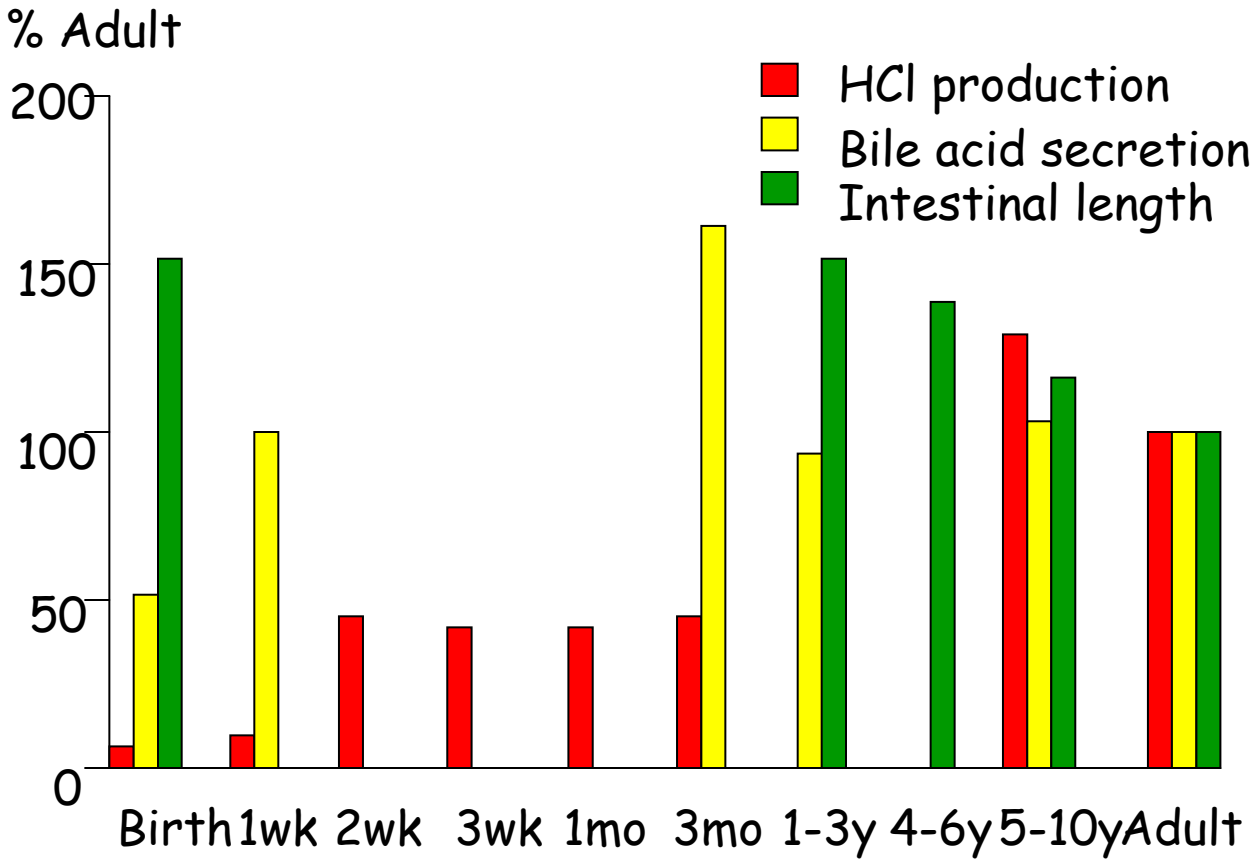
PLASMA PROTEINS

TISSUE COM

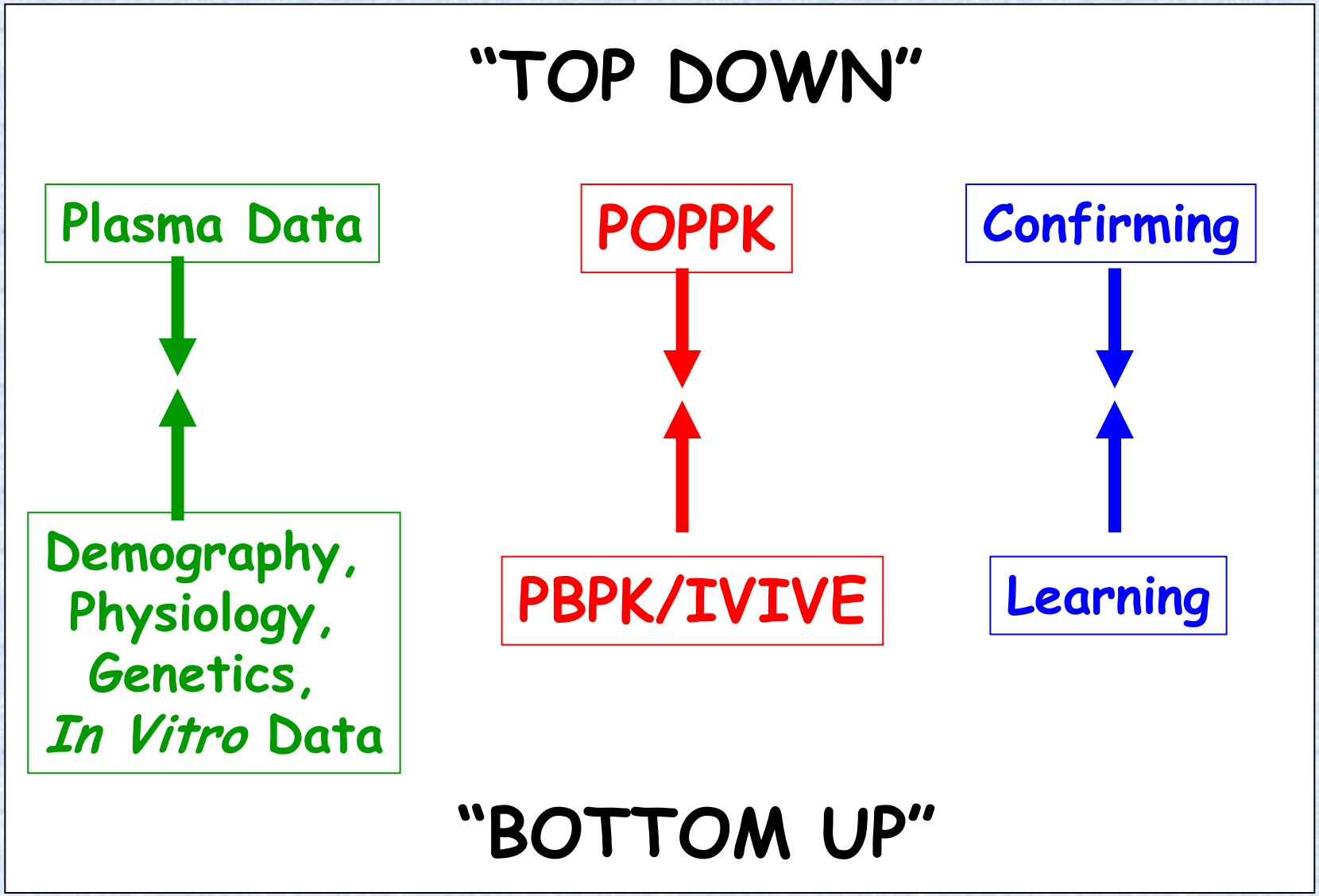
TISSUE C



GASTROINTESTINAL FUNCTION



PK MODELLING



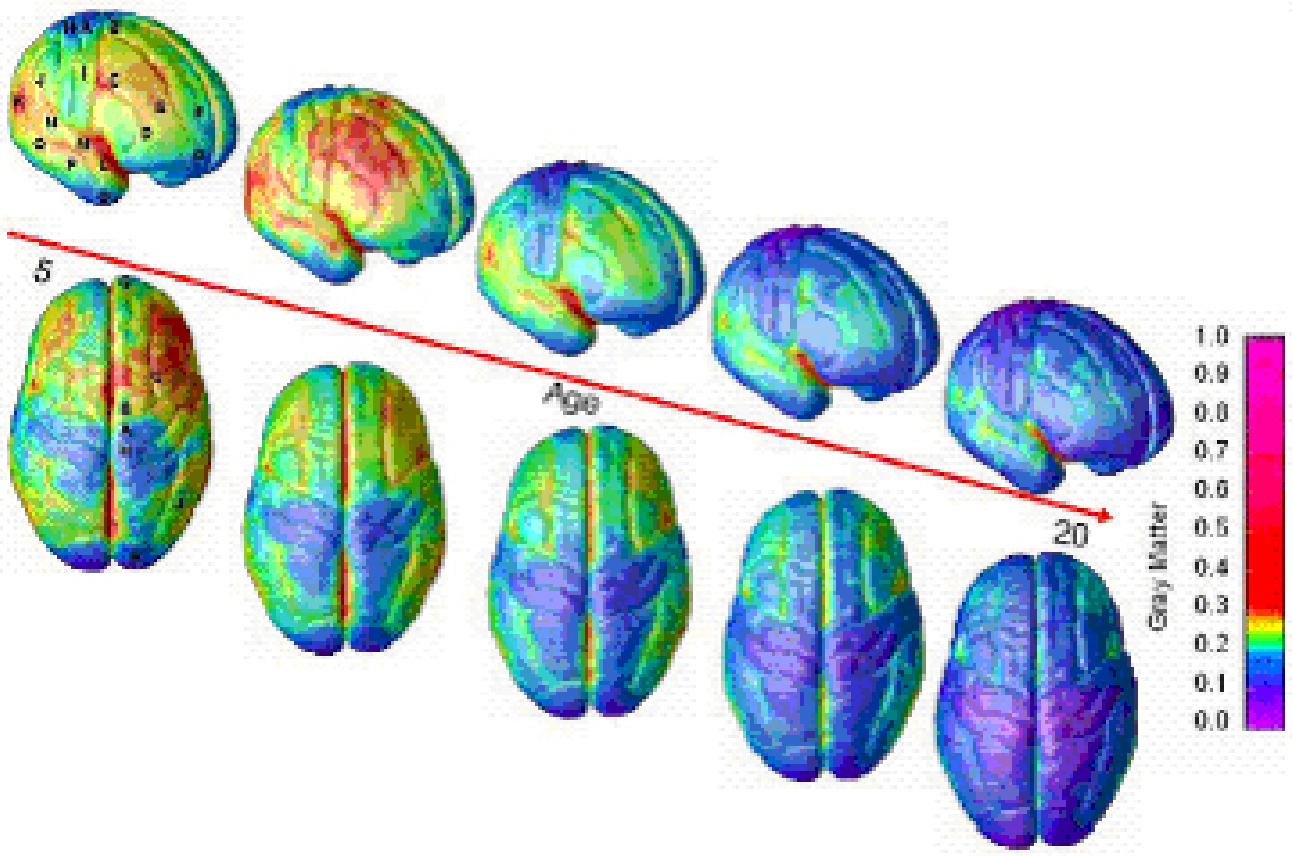
PHARMACODYNAMICS

Age-Related Changes in Concentration-Reponse

Drug	Age Range	n	Observation	Reference
Cyclosporin	3mo – 39y	56	Increased CR effect in <1-4y group	Marshall & Kearns (1999)
Warfarin	1 – 76y	134	Increased CR effect (INR/dose) in 1-11y group	Takahashi et al (2000)
Midazolam	Preterm – 29w	31	Decreased CR (sedation)	De Wildt et al (2001)

MIDAZOLAM (10mg/kg S/C – Rats)

Late



"Dynamic mapping of human cortical development during childhood through early adulthood"
Gogtay *et al* – *PNAS* 101: 8174, 2004

PK-PD MODELLING

"Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis"

Johnson *et al*: *Br J Anaesth* 89:428, 2002

"A 50% increase in dose would increase odds ratio from 4 to 275 in favour of sedation score 2 (drowsy/asleep) at start of surgery"

An indirect response model of homocysteine suppression by betaine: optimising the dosage regimen of betaine in homocystinuria

Angela Matthews,[1] Trevor N. Johnson,[2] Amin Rostami-Hodjegan,[2] Anupam Chakrapani,[3] J. Edward Wraith,[3] Stuart J. Moat,[4] James R. Bonham[1] & Geoffrey T. Tucker[2]

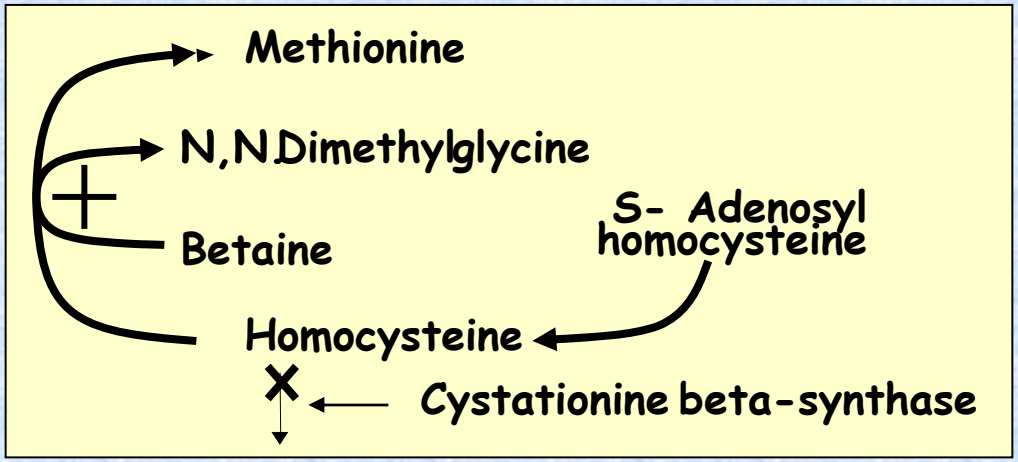
[1]*Department of Chemical Pathology & Neonatal Screening, Sheffield Children's Hospital,* [2]*Molecular Pharmacology & Pharmacogenetics, University of Sheffield, Sheffield,* [3]*The Willink Unit, Royal Manchester Children's Hospital, Manchester and* [4]*Cardiovascular Sciences Research Group, Wales Heart Research Institute, University of Wales College of Medicine, Cardiff*

Br J Clin Pharmacol 54:140,2002

- Homocysteinuria
  (3 in 1 million)
- Betaine
  (orphan drug)

- Limited population of patients to study

- No Pharma funding for large studies



$$\frac{dH}{dt} = k_{in} - k_{out}\, S(t)\, H(t)$$

Solution:
Clinical Trial Simulation

$$S(t) = 1 + \frac{E_{Max} C_{Betaine}(t)}{EC_{50} + C_{Betaine}(t)}$$

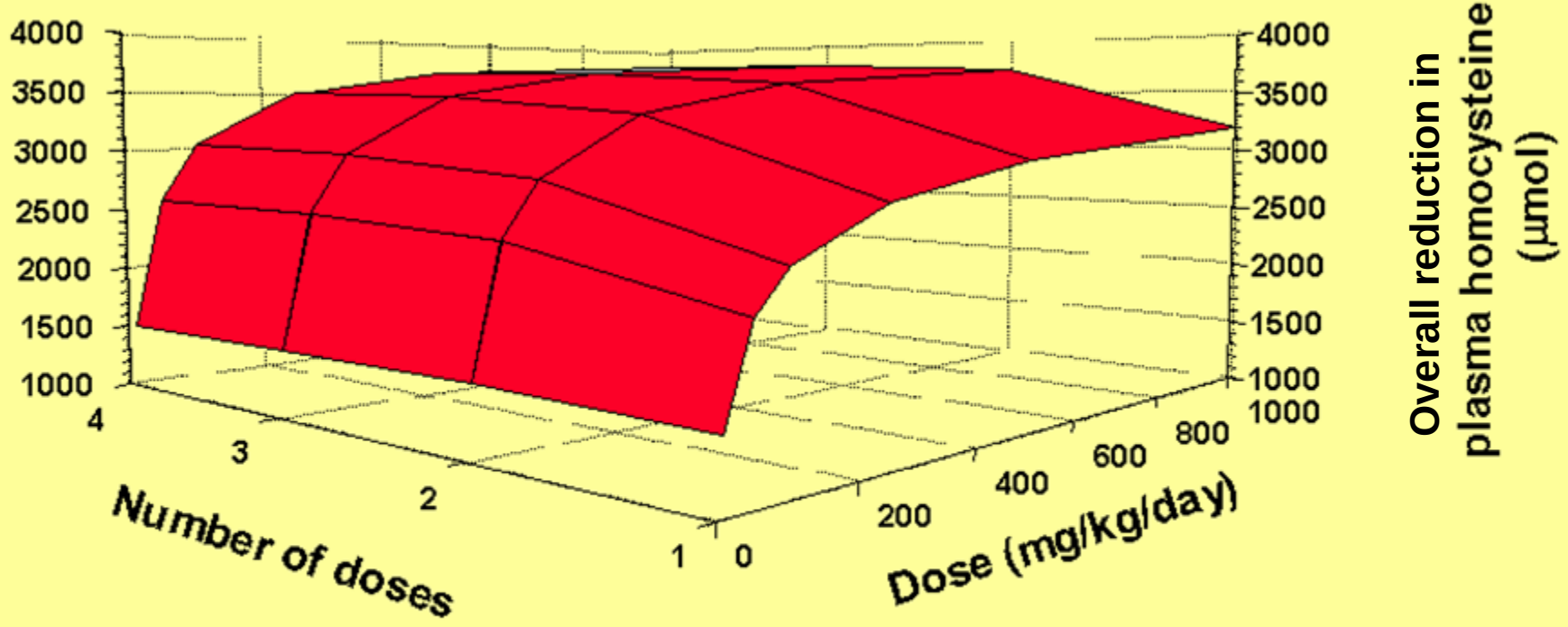


Figure. Predicted effects for the combined dose frequency and total daily dose on the overall 24 hour reduction in plasma homocysteine concentration.

Increase in the usual daily dosage (150 mg/kg) or in dosage frequency greater than twice daily is predicted to give negligible added clinical benefit for an additional cost of £2100 per patient year and potential decrease in compliance.Two divided daily doses may be optimal.

- Concentrate on < 2 year olds
  - More variable
  - High risk
  - Developing systems
- More 'creative' PD evaluation