Neonatal pharmacology

limited size, extensive variability

SAFE PEDRUG

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recent FDA black box warnings
specific to neonates

Conclusions

neonatologists are working at the fast lane of (developmental) life, age or size/weight are the most significant covariates.

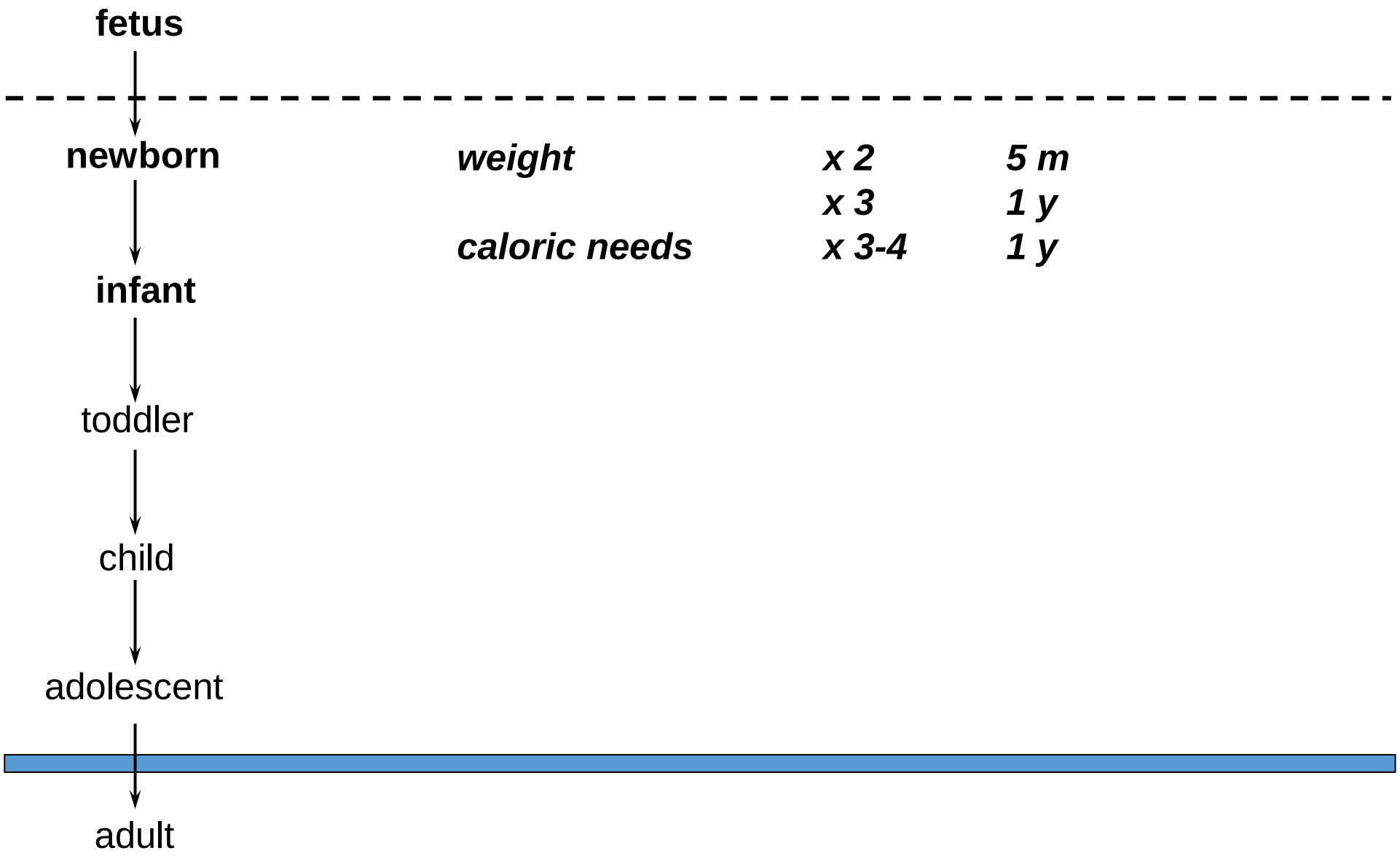
in general, drug clearance is low. This – however – does not exclude extensive interinidividual variability within the neonatal population (size log value).

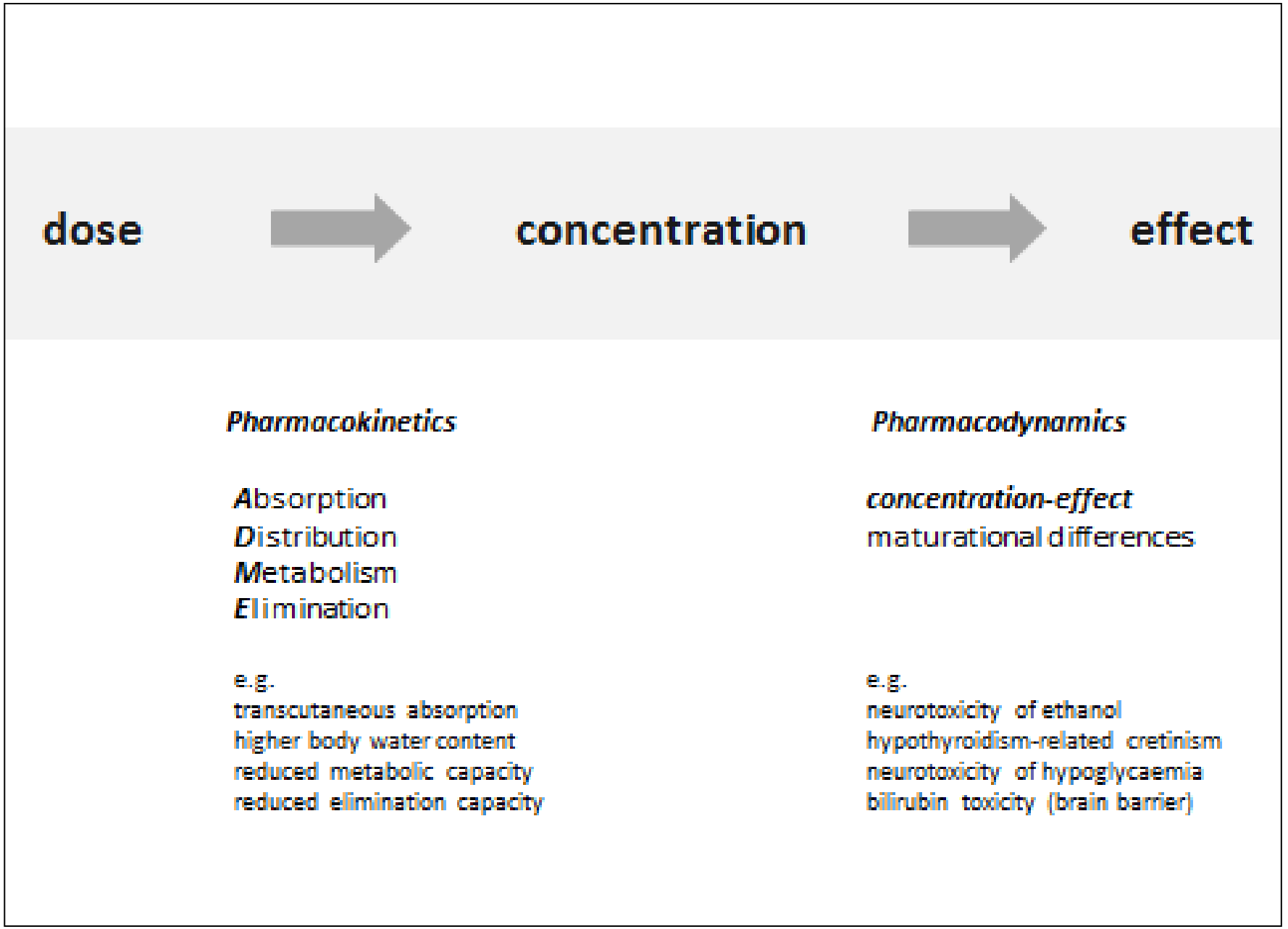
this extensive interindividual variability in drug disposition necessitates the search for covariates within the neonatal population.

there is no such thing as ‘an isolated neonatal liver/kidney’
main route of clearance should not be similar in neonates compared to adults.

pattern recognition matters, and may be used to predict PK for yet unknown drugs.

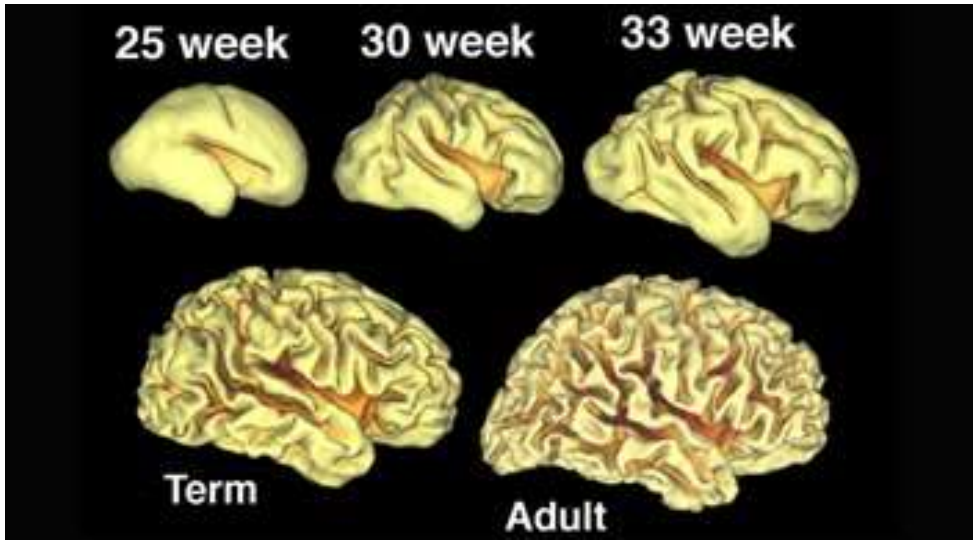
developmental (dis)continuum

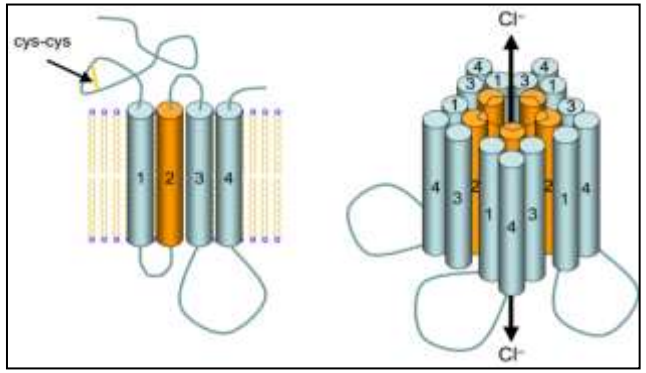


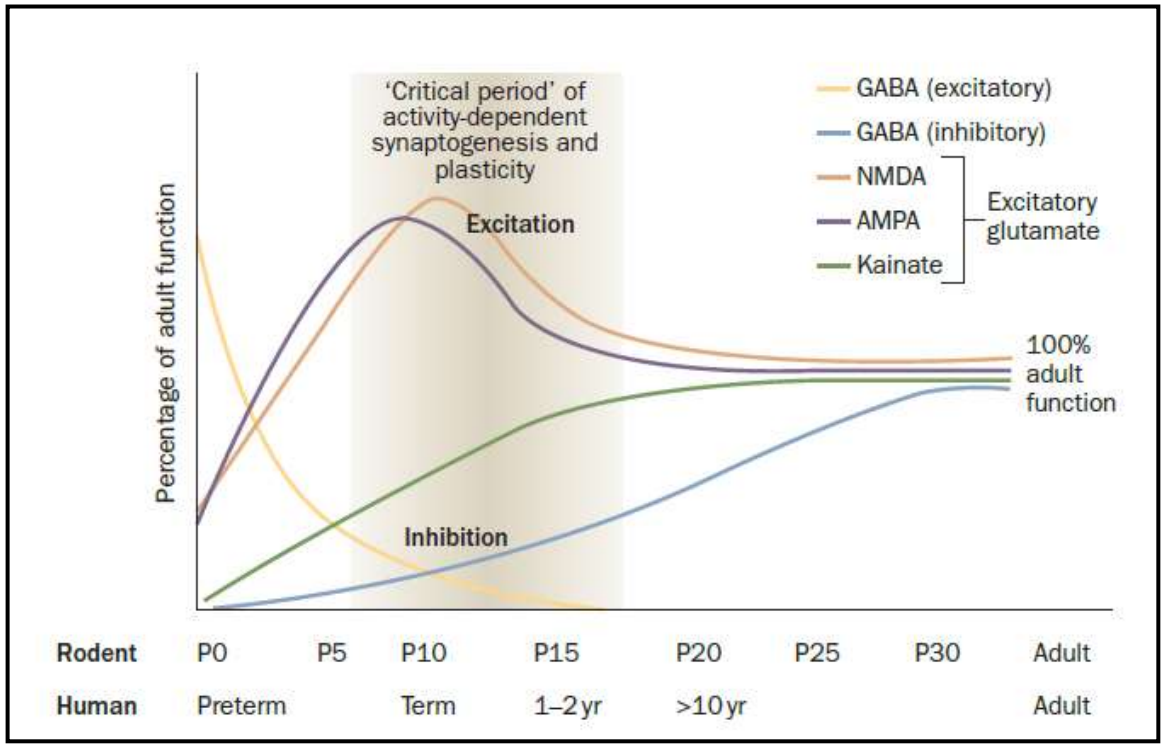

dose
concentration
effect
Pharmacokinetics
Absorption
Distribution
Metabolism
Elimination
e.g.
transcutaneous absorption
higher body water content
reduced metabolic capacity
reduced elimination capacity
Pharmacodynamics
concentration-effect
maturational differences
e.g.
neurotoxicity of ethanol
hypothyroidism-related cretinism
neurotoxicity of hypoglycaemia
bilirubin toxicity (brain barrier)

Epileptogenesis in the immature brain: emerging mechanisms

Sanjay N. Rakhade and Frances E. Jensen







Rakhade et al, Nat Rev Neurol 2009

Effects of Preterm Birth on the Kidney

Mary Jane Black, Megan R. Sutherland and Lina Gubhaju
Department of Anatomy and Developmental Biology, Monash University
Australia

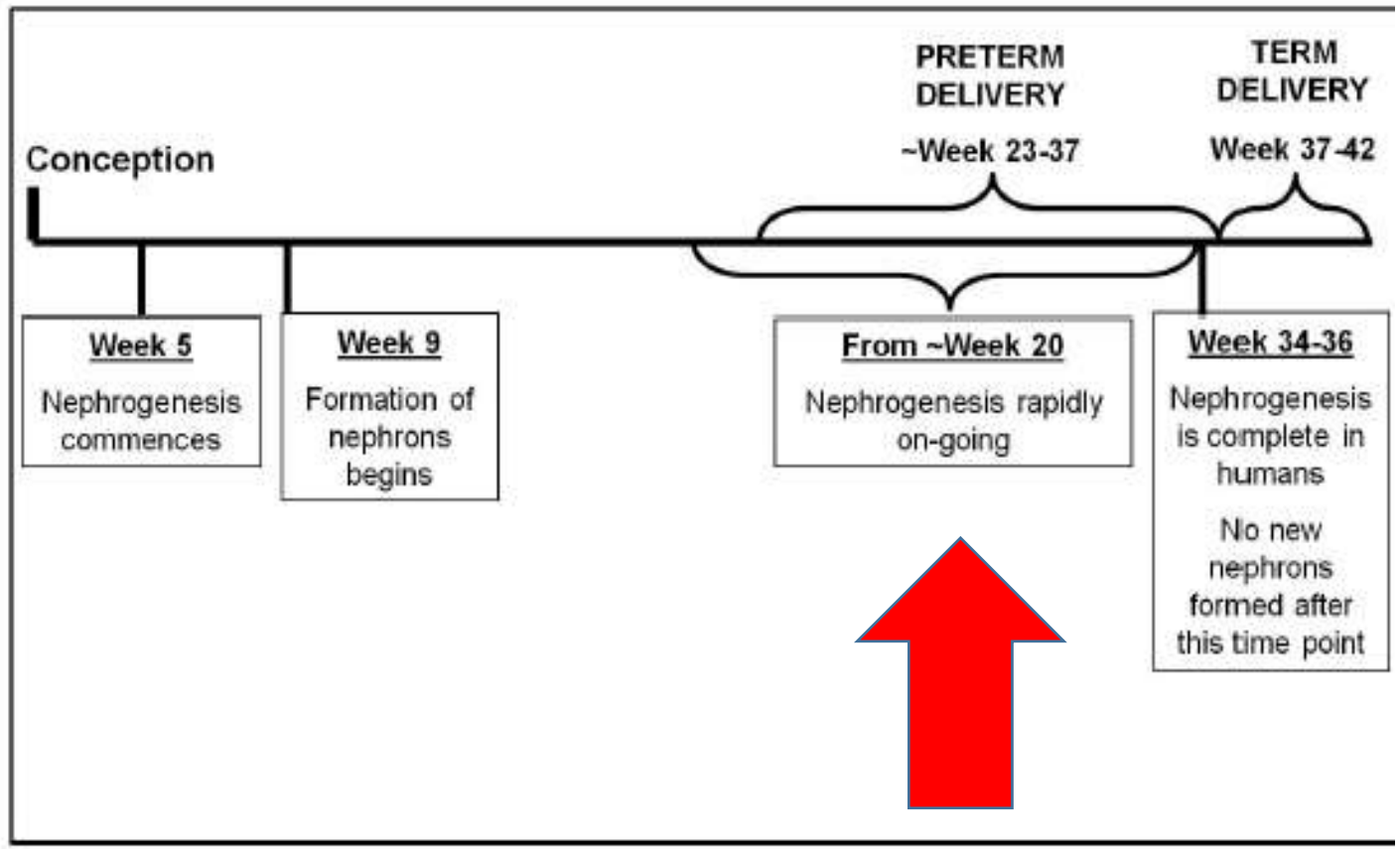


Fig. 1. A timeline of human nephrogenesis during gestation. Nephrogenesis is rapidly on-going at the time when most preterm neonates are delivered.

Platelets contribute to postnatal occlusion of the ductus arteriosus

Katrin Echtler[1], Konstantin Stark[1], Michael Lorenz[1], Sandra Kerstan[1], Axel Walch[2], Luise Jennen[2], Martina Rudelius[3], Stefan Seidl[3], Elisabeth Kremmer[4], Nikla R Emambokus[5], Marie-Luise von Bruehl[1], Jon Frampton[6], Berend Isermann[7], Orsolya Genzel-Boroviczény[8], Christian Schreiber[9], Julinda Mehilli[1], Adnan Kastrati[1], Markus Schwaiger[10], Ramesh A Shivdasani[11] & Steffen Massberg[1,12]

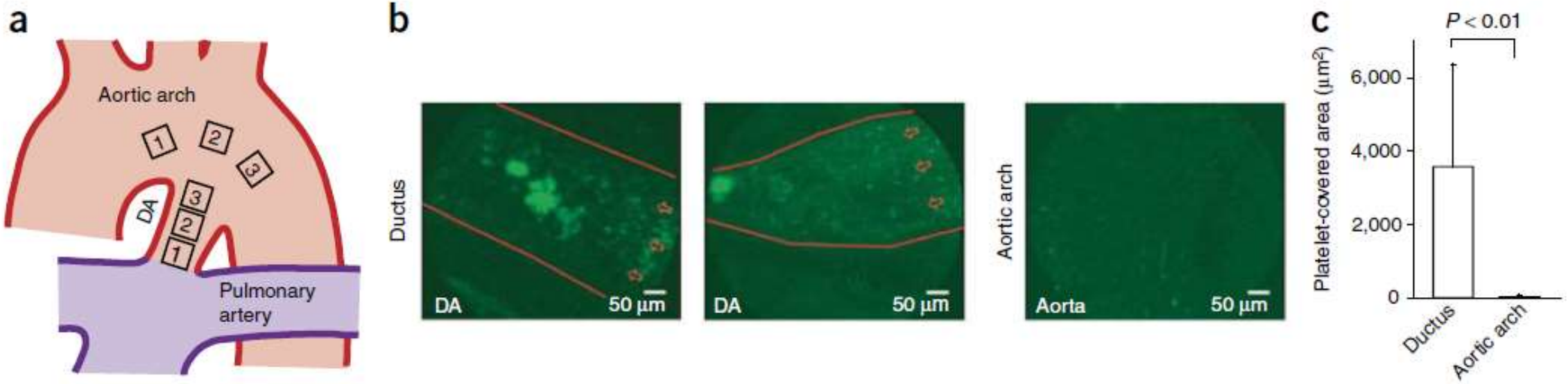
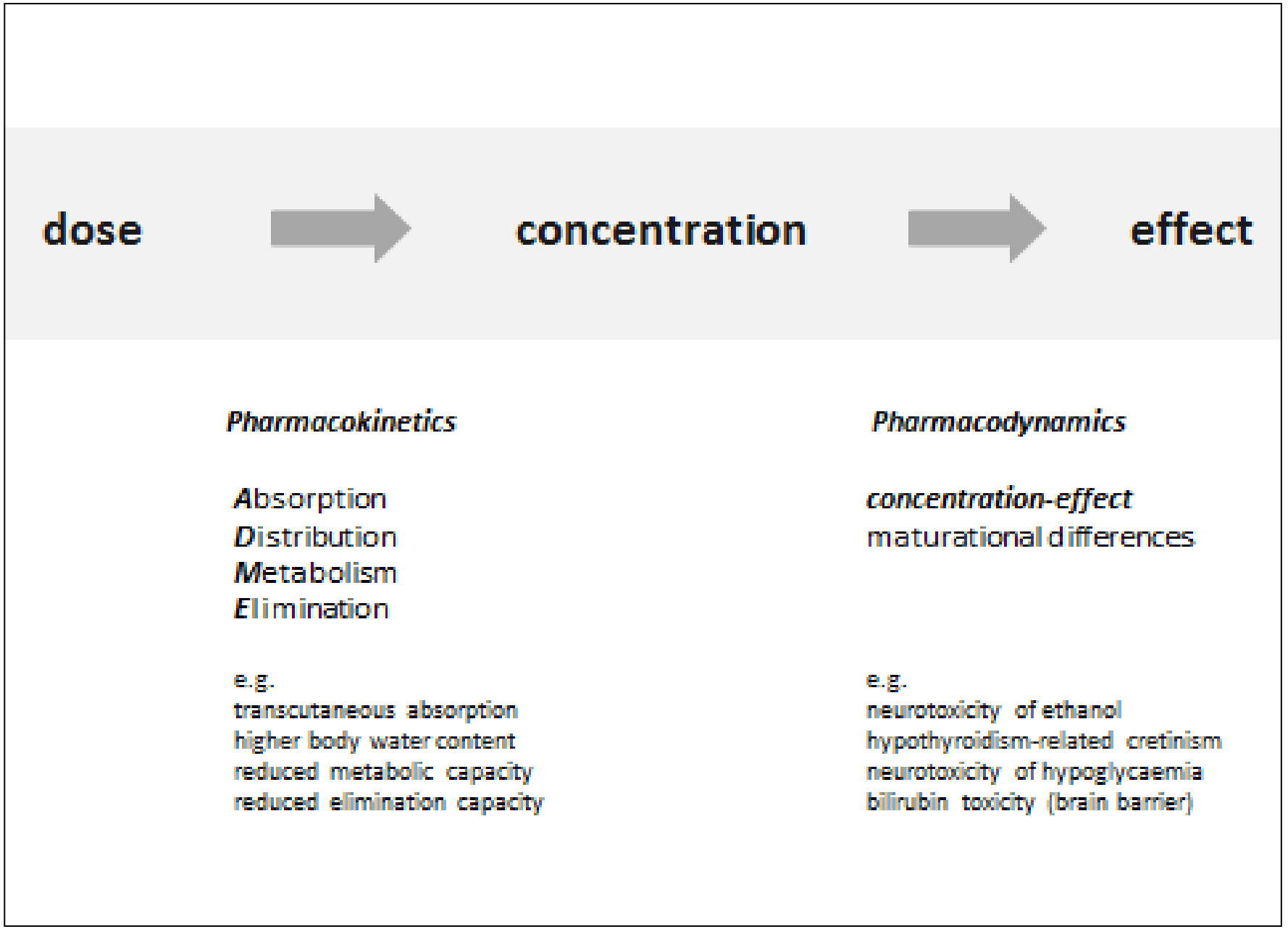


Figure 2 Platelets are recruited rapidly to the closing mouse DA *in vivo*. (**a**) Schematic illustration of the three regions in the aorta and DA (indicated by 1, 2 and 3) in which platelet adhesion was evaluated by ICM. (**b**) Representative ICM images of the DA and aorta (dichlorofluorescein-labeled platelets in green; red line and arrows indicate DA wall and direction of flow, respectively). (**c**) Quantification of the thrombus size (mean values) in the DA and the adjacent aorta as assessed by ICM ($n = 5$ mice per group). Error bars show s.e.m.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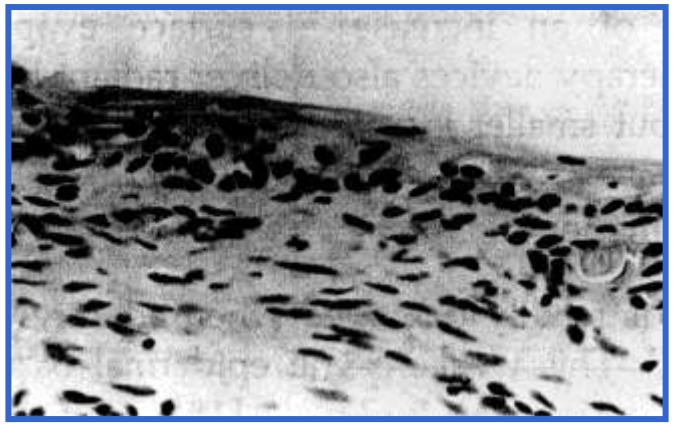
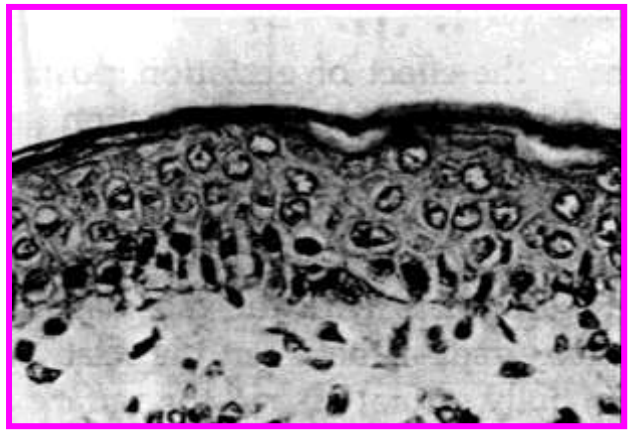
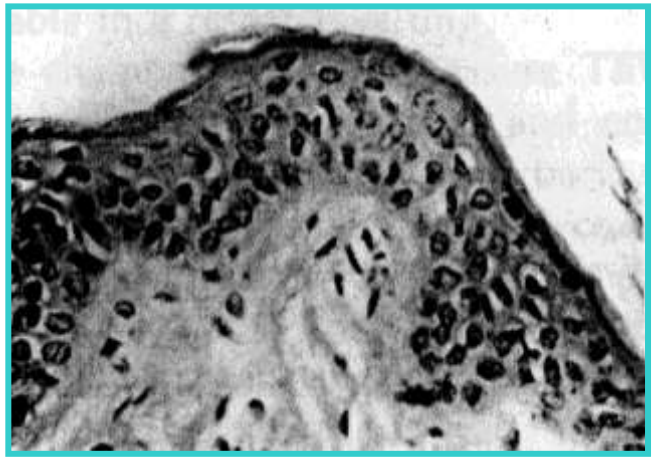






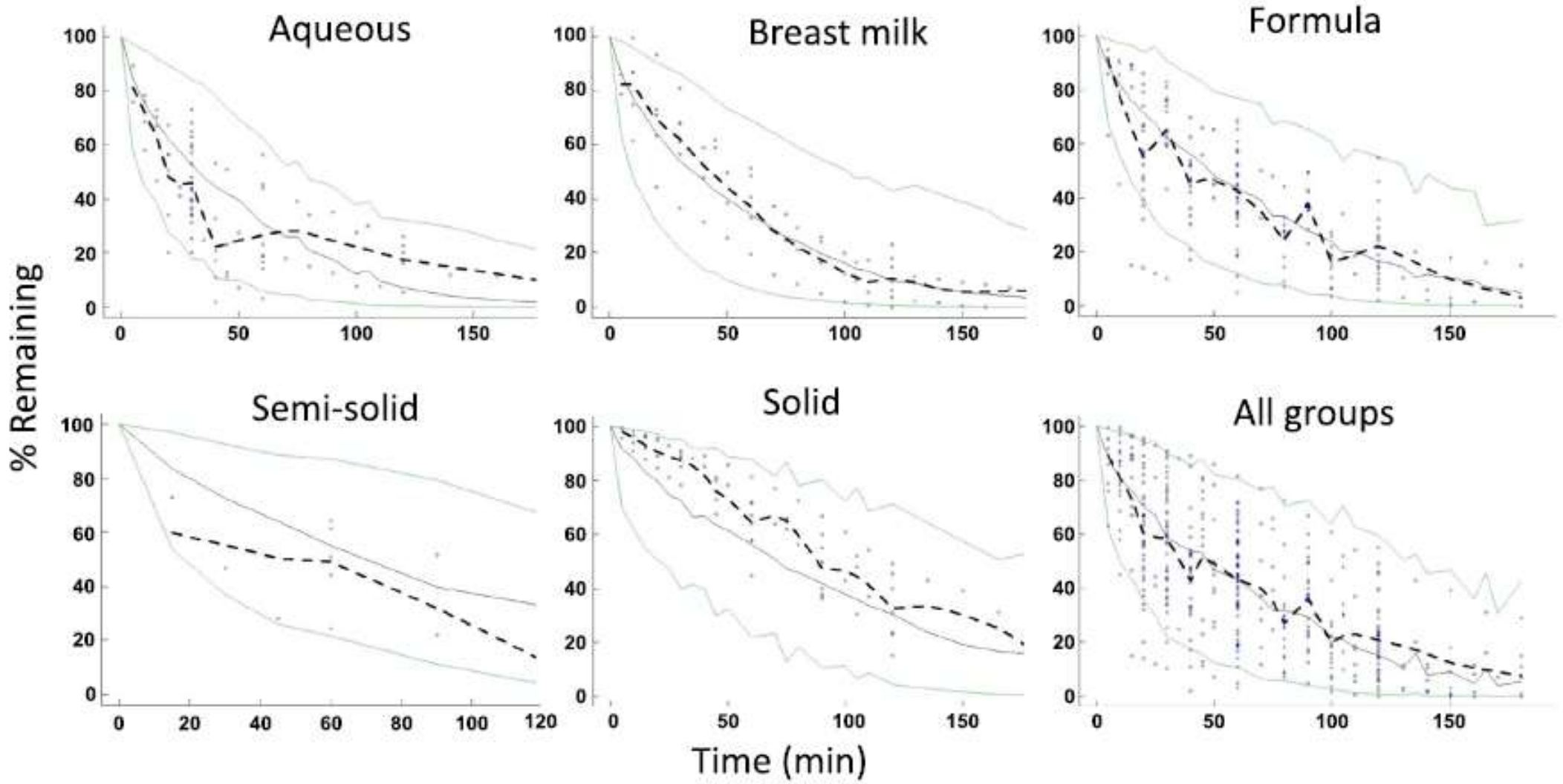


Figure 2. Visual predictive check plots. The green lines represent 2.5th and 97.5th percentiles of model-predicted data. The solid grey line represents the 50th percentile of model-predicted data. The dashed black line represents the median of the observed data

Bonner et al, Biopharm Drug Disp 2015

body water content

Fig. 1. Changes occurring in percentages of body fat and water stores along the continuum of age [16].

Rakhmanina et al, Adv Drug Deliver 2006

distribution volume: hydrophylic drugs

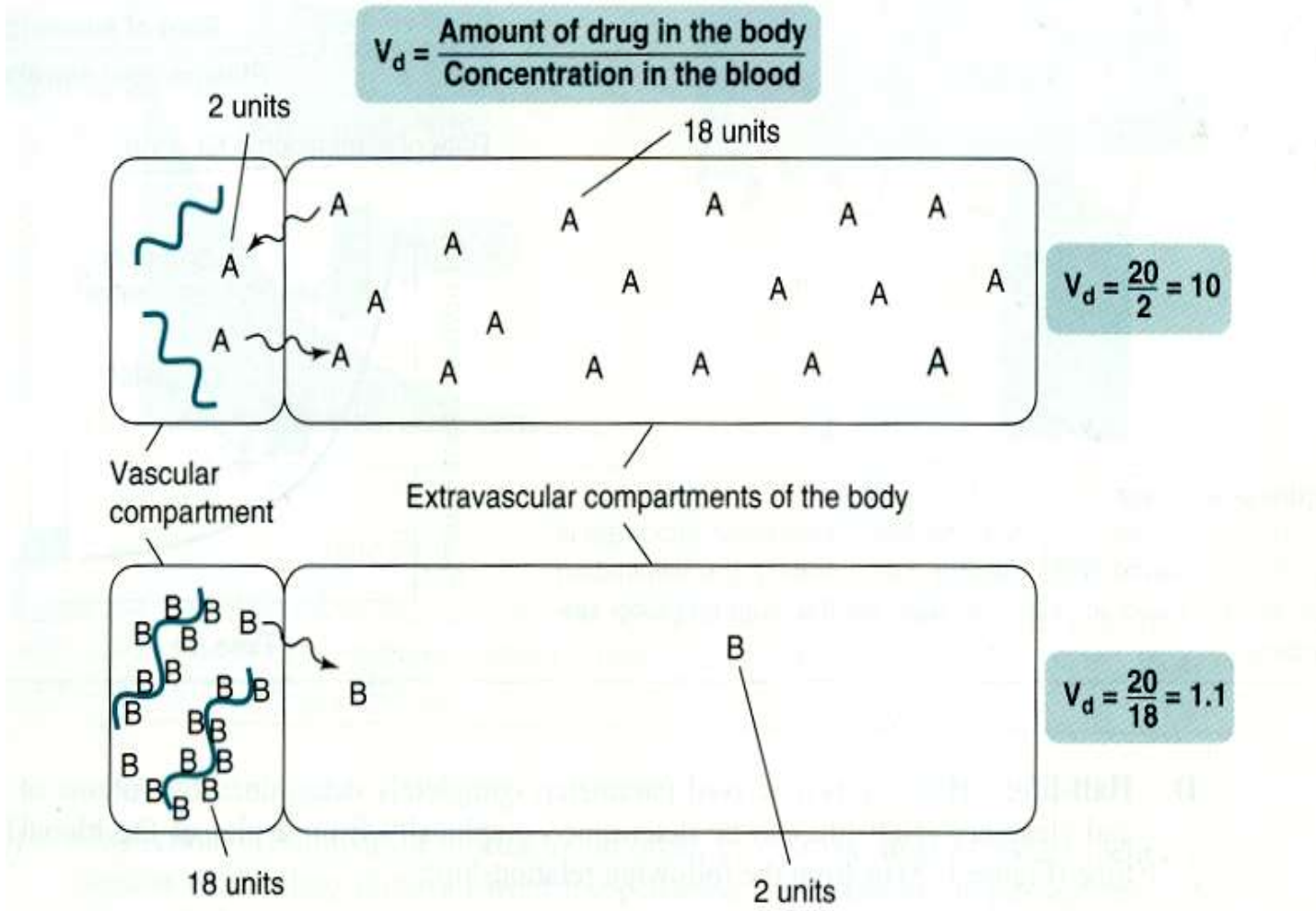
Table 1. Dosing chart recommended with specific doses and intervals according to the GA at birth

	VD, l/kg (mean ± 1 SD)	Half-life, h (mean ± 1 SD)	CL, ml/kg/min (mean ± 1 SD)	Dose mg/kg	Interval h
Group 1a (<28 weeks)	0.700±0.151	12.20±3.83	0.73±0.148	20	42
Group 1b (28 to <31 weeks)	0.660±0.120	8.40±1.36	0.87±0.127	20	36
Group 2 (31 to <34 weeks	0.614±0.013	7.71±0.31	0.98±0.025	18.5	30
Group 3 (34 to <37 weeks)	0.573±0.013	6.77±0.32	1.09±0.061	17	24
Group 4 (37–41 weeks)	0.520±0.021	5.55±0.49	1.15±0.036	15.5	24

The dosing chart was based on population-specific pharmacokinetic parameters calculated during the previous studies, using a pharmacokinetic programme assuming a one-compartment model [27, 28]. Assuming the pharmacokinetic results obtained in the previous study [27] in clinical unstable conditions such as asphyxia, prolonged hypoxia or concomitant treatment by indomethacin, we also recommended in the present study increasing the interval by 6 h, whatever the group, in these encountered clinical situations. For definitions, see text. VD = Volume of distribution; CL = clearance of amikacin.

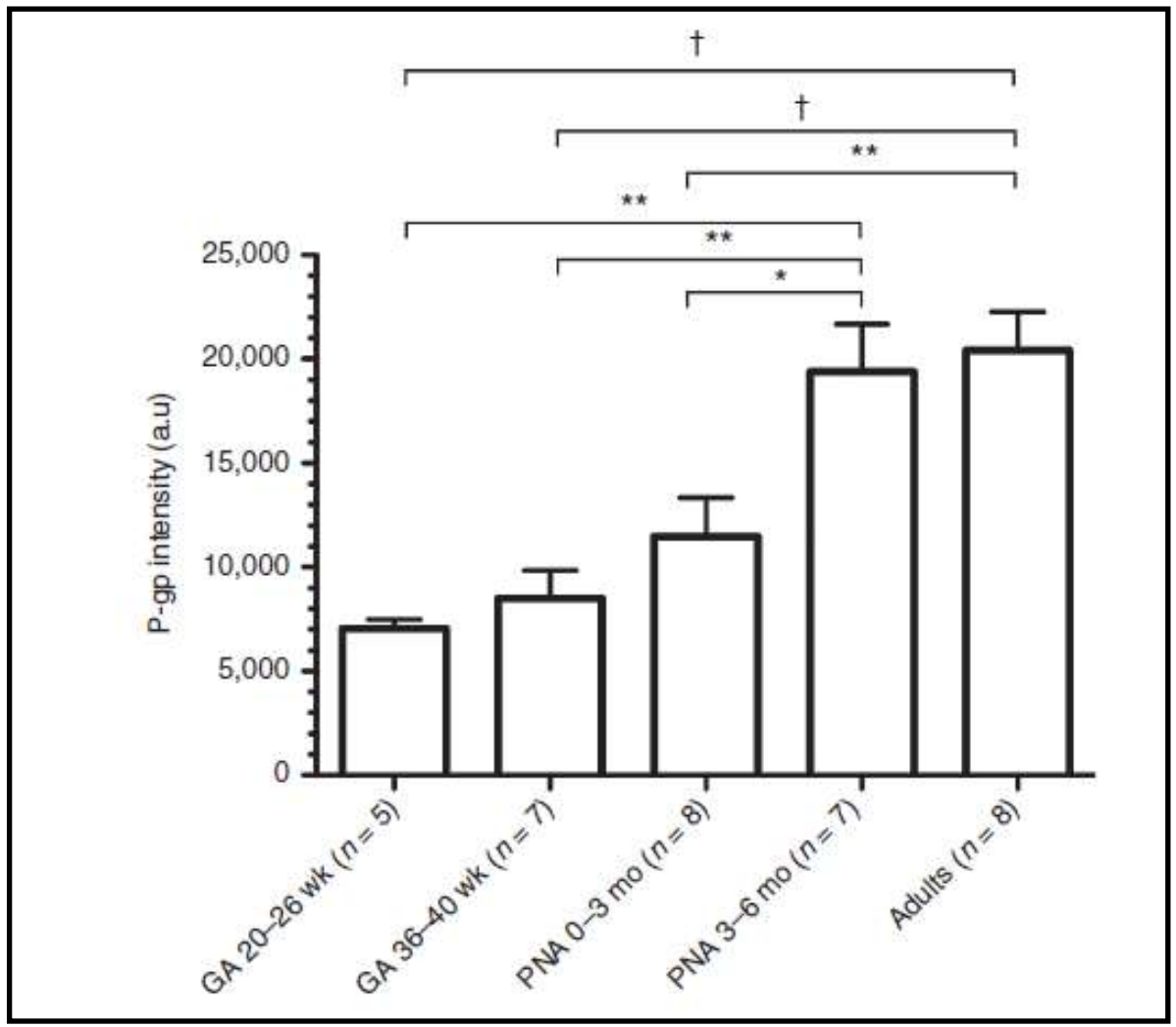
Langhendries et al, Biol Neonate 1998

effect of drug binding on volume of distribution
bilirubin

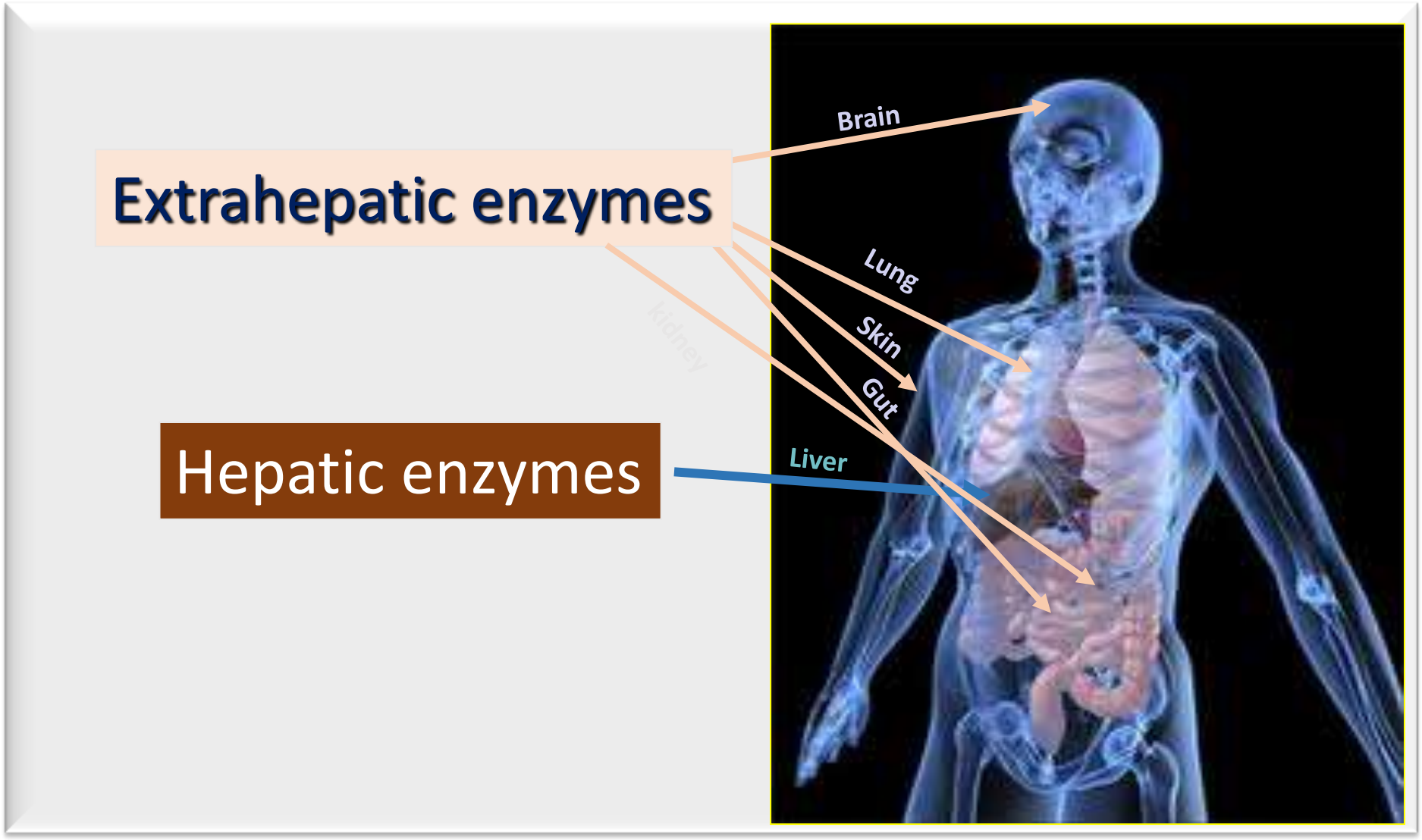


The ontogeny of P-glycoprotein in the developing human blood–brain barrier: implication for opioid toxicity in neonates

Jessica Lam[1,2], Stephanie Baello[3], Majid Iqbal[2], Lauren E. Kelly[4], Patrick T. Shannon[5], David Chitayat[6,7], Stephen G. Matthews[3] and Gideon Koren[1,2,4]

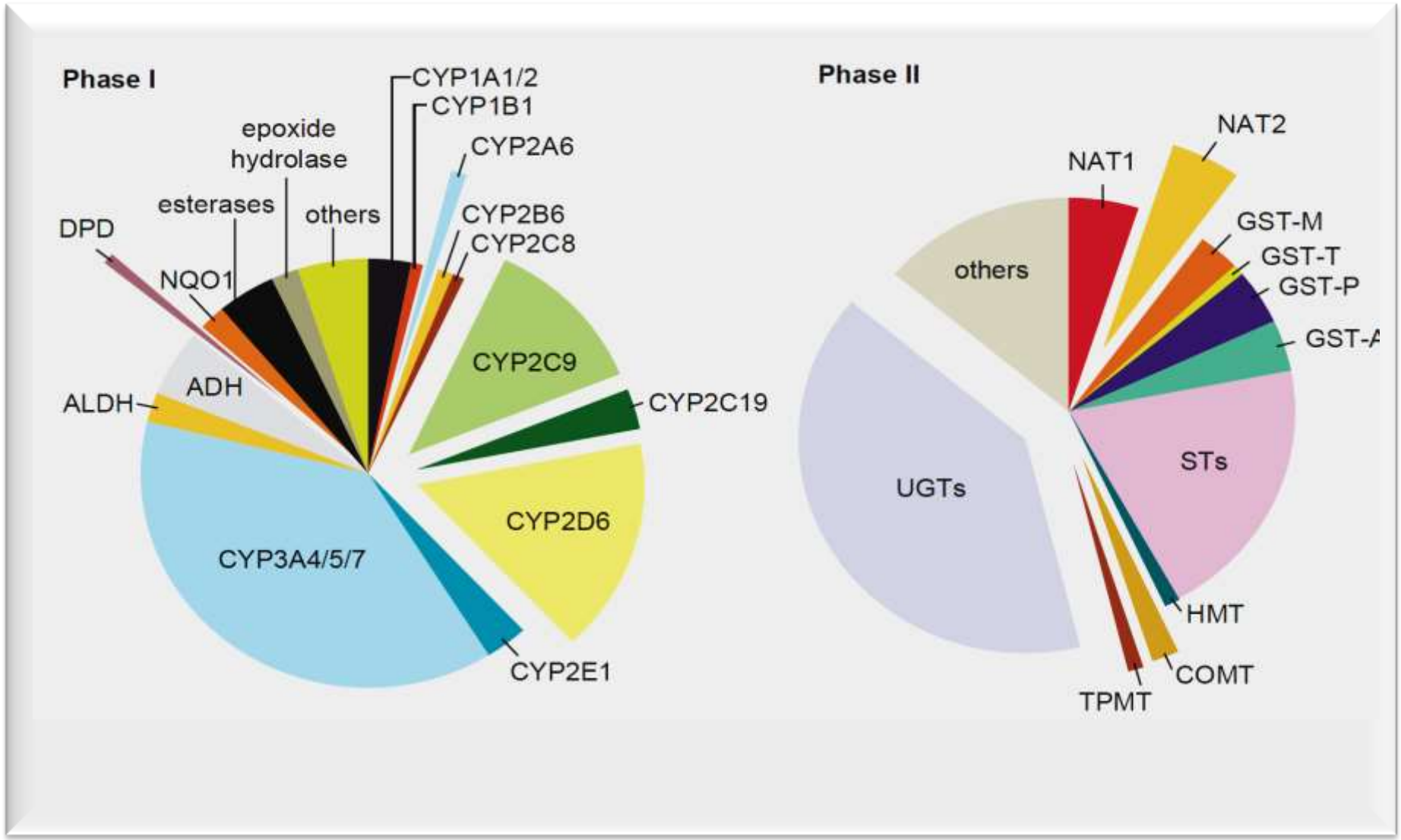


clearance: renal/hepatic

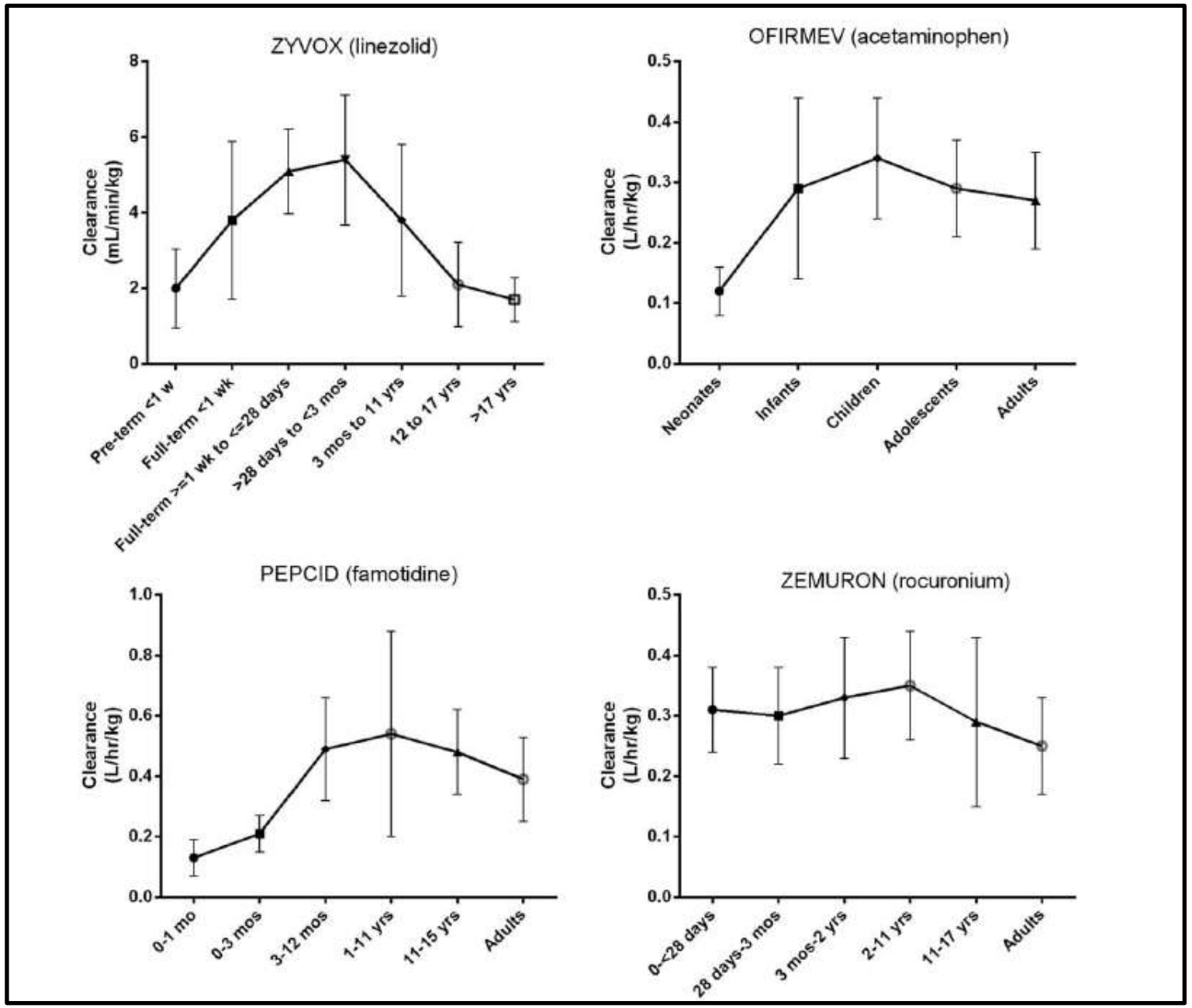


Slide provided by J van den Anker

Phase I and Phase II of drug metabolism



Evans et al, Science 1999



Wang et al, Clin Pharm Ther 2015

developmental toxicology, metabolism driven ?

ORIGINAL ARTICLE

Katarina Aleksa · Doug Matsell · Kris Krausz ·
Harry Gelboin · Shinya Ito · Gideon Koren

Cytochrome P450 3A and 2B6 in the developing kidney: implications for ifosfamide nephrotoxicity

ifosfamide (IF) causes serious renal damage substantially more in younger children (less than 3 years of age) than among older children.

Relates to differences in enzyme activity

covariates of drug metabolism

herbal medicine

disease

drugs

genetics

age

nutrition

Slide provided by J van den Anker

glucuronidation: postnatal age-dependent

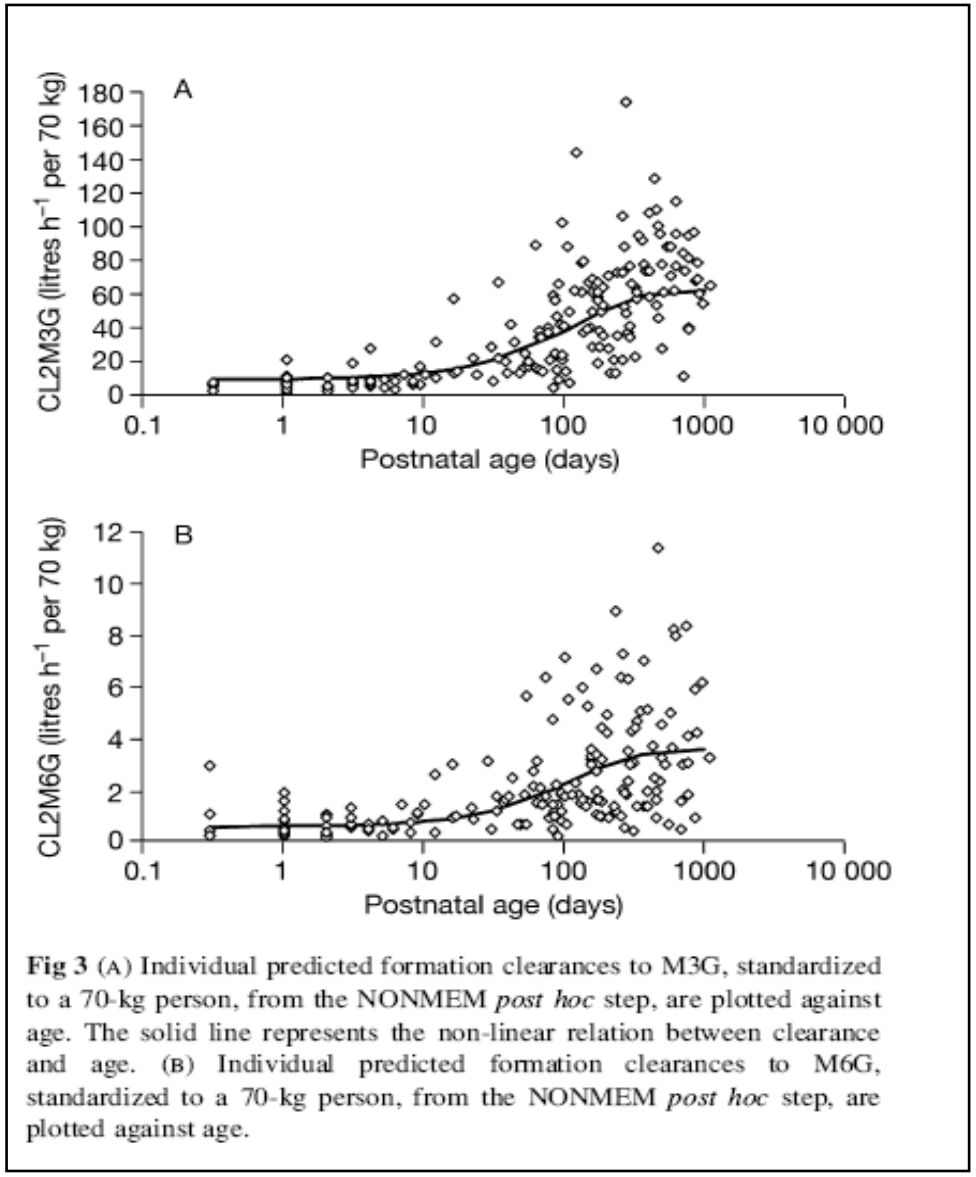
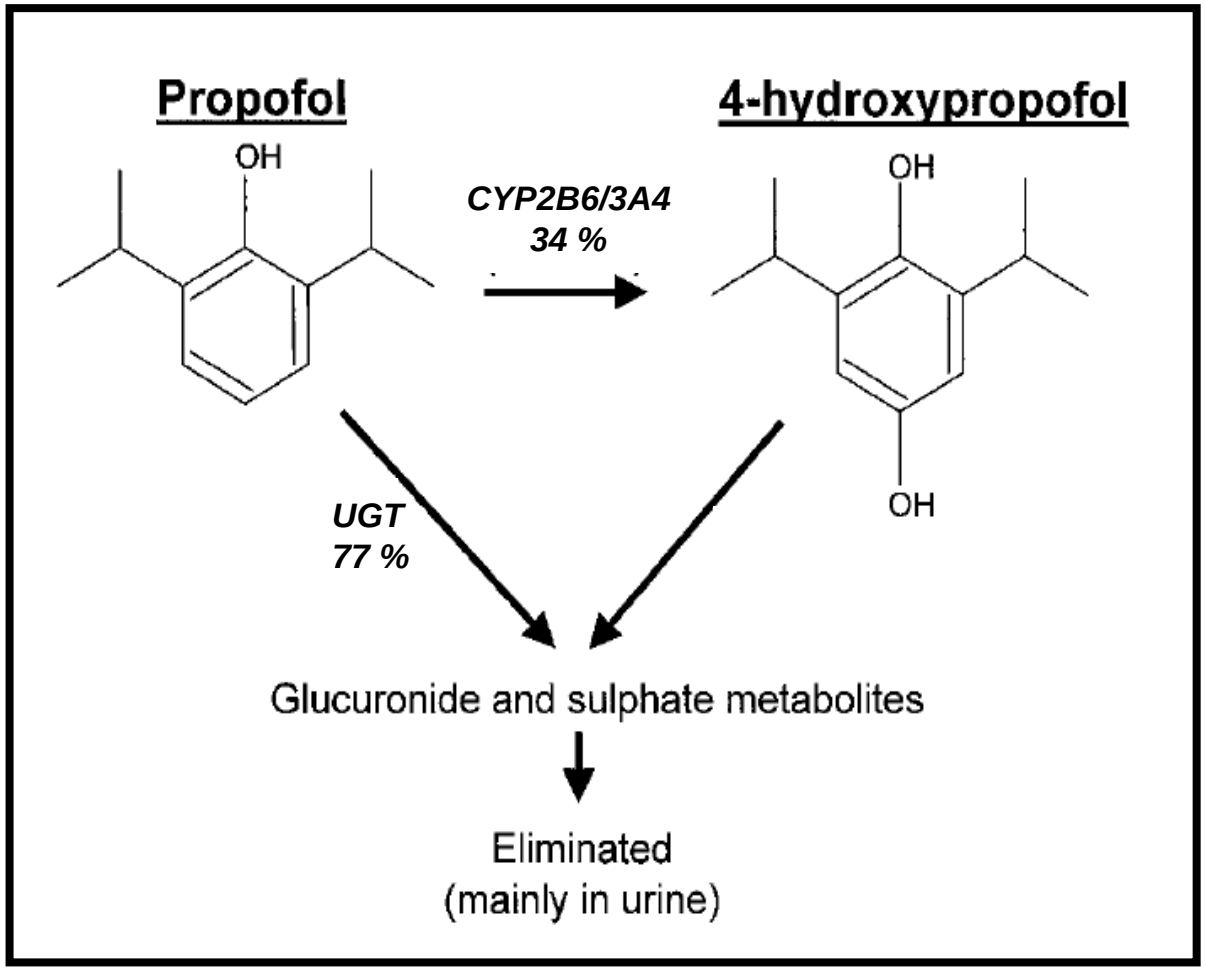


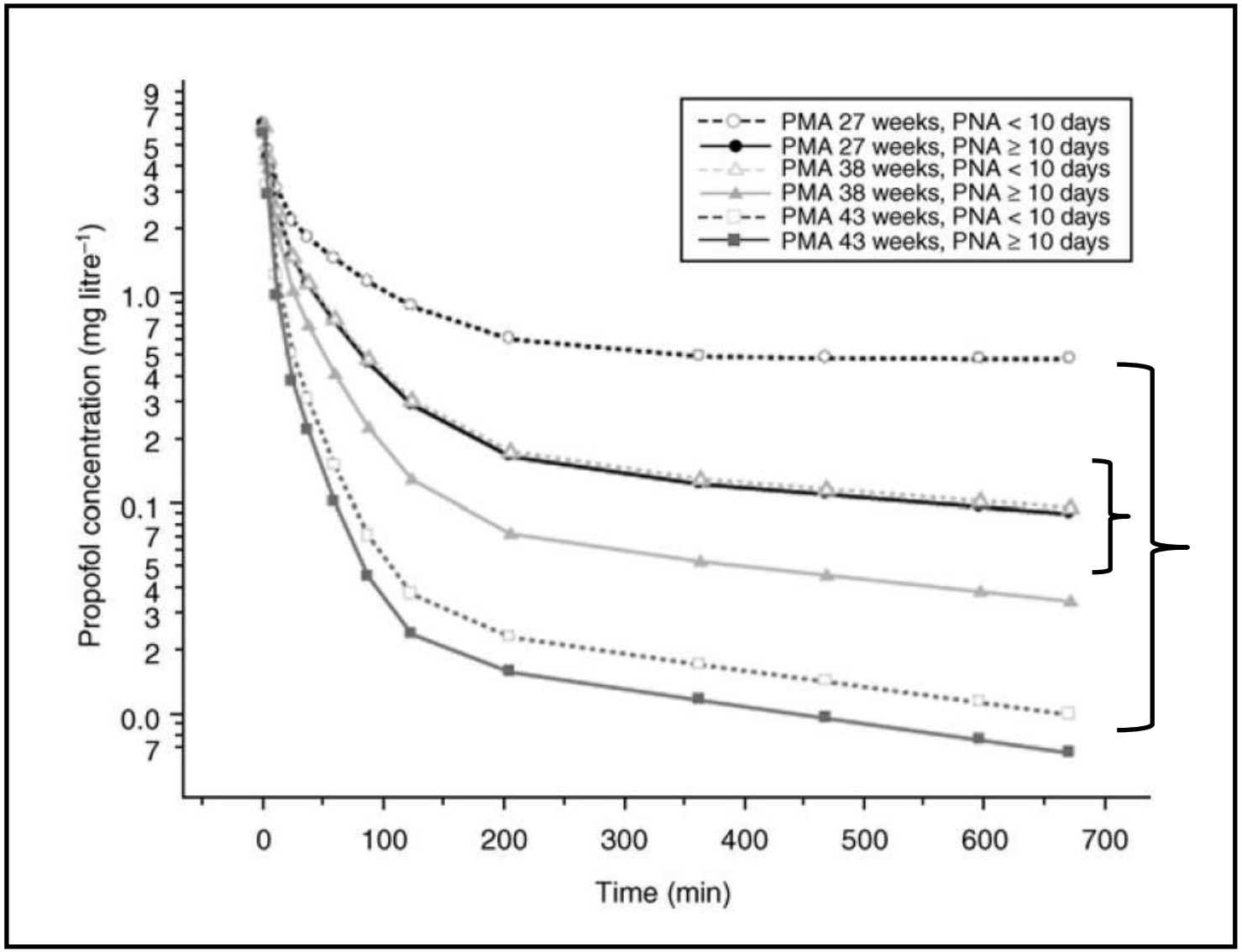
Fig 3 (A) Individual predicted formation clearances to M3G, standardized to a 70-kg person, from the NONMEM *post hoc* step, are plotted against age. The solid line represents the non-linear relation between clearance and age. (B) Individual predicted formation clearances to M6G, standardized to a 70-kg person, from the NONMEM *post hoc* step, are plotted against age.

Bouwmeester et al, Br J Anaesth 2004

propofol clearance is metabolic clearance

High capacity, low specificity : glucuronidation
Low capacity, high specificity: CYP2B6





Allegaert et al, Br J Anaesth 2007

polymorphisms are not limited to metabolic enzymes

Association of *OPRM1* and *COMT* Single-Nucleotide Polymorphisms With Hospital Length of Stay and Treatment of Neonatal Abstinence Syndrome

Wachman et al, JAMA 2015

NAT-2, isoniazid ontogeny

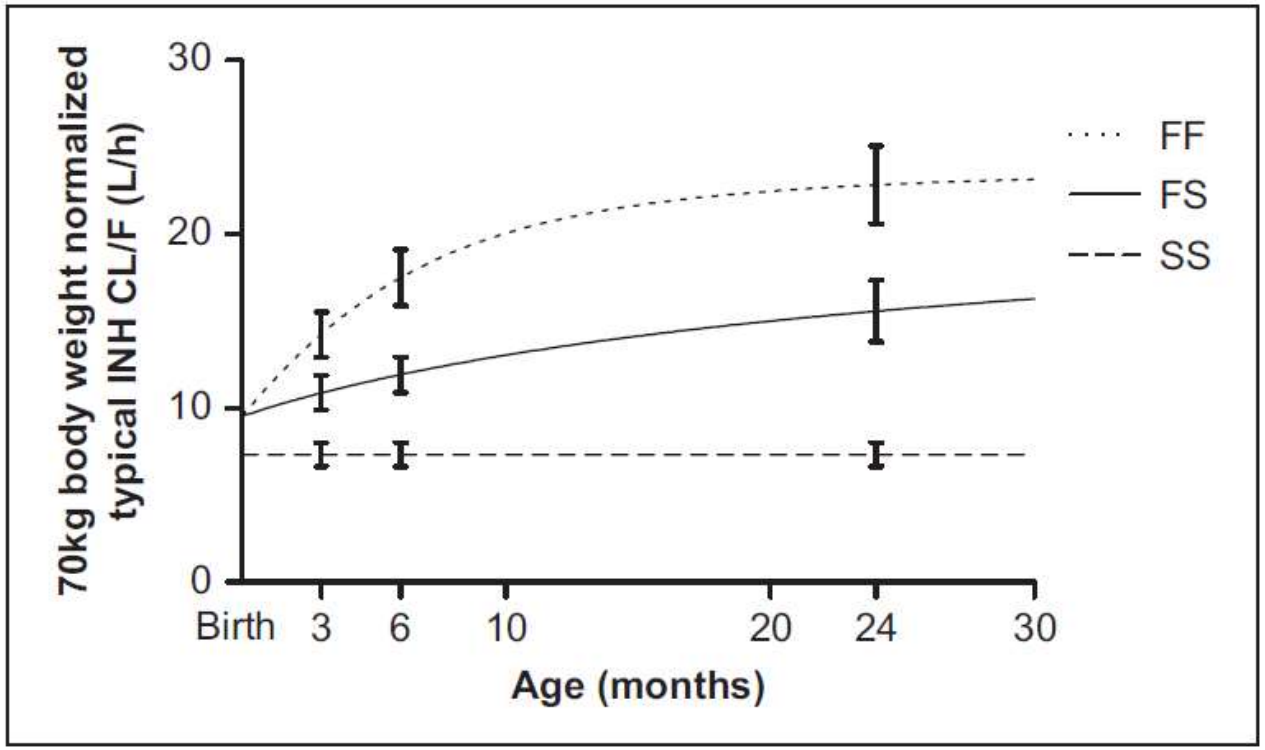
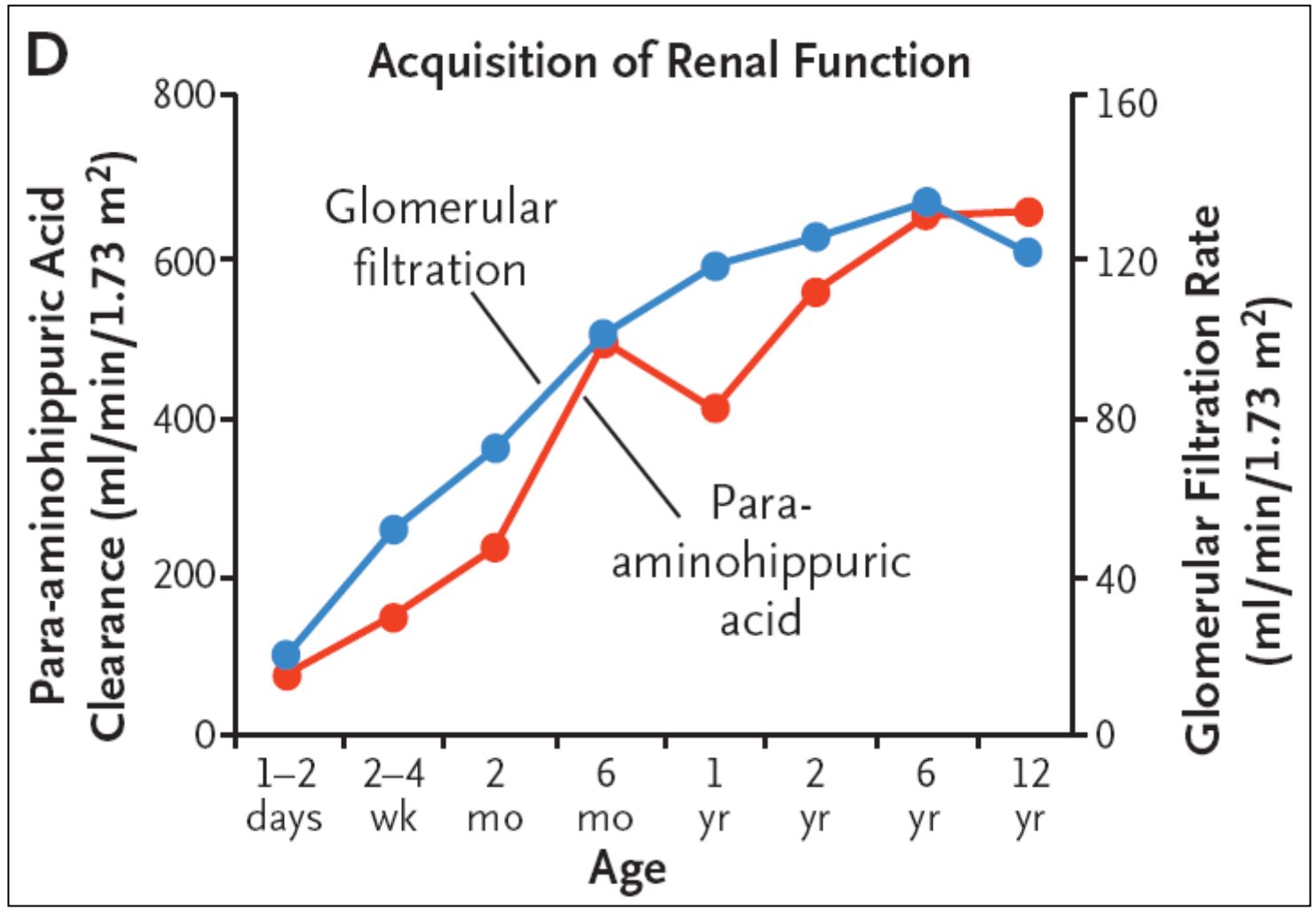


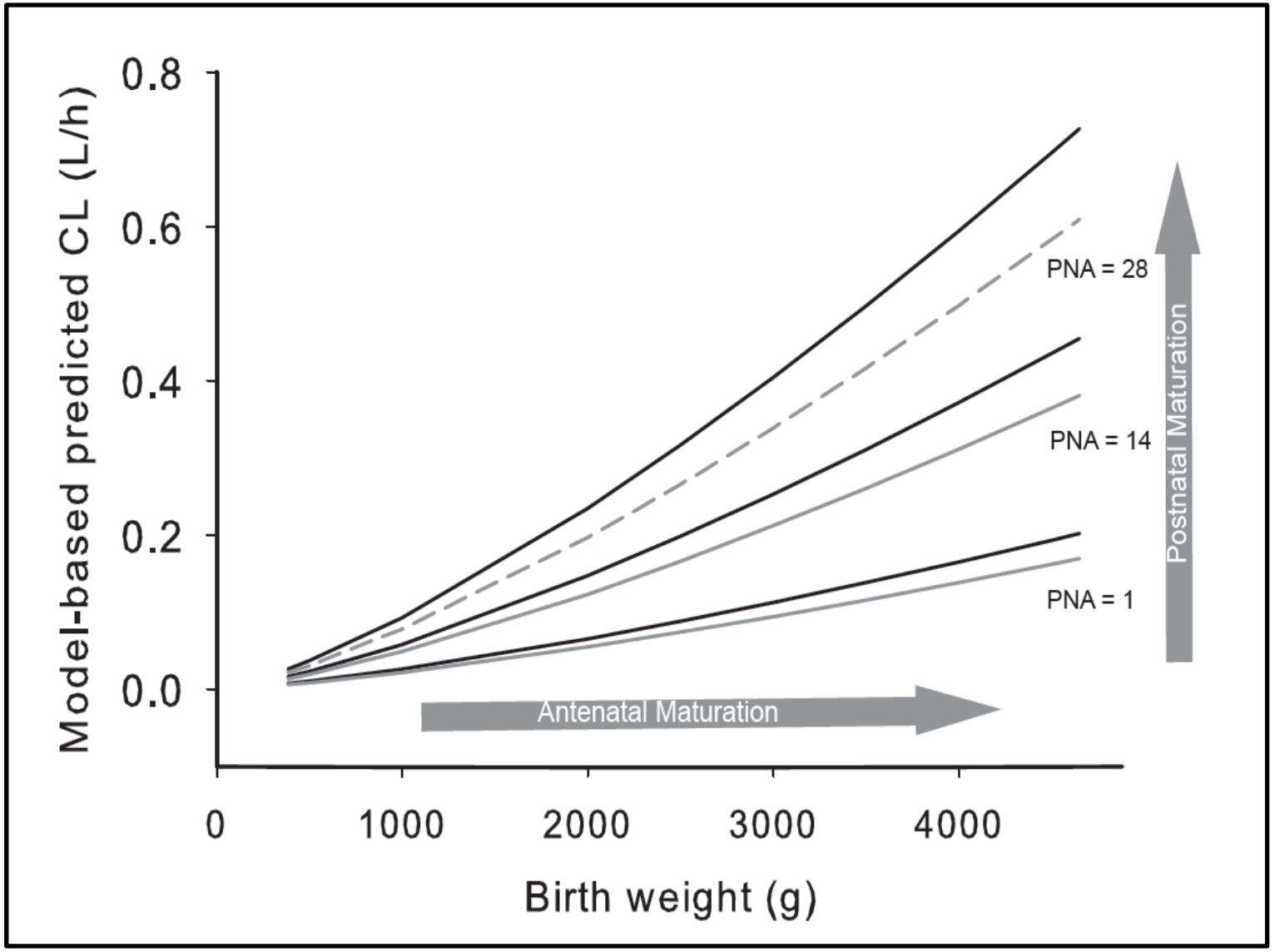
Figure 3. Seventy-kilogram body weight–normalized typical value of isoniazid apparent clearance versus age plot from the final enzyme maturation model with relative bioavailability fixed at 1. Error bars represent standard error of the mean. The curves were obtained from the population covariate model functions with relative bioavailability effect (f_F) fixed at 1.

Zhu et al, J Clin Pharmacol 2012



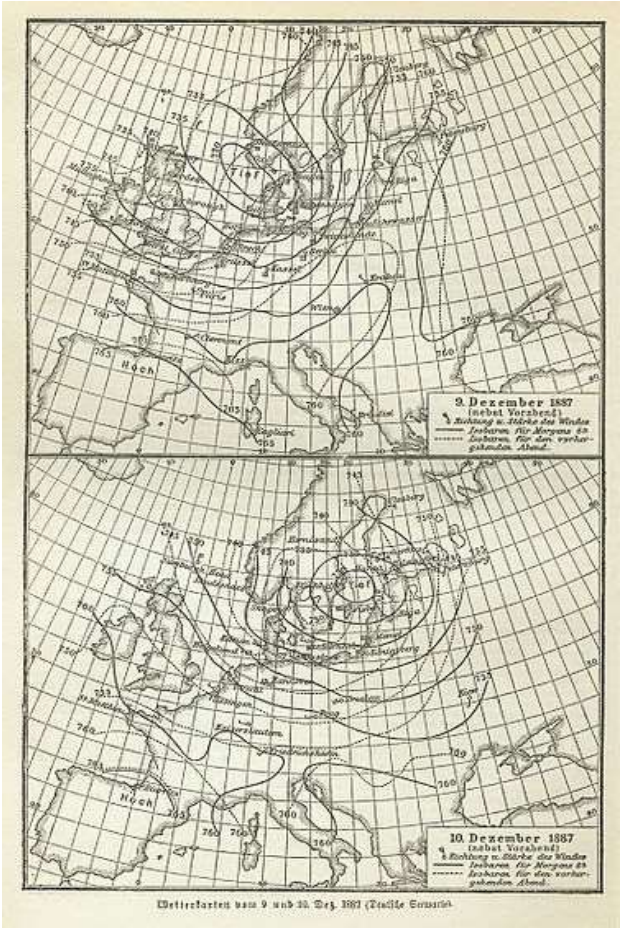
Kearns et al, NEJM 2003

amikacin clearance in neonates: age/weight/NSAIDS/asphyxia



De Cock et al, Clin Pharmacok 2013; Cristea et al, Antimicrob Agents Chemother 2017

models: *let's make things better...*



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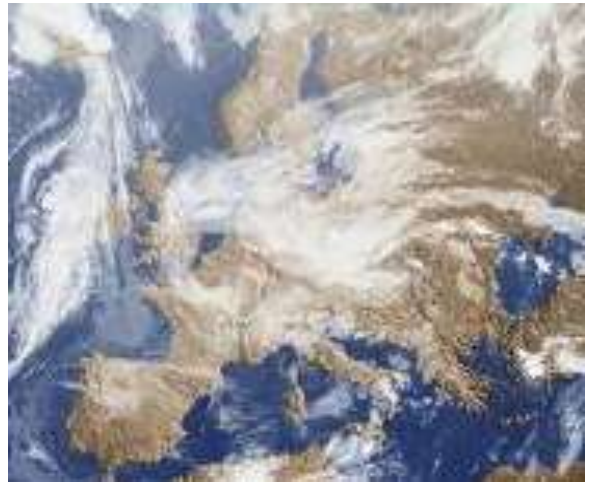
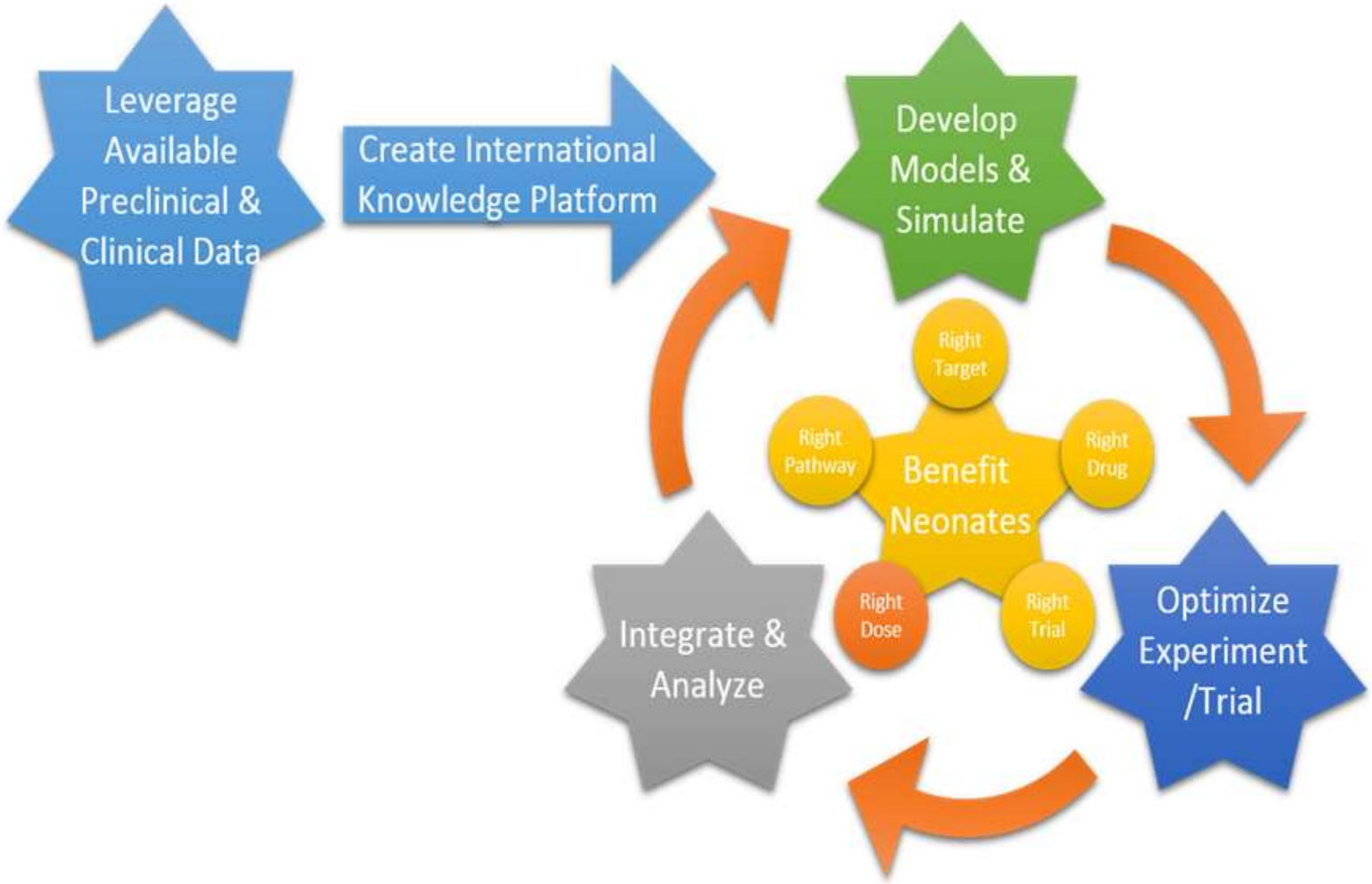


2014

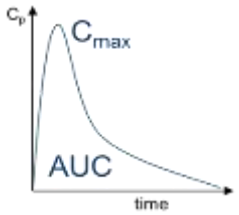
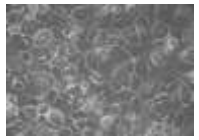
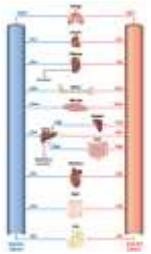
Essentially, all models are wrong, but some are useful.

(George E.P. Box, 1919 - 2013)

drug evaluation studies in neonates: how to overcome the current limitations



integrate neonatal (patho)physiology into neonatal drug development

	Data gathering	Modelling	Clinical implications
"TOP DOWN" **Clinic to mechanistic (population-based)**	Plasma Data  	Population-based PK (Covariates?)	Confirming 
"BOTTOM UP" ***In vitro* to *In vivo* (IVIVE)**	 Demography Physiology Genetics *In vitro* data  	PBPK/IVIVE 	Learning 

Conclusions

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