Type of parameters	Parameters	Values for the different typical patients investigated								[Ref] (Eq)
Age		1 day	1 month	6 months	1 year	2 years	5 years	15 years	35 years	
Demographic values	Bodyweight [1] (kg)	3.45[a]	4.3[a]	7.55[a]	9.9[a]	12.35[a]	18.25[a]	54.25[a]	66.5[b]	[1][a], [2][b]
	Height[1] (cm)	49.75[a]	54.25[a]	66[a]	74.75[a]	86[a]	108.25[a]	166[a]	169.5[b]	[1][a], [2][b]
	Body surface area (m^2)	0.22[c]	0.26[c]	0.38[c]	0.46[c]	0.55[c]	0.74[d]	1.60[d]	1.77[d]	[3](1)[c], [4](2)[d]
Drug properties	CLint,mic ($L.min^{-1}.mg^{-1}$ microsomal protein)	between $0.56.10^{-3}$ and 0.209 with 124 intermediate equidistant values								[5]
	Kp	0, 1, 2, 3 or 4								
	fu in adults	From 0.01 to 1 with 8 intermediate equidistant values								
Size and age independent system specific parameters	Liver density ($g.L^{-1}$)	1080								[6]
	MPPGL ($mg.g^{-1}$)	33								[6]
	D_N	0.17								
System specific parameters influenced by size-related changes	Liver weight (g)	133	159	249	313	385	544	1351	1523	[6](3-5)
	Cardiac output ($L.min^{-1}$)	0.52[e]	0.61[e]	0.92[e]	1.15[e]	1.46[e]	2.33[e]	5.59[e]	6.2[f,2]	[6](6)[e], [2][f]
	Hepatic blood flow ($L.min^{-1}$)	0.14	0.17	0.25	0.32	0.40	0.64	1.54	1.70	[6](7)
	Glomerular filtration rate ($mL.min^{-1}$)	3.97	7.49	18.90	26.56	34.71	51.90	85.84	138.05	[6](8)
System specific influenced by maturational changes	Albumin concentration	27	31	33	34	35	36	37	38	[6](9)
	Alpha 1 glycoprotein concentration	0.04	0.13	0.22	0.27	0.32	0.40	0.49	0.56	[6](10)
	Hematocrit	56	44	36	36	36.5[3]	37	42[2]	44[2]	[7]

Table of the parameters implemented in the PBPK-workflow. Demographic values are typical size parameters correlated to age. Drug properties are parameters chosen for the generation of the different hypothetical drugs. System specific parameters are parameters reflecting the physiology and are categorized based on their dependence on age (maturation) and size (size-dependent changes). CLint,mic stands for unbound microsomal intrinsic clearance, Kp stands for blood to plasma partition coefficient, fu stands for unbound drug fraction in plasma, MPPGL stands for amount of microsomal protein per gram of liver and D_N stands for dispersion number. Superscript letters show the different source of the data between different ages; [1]: mean of the 50^{th} percentile in males and females; [2]: values based on the mean between males and females; [3]: average between two age groups when age corresponds to cut off age for the reported hematocrit value.

Formulas used to obtain the demographic and system specific parameters

Formulas for demographic values

- *Body surface area, as implemented in the PBPK model from Johson et al.[6]:*
  - Body surface area (BSA) based on Haycock et al. formula [3] for children with a bodyweight smaller than 15kg

$$BSA\ (\mathrm{m^2}) = 0.024265 \times \text{Bodyweight (kg)}^{0.5378} \times \text{Height (cm)}^{0.3964} \quad (1)$$

  - Body surface area (BSA) based on Dubois and Dubois formula [4] for children with a bodyweight greater than 15 kg and for adults

$$BSA\ (\mathrm{m^2}) = 0.007184 \times \text{Bodyweight (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \quad (2)$$

Formulas for size related-changes

- *Liver weight based on Johson et al.[6]:*

$$Liver\ weight\ (g) = \text{Liver density } (\mathrm{g}.L^{-1}) \times \text{Liver volume (L)} \quad (3)$$

$$\text{Liver density } (\mathrm{g}.L^{-1}) = 1080 \quad (4)$$

$$Liver\ volume\ (L) = 0.722 \times \mathrm{BSA}^{1.176} \quad (5)$$

- *Cardiac output based on Johson et al.[6]:*

$$Cardiac\ output = \left[u + \frac{(Age - v) \times (w - x)}{y - z}\right] \times BSA \quad (6)$$

where u = 2.5, v = 1, w = 4, x = 2.5, y = 10 and z = 1 for ages ≤10 years, and u = 4, v = 10, w = 3, x = 4, y = 20 and z = 10 for ages >10 years, but ≤20 years.

- *Hepatic blood flow ($\mathrm{Q_H}$) based on Johson et al. [6]:*

$$\mathrm{Q_H} = 0.275 \times Cardiac\ output \quad (7)$$

- *Glomerular filtration rate (GFR) based on Johson et al. [6]:*

$$GFR\ (L) = (-6.1604 \times \mathrm{BSA}^2) + (99.054 \times BSA) - 17.74 \quad (8)$$

Formulas for maturational changes of system specific parameters (independent of drug properties)

- *Plasma protein concentration based on Johson et al. [6]:*
    - Albumin:

$$Plasma\ albumin\ concentration(\mathrm{g}.L^{-1}) = 1.1287\ \times \ln(Age) + 33.746 \quad (9)$$

With Age in years

    - α1-acid glycoprotein (AGP):

$$Plasma\ AGP\ concentration(\mathrm{g}.L^{-1}) = \frac{0.887\ \times \mathrm{Age}^{0.38}}{8.89^{0.38} + \mathrm{Age}^{0.38}} \quad (10)$$

With Age in years

Formulas for the drug and system specific parameters

Clearance is dependent on drug and system specific parameters, that is to say parameters dependent on both drug properties and system specific parameters.

<u>Formulas for maturational changes of system and drug specific parameters (dependent on drug properties)</u>

- *Fraction unbound based on Johson et al.[6]:*

$$fu_{paediatric} = \frac{1}{1 + \frac{(1 - fu_{adult}) \times [P]_{paediatric}}{[P]_{adult}\ \times fu_{adult}}} \quad (11)$$

With maturation in [P] (concentration in plasma protein for either albumin or AGP) driving the maturation of fu

- *Blood to plasma ratio (B:P) based on Maharaj et al. [8]:*

$$B{:}P = 1 + \ [Hematocrit\ \times (fu \times Kp - 1)] \quad (12)$$

With maturation in hematocrit and in plasma protein driving the maturation in B:P.

- *Intrinsic clearance (CLint) based on Johson et al.[6]:*

$$CLint = \mathrm{MPPGL} \times \mathrm{Liver\ weight}\ \times \mathrm{CLint,mic}\ \times \mathrm{enzyme\ maturation} \quad (13)$$

With enzyme maturation (expressed as a percentage of adult CLint,mic) driving the maturation of CLint. In the PBPK-workflow, different enzyme maturation were investigated.

<u>Plasma clearance (CLp) for drugs undergoing glomerular filtration for adults and children, based on Johnson et al. [6]</u>

$$CLp\ = GFR\ \times fu \quad (14)$$

For scenario 1, selection of the drug property fu=1 allows for the simplification equation 14 into an equation only reflecting size related changes:

$$CLp\ = GFR \quad (15)$$

Clearance for drugs undergoing hepatic metabolism based on Naritomi et al. [9]

$$CLp = CL_B \times B{:}P \quad (16)$$

$$CL_B = Q_H \times E_H \quad (17)$$

$$E_H = 1 - F_H \quad (18)$$

$$F_H = \frac{4a}{(1+a)^2 \exp\{(a-1)/2D_N\} - (1-a)^2 \exp\{-(a+1)/2D_N\}} \quad (19)$$

$$a = (1 + 4R_N \times D_N)^{1/2} \quad (20)$$

$$R_N = (fu/B{:}P) \times CLint/Q_H \quad (21)$$

For scenario 1, selection of fu = 1 and Kp =1 (drugs for which B:P=1 for at ages) and enzyme maturation = 100% allows for the simplification equations 16, 23 and 13 into the equations 22,23 and 24 respectively leading to CLp equation only reflecting size related changes:

$$CLp = CL_B \quad (22)$$

$$R_N = CLint/Q_H \quad (23)$$

$$CLint = \text{MPPGL} \times \text{Liver weight} \times \text{CLint, mic} \quad (24)$$

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