Table 1. Pediatric and Adult Physiological parameters for the human BDCM model

Parameter, units	Symbol	Child 0-30 days	Child 31-90 days	Child ~1-2 years	Adult	Note
Height, cm	height	51.8	57.4	81.0	174.7	[1]
Body Weight, kg	BW	3.81	5.22	10.55	80.8	[2]
Alveolar ventilation Rate, L/h-m^2	QPC	391	432	470	419	[3]
Alveolar Deadspace, unitless	deadspace	0.336	0.336	0.336	0.344	[3]
QPC to Cardiac Output (CO) Ratio, unitless	RQPCO	1.0	1.0	1.0	1.0	[4]
Fractional Blood Flows, unitless						
Richly Perfused Tissue Group	FQRP	0.75	0.75	0.75	0.75	[5, 7]
Liver	FQL	0.13	0.13	0.13	0.09	[5 ,6]
Gastrointestinal Tract	FQG	0.15	0.15	0.12	0.16	[5, 6]
Kidney	FQK	0.13	0.13	0.14	0.15	[5, 6]
Poorly Perfused Tissue Group	FQPP	0.25	0.25	0.25	0.25	[5, 7]
Fat	FQF	0.04	0.04	0.05	0.05	[5 ,6]
Blood Flow to Skin, L/min-m^2	QSKSA	0.58	0.58	0.58	0.58	[5, 7]
Compartment Volume, unitless						
Blood fraction of BW	FVBD	0.0671	0.0617	0.0529	0.079	[5,8]
Blood as arterial	FVART	0.25	0.25	0.25	0.25	[5]
Blood as venous	FVVEN	0.75	0.75	0.75	0.75	[5]
Richly perfused fraction of BW	FVRP	0.2	0.2	0.2	0.2	[5]
Poorly perfused fraction of BW	FVPP	0.8	0.8	0.8	0.8	[5]
GI tract fraction of BW	FVGI	0.0146	0.0146	0.0177	0.0165	[5, 8]
Liver fraction of BW	FVL	0.0355	0.0355	0.0382	0.026	[5, 8]
Fat fraction of BW	FVF	0.169	0.174	0.175	0.21	[8]
Kidney fraction of BW	FVK	0.0065	0.0065	0.0066	0.004	[5, 8]
Volume GI tract lumen, L	VLUM	0.14	0.14	0.24	2.1	[5, 9]
Skin thickness, mm	LSK	1.3	1.3	1.3	2.0	[5, 10]

[1]Calculated based on midpoint of age range for 50th percentile from CDC data tables for length-for-age for male and female children. https://www.cdc.gov/growthcharts/who_charts.htm#The WHO Growth Charts. For adult, used mean combined male and female, aged 30-40 years (Table 8-3, USEPA, 2011a).

[2]Calculated based on midpoint of age range for 50th percentile from CDC data tables for weight-for-age for male and female children. https://www.cdc.gov/growthcharts/who_charts.htm#The WHO Growth Charts. For adult used combined male and female, aged 30-40 mean (Table 8-16, USEPA, 2011a).

[3]Derived from mean of alveolar ventilation rate male and female children at ~ 1 month in Brochu *et al.* (2006), and 0.22-0.5 yrs for 30-90 dys group, 1-2 yrs of age and adults (35-40 yrs) in Brochu *et al.* (2011). Deadspace figures from Brochu *et al.*, (2012) with childhood age groups assumed same and set to mean value for youngest age group (5-10 years) and 35-45 year age group for adults. Minute ventilation rate is scaled to skin surface area (SA) in m^2 in the model; QP = QPC* SA * (1-Deadspace). SA = Height $^{(0.725)}$ * Weight $^{(0.425)}$ * 0.007187 in m^2 from (Adams, 1993; also eq. 6-3 in USEPA, 2008) for all childhood age groups. For adults use equation, SA = Height $^{(0.417)}$ * Weight $^{(0.517)}$ * 0.02350 in m^2 (Gehan and George, 1970, also eq. 7A-3 USEPA, 2011a).

[4]Cardiac Output, QC = QP/RQPCO.

[5]Adult value same as in original model.

[6]Blood flows calculated from Edginton *et al.* (2006) for 0-30 (newborn) and one year-old, 31-90 days assumed same as newborn. Fractional blood flows to individual tissues are scaled to cardiac output (QC), i.e. QL = FQL *QC, QG= FQG *QC, QK= FQK * QC, and QF = FQF * QC.

[7]Richly (QRP) and poorly perfused (QPP) tissues calculated by difference subtracting out blood flows from liver, kidney and gut for QRP and subtracting out fat and skin volumes for QPP, i.e., QRP = (FQRP*QC)-QL-QK-QG and QPP = (FQPP*QC)-QF-QSK.. Blood flow to skin (QSK) is scaled on the basis of body surface area, i.e., QSK = QSKSA * SA * 60 min/hr. Total liver blood flow is sum of liver plus gut as shown in Figure S1.

[8]Calculated as fraction of BW using estimated mass based on equations from Haddad *et al.*, (2001) using average of male and female and midpoint of age range. FVL is included for completeness; Monte Carlo analysis uses FVL distributional descriptors specific for each age group in Table 3. Blood volume assumes density of 1 g/L. Fat volume is recalculated from equations of Haddad *et al.*, (2001) based on modifications in Price *et al.* (2003). Volume of blood compartment is scaled to BW and volume of arterial and venous compartments are scaled to total blood volume. Tissue volumes to tissues are scaled to BW with richly (VRP) and poorly perfused (VPP) tissue volumes calculated respectively, as follows: VRP = FVRP*BW-VL-VGI-VBD-VK and VPP = FVPP*BW-VF-VSK. Volume of skin (VSK) is calculated as VSK = LSK*SA.

[9]Estimated based on figures in ICRP (2002, Table 2,8, p. 18) for newborn and 1-year old; age range 31-90 days assumed to be same as 0-30 days.

[10] LSK is average value for thickness of dermis and epidermis for adults (Laurent *et al.*, 2007) and all pediatric age groups (Ploin *et al.*, 2011). Note that skin thickness remains relatively unchanged based on age (up to 5 years), BMI, gender and skin phototype (Ploin *et al.*, 2011).

Table 2. Chemical-specific parameters in the human BDCM model*

Parameter, units	Symbol	Value	Footnote
Partition coefficients, unitless			
Blood:Air	PBBDCM	15.97	[1]
Liver:Blood	PLBDCM	1.93	[1]
Gut:Blood	PGBDCM	1.93	[2]
Kidney:Blood	PKBDCM	2.08	[1]
Fat:Blood	PFBDCM	33.2	[1]
Skin:Blood	PSKBDCM	2.91	[3]
RPTG:Blood	PRPBDCM	1.93	[2]
PPTG:Blood	PPPBDCM	0.78	[1]
Skin diffusion coefficient, cm/h	KBDCM	0.18	[4]
Skin:water partition coefficient	PWSBDCM	5.6	[4]
Oral absorption coefficient, h^{-1}	KABDCM	8.3	[5]
Vmax CYP Liver, µg/h-pmol CYP2E1	IVVMAX	0.201	[6]
KM CYP Liver, µg/L	KM1BDCM	221	[6]
Kf GST Liver, 1/h-kg $BW^{0.75}$	VFCBDCM	0.0079	[7]

[1]Calculated by dividing rat tissue:air partition coefficient (Lilly *et al.* 1997) by human blood:air partition coefficient from Kenyon *et al*. (2016).

[2] Gut:air and rapidly perfused tissue:air partition coefficients were assumed to be the same as liver:air.

[3] Skin:air partition coefficient (Haddad *et al.* 2006) used with human blood air partition coefficient to calculate skin:blood partition coefficient.

[4] Skin diffusion coefficient determined with method using aqueous solution across human skin (Xu *et al.* 2002). Skin:water partition coefficient calculated on basis of water:air partition coefficient (Batterman *et al.* 2002) divided by skin:air partition coefficient (Haddad *et al.* 2006).

[5]Estimated on basis of Tmax from oral time course data of Leavens *et al.* (2007) and assumed to be the same across age groups.

[6]Experimentally determined in pooled adult human microsomes as 1.74 nmoles/min – mg MSP (Kenyon *et al.*, 2016a) and converted to 17.14 µg/h-mg MSP in (Kenyon *et al.*, 2016b) analysis. Converted to basis of CYP 2E1 for this analysis using known average CYP2E1 content (85 pmol CYP2E1/mg MSP) for independent set of adult samples for which both CYP2E1 content and P450 content are known at the level of the individual subject (J. Lipscomb, personal communication).

[7]Estimated from *in vitro* clearance of BDCM from pooled human liver cytosol (Ross and Pegram 2003).

Table 3. Parameter distributions and values used as input to Monte Carlo analysis for pediatric age groups and adults

Parameters[1]	FVL		MPPGL		CYP2E1	
Age Group	Distribution & Descriptors[2]	Value	Distribution & Descriptors	Value	Distribution & Descriptors	Value
0-30 days, neonate	Normal		Log Normal		Gamma	
	Mean	0.0412	GM	25.55	Alpha	0.505
	SD	0.0157	GSD	1.001	Theta	26.6
	Lower Limit	0.0114	Lower Limit	25.53		
	Upper Limit	0.0775	Upper Limit	25.60		
31-90 days, infant	Normal		Log Normal		Gamma	
	Mean	0.0366	GM	25.68	Alpha	10.7
	SD	0.0102	GSD	1.002	Theta	2.24
	Lower Limit	0.0145	Lower Limit	25.61		
	Upper Limit	0.0612	Upper Limit	25.74		
91 days – 2 years, toddler	Normal		Log Normal		Gamma	
	Mean	0.0445	GM	26.35	Alpha	4.82
	SD	0.0159	GSD	1.028	Theta	9.42
	Lower Limit	0.0274	Lower Limit	25.76		
	Upper Limit	0.1200	Upper Limit	27.36		
Adult	Normal		Log Normal		Gamma	
	Mean	0.0239	GM	35.24	Alpha	11.1
	SD	0.0090	GSD	1.094	Theta	5.33
	Lower Limit	0.0136	Lower Limit	29.26		
	Upper Limit	0.0415	Upper Limit	40.19		

[1]FVL (g liver/kg BW, assuming a volumetric density of 1) and CYP2E1 (pmol/mg microsomal protein) were calculated from data in Johnsrud *et al.* (2003) for specific pediatric age groups. FVL for adults was recalculated from Young *et al.* (2009). CYP2E1 for adults is from Lipscomb *et al*. (1997, 2003a, b). MPPGL was estimated on the basis of the equation published in Barter *et al.* (2008) using subject age in years for all age groups.

[2]Lower and upper limits are lowest and highest values from data, respectively. Abbreviations: SD is standard deviation, GM is geometric mean and GSD is geometric standard deviation. GM and GSD are log transformed for input into acslx MC routines. For the gamma distribution, alpha is the shape parameter and theta is the scale parameter.