**Supplementary Material Part 1**

***Height***

******The growth curve for BH in an individual male and female younger than or equal to 3 years old was adapted from Jolicouer, Pontier, Pernin, and Sempre (JPPS) model (1998) and is described by equations 1 and 2:

Equation 1



Equation 2

Where Hi is BH (cm) at age AGE (years) for the ith individual; h1,i is the BH at adult age for the ith individual; D1 is a time-scale factor; C1 is a positive dimensionless exponent, reflecting the shape of the growth curve, 0.75 is the average age since conception in year at birth, H3y,i  is BH at 3 years calculated for the ith individual from Equation 4. H3y,i,JPPS  is BH at 3 years calculated for the ith individual from Equation 1.

The growth curve for BH in an individual male and female older than 3 years old was adapted from the Preece Baines model (1978) and is described by equation 3:

 Equation 3



Equation 4

Where Hi is BH (cm) at age AGE (years) for the ith individual; h1,i is the adult height for the ith individual; θi is a timing parameter controlling the location of the adolescent growth spurt along the time axis for the ith individual. θi is highly correlated with age at peak height velocity, hθ,i is the BH at age θi. The rate constant S0,i controls prepubertal growth velocity and S1,i controls pubertal growth velocity.

S0,i, S1,i, θi, and h1,i were assumed to follow a normal distribution. hθ,i was defined with equation 5 so that birth height (length) could vary given the same adult height and the resulting distribution of BH at early age was reasonable.

 Equation 5

Mean values of S0, S1, θ, h1, hθ, C1, and D1 were estimated based on the median BH curve from NHANES 2005-2006 data for males and NHANES 2003-2004 data for females. The variance of the S0, S1, θ, h1, and error terms were determined when the 5th, 50th and 95th percentiles of BH curves from the simulated data matched the observed corresponding NHANES data for males and females.

***Weight*.** The growth curve for BW was adapted from the O’Flaherty model (1993) and is described by equation 6 (O'Flaherty 1993):



Equation 6

Where Wi is BW (kg) for the ith individual at age AGE (years); WBirth,i represents BW at birth for the ith individual; WChild,i is the maximum weight (kg) for the ith individual during the early hyperbolic section of the growth curve; HALFi is the midpoint age (years) for the ith individual in this hyperbolic growth segment. WChild,i and HALFi define the rapid growth that takes place in early childhood. A logistic growth curve, determined by the empirically determined parameters WAdult,i (kg), Ki, and Li , describing growth during puberty and early adulthood, is superimposed. Among these parameters, WBirth,i was assumed to follow a normal distribution and HALFi was assumed to follow a log normal distribution.

***Linking the height and weight growth curves.*** The age at peak height velocity and age at peak weight velocity were linked in the simulation. The age at peak height velocity was correlated with θ. The age at peak height velocity can be described as the following:

Equation 7

Where

The age at peak weight velocity was not directly represented by any parameters in the equation. To get the weight velocity curve, we took the first derivative of the weight equation and each term in the weight equation. The velocity of total BW change over time was parallel with the velocity of the logistic growth part. So the age at peak weight velocity was derived by taking the second derivative of the logistic growth term in the weight equation. The derived age at peak weight velocity (APWV) is:

Equation 8





So Equation 9

To link the age at peak weight velocity and age at peak height velocity, we have:

Age at peak weight velocity (APWVi) = θi + Diff\_BH\_BW + error\_APWV; where Diff\_BH\_BW represents the lag time between age at peak height velocity and age at peak weight velocity. Mean values of WBirth, WChild, WAdult, K, HALF and L were estimated based on the median weight curve from NHANES 2005-2006 data for males and NHANES 2003-2004 data for females. The variance of WBirth, WChild, WAdult, HALF and Diff\_BH\_BW and error terms were determined by matching the 5th, 50th and 95th percentiles of the weight curves from the simulated data to the corresponding NHANES data for males and females.

Ideally, longitudinal data should be used to develop the growth model during puberty. However, longitudinal data is not available. So we started with reported parameters in the published sources which used longitudinal data and optimized the distribution of parameters based on NHANES data. The average peak height velocity was comparable between simulated (8.21 cm/year) and observed (8.1 cm/year) (Buckler and Wild, 1987). The average peak weight velocity was smaller in simulated (5.25 kg/year) compared to observed (6.1 kg/year) (Buckler and Wild, 1987). So using NHANES data may result in an underestimation of the impact of puberty on PFAS concentrations but this effect may be limited.

***Exclusion criteria*.** To identify and exclude subjects with implausible values of body measurements, we used BMI z-score as a criterion, which has been used in the standard analysis for WHO Global Database (WHO, 2014). Simulated individuals with BMI z-score greater than 5 or less than -5 were excluded from the final dataset. BMI z-score was calculated based on the 50th percentile of the simulated BMI curve and the standard deviation of BMI at each age in the NHANES 2003-2004 dataset (CDC, 2014).

***Body mass index (BMI)***

BMI in an individual male and female is described by the following equation adapted from Taylor et al. (1972):

Where BMIi is BMI (kg/m2) at age AGE (years) for the ith individual; BWi is the body weight at age AGE (years) for the ith individual; BHi is the body height at age AGE (years) for the ith individual.

***Body surface area (BSA)***

BSA in an individual male and female is described by the following equation adapted from Gehan and George (1970):

Where BSAi is BSA (m2) at age AGE (years) for the ith individual; BWi is the body weight at age AGE (years) for the ith individual; BHi is the body height at age AGE (years) for the ith individual.

***Hematocrit***

Hematocrit for a male and a female at different ages was described using the following equations:

Age ≤ 1.0 year:

***HCT = 0.359 • (1+WSV\_HCT)***

Age > 1.0 year:

***HCT = ((1.12815e-06 • Years3) – (1.72362e-04 • Years2) + (8.15264e-03 • Years) + 0.327363) • (1.0 + WSV\_HCT)***

where HCT is the value of hematocrit. WSV\_HCT is a normally distributed random variable, with zero mean and variance σ2, accounting for the difference between the individual Hct and median Hct at a specific age. The equation for males older than 1 year was derived based on data from (Yip et al. 1984). The value of Hct in female younger than 1-year-old was assumed to be the same as that in a 1-year-old.

***Tissue volumes***

VTissue = VTissueC • BW

Where Tissue is brain, fat, liver, gut, rapidly perfused tissue and plasma; VTissue is the volume of the specified tissue in L; VTissuesC is the specified tissue volume as a fraction of body weight; and BW is the body weight in kg.

***Fat volume***

The percentage of body fat has been linked to body measurements such as BMI in many studies. NHANES collected data on body measurements including fat volume (measured by DXA), BW, BH, and BMI in the general population. We obtained these data from the website of the Centers for Disease Control and Prevention (CDC, 2014). Models for predicting percentage of body fat were fitted to the NHANES data by performing multiple linear regression with age, and different forms of BMI including BMI, 1/BMI, BMI2, and combinations of these factors. The relationship between percentage of body fat, age and BMI was best described by the following equation:

*For female:*

***Age ≤ 25 yrs: %FATi = (1.5334 • e -0.103•AGE + 0.67) • BMIi + 0.6276 • AGE + 1.0301***

***Age > 25 yrs: %FATi = 1.9224 • BMIi - 0.018517 • (BMIi2) + 0.05537 • AGE - 0.794894***

Where %FATi is percentage of body fat (%) for the ith individual at age AGE (years); BMIi is BMI for the ith individual at a specific age in years.

*For male:*

***Age ≤ 20 yrs: %FATi = (2.9875 • e -0.129•AGE + 0.67) • BMIi + 0.2635 • AGE - 4.843***

***Age > 20 yrs: %FATi = -5.33798 • BMIi + 0.11149 • (BMIi2) + 0.09795 • AGE + 85.24521***

Where %FATi is percentage of body fat (%) for the ith individual at age AGE (years); BMIi is BMI for the ith individual at a specific age in years.

***Other tissue volumes***

Several studies have reported relationships between body measurements and volume of tissues including liver, brain, plasma, gut and rapidly perfused tissues (Cropp 1971; Noda et al. 1997; Price et al. 2003; Clewell et al. 2004). We selected the most appropriate equations to simulate volumes of liver, brain, plasma, gut and rapidly perfused tissues from these studies. Equations for tissue volumes are summarized in **Supplemental Table 1**.

**Supplemental Table 1: Equations for tissue volumes in Female**

|  |  |  |
| --- | --- | --- |
| **Physiological Parameter** | **Source of equations** | **Relationship** |
| Plasma volume | Cropp, 1971 | VPls = 10(1.2082\*log10(BSA)+3.2869)•(1-Hct) |
| Liver volume | Noda, 1997 | Age ≤ 22 yrs: VLiv = 0.05012•BW 0.78  Age > 22 yrs: VLiv = (1.0728•BSA-0.3457) • S  S = 0.05012•BWAdult 0.78 /(1.0728•BSAAdult-0.3457) |
| Brain volume | Willmann, 2007 | 10• (Years + 0.315)/(9+6.92•Years) |
| GI volume | Price, 2003 | VGut = 0.027 • LBM (kg)  LBM = BW - Vfat |
| Rapidly perfused tissues | Clewell et al. 2004 | Vrap = 2.464 • VGut |

**Supplemental Table 2: Equations for tissue volumes in male**

|  |  |  |
| --- | --- | --- |
| **Physiological Parameter** | **Source of equations** | **Relationship** |
| Plasma volume | Cropp, 1971 | VPls = 10(1.2082\*log10(BSA)+3.2869)•(1-Hct) |
| Liver volume | Noda, 1997 | * Age ≤ 22 yrs: VLiv = 0.05012•BW 0.78 * Age > 22 yrs: VLiv = (1.0728 \* MBSA - 0.3457) \* MVLiv268 / (1.0728 \* MBSA\_268\_303 - 0.3457) * MVLiv268 (Liver volume at age 268 months for an average person) = 0.05012 \* MBWADULT^0.78 * MBSA\_268\_303 (BSA for an average person at 268 (female) or 303 (male) months old) = EXP(-3.751 + 0.422 \* LOG(H1) + 0.515 \* LOG(MBWADULT)) |
| Brain volume | Willmann, 2007 | 10• (Years + 0.315)/(9+6.92•Years) |
| GI volume | Price, 2003 | VGut = 0.021 • LBM (kg)  LBM = BW - Vfat |
| Rapidly perfused tissues | Clewell et al. 2004 | Vrap = 2.596 • VGut |

In this model, a constant density of 1 g/ml was assumed for all tissues, so mass in [kg]) is equal to volume (in [L]).

***Cardiac output***

Cardiac output was calculated for male and female based on body surface area (BSA) using the following equation:

QC (Cardiac output, L/h) = 60 • QCMIN,

QCMIN = 3.5 • BSA • (1+WSV\_QCMIN),

where WSV\_QCMIN is a normally distributed random variable, with zero mean and variance σ2, accounting for the difference between the individual QCMIN and median QCMIN given the same value of BSA.

QCP = QC • (1.0 – HTC),

Where QCP is the plasma cardiac output; and HTC is the hematocrit.

***Tissue blood flows***

The change of tissue blood flow during growth has rarely been reported. In our simulation, tissue blood flows were assumed to change proportionally with the tissue volumes as a fraction of BW across individuals over time.

QTissueC = QTisCAdult • (VTisC/VTisCAdult)

Qtissue = QTissueC • QCP

VTisCAdult = VTisAdult/BW\_Adult

VTisC = VTis/BW

Where tissue is for fat, gut, liver and rapidly perfused tissues; QTissueC is the blood flow to the specified tissue as a fraction of cardiac output; QTisCAdult is the standard fractional blood flow for the specified tissue as a fraction of cardiac output for an adult; VTisC is the volume for the specified tissue as a fraction of body weight; VTisCAdult is the volume for the specified tissue as a fraction of body weight at 25 years old;

For the brain, a nonlinear regression analysis was performed to describe the brain blood flow across ages based on data from yoon et al. 2011. Lognormal, hyperbola, allosteric-sigmoidal, dose-response, exponential and gompertz growth curves were used for fitting. Based on the degree of freedom and visual inspection, the best fit curve was chosen and the equation derived from this curve was used to describe age-dependent changes in brain blood flow.

*For female:*

QBRNC = (3.064/Years) • EXP (-0.5 • (LN(years/47.57)/1.946)2)

QBRN = QBRNC • QCP

*For male:*

QBRNC = (3/Years) • EXP (-0.5 • (LN(years/41.92)/1.876)2)

QBRN = QBRNC • QCP

***Pulmonary parameters***

Based on the data from IRCP, a nonlinear regression analysis was performed to describe the dead space in the lung (DS), the tidal volume (TV) and the breathing rate (RESPR) at resting or during light exercise through ages.

Lognormal, hyperbola, allosteric-sigmoidal, dose-response, exponential and gompertz growth curves were used for fitting. Based on the degree of freedom and visual inspection, the best fit curve was chosen and the equation derived from this curve was used to describe age-dependent changes in DS, TV and RESPR parameters.

**Supplemental Table 3: Equations for tissue volumes in female**

|  |  |  |  |
| --- | --- | --- | --- |
| **Respiratory parameters** | **Unit** | **Conditions** | **Equation from fitting ICRP data** |
| DS (dead space) | L |  | Y = 0.1274 • EXP (LN (0.01345/0.1274) • EXP (-0.161 • age)) |
| TV (Tidal volume) | L | Resting | < 5Y: Y = 0.02712 + (age0.9173) • (0.9599-0.02712)/(age0.9173 + 27.010.9173)  >5Y: Y = 0.4532 • EXP (ln (0.04072/0.4532) • EXP (-0.1909 • age)) |
| Light exercise | <1Y: Y = 1.159 • EXP (ln (0.07248/1.159) • EXP (-0.1362 • age))  >1Y: Y = 0.1036 + (age3.064) • (1.055 - 0.1036)/(age3.064 + 9.583.064) |
| RESPR (Breathing rate) | L/hr | Resting | Y = 0.3255 • EXP (LN (0.08771/0.3255) • EXP (-0.3731•age)) |
| Light exercise | Y = 0.269 + (age3.228) • (1.335 - 0.269)/(age3.228 + 6.6563.228) |

**Supplemental Table 4: Equations for tissue volumes in male**

|  |  |  |  |
| --- | --- | --- | --- |
| **Respiratory parameters** | **Unit** | **Conditions** | **Equation from fitting ICRP data** |
| DS (dead space) | L |  | Y = 0.17 • EXP (LN (0.01371/0.17) • EXP (-0.13 • age)) |
| TV (Tidal volume) | L | Resting | Y = 0.6842 • EXP (ln (0.04306/0.6842) • EXP (-0.1357 • age)) |
| Light exercise | Y = 0.1041 + (age2.727) • (1.478 - 0.1041)/(age2.727 + 12.232.727) |
| RESPR (Breathing rate) | L/hr | Resting | Y = 0.4493 • EXP (LN (0.09919/0.4493) • EXP (-0.175•age)) |
| Light exercise | Y = 0.4493• EXP (LN (0.09919/0.4493) • EXP (-0.175 • age)) |

**FIGURE LEGENDS**

**Supplemental Figure S1.** Comparison of model simulated body fat in female as a function of age with data from NHANES study 2003-2004. Red lines represent the 5th, 50th, and 95th percentiles from simulated data. Black lines represent the 5th, 50th, and 95th percentiles from observed data.

**Supplemental Figure S2.** Comparison of model simulated body fat in male as a function of age with data from NHANES study 2003-2004. Red lines represent the 5th, 50th, and 95th percentiles from simulated data. Black lines represent the 5th, 50th, and 95th percentiles from observed data.

**Supplemental Figure S3.** Comparison of model simulated cardiac outputs as a function of age with published data from William et al. (1994). Red lines represent the 5th, 50th, and 95th percentiles from simulated data. Symbols represent observed individuals. Solid black line represents reference curve for the population. Dashed black lines represent plus or minus 1 standard deviation from the reference curve.

**Supplemental Figure S4.** Comparison of model simulated volumes of liver, kidney, gut and blood in female as a function of age with data from published paper. Red lines represent the 5th, 50th, and 95th percentiles from simulated data. For liver and kidney, black symbols represent individual data from ICRP 2003. For gut, black symbols and line represent median and range of data from ICRP 1975. For blood, black symbols and lines represent mean and SD of data from Williams 1994.

**Supplemental Figure S5.** Comparison of model simulated blood flow of liver, kidney, gut and fat in female as a function of age with data from published paper. Red lines represent the 5th, 50th, and 95th percentiles from simulated data. For liver, black symbols represent mean and percentile data from Zoli et al., 1999. For kidney, black symbols represent mean of data from Dewoskin et al., 2008. For gut and fat, black symbols represent mean of data from ICRP 2003.

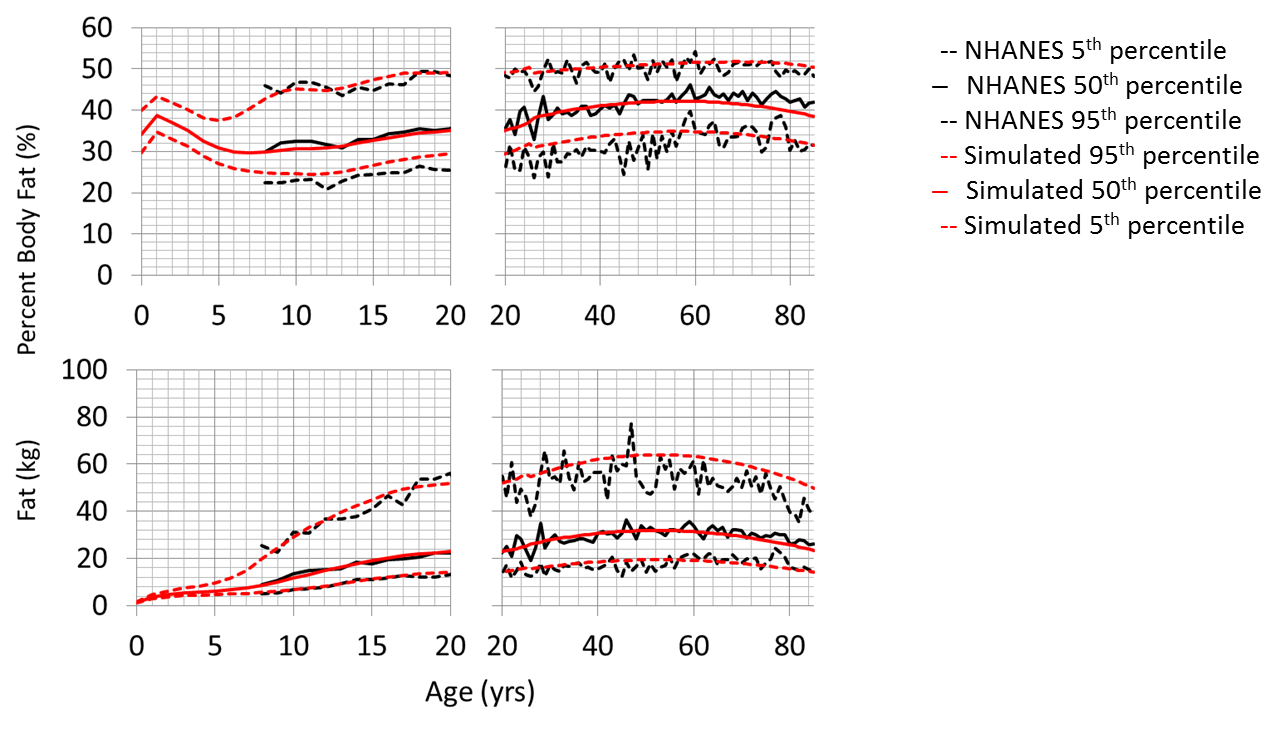
**Supplemental Figure S6.** Comparison of model simulated blood flow of brain in female as a function of age with data from published paper. Red line represents the mean from simulated data. Black symbols represent mean of data from ICRP 2003.

**Supplemental Figure S7.** Comparison of model simulated blood flow of brain in male as a function of age with data from published paper. Red line represents the mean from simulated data. Black symbols represent mean of data from ICRP 2003.

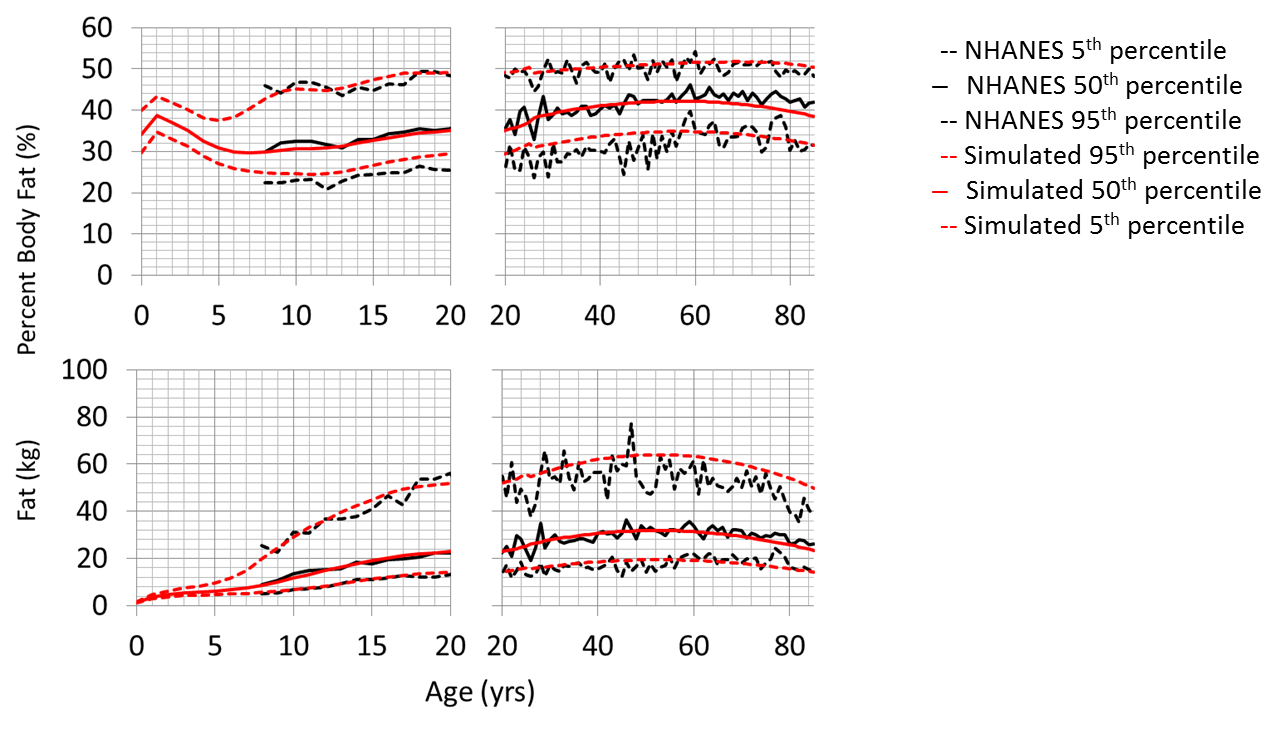
**Supplemental Figure S8.** Comparison of model simulated pulmonary parameters (Dead space DS, tidal volume TD and breathing rate RESPR) in female as a function of age with data from published paper. Red lines represent the mean from simulated data. Black symbols represent mean of data from ICRP 2003.

**Supplemental Figure S9.** Comparison of model simulated pulmonary parameters (Dead space DS, tidal volume TD and breathing rate RESPR) in male as a function of age with data from published paper. Red lines represent the mean from simulated data. Black symbols represent mean of data from ICRP 2003.

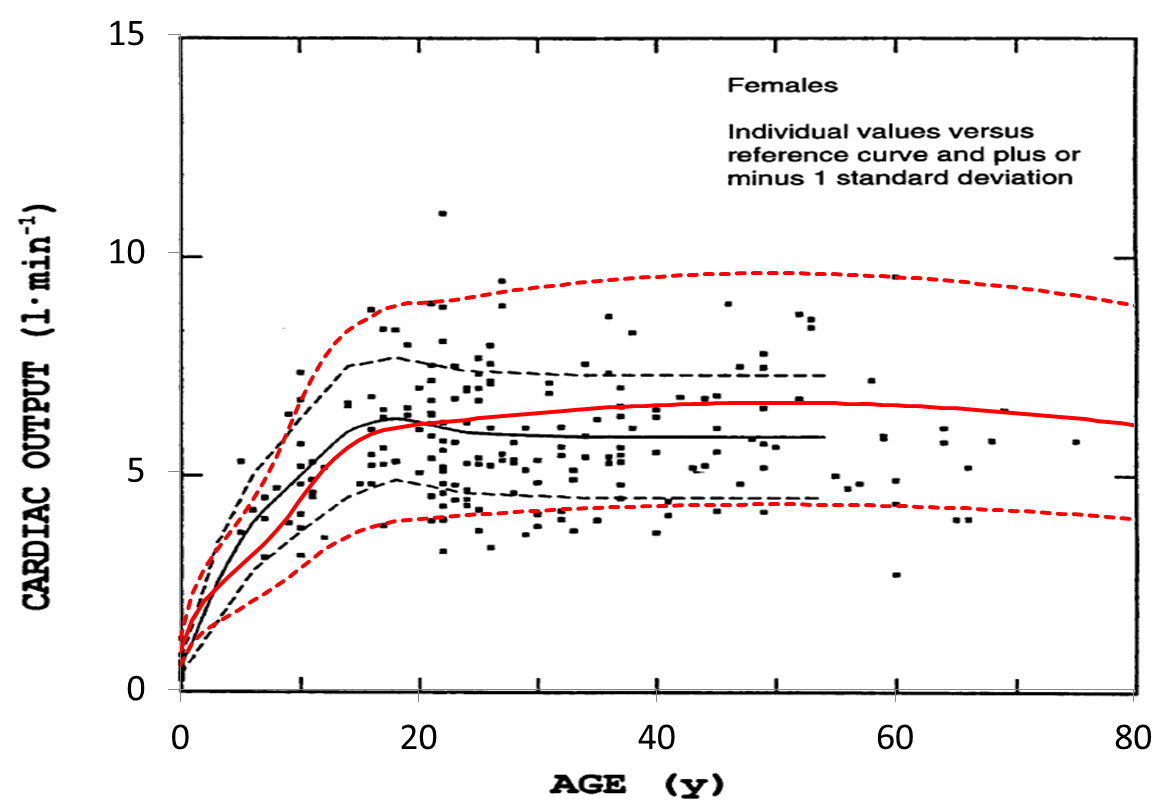
**Supplemental Figure S1.**

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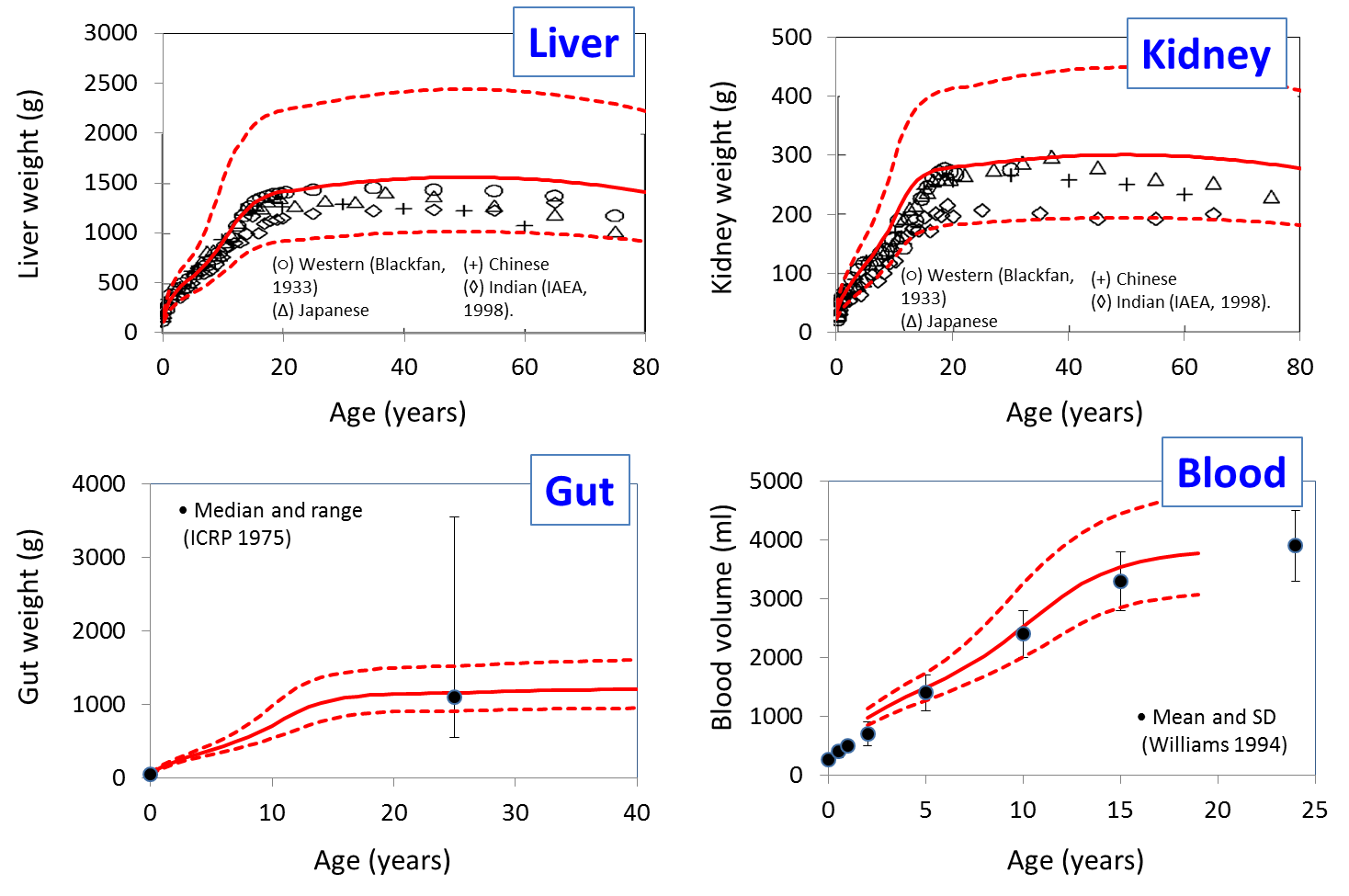
**Supplemental Figure S2.**

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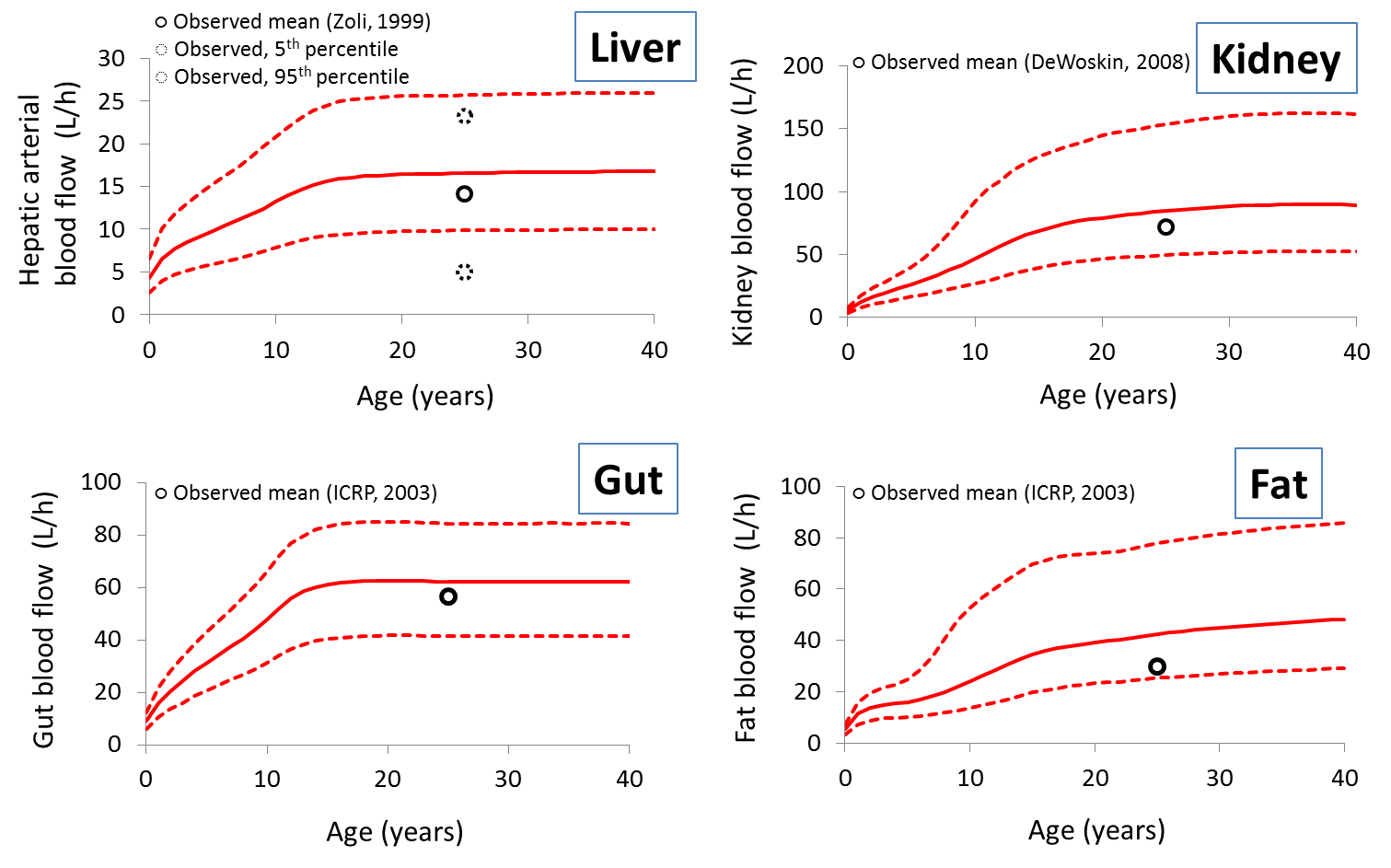
**Supplemental Figure S3.**

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**Supplemental Figure S4.**

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**Supplemental Figure S5.**

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**Supplemental Figure S6.**



**Supplemental Figure S7.**



**Supplemental Figure S8.**

**Supplemental Figure S9.**

**Supplemental Table 5**. Parameter Distributions Used in the Monte Carlo Simulation in female

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | **Mean** | **CV (%)** | **SD** | **Upper bound** | **Lower bound** | **Distribution** |
| **Body height** |  |  |  |  |  |  |
| h1 | 162.15 | 3.4 | 5.5 | 178.65 | 145.65 | Normal |
| θ | 11.2536 | 8.0 | 0.9 | 13 | 9 | Normal |
| S0 | 0.135 | 10 | 0.0135 | 0.1755 | 0.0945 | Normal |
| S1 | 1.27 | 10 | 0.127 | 1.651 | 0.889 | Normal |
| C1 | 0.7 | - |  |  |  |  |
| D1 | 2.3 | - |  |  |  |  |
| Error\_hθ | 0 | - | 0.005 | 0.015 | -0.015 | Normal |
| **Body weight** |  |  |  |  |  |  |
| WBirth | 3.4 | 4.4 |  | 4.42 | 2.38 | Normal |
| HALF | 3 | 5 |  | 3.4 | 2.6 | Lognormal |
| Diff\_BH\_BW | - 0.2 | - |  |  |  |  |
| Error\_APWV | 0 | - | 1.5 | 3 | -4.5 | Normal |
| Error\_WChild | 0 | - | 0.1 | 0.3 | -0.2 | Normal |
| Error\_WAdult | 0 | - | 0.4 | 1.2 | -0.6 | Normal |
| TIME\_GROWTH\_TO\_MENARCHE | 1.6434 | 76.7 | 0.8 | 4.6434 | -0.7566 | Normal |
| **Tissue volume** |  |  |  |  |  |  |
| Error\_VLiv | 0 | - | 0.2 | 0.4 | -0.4 | Normal |
| Error\_Vkid | 0 | - | 0.2 | 0.6 | -0.6 | Normal |
| **Cardiac Output** |  |  |  |  |  |  |
| Error\_QC | 0 | - | 0.2 | 0.6 | -0.6 | normal |
| **GFR** |  |  |  |  |  |  |
| Error\_GFR | 0 | - | 0.05 | 0.15 | -0.15 | normal |
| **Hematocrit (Hct)** |  |  |  |  |  |  |
| Error\_Hct | 0 | - | 0.065 | 0.195 | -0.195 | normal |

**Supplemental Table 6**. Parameter Distributions Used in the Monte Carlo Simulation in male

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | **Mean** | **CV (%)** | **SD** | **Upper bound** | **Lower bound** | **Distribution** |
| **Body height** |  |  |  |  |  |  |
| h1 | 177 | 3.4 | 6.02 | 165.2 | 188.79 | Normal |
| θ | 14.85 | 8.0 | 1.2 | 12.5 | 17.17 | Normal |
| S0 | 0.135 | 10 | 0.0135 | 0.1755 | 0.0945 | Normal |
| S1 | 1.5 | 10 | 0.15 | 1.21 | 1.794 | Normal |
| C1 | 0.9 | - |  |  |  |  |
| D1 | 0.5 | - |  |  |  |  |
| Error\_hθ | 0 | - | 0.005 | 0.015 | -0.015 | Normal |
| **Body weight** |  |  |  |  |  |  |
| WBirth | 4 | 4.4 | 0.18 | 3.66 | 4.35 | Normal |
| HALF | 6 |  | 0.05 | 5.42 | 6.62 | Lognormal |
| Diff\_BH\_BW | - 1.46 | - |  |  |  |  |
| Error\_APWV | 0 | - | 1.5 | 3 | -4.5 | Normal |
| Error\_WChild | 0 | - | 0.1 | 0.3 | -0.2 | Normal |
| Error\_WAdult | 0 | - | 0.4 | 1.2 | -0.6 | Normal |
| TIME\_GROWTH\_TO\_MENARCHE | 1.6434 | 76.7 | 0.8 | 4.6434 | -0.7566 | Normal |
| **Tissue volume** |  |  |  |  |  |  |
| Error\_VLiv | 0 | - | 0.2 | 0.4 | -0.4 | Normal |
| Error\_Vkid | 0 | - | 0.2 | 0.6 | -0.6 | Normal |
| **Cardiac Output** |  |  |  |  |  |  |
| Error\_QC | 0 | - | 0.2 | 0.6 | -0.6 | normal |
| **GFR** |  |  |  |  |  |  |
| Error\_GFR | 0 | - | 0.05 | 0.15 | -0.15 | normal |
| **Hematocrit (Hct)** |  |  |  |  |  |  |
| Error\_Hct | 0 | - | 0.065 | 0.195 | -0.195 | normal |

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