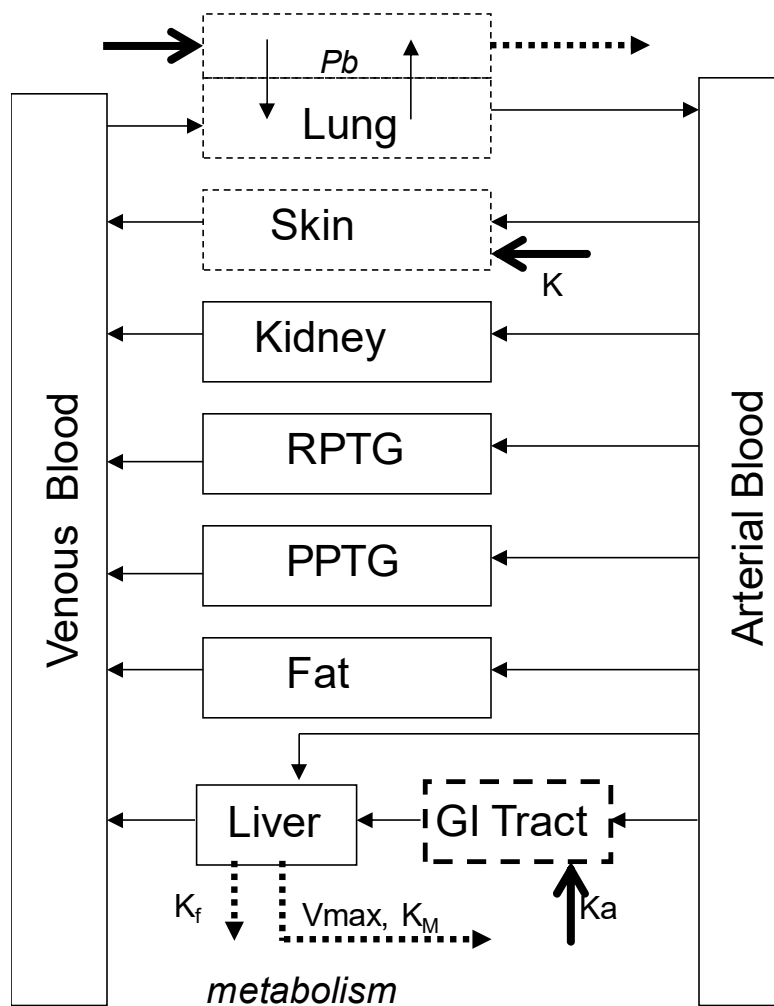


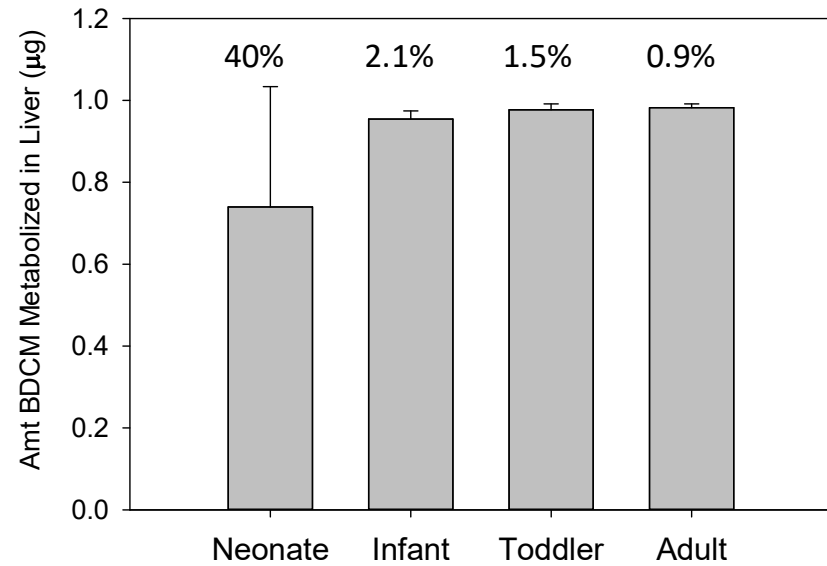
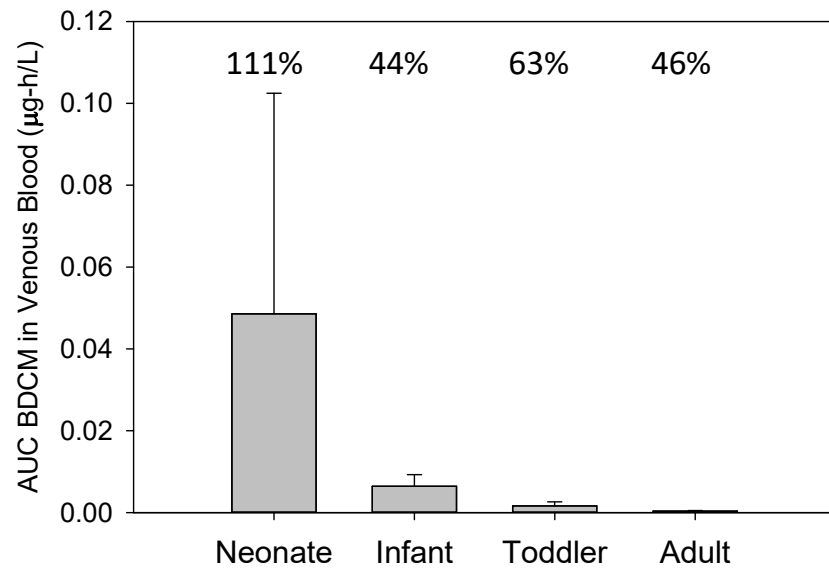
## **Supplemental Material – Inputs and Data**

### Supplemental Description Neonatal Group Pediatric Data

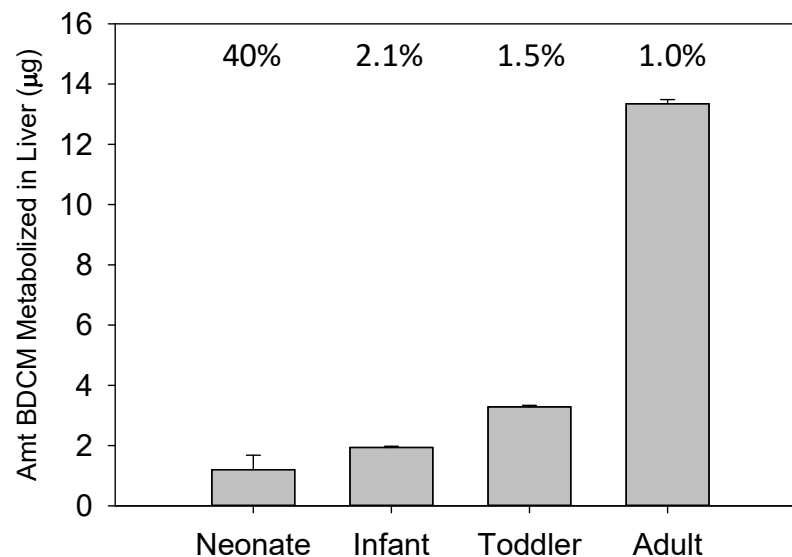
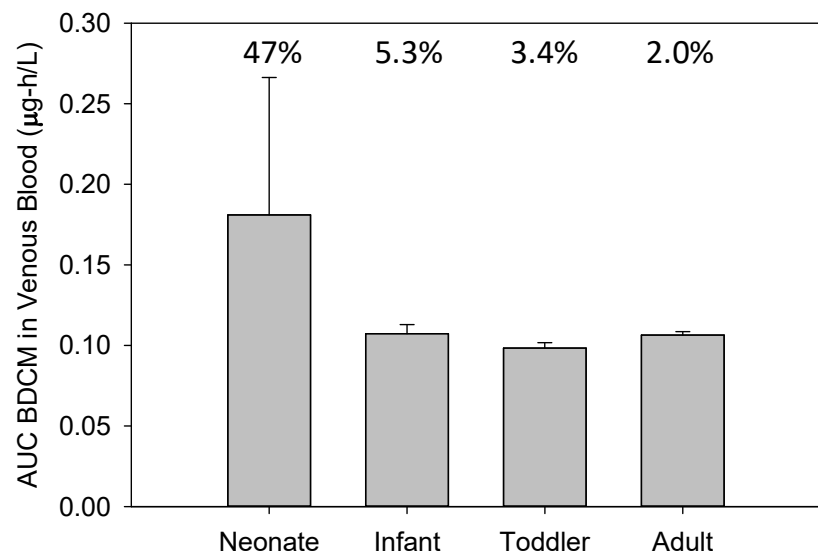
The neonatal group (up to 30 days of age) in this publication and those of Johnsrud et al. (2003) and Nong et al. (2006) included neonates born both prematurely and full term. Postnatal samples with no reported estimated gestational age in McCarver et al. (2017) are term (23/42). Samples from premature births where there was survival for at least one day were included in the neonatal group because previous studies (Koukouritaki et al., 2002) have demonstrated that birth is more important than gestational age in triggering postnatal changes in XME protein expression.



Supplemental Figure S1 - Schematic diagram of the human BDCM Model. Thick black arrows indicate routes of entry to specific tissue compartments (dotted lines). Thin solid lines and arrows indicate blood flow for organs connected by systemic circulation.



Supplemental Figure S2 - Comparison of AUC for (A) venous blood BDCM ( $\mu\text{g}\cdot\text{h}/\text{L}$ ,  $\bar{x} \pm \text{SD}$ ) and (B) amount of BDCM metabolized in liver ( $\mu\text{g}$ ,  $\bar{x} \pm \text{SD}$ ) across age groups based on Monte Carlo simulations (2 hours) utilizing the distributional characteristics for FVL, CYP2E1 and MPPGL shown in Table 3 for an oral exposure to water containing  $20 \mu\text{g}/\text{L}$  BDCM as a single 0.05-liter drink. The number associated with each bar is the coefficient of variation (%).



Supplemental Figure 3. Comparison of AUC for (A) venous blood BDCM ( $\mu\text{g}\cdot\text{h}/\text{L}$ ,  $\bar{x} \pm \text{SD}$ ) and (B) amount BDCM metabolized in liver ( $\mu\text{g}$ ,  $\bar{x} \pm \text{SD}$ ) across age groups based on Monte Carlo simulations (2 hours) utilizing the distributional characteristics for FVL, CYP2E1 and MPPGL shown in Table 3 for a 20-minute bath in water containing  $20 \mu\text{g}/\text{L}$  BDCM. The number associated with each bar is the coefficient of variation (%).

Table S1. Descriptive statistics for input parameters to Monte Carlo analysis and resultant VmaxC ( $\mu\text{g/hr}\cdot\text{kg BW}$ ) from Monte Carlo analysis

Age Group	Statistic	Input Parameters <sup>1</sup>			VmaxC
		FVL	MPPGL	CYP2E1 <sup>2</sup>	
0-30 days, neonate	N	28	42	42	2902 4317 6.05E-05 – 53726 1284 3428
	Mean	0.0412	25.55	13.49	
	Standard Deviation	0.0157	0.0219	15.95	
	Range	0.0114 – 0.0775	25.53 – 25.60	<LD - 70.10	
	Median	0.0438	25.54	8.79	
	IQR	0.0179	0.0374	22.88	
31-90 days, infant	N	18	29	29	4572 1865 506 – 16238 4305 2378
	Mean	0.0366	25.68	24.10	
	Standard Deviation	0.0102	0.0396	7.54	
	Range	0.0145 – 0.0612	25.61 – 25.75	9.95 – 43.25	
	Median	0.0374	25.68	23.81	
	IQR	0.0099	0.0534	7.93	
91 days – 2 years, toddler	N	43	47	47	11857 6402 1064 – 63244 10530 7786
	Mean	0.0445	26.19	45.38	
	Standard Deviation	0.0159	0.5230	20.94	
	Range	0.0274 – 0.1200	25.76 – 27.36	17.92 – 86.07	
	Median	0.0399	25.92	36.59	
	IQR	0.0121	0.6849	38.18	
Adult	N	135	101	134	10722 4707 1301 – 42809 9918 5876
	Mean	0.0239	35.38	59.31	
	Standard Deviation	0.0090	3.136	18.34	
	Range	0.0123 – 0.0863	29.26 – 40.19	23.0 – 130	
	Median	0.0217	35.24	57.5	
	IQR	0.0084	5.84	20.0	

<sup>1</sup>Data Sources – 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.

<sup>2</sup>Approximate limit of detection for CYP2E1 in Johnsrud *et al.* (2003) data was 0.5 pmol/mg microsomal protein. For the neonatal group, 8 of 42 observations were below the limit of detection (LD). LD values were not included in calculations.

Table S2. Akaike information criterion (AIC), corrected AIC (AICC), and Bayesian information criterion (BIC) compared for lognormal and gamma distributions for CYP2E1

Age Group	Distribution	AIC*	AICC*	BIC*
0-30 days, neonate	Lognormal	316.9	317.2	320.3
	Gamma	304.5	304.8	308.0
31-90 days, infant	Lognormal	200.5	200.9	203.2
	Gamma	200.2	200.6	202.9
91 days – 2 years, toddler	Lognormal	414.5	414.8	418.2
	Gamma	415.3	415.5	419.0
Adult	Lognormal	1147	1147	1153
	Gamma	1147	1148	1153

\* A lower value is deemed better

Table S3. Statistical characteristics for maximum concentration of BDCM in blood (CvMax) based on Monte Carlo analysis following oral exposure (single 0.05 L drink, 20 µg/L BDCM in water, 2 hr simulation).

Age Group	Mean ± SD (ng/L)	% CV	5 <sup>th</sup> percentile	95 <sup>th</sup> percentile	Ratio <sup>1</sup>
neonate	96.6 ± 76.5	79.2	10.3	234	22.8
infant	21.6 ± 8.35	38.7	11.3	37.1	3.28
toddler	5.30 ± 3.07	57.9	2.08	11.0	5.29
adult	0.92 ± 0.40	43.4	0.44	1.65	3.75

<sup>1</sup>Ratio of 95<sup>th</sup> to 5<sup>th</sup> percentile values.

Table S4. Statistical characteristics for maximum concentration of BDCM in blood (CvMax) based on Monte Carlo analysis following bathing exposure (20 minutes, 20 µg/L BDCM in water, 2 hr simulation).

Age Group	Mean ± SD (ng/L)	% CV	5 <sup>th</sup> percentile	95 <sup>th</sup> percentile	Ratio <sup>1</sup>
neonate	347 ± 91.9	26.5	254	529	2.08
infant	247 ± 9.40	3.80	236	265	1.12
toddler	226 ± 5.54	2.45	221	236	1.07
adult	196 ± 1.95	1.00	194	199	1.03

<sup>1</sup>Ratio of 95<sup>th</sup> to 5<sup>th</sup> percentile values.

Table S5. Ranking of parameter influence based on Morris screening level global sensitivity analysis for oral exposure scenario of a single 0.05 L ingestion of water containing 5 µg/L BDCM for AUCv in neonate and adult.<sup>1</sup>

Neonate			Adult		
Parameter	μ	σ	Parameter	μ	σ
CYP2E1	1.05E-02	3.82E-03	CYP2E1	1.24E-04	4.32E-05
FVL	3.85E-03	1.31E-03	KM1BDCM	7.90E-05	2.74E-05
KM1BDCM	2.18E-03	7.38E-04	FVL	7.78E-05	2.74E-05
KABDCM	1.26E-03	6.28E-04	PLBDCM	4.29E-05	1.49E-05
PLBDCM	1.16E-03	3.80E-04	IVVMAX1	4.26E-05	1.49E-05
IVVMAX1	1.14E-03	3.86E-04	KABDCM	3.22E-05	1.49E-05
QPC	3.28E-04	1.27E-04	MPPGL	2.09E-05	7.30E-06
PBBDCM	3.12E-04	1.57E-04	FQG	1.24E-05	2.43E-06
RQPCO	2.46E-04	6.57E-05	RQPCO	1.00E-05	2.31E-06
FQG	2.37E-04	4.06E-05	FQL	6.51E-06	1.60E-06
FQF	2.26E-04	1.03E-04	QPC	5.57E-06	1.09E-06
FQL	1.88E-04	4.20E-05	PBBDCM	4.44E-06	2.23E-06
DEADSPACE	1.30E-04	4.66E-05	FQF	4.39E-06	2.41E-06
PPPBDCM	1.09E-04	4.61E-05	PPPBDCM	3.36E-06	1.49E-06
PRPBDCM	4.87E-05	2.64E-05	DEADSPACE	2.52E-06	5.02E-07
PSKBDCM	3.90E-05	1.95E-05	PRPBDCM	1.77E-06	1.06E-06
PFBDCM	3.09E-05	2.44E-05	QSKSA	9.72E-07	6.18E-07
FSASK	3.02E-05	9.84E-06	PSKBDCM	9.44E-07	4.77E-07
LSK	2.89E-05	1.64E-05	FVBD	9.11E-07	5.15E-07
FVF	2.60E-05	1.23E-05	FVF	9.00E-07	4.08E-07
QSKSA	2.42E-05	1.40E-05	FSASK	8.13E-07	2.73E-07
FVBD	1.85E-05	1.04E-05	PGBDCM	7.89E-07	8.07E-07
PGBDCM	1.64E-05	1.44E-05	LSK	7.47E-07	4.51E-07
FVGI	9.04E-06	1.15E-05	FVGI	4.87E-07	7.22E-07
MPPGL	4.75E-06	1.60E-06	PFBDCM	2.27E-07	1.82E-07
PKBDCM	3.61E-06	1.97E-06	PKBDCM	8.47E-08	5.53E-08
FQK	1.14E-06	1.59E-06	FQK	7.72E-08	9.19E-08
VFCBDCM	7.57E-07	3.69E-07	VFCBDCM	3.23E-08	1.14E-08
FVK	5.99E-07	5.14E-07	FVK	2.10E-08	2.40E-08
VLUM	3.87E-10	4.07E-10	VLUM	1.25E-19	4.61E-20

<sup>1</sup>Parameter abbreviations are defined in Tables 1 and 2. μ is the mean sensitivity measure over the course of the simulation and σ is the standard deviation of the sensitivity measure over the course of the simulation. Shading indicates division of parameters into thirds.



Table S6. Ranking of parameter influence based on Morris screening level global sensitivity analysis for oral exposure scenario of a single 0.05 L ingestion of water containing 5 µg/L BDCM for AML in neonate and adult.<sup>1</sup>

Neonate			Adult		
Parameter	μ	σ	Parameter	μ	σ
KABDCM	9.27E-02	6.40E-02	KABDCM	9.82E-02	6.59E-02
CYP2E1	8.39E-02	1.27E-02	CYP2E1	1.22E-02	1.96E-03
FVL	3.13E-02	5.30E-03	KM1BDCM	7.78E-03	1.26E-03
KM1BDCM	1.80E-02	2.50E-03	FVL	7.45E-03	1.42E-03
IVVMAX1	9.80E-03	1.39E-03	IVVMAX1	4.03E-03	6.43E-04
PLBDCM	9.51E-03	1.60E-03	PLBDCM	4.00E-03	7.50E-04
QPC	7.06E-03	1.19E-03	QPC	3.58E-03	2.37E-03
RQPCO	4.36E-03	4.82E-04	RQPCO	2.78E-03	2.55E-03
DEADSPACE	3.19E-03	5.57E-04	FQG	2.15E-03	3.30E-03
PBBDCM	2.82E-03	1.15E-03	PGBDCM	2.14E-03	3.83E-03
FQG	1.65E-03	8.66E-04	FVGI	2.12E-03	3.83E-03
FQF	1.64E-03	6.82E-04	MPPGL	2.07E-03	3.34E-04
FQL	1.44E-03	3.48E-04	DEADSPACE	1.65E-03	1.07E-03
PGBDCM	9.16E-04	1.67E-03	PBBDCM	7.95E-04	3.58E-04
FVGI	8.60E-04	1.64E-03	FQL	5.72E-04	1.86E-04
PPPBDCM	7.84E-04	3.84E-04	FQF	4.94E-04	2.74E-04
PRPBDCM	3.09E-04	2.36E-04	PPPBDCM	3.90E-04	1.75E-04
PSKBDCM	2.45E-04	1.63E-04	PRPBDCM	2.03E-04	1.24E-04
PFBDCM	2.29E-04	1.72E-04	PSKBDCM	1.07E-04	5.47E-05
FSASK	2.18E-04	8.03E-05	FVF	1.04E-04	4.85E-05
FVF	2.13E-04	1.08E-04	FVBD	1.02E-04	5.92E-05
LSK	1.88E-04	1.45E-04	QSKSA	1.01E-04	6.46E-05
QSKSA	1.73E-04	1.12E-04	LSK	8.56E-05	5.19E-05
FVBD	1.24E-04	9.41E-05	FSASK	8.46E-05	2.94E-05
MPPGL	3.94E-05	5.47E-06	PFBDCM	2.57E-05	2.08E-05
PKBDCM	2.27E-05	1.82E-05	PKBDCM	9.67E-06	6.24E-06
FQK	9.22E-06	1.39E-05	FQK	8.82E-06	1.03E-05
VFCBDCM	6.05E-06	1.41E-06	VFCBDCM	3.16E-06	5.09E-07
FVK	4.56E-06	5.09E-06	FVK	2.31E-06	2.59E-06
VLUM	1.36E-08	1.40E-08	VLUM	4.03E-16	1.07E-16

<sup>1</sup>Parameter abbreviations are defined in Tables 1 and 2. μ is the mean sensitivity measure over the course of the simulation and σ is the standard deviation of the sensitivity measure over the course of the simulation. Shading indicates division of parameters into thirds.

Table S7. Ranking of parameter influence based on Morris screening level global sensitivity analysis for bathing exposure for 20 minutes in water containing 5 µg/L BDCM for AUCv in neonate and adult.<sup>1</sup>

Neonate			Adult		
Parameter	µ	σ	Parameter	µ	σ
FSASK	1.39E-02	5.33E-03	FSASK	1.11E-02	4.76E-03
KBDCM	1.22E-02	4.69E-03	KBDCM	9.83E-03	4.26E-03
CYP2E1	1.20E-02	5.88E-03	QPC	8.04E-03	3.72E-03
QPC	9.64E-03	3.94E-03	RQPCO	7.69E-03	3.38E-03
RQPCO	8.88E-03	3.42E-03	FQG	3.73E-03	1.93E-03
FVL	4.35E-03	2.29E-03	DEADSPACE	3.69E-03	1.71E-03
DEADSPACE	4.33E-03	1.77E-03	FQL	2.11E-03	1.09E-03
FQG	3.67E-03	1.62E-03	QSKSA	1.39E-03	1.10E-03
FQL	3.18E-03	1.41E-03	PSKBDCM	1.38E-03	9.51E-04
KM1BDCM	2.74E-03	1.29E-03	LSK	1.21E-03	1.01E-03
PBBDCM	1.93E-03	9.58E-04	PBBDCM	1.19E-03	6.72E-04
FQF	1.56E-03	7.58E-04	CYP2E1	1.16E-03	6.10E-04
PLBDCM	1.45E-03	6.76E-04	FQF	1.10E-03	6.90E-04
IVVMAX1	1.42E-03	6.71E-04	PPPBDCM	8.86E-04	4.68E-04
PSKBDCM	1.25E-03	1.05E-03	KM1BDCM	7.22E-04	3.81E-04
QSKSA	1.04E-03	1.13E-03	FVL	5.65E-04	3.39E-04
LSK	9.32E-04	1.06E-03	PRPBDCM	4.94E-04	3.17E-04
PPPBDCM	7.88E-04	4.19E-04	IVVMAX1	3.89E-04	2.05E-04
PRPBDCM	3.03E-04	2.57E-04	PLBDCM	3.89E-04	2.04E-04
PWSBDCM	2.50E-04	1.05E-04	FVBD	2.47E-04	1.65E-04
PFBDCM	2.04E-04	1.61E-04	FVF	2.42E-04	1.27E-04
FVF	1.88E-04	9.70E-05	MPPGL	1.93E-04	1.02E-04
FVBD	1.30E-04	1.12E-04	PWSBDCM	1.54E-04	7.21E-05
FVGI	3.63E-05	3.32E-05	FVGI	8.44E-05	5.40E-05
PKBDCM	2.32E-05	2.05E-05	PFBDCM	5.27E-05	4.53E-05
PGBDCM	1.37E-05	9.11E-06	PKBDCM	2.34E-05	1.56E-05
FQK	9.89E-06	1.00E-05	FQK	2.21E-05	1.95E-05
MPPGL	5.96E-06	2.79E-06	FVK	5.92E-06	5.33E-06
FVK	4.67E-06	4.39E-06	PGBDCM	5.48E-06	3.61E-06
VFCBDCM	7.63E-07	4.28E-07	VFCBDCM	3.00E-07	1.60E-07

<sup>1</sup>Parameter abbreviations are defined in Tables 1 and 2. µ is the mean sensitivity measure over the course of the simulation and σ is the standard deviation of the sensitivity measure over the course of the simulation. Shading indicates division of parameters into thirds.

Table S8. Ranking of parameter influence based on Morris screening level global sensitivity analysis for bathing exposure for 20 minutes in water containing 5 µg/L BDCM for AML in neonate and adult.<sup>1</sup>

Neonate			Adult		
Parameter	$\mu$	$\sigma$	Parameter	$\mu$	$\sigma$
FSASK	1.53E-01	5.94E-02	FSASK	1.25E+00	5.52E-01
KBDCM	1.35E-01	5.26E-02	KBDCM	1.11E+00	4.96E-01
CYP2E1	1.03E-01	3.31E-02	RQPCO	3.80E-01	1.45E-01
FVL	3.99E-02	1.22E-02	QSKSA	1.54E-01	1.24E-01
RQPCO	3.51E-02	1.21E-02	FQG	3.67E-01	1.24E-01
PBBDCM	2.90E-02	1.30E-02	LSK	1.37E-01	1.13E-01
FQG	2.80E-02	8.45E-03	PBBDCM	2.12E-01	1.10E-01
QPC	2.72E-02	8.06E-03	PSKBDCM	1.58E-01	1.09E-01
FQL	2.43E-02	7.31E-03	QPC	3.46E-01	1.07E-01
KM1BDCM	2.25E-02	6.88E-03	FQF	1.27E-01	8.00E-02
FQF	1.61E-02	7.64E-03	FQL	2.07E-01	6.87E-02
PSKBDCM	1.33E-02	1.17E-02	PPPBDCM	1.02E-01	5.40E-02
DEADSPACE	1.21E-02	3.61E-03	DEADSPACE	1.61E-01	4.98E-02
IVVMAX1	1.16E-02	3.56E-03	CYP2E1	1.14E-01	3.77E-02
PLBDCM	1.13E-02	3.68E-03	FVL	9.88E-02	3.54E-02
QSKSA	1.12E-02	1.24E-02	PRPBDCM	5.45E-02	3.51E-02
LSK	1.01E-02	1.18E-02	KM1BDCM	7.43E-02	2.44E-02
PPPBDCM	7.97E-03	4.62E-03	FVBD	2.72E-02	1.83E-02
PRPBDCM	2.97E-03	2.77E-03	PGBDCM	1.58E-02	1.54E-02
PWSBDCM	2.70E-03	1.14E-03	FVF	2.76E-02	1.47E-02
PFBDCM	2.28E-03	1.79E-03	PLBDCM	3.81E-02	1.36E-02
FVF	2.12E-03	1.15E-03	IVVMAX1	3.95E-02	1.30E-02
FVBD	1.27E-03	1.20E-03	FVGI	7.96E-03	1.04E-02
PGBDCM	6.82E-04	8.31E-04	PWSBDCM	1.71E-02	8.28E-03
FVGI	3.06E-04	4.51E-04	MPPGL	1.95E-02	6.42E-03
PKBDCM	2.32E-04	2.22E-04	PFBDCM	6.03E-03	5.24E-03
FQK	9.84E-05	1.02E-04	FQK	2.37E-03	2.08E-03
MPPGL	4.91E-05	1.50E-05	PKBDCM	2.62E-03	1.75E-03
FVK	4.53E-05	4.61E-05	FVK	6.32E-04	5.62E-04
VFCBDCM	7.21E-06	2.86E-06	VFCBDCM	2.96E-05	9.78E-06

<sup>1</sup>Parameter abbreviations are defined in Tables 1 and 2.  $\mu$  is the mean sensitivity measure over the course of the simulation and  $\sigma$  is the standard deviation of the sensitivity measure over the course of the simulation. Shading indicates division of parameters into thirds.

Table S9. Descriptive statistics for CYP2E1 Neonate simulations for oral exposure using 10 different random seeds (10,000 simulations each set)

<b>Mean</b>	<b>Std</b>	<b>Min</b>	<b>Max</b>	<b>5 %ile</b>	<b>95 %ile</b>	<b>IQR</b>	<b>%CV</b>	<b>Max/Min</b>	<b>Ratio95_5</b>
13.1	18.5	0.000000182	184.2	0.0582	49.2	16.0	141%	1,010,000,000	844.54
13.4	18.2	0.000000212	217.3	0.0583	50.7	16.8	136%	1,020,000,000	870.17
13.6	19.0	0.000000000	230.9	0.0579	51.7	16.8	139%	987,000,000,000	891.87
13.2	18.5	0.000000187	289.8	0.0562	49.2	16.3	141%	1,550,000,000	873.95
13.5	19.4	0.000001620	192.8	0.0513	51.9	16.0	144%	119,000,000	1011.11
13.3	18.7	0.000000110	192.1	0.0578	51.0	16.3	140%	1,740,000,000	882.5
13.3	18.4	0.000000002	169.6	0.0599	50.7	16.6	138%	90,400,000,000	845.76
13.6	19.3	0.000000072	204.3	0.0548	54.1	16.3	142%	2,860,000,000	986.48
13.6	19.3	0.000002230	299.3	0.0613	52.1	16.5	142%	134,000,000	848.72
13.3	19.2	0.000003610	234.8	0.0490	51.6	16.3	144%	65,100,000	1054.86