Supplemental Material

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.

Table S1. Descriptive statistics for input parameters to Monte Carlo analysis and resultant VmaxC (µg/hr-kg BW) from Monte Carlo analysis

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

[1]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.

[2]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	5th percentile	95th percentile	Ratio[1]
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

[1]Ratio of 95th to 5th 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	5th percentile	95th percentile	Ratio[1]
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

[1]Ratio of 95th to 5th 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.[1]

| | 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

[1]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.[1]

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

[1]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.[1]

	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

[1]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.[1]

Neonate			Adult		
Parameter	μ	σ	Parameter	μ	σ
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

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

| Mean	Stdev	Min	Max	5 %ile	95 %ile	IQR	%CV	Max/Min	Ratio95_5
13.1	18.5	1.82E-07	184.2	0.0582	49.2	16.0	141	1.01E+09	844.54
13.4	18.2	2.12E-07	217.3	0.0583	50.7	16.8	136	1.02E+09	870.17
13.6	19.0	1.00E-08	230.9	0.0579	51.7	16.8	139	9.87E+11	891.87
13.2	18.5	1.87E-07	289.8	0.0562	49.2	16.3	141	1.55E+09	873.95
13.5	19.4	1.62E-06	192.8	0.0513	51.9	16.0	144	1.19E+08	1011.11
13.3	18.7	1.10E-07	192.1	0.0578	51.0	16.3	140	1.74E+09	882.5
13.3	18.4	2.00E-09	169.6	0.0599	50.7	16.6	138	9.04E+10	845.76
13.6	19.3	7.20E-08	204.3	0.0548	54.1	16.3	142	2.86E+09	986.48
13.6	19.3	2.23E-06	299.3	0.0613	52.1	16.5	142	1.34E+08	848.72
13.3	19.2	3.61E-06	234.8	0.0490	51.6	16.3	144	6.51E+07	1054.86
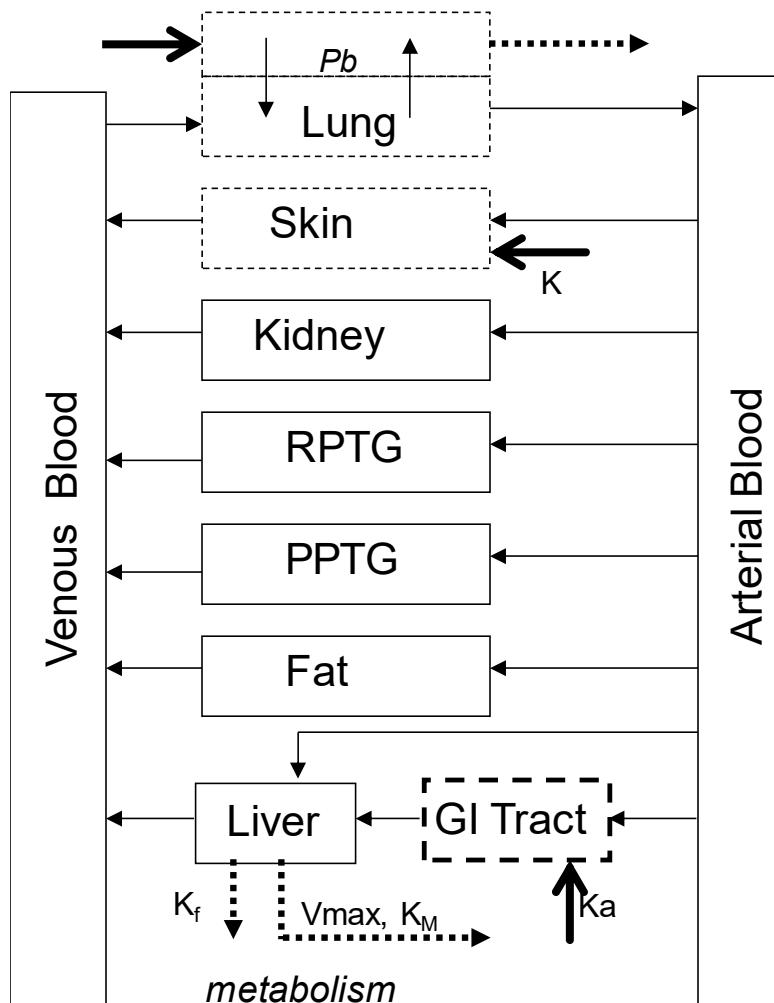
Fig S1. Schematic diagram of the human BDCM Model. Thick black arrows indicate routes of entry to specific tissue compartments (dotted lines). Thin solid lines and arrows indicate blood flow for organs connected by systemic circulation. Distribution is blood flow limited and there is no binding of BDCM to blood proteins.
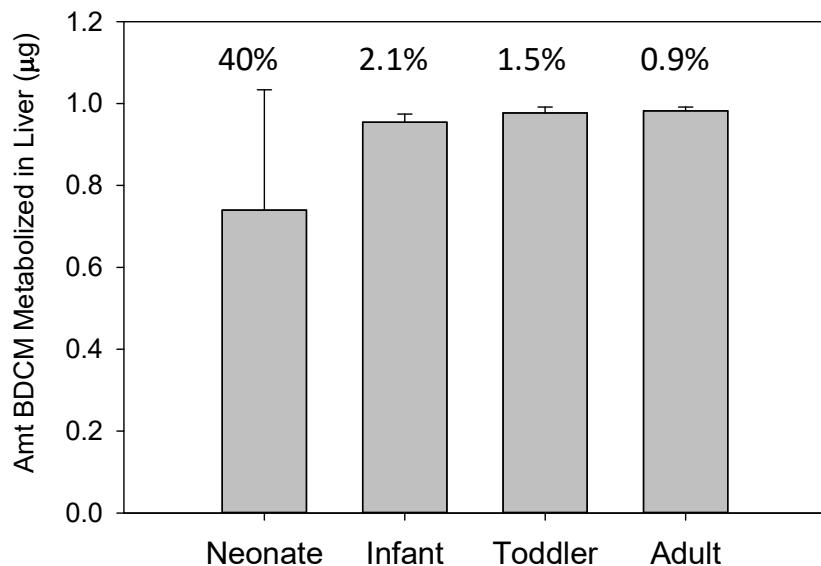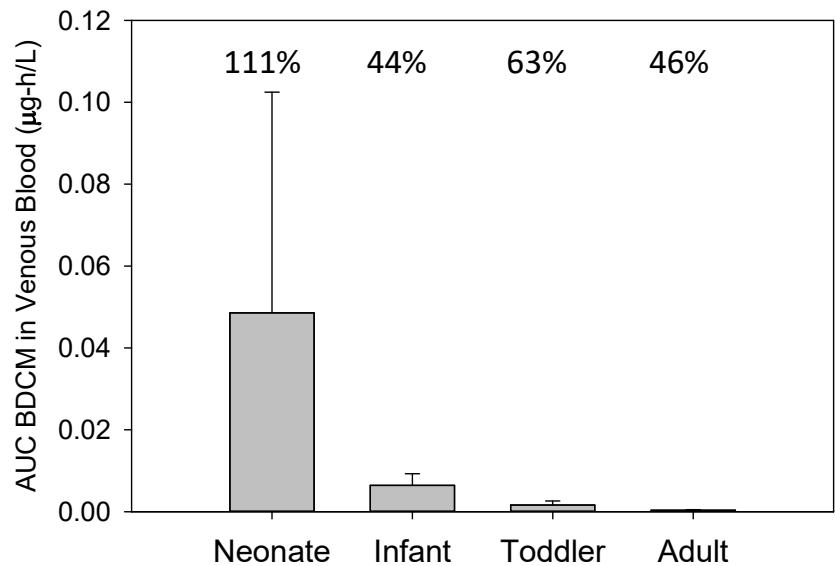
Fig S2. Comparison of AUC for (A) venous blood BDCM (µg-h/L, $\bar{x} \pm$ SD) and (B) amount of BDCM metabolized in liver (µg, $\bar{x} \pm$ SD) across age groups based on Monte Carlo simulations (2 hours) utilizing the distributional characteristics for FVL, CYP2E1 and MPPGL shown in Table 3 for an oral exposure to water containing 20 µg/L BDCM as a single 0.05-liter drink. The number associated with each bar is the coefficient of variation (%).
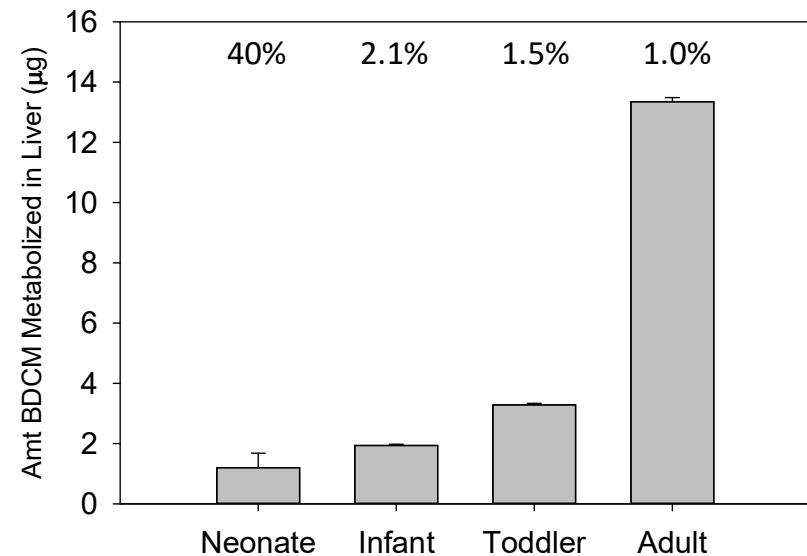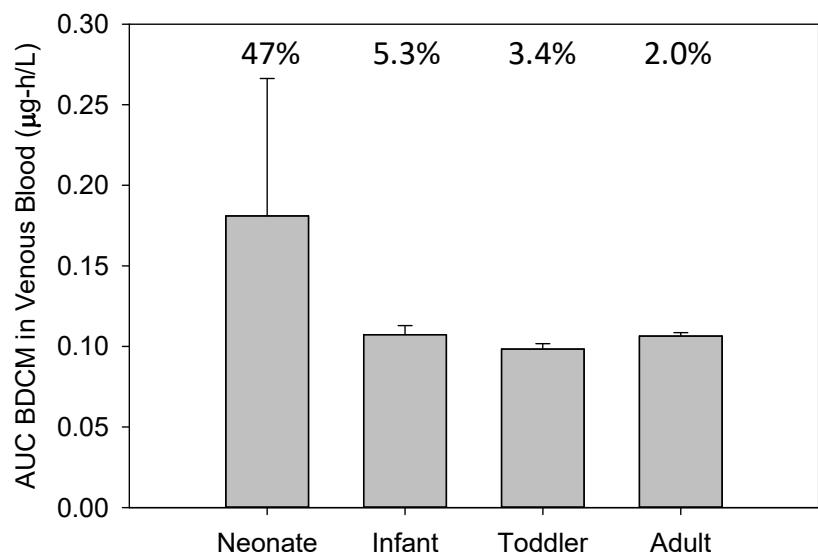
Fig S3.   Comparison of AUC for (A) venous blood BDCM (µg-h/L, $\bar{x} \pm$ SD) and (B) amount BDCM metabolized in liver (µg, $\bar{x} \pm$ SD) across age groups based on Monte Carlo simulations (2 hours) utilizing the distributional characteristics for FVL, CYP2E1 and MPPGL shown in Table 3 for a 20-minute bath in water containing 20 µg/L BDCM. The number associated with each bar is the coefficient of variation (%).