

**Supplemental Material for Carignan et al., “Contribution of breast milk and formula to arsenic exposure during the first year of life in a US prospective cohort”**

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## APPENDIX 1 - EXPOSURE MODELS

### 1. Equations for estimated arsenic exposure via breast milk and formula for NHBCS infants, by feeding type

Formula-fed (consume only formula, no breast milk):

$$AsE_F = IR_{BW} \times (C_W + C_P)$$

Breastfed (consume only breast milk, no formula):

$$AsE_B = IR_{BW} \times (C_B)$$

Mixed formula and breast milk (assuming a 50/50 mix of these diet items):

$$AsE_M = [(IR_{BW} \div 2) \times (C_W + C_P)] + [(IR_{BW} \div 2) \times C_B]$$

where:

AsE = Arsenic exposure; subscript indicates feeding mode (F=Formula-Fed,

B=Breastfed, and M=mixed)

$IR_{BW}$  = Age specific, average body weight-adjusted ingestion rate<sup>1</sup>,  $L\ kg^{-1}\ d^{-1}$

$C_W$  = NHBCS subject-specific concentration of arsenic in home tap water,  $\mu g/L$

$C_P$  = Median or maximum concentration of arsenic in formula powder<sup>2</sup>,  $\mu g/L$

$C_B$  = Median or maximum concentration of arsenic in breast milk<sup>3</sup>,  $\mu g/L$

**APPENDIX 2. SUPPLEMENTAL TABLES & FIGURES CITED IN RESULTS**

**Table S1.** Concentrations of arsenic in home tap water ( $\mu\text{g/L}$ ) among our study subset ( $n=356$ ), based on samples taken at enrollment.

	n	Minimum <sup>a</sup>	5 <sup>th</sup> percentile	25 <sup>th</sup> percentile	50 <sup>th</sup> percentile	75 <sup>th</sup> percentile	95 <sup>th</sup> percentile	Maximum
<i>All feeding types</i>	356	<LOD	0.014	0.079	0.48	3.22	24.7	79.7
<i>Formula-Fed</i>								
4 months	112	<LOD	0.010	0.070	0.31	2.65	26.7	79.7
8 months	179	<LOD	0.010	0.090	0.48	3.33	26.7	79.7
12 months	235	<LOD	0.011	0.092	0.51	3.49	24.7	79.7
<i>Mix of Formula and Breast Milk</i>								
4 months	85	<LOD	0.014	0.149	1.21	5.29	54.7	63.4
8 months	58	<LOD	0.014	0.080	0.86	5.41	33.0	57.0
12 months	48	<LOD	0.014	0.053	0.44	2.65	18.8	33.0
<i>Breast Fed</i>								
4 months	159	<LOD	0.015	0.070	0.48	2.57	18.8	70.8
8 months	119	<LOD	0.014	0.070	0.45	2.57	18.3	70.8
12 months	73	<LOD	0.014	0.064	0.79	2.57	30.4	70.8

<sup>a</sup> <LOD = less than the limit of detection

**Table S2.** Formula ingestion rates (L/d) for our study subset (n=356) at select time points during the first year of life, as reported by parents during our telephone questionnaire.

	n	Minimum	5 <sup>th</sup> percentile	25 <sup>th</sup> percentile	50 <sup>th</sup> percentile	75 <sup>th</sup> percentile	95 <sup>th</sup> percentile	Maximum	Mean	StdDev
<i>FORMULA-FED</i>										
4 months	111	0.15	0.53	0.71	0.83	0.95	1.18	1.77	0.84	0.22
8 months	178	0.12	0.30	0.71	0.83	0.95	1.18	1.36	0.81	0.22
12 months	233	0.06	0.30	0.53	0.71	0.83	1.07	2.13	0.71	0.26
<i>MIXED FEEDING: Received both formula and breast milk</i>										
4 months	85	0.030	0.03	0.12	0.24	0.47	1.07	1.18	0.34	0.32
8 months	58	0.030	0.06	0.18	0.24	0.65	0.95	1.18	0.34	0.30
12 months	48	0.030	0.06	0.12	0.24	0.36	0.71	0.71	0.28	0.20

**Table S3.** Number of breast-feedings per day for our study subset (n=356) at select time points during the first year of life, as reported by parents during our telephone questionnaire.

	n	Minimum	5 <sup>th</sup> percentile	25 <sup>th</sup> percentile	50 <sup>th</sup> percentile	75 <sup>th</sup> percentile	95 <sup>th</sup> percentile	Maximum	Mean	StdDev
<i>BREASTFED</i>										
4 months	156	2	4	6	8	8	10	15	7.2	1.9
8 months	119	2	3	5	5	7	8	12	5.6	1.7
12 months	73	1	1	3	4	5	8	8	4.2	1.7
<i>MIXED FEEDING: Received both formula and breast milk</i>										
4 months	85	1	1	4	6	8	10	12	5.8	2.7
8 months	57	1	1	2	4	6	8	15	4.3	2.9
12 months	48	1	1	2	3	4	10	24	3.9	3.6

**Table S4.** Comparison of age-specific, body weight adjusted ingestion rates ( $IR_{BW}$ ,  $L\ kg^{-1}\ d^{-1}$ ) used in our sensitivity analyses.

Model	Source	Feeding mode for which the $IR_{BW}$ was generated	Age (months)		
			4	8	12
Central Tendency Model			Mean $IR_{BW}$ ( $L\ kg^{-1}\ day^{-1}$ )		
Breast milk $IR_{BW}$	EPA EFH (Table 15-4)	Exclusively breastfed	0.112	0.075	0.047
Tap water $IR_{BW}$	EPA EFH (Table 3-22)	Formula plus direct and indirect consumption of tap water	0.090	0.063 <sup>a</sup>	0.063 <sup>a</sup>
NHBCS $IR_{BW}$ for formula	NHBCS subset <sup>a</sup>	Exclusively formula-fed	0.127	0.079	0.064
Upper Bound Model			Upper Percentile $IR_{BW}$ ( $L\ kg^{-1}\ day^{-1}$ ) <sup>b</sup>		
Breast milk $IR_{BW}$	EPA EFH (Table 15-4)	Exclusively breastfed	0.148	0.125	0.101
Tap water $IR_{BW}$	EPA EFH (Table 3-22)	Formula plus direct and indirect consumption of tap water	0.195	0.152 <sup>a</sup>	0.152 <sup>a</sup>
NHBCS $IR_{BW}$ for formula	NHBCS subset <sup>c</sup>	Exclusively formula-fed	0.197	0.148	0.136

<sup>a</sup> Infants were grouped as 6 to <12 months of age

<sup>b</sup> Upper percentile values are based on the mean + 2 standard deviations.

<sup>c</sup> Subset of those infants with abstracted body weight data (ongoing effort): n=34 (4 months); n=48 (8 months); n=58 (12 months)

**Table S5.** Estimated exposure to arsenic ( $\mu\text{g kg}^{-1} \text{d}^{-1}$ ) among our study subset (n=356) during the first year of life via A) all feeding types and B) Mixed and Formula-fed feeding types using the central tendency model and upper bound model, which use central tendency or upper bound inputs, respectively, for the body-weight adjusted ingestion rate, arsenic in infant formula powder, and arsenic in breast milk. At the population-level, variability between infants is due to individual-level concentrations of arsenic in home tap water and the change in feeding type over time; however, there was no variability among Breastfed infants since only median and maximum values were modeled.

A)

	All Feeding Types					
	Minimum	25 <sup>th</sup> percentile	50 <sup>th</sup> percentile	75 <sup>th</sup> percentile	95 <sup>th</sup> percentile	Maximum
<b>Central Tendency Model</b>						
4 months	0.03	0.03	0.09	0.17	1.62	9.05
8 months	0.02	0.02	0.09	0.16	1.39	6.06
12 months	0.01	0.04	0.06	0.13	0.88	3.80
<b>Upper Bound Model</b>						
4 months	0.09	0.09	0.19	0.31	2.24	12.1
8 months	0.08	0.08	0.23	0.36	2.40	10.2
12 months	0.06	0.13	0.20	0.35	1.96	8.23

B)

	Mixed Fed <sup>1</sup>						Formula Fed					
		25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>		25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>		
	Min	%tile	%tile	%tile	%tile	Max	Min	%tile	%tile	%tile	%tile	Max
<b>Central Tendency Model</b>												
4 months	0.08	0.09	0.15	0.38	3.14	3.63	0.12	0.13	0.16	0.42	3.11	9.05
8 months	0.05	0.06	0.09	0.26	1.29	2.19	0.08	0.09	0.12	0.33	2.08	6.06
12 months	0.03	0.03	0.04	0.10	0.48	0.81	0.05	0.06	0.08	0.22	1.21	3.80
<b>Upper Bound Model</b>												
4 months	0.18	0.19	0.27	0.57	4.23	4.87	0.27	0.28	0.31	0.66	4.21	12.1
8 months	0.15	0.16	0.21	0.49	2.21	3.71	0.23	0.24	0.28	0.64	3.56	10.2
12 months	0.12	0.12	0.14	0.26	1.07	1.79	0.18	0.19	0.23	0.53	2.67	8.23

<sup>1</sup> Assumed to receive 50:50 breastmilk and formula, see Appendix 1 and main text



**Table S6.** Sensitivity analysis comparing geometric mean (GM) estimated arsenic exposures ( $\mu\text{g kg}^{-1} \text{d}^{-1}$ ) for infants during the first year of life for different assumptions regarding the ingestion rate per unit body mass ( $\text{IR}_{\text{BW}}$ ) using the A) central tendency model and B) upper bound model.

A) Central Tendency Model

	All		Mixed		Formula-fed	
	GM	% Change	GM	% Change	GM	% Change
<b>4 months</b>						
Main model <sup>a</sup>	0.10	Referent	0.20	Referent	0.28	Referent
Tap water arsenic <10 ppb <sup>b</sup>	0.08	-18%	0.14	-29%	0.19	-31%
Tap water $\text{IR}_{\text{BW}}$ <sup>c</sup>	0.09	-11%	0.17	-17%	0.22	-20%
NHBCS $\text{IR}_{\text{BW}}$ for formula <sup>d</sup>	0.11	7%	0.23	12%	0.32	13%
<b>8 months</b>						
Main model	0.09	Referent	0.13	Referent	0.20	Referent
Tap water arsenic <10 ppb	0.07	-23%	0.09	-31%	0.14	-31%
Tap water $\text{IR}_{\text{BW}}$	0.08	-11%	0.11	-14%	0.17	-16%
NHBCS $\text{IR}_{\text{BW}}$ for formula	0.09	3%	0.14	5%	0.21	5%
<b>12 months</b>						
Main model	0.07	Referent	0.07	Referent	0.13	Referent
Tap water arsenic <10 ppb	0.06	-23%	0.06	-17%	0.09	-30%
Tap water $\text{IR}_{\text{BW}}$	0.09	26%	0.09	29%	0.17	34%
NHBCS $\text{IR}_{\text{BW}}$ for formula	0.09	27%	0.09	31%	0.17	36%

$\text{IR}_{\text{BW}}$  = Age specific, average body weight-adjusted ingestion rate<sup>1</sup>,  $\text{L kg}^{-1} \text{d}^{-1}$

B) Upper Bound Model

	All		Mixed		Formula-fed	
	GM	% Change	GM	% Change	GM	% Change
<b>4 months</b>						
Main model <sup>a</sup>	0.22	Referent	0.37	Referent	0.51	Referent
Tap water arsenic <10 ppb <sup>b</sup>	0.18	-16%	0.27	-26%	0.37	-28%
Tap water IR <sub>BW</sub> <sup>c</sup>	0.25	15%	0.47	27%	0.67	32%
NHBCS IR <sub>BW</sub> for formula <sup>d</sup>	0.25	16%	0.47	28%	0.68	33%
<b>8 months</b>						
Main model	0.24	Referent	0.30	Referent	0.45	Referent
Tap water arsenic <10 ppb	0.19	-20%	0.22	-27%	0.33	-28%
Tap water IR <sub>BW</sub>	0.27	13%	0.36	18%	0.55	22%
NHBCS IR <sub>BW</sub> for formula	0.26	11%	0.35	15%	0.54	18%
<b>12 months</b>						
Main model	0.24	Referent	0.21	Referent	0.37	Referent
Tap water arsenic <10 ppb	0.19	-20%	0.18	-15%	0.27	-27%
Tap water IR <sub>BW</sub>	0.33	37%	0.29	41%	0.55	50%
NHBCS IR <sub>BW</sub> for formula	0.30	26%	0.27	28%	0.50	35%

IR<sub>BW</sub> = Age specific, average body weight-adjusted ingestion rate<sup>1</sup>, L kg<sup>-1</sup> d<sup>-1</sup>

<sup>a</sup>Applies the breast milk IR<sub>BW</sub> to all feeding types

<sup>b</sup>Restricts sample to infants in homes with tap water arsenic <10 ppb

<sup>c</sup>Applies tap water IR<sub>BW</sub> (reference [1]) to formula ingestion

<sup>d</sup>Applies formula IR<sub>BW</sub> calculated from NHBCS formula-fed infants to formula ingestion by formula-fed and mixed-fed infants.

**Table S7.** Sensitivity analysis comparing 95<sup>th</sup> percentile estimated arsenic exposures ( $\mu\text{g kg}^{-1} \text{d}^{-1}$ ) for infants during the first year of life for different assumptions regarding the ingestion rate per unit body mass ( $\text{IR}_{\text{BW}}$ ) using the A) central tendency model and B) upper bound model

A) Central Tendency Model

	All		Mixed		Formula-fed	
	95 %tile	% Change	95 %tile	% Change	95 %tile	% Change
<b>4 months</b>						
Main model <sup>a</sup>	1.62	Referent	3.14	Referent	3.11	Referent
Tap water arsenic <10 ppb <sup>b</sup>	0.43	73%	0.67	79%	1.15	63%
Tap water $\text{IR}_{\text{BW}}$ <sup>c</sup>	1.30	20%	2.53	20%	2.50	20%
NHBCS $\text{IR}_{\text{BW}}$ for formula <sup>d</sup>	1.84	-13%	3.56	-13%	3.53	-13%
<b>8 months</b>						
Main model	1.39	Referent	0.48	Referent	1.21	Referent
Tap water arsenic <10 ppb	0.43	69%	0.50	-4%	0.78	36%
Tap water $\text{IR}_{\text{BW}}$	1.16	16%	0.64	-34%	1.62	-34%
NHBCS $\text{IR}_{\text{BW}}$ for formula	1.46	-5%	0.65	-36%	1.65	-36%
<b>12 months</b>						
Main model	0.88	Referent	0.48	Referent	1.21	Referent
Tap water arsenic <10 ppb	0.29	67%	0.50	-4%	0.78	36%
Tap water $\text{IR}_{\text{BW}}$	1.18	-34%	0.64	-34%	1.62	-34%
NHBCS $\text{IR}_{\text{BW}}$ for formula	1.20	-36%	0.65	-36%	1.65	-36%

$\text{IR}_{\text{BW}}$  = Age specific, average body weight-adjusted ingestion rate<sup>1</sup>,  $\text{L kg}^{-1} \text{d}^{-1}$

B) Upper Bound Model

	All		Mixed		Formula-fed	
	95 %tile	% Change	95 %tile	% Change	95 %tile	% Change
<b>4 months</b>						
Main model <sup>a</sup>	2.24	Referent	4.23	Referent	4.21	Referent
Tap water arsenic <10 ppb <sup>b</sup>	0.67	70%	0.67	84%	1.15	73%
Tap water IR <sub>BW</sub> <sup>c</sup>	2.96	-32%	5.56	-31%	5.55	-32%
NHBCS IR <sub>BW</sub> for formula <sup>d</sup>	2.99	-33%	5.61	-33%	5.61	-33%
<b>8 months</b>						
Main model	2.40	Referent	1.07	Referent	2.67	Referent
Tap water arsenic <10 ppb	0.78	68%	0.50	54%	0.78	71%
Tap water IR <sub>BW</sub>	2.92	-22%	1.60	-49%	4.02	-50%
NHBCS IR <sub>BW</sub> for formula	2.84	-18%	1.43	-34%	3.60	-35%
<b>12 months</b>						
Main model	1.96	Referent	1.07	Referent	2.67	Referent
Tap water arsenic <10 ppb	0.70	64%	0.50	54%	0.78	71%
Tap water IR <sub>BW</sub>	2.95	-50%	1.60	-49%	4.02	-50%
NHBCS IR <sub>BW</sub> for formula	2.64	-35%	1.43	-34%	3.60	-35%

IR<sub>BW</sub> = Age specific, average body weight-adjusted ingestion rate<sup>1</sup>, L kg<sup>-1</sup> d<sup>-1</sup>

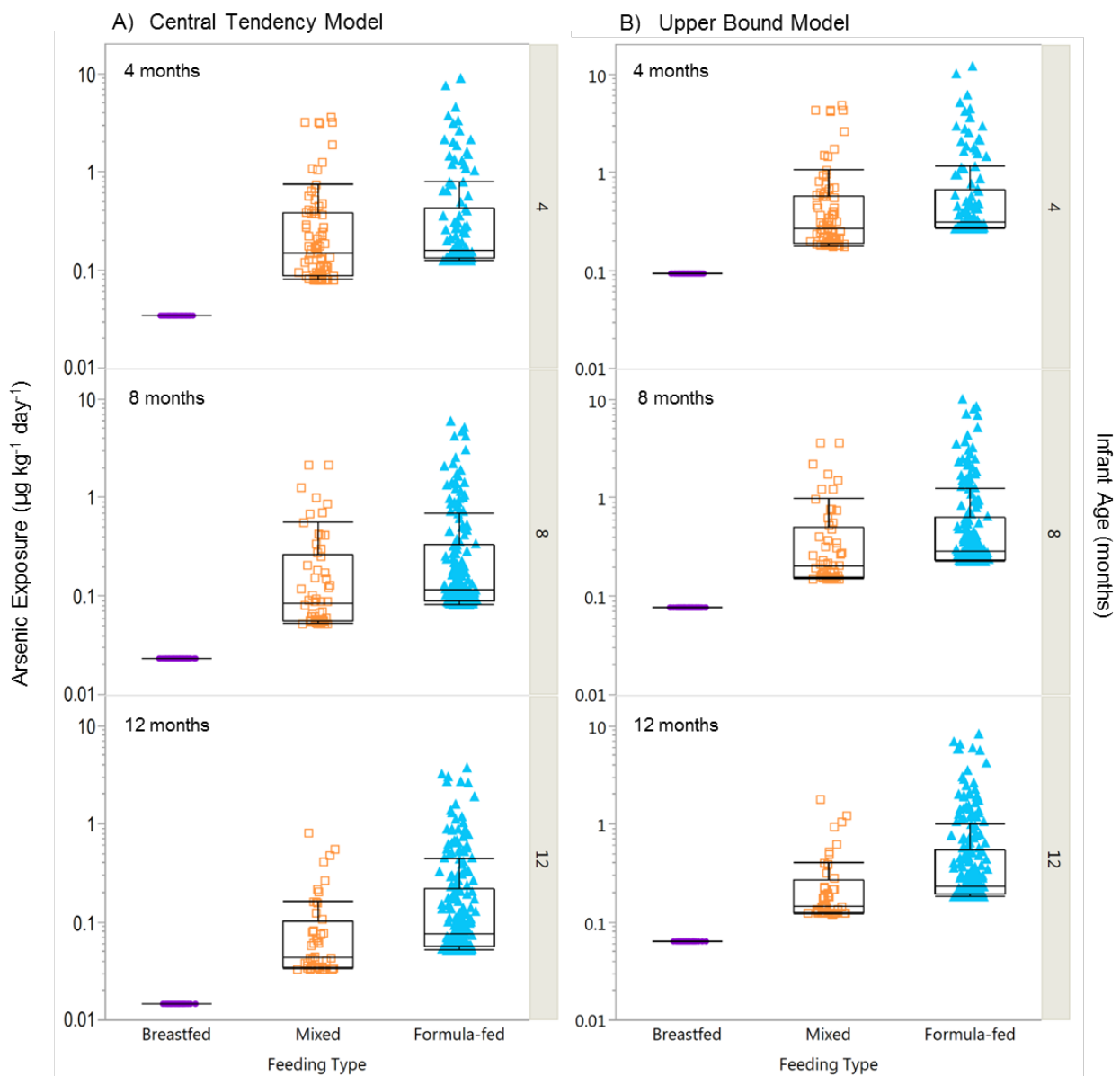
<sup>a</sup>Applies the breast milk IR<sub>BW</sub> to all feeding types

<sup>b</sup>Restricts sample to infants in homes with tap water arsenic <10 ppb

<sup>c</sup>Applies tap water IR<sub>BW</sub> (reference [1]) to formula ingestion

<sup>d</sup>Applies formula IR<sub>BW</sub> calculated from NHBCS formula-fed infants to formula ingestion by formula-fed and mixed-fed infants.

**Figure S1.** Estimated arsenic exposure ( $\mu\text{g kg}^{-1} \text{d}^{-1}$ ) for NHBCS infants by feeding mode and age. using the A) central tendency model and B) upper bound model, which use central tendency or upper bound inputs, respectively, for the body-weight adjusted ingestion rate, infant formula powder, and breast milk. Variability between infants is due to individual-level concentrations of arsenic in home tap water and the change in feeding type over time. Colors indicate the different feeding types.



## REFERENCES

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