C SUPPLEMENTAY MATERIAL eAppendix C

Exposure to Trihalomethanes in Drinking Water and Small for Gestational Age Births <3rd and 10th Percentile Birthweight in Hunter region 1997-2004.

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Objective: We investigated the association between trihalomethanes (THM) in drinking water and small for gestational age (SGA) births in the Hunter metropolitan water supply in New South Wales (NSW), Australia.

Method: We geocoded mother's residential address for live, singleton, term births to nine distribution systems in the neighbouring Hunter region of NSW (37,944 births between 1997-2004). We classified births into <3rd and <10th percentile SGA. Mean trimester and entire pregnancy exposure was estimated for trihalomethanes based on monthly sampling in each distribution system. We estimated the Relative Risk (RR) of SGA for exposure to THM's using log-binomial regression controlling for confounders.

Results: We found the effect estimates for the smaller study population in the Hunter region were similar to the Sydney/Illawarra results for SGA <3rd percentile but with wider confidence intervals, while no associations with SGA <10th percentile were found in the

Conclusion: Our study indicates small but not significant association between SGA births in the Hunter region and mother's exposure to total THM during pregnancy, as well as exposure to some specific THM species.

METHOD

The birth data for Hunter was geocoded and assigned to the water distribution system boundaries in the same method as described in the Main Paper. Birth outcomes SGA< 3^{d}% was a subset of the same population for the SGA<10%. The same birth exclusion protocol as described in the main paper was used (eAppendix C1).

Exposure Estimation

The Hunter water supply includes nine distribution systems with fixed site sampling points operating continuously with complete monthly THM values for the study period. Six systems received surface water and three received ground water most of the study period. Blending of

surface and ground waters occurred within some distribution systems from 2003 and we identified these periods with dates supplied by the water supply. Less than 15% of distribution/month concentrations were below detection limit for chloroform, less than 10% for DBCM and DBCM, however more than 50% of bromoform values were below detection limit.

We used distribution/month data to calculate trimester and entire pregnancy average chloroform, BDCM, DBCM BrTHM and THM4 exposure for each birth. All calculations were conducted using log transformed THM concentrations due to the skewed THM distribution and the monthly values were back-transformed for regression modeling and reporting.

RESULTS

There were 43,532 births geocoded to Hunter distribution systems. We excluded 5,588 infants (12.8% of the study population). This left 37,944 live, singleton term births available for analysis (eAppendix C1).

In the Hunter water supply area, a smaller proportion of teenage mothers (2.6%) had a term SGA<3% baby compared to Sydney/Illawarra region, while a larger proportion (22.0%) of mothers smoked during pregnancy (eAppendix C2). Otherwise the Hunter region had similar proportions of SGA<3% and 10% babies compared to Sydney/Illawarra for the various study factors (eAppendix B1).

In the Hunter there was considerable variation in entire pregnancy THM exposures between surface water compared to ground or mixed water. Details of the entire pregnancy DBP exposure for all births in Hunter region stratified by water source are provided in eAppendix C4.

The mean THM exposure for each birthweight category for Hunter regions and trimester, shows in all instances the mean concentration for each THM for entire pregnancy and each trimester is marginally higher for mothers who had SGA<3% births compared to AGA births (eAppendix C5).

We examined the linear exposure-response relationship for SGA <3% and SGA<10% for unadjusted models and models adjusted for covariates. Overall, results indicate that exposure to THM's a weak non-significant association with SGA<3% births. In the Hunter there was no association between THM exposures and SGA<10% births but this may be related to the relatively low numbers of study subjects (eAppendix C6).

DISCUSSION

Our results suggest a similar pattern of association between maternal exposure to chloroform, BDCM and THM4 during pregnancy and reduced foetal weight in Hunter to that reported in the Main Paper for Sydney/Illawarra. However the magnitude of the association was smaller with wider confidence interval and not significant.

Appendix C-1: Exclusion criteria for births within the Hunter water supply study area and time periods

Scope	Births in Hunter Water Supply			
Characteristics	**Exclusion**		**Inclusion**	
N	**%**	**N**	**%**	
Study Area and Period				
Hunter (a)			43,532	100.0
Birth defect present	948	2.2	42,584	97.8
Stillborn	243	0.6	42,341	97.3
Discharge status missing	3	0.0	42,338	97.3
Multiple births	1,283	2.9	41,055	94.3
Missing birthweight or gestational age	10	0.0	41,045	94.3
Extreme birthweight (c)	15	0.0	41,030	94.3
Extreme gestational age (d)	96	0.2	40,943	94.1
Pre-term births (e)	2,636	6.1	38,307	88.0
Missing covariate data	354	0.8	37,944	87.2
Missing exposure data	0	0.0	-	-
Total subjects	**5,588**	**12.8**	**37,944**	**87.2**

(a) January 1997 to December 2004
(b) <>5SD from mean for gestational age
(c) Births outside 22 to 42 gestational weeks inclusive
(d) <37 weeks gestation

Appendix C-2: Descriptive statistics of births included in the analysis of term SGA <3rd and 10th percentile births and maternal exposure to THM's, Hunter 1997-2004.

Characteristics	Total Births	Total Births	SGA<3%		SGA<10%		AGA (a)	
		N	N	row%	N	row%	N	row%
Maternal Age								
	<20yrs	5,154	135	2.6	433	8.4	4,721	91.6
	20-24yrs	2,221	90	4.1	330	14.9	1,891	85.1
	25-29yrs	6,941	251	3.6	817	11.8	6,124	88.2
	30-34yrs	12,616	331	2.6	1,115	8.8	11,501	91.2
	35+yrs	11,012	250	2.3	894	8.1	10,118	91.9
Indigenous Mother								
	No	37,191	1,016	2.7	3,475	9.3	33,716	90.7
	Yes	753	41	5.4	114	15.1	639	84.9
Country of Birth								
	Australia	35,737	991	2.8	3,348	9.4	32,025	89.6
	Asia	665	30	4.5	81	12.2	584	87.8
	Other	1,906	36	1.9	160	8.4	1,746	91.6
Gender								
	Male	19,595	504	2.6	1,800	9.2	17,795	90.8
	Female	18,349	553	3.0	1,789	9.7	16,560	90.3
Smoking during pregnancy								
	No	29,600	533	1.8	2,019	6.8	27,581	93.2
	Yes	8,344	524	6.3	1,570	18.8	6,774	81.2
First pregnancy								
	No	22,776	508	2.2	1,773	7.8	21,003	92.2
	Yes	15,168	549	3.6	1,816	12.0	13,352	88
Maternal Hypertension								
	No	37,263	1,043	2.8	3,534	9.5	33,729	90.5
	Yes	681	14	2.1	55	8.1	626	91.9
Maternal Diabetes								
	No	37,775	1,055	2.8	3,581	9.5	34,194	90.5
	Yes	169	2	1.2	8	4.7	161	95.3
Pre-eclampsia								
	No	34,819	947	2.7	3,239	9.3	31,580	90.7
	Yes	3,125	110	3.5	350	11.2	2,775	88.8
Gestational Diabetes								
	No	36,860	1,036	2.8	3,521	9.6	33,339	90.4
	Yes	1,084	21	1.9	68	6.3	1,016	93.7
First Ante-natal Care Visit								
	<12 wks	20,650	503	2.4	1,721	8.3	18,929	91.7
	12+ wks	17,294	554	3.2	1,868	10.8	15,426	89.2
Year of Birth								
	1997	1,339	26	1.9	111	8.3	1,228	91.7
	1998	5,254	131	2.5	492	9.4	4,762	90.6
	1999	5,333	131	2.5	454	8.5	4,879	91.5
	2000	5,354	163	3.0	519	9.7	4,835	90.3
	2001	5,101	163	3.2	504	9.9	4,597	90.1
	2002	5,219	150	2.9	500	9.6	4,719	90.4
	2003	5,194	127	2.4	484	9.3	4,710	90.7
	2004	5,150	166	3.2	525	10.2	4,625	89.8
Season of Birth								
	Summer	9,201	256	2.8	868	9.4	8,333	90.6
	Autumn	9,320	281	3.0	920	9.9	8,400	90.1
	Winter	9,220	274	3.0	872	9.5	8,348	90.5
	Spring	10,203	246	2.4	929	9.1	9,274	90.9
Index of Relative Socio-Economic Disadvantage								
	1st quartile	13,538	473	3.5	1,538	11.4	12,000	88.6
	2nd quartile	12,191	317	2.6	1,109	9.1	11,082	90.9
	3rd quartile	8,704	201	2.3	694	8.0	8,010	92.0
	4th quartile	3,511	66	1.9	248	7.1	3,263	92.9
TOTAL		**37,944**	**1,057**	**2.8**	**3,589**	**9.5**	**34,355**	**90.5**

(a) AGA average for gestational age ≥10th percentile birthweight

(b) IRSD: Index of Relative Socio-Economic Disadvantage. Quartiles (QTL) go from most socio-economically disadvantaged (1st quartile) to least socio-economically disadvantaged (4th quartile)

Appendix C-3: Descriptive statistics of births excluded in the analysis of term SGA <3rd and 10th percentile births and maternal exposure to THM's, Hunter 1997-2004.

Characteristics	Total N	SGA<3% N	%	SGA<10% N	%	AGA (a) N	%
Maternal Age							
<20yrs	35	3	8.6	5	14.3	30	85.7
20-24yrs	96	2	2.1	13	13.5	83	86.5
25-29yrs	99	6	6.1	18	18.2	81	81.8
30-34yrs	81	7	8.6	10	12.3	71	87.7
35+yrs	35	3	8.6	5	14.3	30	85.7
Indigenous Mother							
Non- Indigenous	320	19	5.9	48	15.0	272	85.0
Indigenous	22	2	9.1	3	13.6	19	86.4
Missing	12	0	0	0	0	12	100
Country of Birth							
Australia	338	20	5.9	50	14.8	288	85.2
Asia	1	1	100	1	100	0	0
Other	15	0	0	0	0	15	100.0
Gender							
Male	167	10	6.0	26	15.6	141	84.4
Female	177	10	5.6	24	13.6	153	86.4
Indeterminant	2	1	50.0	1	50.0	1	50.0
Missing	8	0	0	0	0	8	100.0
Smoking during pregnancy							
No	197	4	2.0	14	7.1	183	92.9
Yes	154	17	11.0	37	24.0	117	76.0
Missing	3	0	0	0	0	3	100.0
First pregnancy							
No	241	12	5.0	34	14.1	207	85.9
Yes	106	9	8.5	17	16.0	89	84.0
Missing	7	0	0	0	0	7	100.0
Maternal Hypertension							
No	351	21	6.0	50	14.2	301	85.8
Yes	3	0	0	1	33.3	2	66.7
Maternal Diabetes							
No	352	21	6.0	51	14.5	301	85.5
Yes	2	0	0	0	0	2	100.0
Pre-eclampsia							
No	340	20	5.9	48	14.1	292	85.9
Yes	14	1	7.1	3	21.4	11	78.6
Gestational Diabetes							
No	350	21	6.0	51	14.6	299	85.4
Yes	4	0	0	0	0	4	100.0
First Ante-natal Care Visit							
<12 wks	83	1	1.2	7	8.4	76	91.6
12+ wks	84	4	4.8	8	9.5	76	90.5
Missing	187	16	8.6	36	19.3	151	80.7
Year of Birth							
1997	23	0	0	3	13.0	20	87.0
1998	54	3	5.6	6	11.1	48	88.9
1999	48	2	4.2	7	14.6	41	85.4
2000	53	4	7.5	11	20.8	42	79.2
2001	43	1	2.3	4	9.3	39	90.7
2002	63	4	6.3	8	12.7	55	87.3
2003	25	4	16.0	6	24.0	19	76.0
2004	42	3	7.1	6	14.3	36	85.7
Season of Birth							
Summer	86	4	4.7	11	12.8	75	87.2
Autumn	92	6	6.5	10	10.9	82	89.1
Winter	86	5	5.8	16	18.6	70	81.4
Spring	90	6	6.7	14	15.6	76	84.4
Index of Relative Socio-Economic Disadvantage (IRSD[b])							
1st quartile	118	8	6.8	19	16.1	99	83.9
2nd quartile	62	6	9.7	12	19.4	50	80.6
3rd quartile	32	3	9.4	6	18.8	26	81.3
4th quartile	13	0	0	0	0	13	100.0
Missing	129	0	0	14	10.9	115	89.1
TOTAL	354	21	5.9	51	14.4	303	85.6

Appendix C-4: Average THM (µg/L) Exposure across entire pregnancy for all births by water source for Hunter 1997-2004

DBP	Births	Mean	Std Dev	Min.	25th Percentile	Median	75th Percentile	Max.
N	µg/L	µg/L	µg/L	µg/L	µg/L	µg/L	µg/L	
Hunter Water Supply								
Chloroform	37,944	41.48	18.36	0.62	28.10	37.25	53.68	101.61
BDCM	37,944	17.76	6.92	0.62	12.83	17.35	23.40	34.57
DBCM	37,944	9.94	7.97	0.65	2.49	6.52	17.68	27.95
BrTHM	37,944	29.50	15.01	2.94	16.38	24.68	43.21	64.13
THM4	37,944	70.98	17.38	7.01	62.03	73.07	81.84	120.34
HWC Ground								
Chloroform	1,299	11.91	16.27	0.62	0.77	1.01	31.04	48.22
BDCM	1,299	6.56	7.64	0.66	1.22	1.55	16.16	22.22
DBCM	1,299	5.89	1.54	2.37	4.84	6.21	6.95	8.98
BrTHM	1,299	19.34	6.01	6.22	14.87	19.25	24.69	31.11
THM4	1,299	31.25	20.48	7.01	16.06	21.44	54.38	76.74
HWC Surface								
Chloroform	11,670	54.86	18.91	17.81	41.04	55.75	67.95	101.60
BDCM	11,670	12.84	5.19	1.51	10.48	12.07	13.95	30.94
DBCM	11,670	2.71	3.10	0.65	1.37	1.65	2.20	17.17
BrTHM	11,670	16.29	8.09	2.94	12.53	14.52	16.66	49.64
THM4	11,670	71.14	18.36	20.75	58.88	70.73	82.00	120.33
HWC Mixed								
Chloroform	24,975	36.77	13.45	0.64	27.41	32.71	47.64	72.59
BDCM	24,975	20.65	5.56	0.62	16.51	20.90	24.85	34.57
DBCM	24,975	13.53	7.33	2.42	5.86	14.09	20.78	27.95
BrTHM	24,975	36.20	13.35	7.29	23.15	36.15	48.60	64.13
THM4	24,975	72.97	13.95	7.95	65.28	74.29	82.16	104.86

Min = minimum, Max= maximum

Appendix C-5: Mean THM exposure for entire pregnancy by SGA category for Hunter 1997-2004.

	Hunter Water Supply					
	SGA <3rd percentile		SGA <10th percentile		AGA ≥10th percentile	
	Mean (µg/L)	Std	Mean (µg/L)	Std	Mean (µg/L)	Std
Term						
Chloroform	41.97	18.11	41.71	18.57	41.46	18.36
BDCM	18.03	6.79	17.7	6.96	17.77	6.92
DBCM	10.03	7.98	9.8	7.93	9.95	7.97
Brom. THM	29.76	15.06	29.28	15.03	29.53	15.01
THM4	71.74	16.61	70.98	17.59	70.98	17.38
1st Trimester						
Chloroform	43.09	21.47	42.65	21.9	42.57	22.01
BDCM	18.29	7.48	18.02	7.69	17.98	7.64
DBCM	10.26	8.34	10.14	8.39	10.24	8.46
Brom. THM	30.33	15.94	30.04	16.12	30.11	16.18
THM4	73.43	21.3	72.69	22.14	72.68	21.94
2nd Trimester						
Chloroform	43.49	22.45	43.18	22.58	42.72	21.87
BDCM	18.41	7.52	18.1	7.63	18.13	7.6
DBCM	10.42	8.52	10.22	8.49	10.37	8.52
Brom. THM	30.61	16.33	30.21	16.24	30.41	16.21
THM4	74.1	21.59	73.39	22.06	73.12	21.52
3rd Trimester						
Chloroform	42.67	22.07	42.48	22.45	42.25	22.13
BDCM	18.14	7.48	17.74	7.63	17.99	7.63
DBCM	10.49	8.49	10.16	8.38	10.42	8.45
Brom. THM	30.41	16.23	29.72	16.14	30.27	16.17
THM4	73.08	21.46	72.2	22.42	72.53	22.12

Appendix C-6: Association between SGA (3rd & 10th percentiles) and Trimester average THM Exposure 1997-2004 Hunter Water

		3rd Percentile						10th Percentile					
		Unadj RR			Adj RR[1]			Unadj RR			Adj RR[1]		
	IQR	Est	Lower CI	Upper CI	Est	Lower CI	Upper CI	Est	Lower CI	Upper CI	Est	Lower CI	Upper CI
Chloroform													
Trimester 1	25	1.03	0.96	1.10	1.02	0.95	1.11	1.00	0.97	1.04	1.00	0.96	1.04
Trimester 2	25	1.04	0.97	1.11	1.02	0.94	1.09	1.02	0.99	1.06	1.01	0.97	1.05
Trimester 3	25	1.02	0.95	1.09	0.99	0.92	1.06	1.01	0.98	1.05	0.99	0.95	1.03
Term	25	1.04	0.96	1.12	1.01	0.92	1.11	1.02	0.97	1.06	1.00	0.95	1.05
BDCM													
Trimester 1	5	1.03	0.99	1.07	1.03	0.99	1.07	1.00	0.98	1.02	1.00	0.98	1.02
Trimester 2	5	1.02	0.98	1.06	1.03	0.98	1.07	1.00	0.98	1.02	1.00	0.97	1.02
Trimester 3	5	1.01	0.97	1.05	1.02	0.98	1.06	0.98	0.96	1.00	0.98	0.96	1.00
Term	5	1.03	0.98	1.07	1.03	0.98	1.08	0.99	0.97	1.02	0.99	0.97	1.01
DBCM													
Trimester 1	2	1.00	0.99	1.01	1.01	0.99	1.02	1.00	0.99	1.00	1.00	0.99	1.01
Trimester 2	2	1.00	0.99	1.02	1.00	0.99	1.02	1.00	0.99	1.00	1.00	0.99	1.00
Trimester 3	2	1.00	0.99	1.02	1.01	0.99	1.02	0.99	0.99	1.00	0.99	0.99	1.00
Term	2	1.00	0.99	1.02	1.01	0.99	1.02	1.00	0.99	1.00	1.00	0.99	1.01
BrTHM													
Trimester 1	5	1.00	0.99	1.02	1.01	0.99	1.03	1.00	0.99	1.01	1.00	0.99	1.01
Trimester 2	5	1.00	0.99	1.02	1.01	0.99	1.03	1.00	0.99	1.01	1.00	0.99	1.01
Trimester 3	5	1.00	0.98	1.02	1.01	0.99	1.03	0.99	0.98	1.00	0.99	0.98	1.00
Term	5	1.01	0.99	1.03	1.01	0.99	1.03	0.99	0.98	1.01	1.00	0.99	1.01
THM4													
Trimester 1	25	1.04	0.97	1.11	1.07	0.98	1.16	1.00	0.97	1.04	0.99	0.95	1.04
Trimester 2	25	1.05	0.98	1.13	1.05	0.97	1.14	1.01	0.98	1.05	1.01	0.96	1.05
Trimester 3	25	1.03	0.96	1.10	1.01	0.94	1.09	0.98	0.95	1.02	0.96	0.92	1.00
Term	25	1.06	0.98	1.16	1.07	0.96	1.20	1.00	0.96	1.05	0.98	0.93	1.03

[1]Adjusted for maternal age, indigenous status, country of birth, gender, smoking during pregnancy, parity, hypertension, maternal diabetes, pre-eclampsia, gestational diabetes, antenatal visit, year of birth, season and socio-economic status

Appendix C-7: Mean THM concentrations and proportions by Water Source for Hunter and Sydney/Illawarra