

eAppendix 1

SUPPLEMENTARY MATERIAL LITERATURE SEARCH METHODOLOGY

We carried out a systematic, comprehensive bibliographic search using the US National Library of Medicine (USNLM) Medline database for the years 1980-2007, using the PubMed interface. Search terms used were chosen from the USNLM Institutes of Health list of Medical Subject Headings (MeSH) for 2007.

The search terms were: “birth weight”; “chloroform”; “disinfection”; “foetal growth retardation”; “gestational age”; “infant, low birth weight”; “infant, small for gestational age”; “parturition”; “stillbirth”; “trihalomethanes”; and “water”.

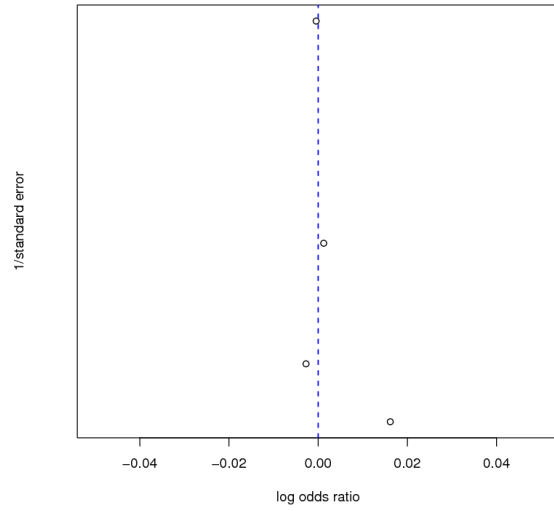
In order to maximise the potential of the search, non-MeSH terms were added as follows: “disinfection by-products”; “low birth weight”; “small for gestational age”; “adverse birth outcomes”; “pre term delivery”; and “drinking water”. Each term was assigned to a group A, B or C, depending on whether it primarily related to exposure agent, health outcome, or exposure media, respectively. These three groups were defined as follows:

- A: (“trihalomethanes” OR “chloroform” OR “disinfection” OR “disinfection by-products”)
- B: (“foetal growth retardation” OR “gestational age” OR “infant, low birth weight” OR “infant, small for gestational age” OR “parturition” OR “stillbirth” OR “low birth weight” OR “pre term delivery” OR “adverse birth outcome”)
- C: (“water” OR “drinking water”)

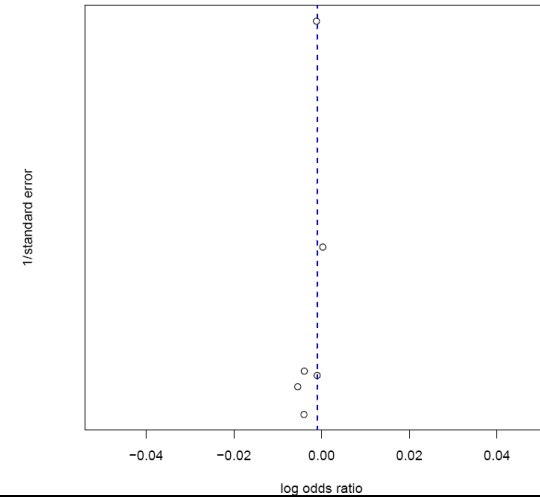
The search was carried out thus [“A” AND “B” AND “C”], with one term from each group substituted for each iteration of the search. Retrieved studies were checked against a broad list of eligibility criteria. Bibliographies of each retrieved study were also checked by hand for any additional studies that met broad eligibility criteria. The same search method was repeated using the Thomson Scientific ISI Web of Knowledge database, as well as with Google Inc.'s Google Scholar and Google search engines. We checked the studies identified thus far against studies referenced in four existing reviews (Nieuwenhuijsen 2000b; ICPS 2000; Graves et al. 2001; Tardiff et al. 2006).

eFigure 1 – FUNNEL PLOTS

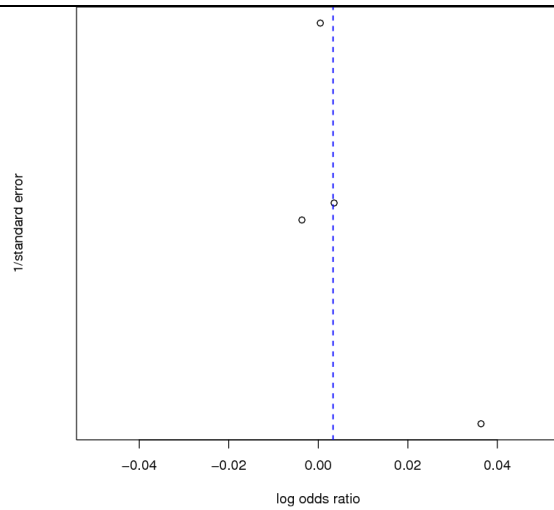
Funnel plots of log OR slopes per 10 μ g/L TTHM against 1/standard error on those slopes for third trimester exposure to TTHM only



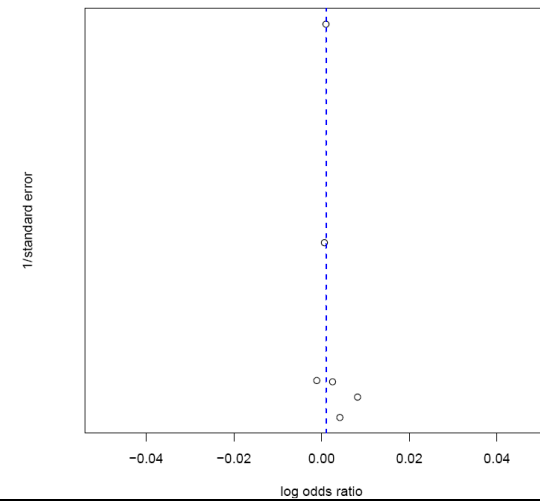
a. Low birth weight



c. Pre-term delivery



b. Term low birth weight



d. Small for gestational age

eTable 1 – RESULTS OF EGGER’S TEST FOR HETEROGENEITY

Exposure agent	Exposure timing	Health outcome	Egger's test (unweighted p-value for intercept)	Egger's test (weighted value for intercept)
<i>Only TTHM</i>	<i>Third trimester</i>	LBW	0.394	0.387
		TLBW	0.180	0.461
		PTD	0.447	0.222
		SGA	0.365	0.639
	<i>Any exposure timing</i>	LBW	0.229	0.229
		TLBW	0.088	0.348
		PTD	0.449	0.273
		SGA	0.818	0.669
	<i>Entire pregnancy only</i>	SGA	0.761	0.862
	<i>TTHM and chloroform</i>	<i>Any exposure timing</i>	LBW	0.239
PTD			0.467	0.235
<i>Entire pregnancy only</i>		PTD	0.495	0.223

eTable 2 – FULL RESULTS OF THE LEAVE-ONE-OUT SENSITIVITY ANALYSIS

Exposure agent	Exposure timing	Health outcome	Study removed	OR per 10µg/L	Lower 95% CI	Upper 95% CI	p-value	Difference from full analysis (%)	Significance at 95%	Direction of effect
<i>Only TTHM</i>	<i>3rd trimester</i>	LBW	none	0.9999	0.9735	1.0270	0.9933	0.0000	not significant	negative
			Savitz et al. (1995)	1.0016	0.9735	1.0306	0.9111	-0.0002	not significant	positive
			Gallagher et al. (1998)	0.9978	0.9713	1.0250	0.8715	0.0002	not significant	negative
			Dodds et al. (1999)	1.0125	0.9608	1.0670	0.6434	-0.0013	not significant	positive
			Toledano et al. (2005)	0.9970	0.9650	1.0301	0.8583	0.0003	not significant	negative
		TLBW	none	1.0337	0.9272	1.1525	0.5501	0.0000	not significant	positive
			Gallagher et al. 1998	1.0027	0.9139	1.1002	0.9538	0.0030	not significant	positive
			Wright et al. 2003	1.0713	0.8942	1.2834	0.4550	-0.0036	not significant	positive
			Hinckley et al. 2005	1.0500	0.8898	1.2389	0.5637	-0.0016	not significant	positive
			Lewis et al. 2006	1.0702	0.9211	1.2434	0.3754	-0.0035	not significant	positive
		PTD	none	0.9896	0.9781	1.0013	0.0814	0.0000	not significant	negative
			Savitz et al. (1995)	0.9888	0.9738	1.0040	0.1478	0.0001	not significant	negative
			Gallagher et al. (1998)	0.9882	0.9733	1.0032	0.1229	0.0002	not significant	negative
			Dodds et al. (1999)	0.9827	0.9655	1.0003	0.0540	0.0007	not significant	negative
			Wright et al. (2003)	0.9867	0.9706	1.0030	0.1097	0.0003	not significant	negative
			Wright et al. (2004)	0.9954	0.9738	1.0175	0.6808	-0.0006	not significant	negative
		Lewis et al. (2007)	0.9889	0.9739	1.0042	0.1552	0.0001	not significant	negative	
		SGA*	None	1.0100	1.0006	1.0194	0.0361	0.0000	significant	positive
			Dodds et al. (1999)	1.0108	1.0005	1.0212	0.0402	-0.0001	significant	positive
			Wright et al. (2003)	1.0097	1.0003	1.0192	0.0433	0.0000	significant	positive
			Wright et al. (2004)	1.0102	0.9908	1.0301	0.3036	0.0000	not significant	positive
			Porter et al. (2005)	1.0104	1.0010	1.0199	0.0309	0.0000	significant	positive
			Hinckley et al. (2005)	1.0092	0.9999	1.0187	0.0536	0.0001	not significant	positive
			Hoffman et al. (2008a)	1.0099	1.0005	1.0193	0.0385	0.0000	significant	positive
	<i>Any exposure timing</i>	TLBW	none	1.0228	0.9456	1.1063	0.5733	0.0000	not significant	positive
			Gallagher et al. 1998	1.0051	0.9275	1.0892	0.9005	0.0017	not significant	positive
			Wright et al. 2003	1.0397	0.9271	1.1659	0.5058	-0.0016	not significant	positive
			Hinckley et al. 2005	1.0262	0.9242	1.1395	0.6278	-0.0003	not significant	positive
			Lewis et al. 2006	1.0401	0.9444	1.1456	0.4244	-0.0017	not significant	positive
			Yang et al. 2007	1.0337	0.9272	1.1525	0.5501	-0.0011	not significant	positive
		PTD	none	0.9891	0.9777	1.0007	0.0653	0.0000	not significant	negative
			Savitz et al. (1995)	0.9896	0.9781	1.0012	0.0784	0.0000	not significant	negative
Gallagher et al. (1998)			0.9892	0.9777	1.0008	0.0667	0.0000	not significant	negative	
Dodds et al. (1999)			0.9866	0.9741	0.9992	0.0369	0.0003	significant	negative	
Wright et al. (2003)			0.9891	0.9776	1.0008	0.0671	0.0000	not significant	negative	
Wright et al. (2004)			0.9921	0.9677	1.0170	0.5309	-0.0003	not significant	negative	
Lewis et al. (2007)			0.9896	0.9781	1.0013	0.0819	-0.0001	not significant	negative	

		SGA*	Yang et al. (2007)	0.9888	0.9773	1.0004	0.0574	0.0000	not significant	negative	
			Hoffman et al. (2008b)	0.9900	0.9785	1.0016	0.0918	-0.0001	not significant	negative	
			none	1.0096	1.0009	1.0184	0.0309	0.0000	significant	positive	
			Bove et al. (1995)	1.0094	1.0001	1.0187	0.0476	0.0000	significant	positive	
			Dodds et al. (1999)	1.0102	1.0007	1.0199	0.0349	-0.0001	significant	positive	
			Wright et al. (2003)	1.0094	1.0006	1.0183	0.0368	0.0000	significant	positive	
			Wright et al. (2004)	1.0091	0.9937	1.0246	0.2482	0.0001	not significant	positive	
			Porter et al. (2005)	1.0100	1.0012	1.0188	0.0267	0.0000	significant	positive	
			Hinckley et al. (2005)	1.0090	1.0002	1.0178	0.0452	0.0001	significant	positive	
			Yang et al. (2007)	1.0101	1.0014	1.0190	0.0234	-0.0001	significant	positive	
		Hoffman et al. (2008a)	1.0095	1.0008	1.0183	0.0328	0.0000	significant	positive		
		none	1.0105	0.9712	1.0514	0.6059	0.0000	not significant	positive		
		Bove et al. (1995)	1.0025	0.9271	1.0841	0.9495	0.0008	not significant	positive		
		Wright et al. (2003)	1.0053	0.9812	1.0300	0.6699	0.0005	not significant	positive		
Porter et al. (2005)	1.0152	0.9678	1.0650	0.5352	-0.0005	not significant	positive				
Yang et al. (2007)	1.0201	0.9815	1.0603	0.3123	-0.0010	not significant	positive				
<i>TTHM and chloroform</i>	<i>Any exposure timing</i>	LBW	none	1.0001	0.9737	1.0272	0.9920	0.0000	not significant	positive	
			Kramer et al. (1992)	0.9999	0.9735	1.0270	0.9933	0.0000	not significant	negative	
			Savitz et al. (1995)	1.0015	0.9744	1.0294	0.9124	-0.0001	not significant	positive	
			Gallagher et al. (1998)	0.9980	0.9715	1.0253	0.8863	0.0002	not significant	negative	
			Dodds et al. (1999)	1.0134	0.9617	1.0678	0.6186	-0.0013	not significant	positive	
			Toledano et al. (2005)	0.9971	0.9677	1.0273	0.8483	0.0003	not significant	negative	
		none	0.9891	0.9777	1.0007	0.0653	0.0000	not significant	negative		
		Kramer et al. (1992)	0.9859	0.9702	1.0017	0.0807	0.0003	not significant	negative		
		Savitz et al. (1995)	0.9867	0.9709	1.0027	0.1022	0.0003	not significant	negative		
		Gallagher et al. (1998)	0.9860	0.9703	1.0019	0.0831	0.0003	not significant	negative		
		Dodds et al. (1999)	0.9788	0.9602	0.9976	0.0276	0.0011	significant	negative		
		Wright et al. (2003)	0.8664	0.7368	1.0188	0.0828	0.0132	not significant	negative		
		Wright et al. (2004)	0.9921	0.9678	1.0170	0.5312	-0.0003	not significant	negative		
		Lewis et al. (2007)	0.9867	0.9709	1.0029	0.1076	0.0002	not significant	negative		
		Yang et al. (2007)	0.9852	0.9695	1.0011	0.0679	0.0004	not significant	negative		
		Hoffman et al. (2008b)	0.9875	0.9717	1.0035	0.1256	0.0002	not significant	negative		
		<i>Entire pregnancy only</i>	PTD	none	0.9696	0.9139	1.0286	0.3051	0.0000	not significant	negative
					Kramer et al. (1992)	0.9692	0.9133	1.0286	0.3024	0.0000	not significant
Wright et al. (2003)	0.9831				0.9115	1.0604	0.6598	-0.0014	not significant	negative	
Lewis et al. (2007)	0.9768				0.9012	1.0587	0.5678	-0.0007	not significant	negative	
Yang et al. (2007)	0.9560				0.8971	1.0188	0.1657	0.0014	not significant	negative	

*Subset analysis results with statistically significant results at the 95% level of confidence

eTable 3

Exposure agent	Exposure timing	Health outcome	OR at US guideline level (80µg TTHM/L)	Lower 95% CI	Upper 95% CI	OR at EU guideline level (100µg TTHM/L)	Lower 95% CI	Upper 95% CI	
<i>Only TTHM</i>	<i>Third trimester</i>	LBW	1.00	0.81	1.24	1.00	0.76	1.31	
		TLBW	1.30	0.55	3.11	1.39	0.47	4.13	
		PTD	0.92	0.84	1.01	0.90	0.80	1.01	
		SGA	1.08	1.01	1.17	1.10	1.01	1.21	
		TLBW	1.20	0.64	2.24	1.25	0.57	2.75	
	<i>Any exposure timing</i>	PTD	0.92	0.83	1.01	0.90	0.80	1.01	
		SGA	1.08	1.01	1.16	1.10	1.01	1.20	
	<i>Entire pregnancy only</i>	SGA	1.09	0.79	1.49	1.11	0.75	1.65	
		<i>Any exposure timing</i>	LBW	1.00	0.81	1.24	1.00	0.77	1.31
			PTD	0.92	0.83	1.01	0.90	0.80	1.01
<i>TTHM and chloroform</i>	<i>Entire pregnancy only</i>	PTD	0.78	0.49	1.25	0.73	0.41	1.33	