Aplinkos tyrimai, inžinerija ir vadyba, 2012. Nr. 3(61), P. 26-34 *ISSN 1392-1649 (print)*
Environmental Research, Engineering and Management, 2012. No. 3(61), P. 26-34 *ISSN 2029-2139 (online)*
http://erem.ktu.lt

Water Disinfection By-products and the Risk of Congenital Anomalies in Kaunas

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crossref http://dx.doi.org/10.5755/j01.erem.61.3.1147

(received in February, 2012, accepted in September, 2012)

There is growing evidence from epidemiological studies that maternal exposure to increased drinking water chlorination with by-products – trihalometane (THM) may be associated with congenital anomalies. The aim of this study was to evaluate the impact of maternal exposure during pregnancy to individual THM internal dose effect on the risk of congenital anomalies.

We conducted a population-based prospective study of 3074 Kaunas residents births in 2007–2009, using THM exposure estimated as internal dose. We used multivariate logistic regression analysis and compared the risk of any congenital anomalies in four exposure categories of THM internal dose quartiles. In addition, we conducted a linear regression models analysis with adjustment for maternal physiology, lifestyle and sociodemographic characteristics.

Effect estimates based on total THMs and chloroform quartiles tended to increase congenital anomalies risk, but there was no statistically significant effect. However, we found dose–response relationships for the bromodichloromethane (BDCM) internal dose and risk for any congenital anomalies. The adjusted odds ratio for fourth quartile vs. first quartile was 1.5, 95% CI 1.00–2.55. The OR per every 0.01 μg/d increase in BDCM internal dose was 1.03, 95% CI 1.00–1.07. Effect estimates associated with dibromochloromethane (DBCM) exposure levels also revealed statistically significant association with the congenital anomalies risk (OR 1.23, 95% CI 1.02-1.48).

The present study suggests that prenatal exposure to total THM has tendency to increase the risk of any congenital anomalies, while exposure to BDCM and DBCM statistically represents a significant increase in the risk of any congenital anomaly.

Keywords: *drinking water by-products, THM, internal dose, congenital anomalies.*

1. Introduction

Water chlorination is a widely used and efficient method to reduce the occurrence of water-borne infectious diseases, and has been one of the most successful public health measures introduced in the 20th century. Disinfection by-products trihalomethanes (THMs) are a major group of water contaminants, and their role in causing adverse birth outcomes has been subject to extensive epidemiologic and toxicologic research and review (Bove et al. 2002; Butterworth 2005; Goebell et al. 2004; Nieuwenhuijsen et al. 2009; Tardiff et al. 2006;). Generally, the THMs, including chloroform, bromodicholormethane, dibromochlormethane, and bromoform are the most prevalent in chlorinated surface water (Nieuwenhuijsen et. al. 2000). A meta-analysis of the epidemiological studies has indicated that exposure to THMs may increase the risk of birth defects in general, especially neural tube and urinary tract defects (Hwang and Jaakkola 2003). A Swedish study provided some evidence of an elevated risk of cardiac defects (Cedergren et al. 2002), whereas Californian case-control study provided inconsistent results (Shaw et al. 2003). In a Norwegian nationwide cross-sectional study, the risk of specific birth defects was related to exposure to THMs (Hwang et al. 2002). A recent study in England and Wales reported that the risk of ventricular septal defects was associated with exposure to THMs while total brominated THM exposure in the first trimester of pregnancy did not trigger significant excess risks of congenital anomalies in the high-exposure categories. (Nieuwenhuijsen et al. 2008).

A major challenge of these studies was the imprecision of exposure assessment from using aggregate municipal drinking water measures for classifying THM exposures. Most of the previous research has focused on exposure to concentrations of total THMs. As the researchers had no information on individual patterns of water consumption, showering, or bathing, the assigned category of THM exposure might not accurately reflect the actual THM uptake. Moreover, the epidemiological studies differed in the control of maternal characteristics that could also be associated with adverse pregnancy outcomes. Such differences present difficulties in making comparisons between research and generalised results.

Seeking to improve the estimation of THM exposure at the personal level, we conducted a prospective Kaunas pregnant women cohort study, which incorporated different routes of THMs uptake. This is the first epidemiological study that evaluates individual internal dose impact of THM constituents on congenital anomalies. Previously, we reported dose–response relationships for entire pregnancy and trimester-specific gestational THMs and chloroform internal dose for low birth weight and reduction in birth weight (Grazuleviciene et al. 2011).

In that case-control study we used individual maternal data from the prospective pregnant women cohort study to evaluate individual THM uptake during pregnancy and to assess the effect of internal dose of total THMs and individual THM on the risk of any congenital anomalies, adjusting for many important risk factors for congenital anomalies. Individual exposure to THM was estimated as the total internal dose based on the monitoring of drinking water THM levels and detailed water use behaviours.

2. Materials and methods

2.1. Participant characteristics

The epidemiological study in Kaunas city, Lithuania (KANC study) enrolled 4,161 pregnant women at the third month of pregnancy (2007-2009), residents of the municipality of Kaunas. The study ethics complied with the Declaration of Helsinki (1996). The research protocol was approved by the Lithuanian Bioethics Committee and an oral informed consent was obtained from all subjects. In total 5,405 women were approached; 79% of them agreed to participate in the study.

Exposures were assessed through questionnaires administered during pregnancy, requesting extensive information on personal characteristics and water-related habits. The first interview was completed during the first pregnancy trimester. The medium gestational age at the interview was 8 weeks. The interview queried women regarding demographics, residence and job characteristics, chronic diseases (cardiovascular, hypertension, diabetes, renal), reproductive history, including the date of last menstrual period, previous preterm delivery. We also asked the women to report their age (younger than 20 years, 20–29 years, 30 years, and over), educational level (primary, secondary, university), family status (married, not married), smoking (non-smoker, smoker at least one cigarette per day), alcohol consumption (0 drinks per week, at least one drink per week), blood pressure (<140/90 mm/Hg, ≥140 or ≥ 90 mm/Hg), body mass index (<25 kg/m2, 25–30 kg/m2, >30 kg/m2), and other potential risk factors for congenital anomalies. Adjustment for these variables was made for the studies of various subgroups. The women also were examined by ultrasound to determine the gestational age of the foetus.

A special questionnaire on water consumption and water use habits was used to interview 4,260 women who agreed to participate in the study; 76.4% of them were interviewed during the third pregnancy trimester before delivery at the hospital and 23.6% by telephone within the first month after delivery. Consumption was ascertained for three types of water: cold tape water or drinks made of cold tap water; boiled tap water (tea, coffee, and other); and bottled water, used at home, at work, etc. In addition, number of showers, baths, swimming pools weekly, and their average length was asked of all subjects. The interviews were conducted by trained nurses who did not know the THM exposure status and birth outcome.

Pregnancy outcomes were abstracted from the medical records. We obtain registry-based data on any congenital anomalies from medical records. The birth defects studied were those reported in other studies and included cardiac anomalies, neural tube defects, cleft defects, chromosomal abnormalities, and others. The diagnoses of birth defects in this study were limited to those detectable before an infant is discharged from hospital after delivery. The reference group was defined as all term births (born at >37 weeks of gestation).

Women with multiple pregnancies (150), having inconsistent or invalid data for dating the pregnancy (5) or estimating THM exposure mostly students moved out of the city during pregnancy (839), parity more than 3 children (117) or with newborn birth weight above 4,500 g (75) were excluded. We restricted our analyses to infants born with a birth weight below 4,500 g, leaving the data for 3,074 women in the final analysis.

2.2. THM exposure assessment

The Kaunas city municipal drinking water is supplied by the four water treatment plants system. Groundwater sources are used for the whole water supply system. However, the four water treatment plants, which disinfected ground water with sodium hypochlorite (chlorine dose 0.26–0.91 mg/L, residual chlorine 0–0.22 mg/L), produce different concentrations of THMs in finished water. One treatment plant (Petraiunai) supplies finished water with higher levels of THMs (“high level THM site,” 54.9% subjects), and the three other plants supply

finished water with lower levels of all THMs ("low level THM site"). Water samples were collected four times per year over a 3-year study period (2007–2009) in the morning in three locations: close to the treatment plant, at 5 km, and at 10 km or more from every treatment plant. A total of 85 water samples were collected from 12 monitoring sites in four water supply zones for THM analysis. Samples were analysed at the University of the Aegean, Greece, by using gas chromatography with electron captures detection (Nikolaou et al. 2005). Measurements included specific values for the four regulated THMs (total trihalomethane (TTHM), chloroform (CH), bromodicholormethane (BDCM) and dibromochloromethane (DBCM). We calculated the mean quarterly THM constituent concentrations for water zones and, subsequently depending on the TTHM levels within each zone, assigned "low level" and "high level" sites. We used tap water THM concentration, derived as the average of quarterly sample values over the time that the pregnancy occurred from all sampling sites located in the each distribution system, and geocoded maternal address at birth to assign the individual women residential exposure index. Estimates of exposure index to total and specific THMs from drinking water were tabulated first as an average level at the tap over the pregnancy period; this measure was then categorised at the quartiles of the distribution for birth outcomes. We combined every subject's residential exposure index and water-use questionnaire data to assess individual exposure through ingestion of THMs. Women were asked to indicate the cup or glass size and number of cups or glasses of tap water consumed per day, including hot and cold beverages made from tap water. With this information, we calculated daily amounts of hot and cold tap water ingested. Integration of the information was carried out on residential THM levels (μg/L), ingested amounts (L/day) and modifications by heating using an estimated uptake factor of 0.00490 to derive an integrated index of blood concentration expressed in micrograms per day (μg/d) (Savitz et al. 2006; Whitaker et al. 2003).

The actual algorithms of internal dose from ingestion were:

- chloroform level (μg/L) × water consumption (L/day) × 0.00490196 μg/μg/L;
- brominated THM level (μg/L) × water consumption (L/day) × 0.00111848 μg/μg/L.

We assumed a null THM level for any bottled water consumption since chlorination and ozonation in local bottled water production were not used.

Finally, we addressed dermal absorption and inhalation by considering showering and bathing alone and combined with ingestion. We multiplied residential THM levels (μg/L) by frequency and average duration of bathing or showering per day (min/day) and calculated each mother's entire pregnancy average daily uptake of THM internal dose (μg/d). We derived indices of daily uptake by integrating THM concentrations, duration of bathing and showering reported in a questionnaire administered to study participants and estimated uptake factors of 0.001536 and 0.001321 of THMs in blood per minute per microgram from showering and bathing, respectively (Backer et al. 2000; Lynberg et al. 2001). The uptake factors of THMs individual constituents were assessed on the relative changes in blood levels after 10 minute exposure (after versus before ingestion 1 L of tap water, 10 minute showering, and 10 minute bathing). The actual algorithms of internal dose from showering and bathing were:

- min/day showering × μg/L chloroform in water × 0.001536261 μg/min/μg/L,
- min/day showering × μg/L brominated THM in water × 0.001352065 μg/min/μg/L,
- min/day bathing × μg/L chloroform in water × 0.001320755 μg/min/μg/L,
- min/day bathing × μg/L brominated THM in water × 0.00129571 μg/min/μg/L

We then used average daily total uptakes in our analysis as continuous and categorised variables. We calculated quartiles of total THM internal dose. This gave first (0.0025–0.0295 μg/d), second (0.0295–0.1899 μg/d), third (0.1899–0.4492 μg/d) and forth (0.4492 –2.404 μg/d) quartiles for average TTHM uptake. To reduce exposure misclassification errors in the subsequent analysis, we used a subset of women who through the entire pregnancy did not change their address.

2.3. Statistical analysis

The data analysis compared the any congenital anomalies of exposed women to total THMs and specific THM constituents. We used logistic regression to estimate the adjusted odds ratios (ORs) and the 95-percent confidence intervals (CIs) for congenital anomalies and the various exposure indices. We categorized TTHM internal dose in quartiles and evaluated the possible relationship between increases in congenital anomalies risk for an increase in estimated TTHM internal dose. We ran multivariate logistic regression models for the TTHMs, CH, DBCM, and BDCM for the pregnancy. We also used multiple linear regressions for TTHM internal dose analysis as a continuous variable to evaluate the relationship, if any between congenital anomalies and every 0.1 μg/d increase in TTHM internal dose.

In the logistic regression models for congenital anomalies outcomes, using personal data of the pregnant women sample, we assessed a variety of potential confounders identified by univariate analysis. Further, we examined the association of THM exposure and congenital anomalies with a multivariable analysis controlling for the effect of major covariates that changed the adjusted ORs for THM by 10% or more. The adjusted congenital anomalies analyses included maternal education, age, body mass index, alcohol consumption, smoking, blood pressure, stress, foetus number, infant gender and premature birth.

Table 1. Mean THM levels (μg/L) by sampling site and water supply zone

Tap water sampling sites	TTHMs[c] Mean (SD[d])	CH Mean (SD)	DBCM Mean (SD)	BDCM Mean (SD)
All sites	9.8 (12.4)	7.8 (10.2)	0.3 (0.5)	1.7 (2.2)
Low THM level[a]	1.3 (1.2)	0.9 (1.0)	0.1 (0.2)	0.3 (0.5)
High THM level[b]	21.9 (10.9)	17.7 (9.0)	0.5 (0.6)	3.6 (2.1)

[a]Viciunai, Eiguliai, Kleboniskis. [b]Petrasiunai.
[c]TTHMs = total trihalomethanes: the sum of CH (chloroform), DBCM (dibromochloromethane), and BDCM (bromodichloromethane).
[d]SD = standard deviation.

3. Results

3.1. Daily THM uptake

The mean tap water THM level in the low level site from three water treatment plants was 1.3 μg/L, and in the high level site (Petrasiunai) 21.9 μg/L (Table 1).

The highest proportion of THM made chloroform. Bromoform was below the limit of detection. There was little spatial and seasonal variability in the THMs levels within the high and low areas. The estimated individual total uptake of THMs ranged between 0.0025 and 2.404 μg/d. The total CH uptake ranged between 0.0013 and 2.1328 μg/d. Mothers supplied with water who had a higher CH concentration generally also had a higher total internal dose. Daily uptake of BDCM ranged between 0.0001 and 0.3359 μg/d and DBCM ranged between 0 and 0.0683 μg/d.

3.2. Congenital anomalies risk factors

The women recruited were predominantly Lithuanians in ethnic origin (97.5%) and did not smoke (93.5%) (Table 2).

The mean age was 28.4 years, and the women tended to be highly educated (55.6% with a university degree). In general, mothers who were single, had preterm delivery, or reported a chronic stress delivered a higher proportion of congenital anomalies newborns.

Table 2. Distribution of Kaunas cohort study subjects for various characteristics among congenital anomalies cases and controls, crude odds ratios (OR) and 95% confidence intervals (CI)

Risk factors	All participants		Cases		Controls		Crude Odds ratios	
	No	%	No	%	No	%	OR	95% CI
Maternal age								
< 20 years	94	3.1	3	1.8	91	3.1	1	
20–29 years	1895	61.6	100	58.5	1795	61.8	0.59	0.18-1.90
≥ 30 years	1085	35.3	68	39.8	1017	35.0	1.20	0.87-1.65
Family status*								
Married	2554	83.1	129	75.4	2425	83.5	1	
Not married	520	16.9	42	24.6	478	16.5	1.65	1.15-2.37
Maternal education								
Primary school	147	4.8	9	5.3	138	4.8	1	
Secondary school	1217	39.6	57	33.3	1160	40.0	0.75	0.37-1.56
University degree	1710	55.6	105	61.4	1605	55.3	1.00	0.50-2.03
Maternal active smoking								
Non-smoker	2874	93.5	162	94.7	2712	93.4	1	
Smoker	200	6.5	9	5.3	191	6.6	0.79	0.40-1.56
Passive smoking								
Non-smoker	1664	54.7	82	48.8	1582	55.0	1	
Smoker	1378	45.3	86	51.2	1292	45.0	1.28	0.94-1.75
Alcohol consumption								
No	2889	94.0	165	96.5	2729	93.8	1	
Yes	185	6.0	6	3.5	179	6.2	0.55	0.24-1.27
Blood pressure*								
<140/80 mm/Hg	2643	86.0	157	91.8	2486	85.6	1	
≥140 or ≥ 90 mm/Hg	431	14.0	14	8.2	417	14.4	0.53	0.31-0.93
Ethnic group								
Lithuanian	2997	97.5	168	98.2	2829	97.5	1	
Other	77	2.5	3	1.8	74	2.5	0.68	0.21-2.19
Parity								
No child	1515	49.3	86	50.3	1429	49.2	1	
≥ 1 child	1559	50.7	85	49.7	1474	50.8	0.96	0.70-1.30
Infant gender								

Risk factors	All participants		Cases		Controls		Crude Odds ratios	
	No	%	No	%	No	%	OR	95% CI
Male	1558	50.7	91	53.2	1467	50.5	1	
Female	1516	49.3	80	46.8	1436	49.5	0.90	0.66-1.22
Current residence								
2–4 years	1301	42.3	72	41.7	1229	42.3	1	
5–9 years	763	24.8	43	25.1	720	24.8	1.02	0.69-1.50
≥ 10 years	1010	32.9	56	32.7	954	32.9	1.00	0.70-1.44
Work exposure								
No	1089	35.4	55	32.2	1034	35.6	1	
Yes	1985	64.6	116	67.8	1869	64.4	1.17	0.84-1.62
Chronic disease								
No	2333	75.9	125	73.1	2208	76.1	1	
Yes	741	24.2	46	26.9	695	23.9	1.17	0.83-1.66
Previous preterm delivery								
No	3023	98.3	167	97.7	2856	98.4	1	
Yes	51	1.7	4	2.3	47	1.6	0.48	0.52-4.09
Socio economic status								
Low income	906	30.6	52	31.7	854	30.6	1	
Medium income	1594	53.9	78	47.6	1516	54.2	0.85	0.59-1.21
High income	459	15.5	34	20.7	425	15.2	1.31	0.84-2.06
Body mass index (kg/m^2)*								
<25 Normal	1812	58.9	127	74.3	1685	58.0	1	
25–30 Overweight	866	28.2	27	15.8	839	28.9	0.43	0.28-0.65
30 Obesity	396	12.9	17	9.9	379	13.1	0.60	0.35-1.00
Water filter								
Yes	931	30.3	53	31.0	878	30.2	1	
No	2143	69.7	118	69.0	2025	69.8	0.97	0.69-1.35
Water supply area								
Petrasiunai	1681	54.7	103	60.2	1578	54.4	1	
Other	1693	45.3	68	39.8	1325	45.6	1.27	0.93-1.74
Gestation age*								
≥37 weeks	2851	92.7	147	86.0	2704	93.1	1	
<37 weeks	223	7.3	24	14.0	199	6.9	2.22	1.41-3.50
Maternal stress*								
No	2588	84.2	132	77.2	2456	84.6	1	
Yes	486	15.8	39	22.8	447	15.4	1.62	1.12-2.35

**: $p<0.05$*

3.3. Association between THM internal dose during pregnancy and congenital anomalies risk

Using total gestational daily uptakes quartiles of TTHM and individual THMs continuous variables, we examined the association between internal dose for the entire pregnancy and any congenital anomalies risk (Table 3). Effect estimates based on TTHMs and CH quartiles tended to increase by an increase in the exposure quartiles compared with the first quartile, but there were no statistically significant effect for entire pregnancy. TTHM and CH analysed as continuous variables (increase in 0.1 μg/d) also showed slightly elevated, but statistically non-significant increase in risk of any congenital anomalies. However, we found dose–response relationships for the BDCM internal dose and risk for any congenital anomalies for crude and adjusted ORs. The adjusted ORs for fourth quartile vs. first quartile was 1.5, 95% CI 1.00–2.55. The ORs per every 0.01 μg/d increase in BDCM internal dose was 1.03, 95% CI 1.00–1.07. Effect estimates from continuous model associated with DBCM exposure levels during entire pregnancy also revealed statistically significant association with the any congenital anomalies risk (OR 1.23, 95% CI 1.02-1.48).

4. Discussion

Assessment of potential effects of exposure to drinking water disinfection by-products on the risk of congenital anomalies is problematic because of rarity and diversity of the congenital malformations.

In this study the outcome assessment was based on birth registration, as in the vast majority of the previous studies of disinfection by-products and birth defects. However, THM exposure assessment has included personal exposure estimation through multiple routes such as bathing, showering and water consumption. Also we have personal information on alcohol consumption, cigarette smoking, other behaviour factors, residential history, mobility during pregnancy and other variables whose influence we controlled during assessment impact of individual THM constituents exposure on congenital anomalies.

We conducted a prospective epidemiological study to examine the effects of internal dose of THM during the entire pregnancy on the risk of any

congenital anomalies. We found little indication of a dose-response relationship for total THM and CH and congenital anomalies. Total THMs and CH analysed as continuous variables (increase in 0.1 μg/d) showed slightly elevated, but statistically non-significant increase in risk of any congenital anomalies. For the BDCM association with the any congenital anomalies the dose-response relationship was evident for entire pregnancy. The adjusted ORs for fourth quartile vs. first quartile was 1.5, 95% CI 1.00–2.55 and the probability of delivering any congenital anomalies infant was elevated by 3% per every 0.01 μg/d increase in the pollutant internal dose (OR 1.03, 95% CI 1.00–1.07). Effect estimates from continuous model associated with DBCM exposure levels during entire pregnancy also revealed statistically significant association with the any congenital anomalies risk (OR 1.23, 95% CI 1.02-1.48). The lack of statistically significant effects for other THMs constituents may be due to low exposure because of low THM levels and lack of power in our study sample.

Table 3. Congenital anomalies crude and adjusted odds (OR) ratios and 95% confidence intervals (CI) for entire pregnancy exposure to internal dose THM quartiles

THM dose quartiles limits (μg/d)	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
THM				
0.0025-0.0295	35 (4.6)	726 (95.4)	1	1
0.0295-0.1899	39 (4.9)	752 (95.1)	1.08 (0.67-1.72)	1.05 (0.65-1.69)
0.1899-0.4492	45 (5.8)	731 (94.2)	1.28 (0.81-2.01)	1.28 (0.81-2.02)
0.4492-2.4040	52 (7.0)	694 (93.0)	1.55 (1.00-12.42)	1.45 (0.92-2.27)
Continuous (0.1μg/d)				1.03 (0.98-1.08)
Chloroform				
0.0013-0.1807	38 (5.0)	724 (95.0)	1	1
0.1807-0.1457	36 (4.6)	753 (5.4)	0.91 (0.57-1.45)	0.89 (0.56-1.43)
0.1457-0.3707	47 (6.0)	730 (94.0)	1.23 (0.79-1.90)	1.22 (0.78-1.91)
0.3707-2.1328	50 (6.7)	696 (93.3)	1.37 (0.89-2.11)	1.27 (0.82-1.99)
Continuous (0.1μg/d)				1.02 (0.97-1.08)
BDCM				
0.0001-0.01	31 (4.0)	742 (96.0)	1	1
0.01-0.0291	45 (5.8)	732 (94.2)	1.47 (0.92-2.35)	1.44 (0.89-2.32)
0.0291-0.0609	43 (5.7)	710 (94.3)	1.45 (0.90-2.33)	1.49 (0.92-2.41)
0.0609-0.3359	52 (6.7)	719 (93.3)	1.73 (1.10-2.73)	1.59 (1.00-2.55)
Continuous (0.01μg/d)				1.03 (1.00-1.07)
DBCM				
0.0000-0.00101	37 (5.2)	674 (94.8)	1	1
0.00101-0.00267	37 (4.8)	738 (95.2)	0.91 (0.57-1.46)	0.94 (0.59-1.52)
0.00267-0.00809	41 (5.2)	750 (94.8)	1.00 (0.63-1.57)	1.00 (0.63-1.59)
0.00809-0.0683	56 (7.0)	741 (93.0)	1.38 (0.90-2.11)	1.32 (0.85-2.05)
Continuous (0.01μg/d)				1.23 (1.02-1.48)

**Adjusted for maternal education, age, body mass index, alcohol consumption, passive smoking, blood pressure, stress, foetus number, infant gender and premature birth.*
TTHM, total trihalomethane; DBCM–dibromochloromethane, BDCM– bromodichloromethane

5. Discussion

Assessment of potential effects of exposure to drinking water disinfection by-products on the risk of congenital anomalies is problematic because of rarity and diversity of the congenital malformations.

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We conducted a prospective epidemiological study to examine the effects of internal dose of THM during the entire pregnancy on the risk of any congenital anomalies. We found little indication of a dose-response relationship for total THM and CH and congenital anomalies. Total THMs and CH analysed as continuous variables (increase in 0.1 μg/d) showed slightly elevated, but statistically non-significant increase in risk of any congenital anomalies. For the BDCM association with the any congenital anomalies the dose-response relationship was evident for entire pregnancy. The adjusted ORs for fourth quartile vs. first quartile was 1.5, 95% CI 1.00–2.55 and the probability of delivering any congenital anomalies infant was elevated by 3% per every 0.01 μg/d increase in the pollutant internal dose (OR 1.03, 95% CI 1.00–1.07). Effect estimates from continuous model associated with DBCM exposure levels during entire pregnancy also revealed statistically significant association with the any congenital anomalies risk (OR 1.23, 95% CI 1.02-1.48). The lack of statistically significant effects for other THMs constituents may

be due to low exposure because of low THM levels and lack of power in our study sample.

Reconciling our results with previous findings is not straightforward because there are substantial differences in the THMs levels, individual THMs constituents in drinking water, measurement of personal exposures, its classification, variation of exposure during pregnancy and controlling for confounding variables. Also the vast majority of epidemiological studies for the exposure assessment use THM concentration in drinking water as an exposure index without estimation of personal water consumption habits and estimation of THM uptake. These shortcomings may lead to the misclassification of exposure.

Only few previous studies have focused on the study associations between THM exposure and the risk of all the most common congenital anomalies. The authors of a nationwide cross-sectional study of Norwegian births (Hwang et al. 2002) to assess the effect of water chlorination by-products on congenital anomalies compared risks of birth defects according to four exposure categories. The exposure categories were estimated on the basis of chlorination (yes/no) and the level of water colour, representing the amount of natural organic matter. In logistic regression analysis, the risks of any congenital anomalies were significantly associated with increased exposure (OR 1.13, 95% CI 1.01-1.25). In a registry-based study to determine the relationship between THM concentrations and the risk of congenital anomalies in England and Wales (Nieuwenhuijsen et al. 2008) THM data were obtained from water companies. In this large national study the authors found little evidence for a relationship between THM concentrations in drinking water and risk of any congenital anomalies. A population-based cross-sectional Taiwanese births study (Hwang et al. 2008) compared the risk of congenital anomalies in four THM exposure categories, based on the levels of total THM. The study results showed no consistent association between exposure and the risk of any congenital anomalies in general.

A major challenge of these studies is the imprecision of exposure assessment from using aggregate municipal measures for classifying THM exposures. These studies also have no information on the amounts of beverage and tap water consumption by pregnant women and exposure to volatile disinfection by-products through inhalation and dermal absorption, which introduce non-differential misclassification and decrease the accuracy of exposure assessment. The studies have no information on residential mobility during pregnancy that may have produced exposure classification errors.

An epidemiological Australian communities study reported a statistically significant increased risk of any congenital anomalies (OR 1.22, 95% CI 1.01–1.48) among women users of high levels of TTHMs in drinking water with the highest proportion (on average, 92%) of brominated THMs (Chisholm et al. 2008). These results are consistent with our data that the highest effect of total THMs on congenital anomalies comes from brominated THMs.

The strengths of our study include the THM exposure assessment during pregnancy, a population-based assessment of cases and controls, control for residential mobility effects. This study also offers advancement in individual internal dose calculation based on residential THM levels, detailed water use behaviours and exposure during pregnancy. Every subject's exposure indices were estimated as daily internal dose of the THM constituents (μg/d), and birth outcome effects were assessed by using indices categorical variable and also as a continuous variable. An additional strength of our study is that pregnant women were prospectively followed, and did not move during pregnancy. That allowed collection of self reported data on potential confounding covariates and decrease in exposure misclassification errors.

We acknowledge several limitations in this study. Because of the lack of information regarding the validity of the internal dose assessment models that we used in our study, there is a possibility that the effect estimates that we have observed may be biased owing to non-differential misclassification of internal dose. Also we have not studied epigenetic and genetic interaction as part of the mechanism participating in metabolism of environmental contaminants.

Further epidemiological studies to determine whether an association exists between exposure to THMs and developmental effects must consider the individual THM, its concentrations, since the mechanisms of toxic action differ in individual THMs compounds (Bull et al. 2009; Richardson et al. 2007; Health Canada 2006). The influence of the water distribution system structure and the spatial variability of DBPs on the population exposure to water disinfection by-products also should be accounted for the exposure assessment (Legay et al. 2010). A recent workshop highlighted the current challenges and new opportunities for studying the role of genetic factors in the etiology of human birth defects (Olshan et al. 2011). In future studies personal estimation of the uptake substances and research into gene-environmental interaction could be a challenge.

Given the controversy surrounding THM levels in drinking water and adverse pregnancy outcomes, especially regarding associated congenital anomalies, a precautionary approach to brominated THM exposure during pregnancy is somewhat justified.

6. Conclusions

The present study suggests that prenatal exposure to drinking water THM may increase the risk of any congenital anomalies. Our findings demonstrate the importance of focusing on exposure of individual THM constituents at the personal level of the studies' impact on pregnancy outcomes, rather than using total THM concentrations in drinking water. A precautionary approach to brominated THM exposure during pregnancy should be used to decrease risk of congenital anomalies.

Acknowledgment

This work was supported in part by grant FP6-036224 from the European Commission. We acknowledge the contribution of the Clinics of Kaunas University of Medicine involved in registration of pregnancy outcomes. We also thank Maria Kostopoulou-Karadanelli and Stuart W Krasner for THM analyses and consultations.

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Vandens dezinfekcijos pašaliniai produktai ir įgimtų anomalijų rizika Kaune

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(gauta 2012 m. vasario mėn., priimta spaudai 2012m. rugsėjo mėn.)

Remiantis epidemiologinių tyrimų duomenimis, motinos ekspozicija geriamojo vandens chloravimo pašaliniais produktais trihalometanais (THM) gali būti susijusi su įgimtomis anomalijomis. Šio tyrimo tikslas buvo nustatyti motinos ekspozicijos į atskirų THM vidinės dozės nėštumo metu poveikį įgimtų anomalijų rizikai. Buvo atliktas populiacinis perspektyvusis tyrimas, į kurį 2007–2009 m. įtrauktos 3074 nėščiosios kaunietės, kurioms ekspozicijai nustatyti buvo apskaičiuota THM vidinė dozė. Naudojant daugiaveiksnę logistinę regresiją, keturiuose vidinės dozės ekspozicijos kvartiliuose palyginta įgimtų anomalijų rizika. Be to, taikant tiesinės regresijos modelius kontroliuota moterų fiziologinių, elgsenos, socialinių ir demografinių veiksnių įtaka.

Visų dėl THM ir chloroformo įgimtų anomalijų rizika didėjant ekspozicijos kvartiliui turėjo tendenciją didėti. Nustatytas ryšys tarp bromodichlorometano (BDCM) vidinės dozės ir įgimtų anomalijų rizikos. Standartizuotas galimybių santykis (GS) tarp pirmo ir ketvirto kvartilio buvo 1,5, 95%PI 1,00–2,55, o padidėjus 0,01 µg/d BDCM vidinei dozei reikšmingai padidėjo įgimtų anomalijų rizika (GS 1,03, 95% PI 1,00–1,07). Dibromochlorometano (DBCM) ekspozicija taip pat reikšmingai didino įgimtų anomalijų riziką (GS 1,23, 95% PI 1,02–1,48).

Gauti tyrimai rodo, kad dėl visų THM įgimtų anomalijų yra tendencija, kad rizika gali didėti, tačiau esant BDCM ir DBCM ekspozicijai statistiškai reikšmingai didėja įgimtų anomalijų rizika.