

The Effect of Disinfection By-products and Mutagenic Activity on Birth Weight and Gestational Duration

J. Michael Wright,¹ Joel Schwartz,² and Douglas W. Dockery²

¹Office of Research and Development, U.S. Environmental Protection Agency, National Center for Environmental Assessment, Cincinnati, Ohio, USA; ²Exposure, Epidemiology, and Risk Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA

Epidemiologic studies of disinfection by-products have traditionally focused on total trihalomethane (TTHM) concentration as a surrogate for maternal exposure during pregnancy. We used birth certificate data on 196,000 infants to examine the effect of third-trimester exposures on various indices of fetal development. We examined the effect of town-average concentrations of TTHM and additional exposure metrics in relation to mean birth weight, mean gestational age, small for gestational age (SGA) infancy, and preterm delivery. Trihalomethane data (TTHM, chloroform, and bromodichloromethane) from 1995–1998 were available for 109 towns in Massachusetts. Data from 1997–1998 on haloacetic acid (total haloacetic acids, dichloroacetic acid, and trichloroacetic acid), 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX), and mutagenicity were available for a limited number of towns. We observed reductions in mean birth weight (12–18 g) for maternal trihalomethane exposures > the 90th percentile compared with those < the 50th percentile. Birth weight reductions were detected for chloroform exposures > 20 µg/L and TTHM exposures > 40 µg/L. Elevated trihalomethanes were associated with increases in gestational duration and a reduced risk of preterm delivery. We found evidence of an exposure–response effect of trihalomethanes on risk of SGA, with odds ratios (ORs) ranging from 1.09 to 1.23 for bromodichloromethane exposures > 5 µg/L. Elevated mutagenic activity was associated with SGA [OR = 1.25; 95% confidence interval (CI), 1.04 to 1.51] and mean birth weight (–27 g; 95% CI, –54 to –1). Although smaller in magnitude, our findings are consistent with previous studies reporting associations between trihalomethanes and SGA. These data also suggest a relationship between fetal development indices and mutagenic activity independent of exposure to trihalomethanes, haloacetic acids, and MX. **Key words:** birth weight, bromodichloromethane, chloroform, gestational age, haloacetic acids, mutagenic activity, MX, preterm delivery, small for gestational age, trihalomethanes. *Environ Health Perspect* 112:920–925 (2004). doi:10.1289/ehp.6779 available via <http://dx.doi.org/> [Online 18 February 2004]

Disinfection by-products (DBPs) are formed when organic and inorganic matter react with disinfectants used to treat drinking water. Some DBPs are known reproductive and developmental toxins. Teratogenicity has been reported in animals exposed to haloacetic acids (HAAs) (Epstein et al. 1992; Smith et al. 1989a, 1992) and haloacetoneitriles (Smith et al. 1988, 1989b), and there is evidence that 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX) may be a direct-acting teratogen *in vitro* (Teramoto et al. 1998). The trihalomethanes (THMs) are not considered teratogenic, but growth retardation has been reported in mice exposed to chloroform (Murray et al. 1979; Ruddick et al. 1983; Schwetz et al. 1974; Thompson et al. 1974). Growth retardation has also been reported in mice exposed to dichloroacetic acid (Smith et al. 1992) and trichloroacetic acid (Smith et al. 1989a) and in rats exposed to dichloroacetonitrile (Smith et al. 1989b) and trichloroacetonitrile (Smith et al. 1987).

Epidemiologic data suggest an association between DBPs and adverse developmental outcomes (Graves et al. 2001; Nieuwenhuijsen et al. 2000; Reif et al. 1996). Bove et al. (1995) observed a 42% increased risk of low birth weight associated with total THM (TTHM)

concentrations > 100 µg/L compared with those ≤ 20 µg/L. Savitz et al. (1995) reported a 30% increased risk of low birth weight for TTHM exposures ≥ 82.8 µg/L compared with those < 40.8 µg/L but found no effect for maternal dose estimated from TTHM concentration and the number of glasses of water consumed per day. Gallagher et al. (1998) reported associations between > 60 µg/L TTHM (vs. ≤ 20 µg/L) and low birth weight in term births [odds ratio (OR) = 5.9; 95% confidence interval (CI), 2.0 to 17.0] and all births (OR = 2.1; 95% CI, 1.0 to 4.8). Wright et al. (2003) found an increased risk of infants' being small for gestational age (SGA) associated with TTHM concentrations > 80 µg/L (OR = 1.14; 95% CI, 1.02 to 1.26) compared with ≤ 60 µg/L. A 50% increased risk of SGA was reported by Bove et al. (1995) for TTHM concentrations > 100 µg/L (OR = 1.50; 95% CI, 1.14 to 1.94) compared with ≤ 20 µg/L. An 8% increased risk (OR = 1.08; 95% CI, 0.99 to 1.18) of SGA was reported by Dodds et al. (1999) for TTHM ≥ 100 µg/L compared with < 50 µg/L. No associations between preterm delivery and DBP concentrations have been reported (Bove et al. 1995; Dodds et al. 1999; Gallagher et al. 1998; Kramer et al. 1992; Savitz et al. 1995; Wright et al. 2003).

TTHM concentration is the most common surrogate of DBP exposure used in epidemiologic studies, but independent effects of individual THMs have been reported. Waller et al. (1998) found an increased risk of spontaneous abortions in women drinking five or more glasses per day of cold tap water containing ≥ 75 µg/L TTHM (OR = 1.8; 95% CI, 1.1 to 3.0) and ≥ 18 µg/L bromodichloromethane (BDCM; OR = 3.0; 95% CI, 1.4 to 6.6). King et al. (2000) detected a 98% (OR = 1.98; 95% CI, 1.23 to 3.49) increased risk for stillbirths among mothers exposed to ≥ 20 µg/L BDCM (vs. < 5 µg/L) and a 66% increased risk (OR = 1.66; 95% CI, 1.09 to 2.54) for TTHM ≥ 100 µg/L (vs. < 50 µg/L). Few epidemiologic studies have evaluated the impact of non-volatile DBPs on fetal development. Kramer et al. (1992) examined the impact of total organic halides but reported difficulty distinguishing between the effects of this surrogate with highly correlated DBPs. The relationship between fetal development outcomes and individual nonvolatile DBPs has not been examined, but these DBPs are likely even less correlated with TTHM concentrations (Wright et al. 2002). We previously detected high levels of MX and mutagenic activity in drinking water from Massachusetts (Wright et al. 2002), as well as associations between TTHM and different fetal development indices (Wright et al. 2003). In the present study, we used several years of birth certificate data to examine the relationship between indices of fetal development and various town average exposure metrics. Exposure measures included previously collected MX and

Address correspondence to J.M. Wright, 26 W. Martin Luther King Dr. (MS-190), Cincinnati, OH 45268 USA. Telephone: (513) 569-7922. Fax: (513) 569-7916. E-mail: wright.michael@epa.gov

We thank the individual water departments and the Massachusetts Department of Public Health for their interest and cooperation in this study. Special thanks to D. Guterman, J. Dillon, A. Zaharias, and P. Caron at the Massachusetts Department of Environmental Protection for their assistance in the data collection effort.

This work was supported in part by a pilot study grant from the Kresge Center for Environmental Health (National Institute of Environmental Health Sciences grant ES-00002).

The authors declare they have no competing financial interests.

Received 1 October 2003; accepted 18 February 2004.

mutagenicity data, as well as TTHM, BDCM, chloroform, total HAA, dichloroacetic acid, and trichloroacetic acid concentrations.

Materials and Methods

Study population. The Massachusetts Department of Public Health (Boston, MA) supplied 1995–1998 birth certificate data ($n = 282,645$) for towns with populations $> 10,000$. These data contained detailed maternal and infant information including birth weight and gestational age. We excluded infants with implausible values for birth weight (< 200 g) and gestational age (< 22 or > 45 weeks) and those born to nonresidents. The remaining birth data were linked with drinking water DBP and mutagenicity measurements to examine the effect of maternal third-trimester exposure on mean birth weight and SGA in term births and preterm delivery and mean gestational age in all births.

Outcome data. Gestational age recorded on the birth certificates was based on clinician estimate. SGA infancy was defined as the lowest decile of birth weight for each gestational week stratified by infant sex and maternal race. We restricted the SGA and birth weight analyses to term births from 37–45 gestational weeks. Preterm delivery was defined as < 37 gestational weeks, whereas very preterm was defined as < 34 weeks. Infants at least 37 gestational weeks and weighing at least 2,500 g served as the comparison group for the estimated ORs.

Exposure data. We used town-specific aggregate data to estimate maternal exposure to THMs, HAAs, MX, and mutagenic activity in drinking water. We abstracted 1995–1998 THM data from the Massachusetts Department of Environmental Protection (Boston, MA) records. Community systems that use disinfectants and serve populations $> 10,000$ were required to monitor THMs on a quarterly basis. Of the 109 towns with THM data, nine towns were granted waivers allowing annual monitoring. The THM samples collected by each town were analyzed by laboratories certified by the U.S. Environmental Protection Agency (EPA) or the Massachusetts Department of Environmental Protection, by means of gas chromatography (U.S. EPA method 502.2) and gas chromatography/mass spectrometry (U.S. EPA Method 524.2; U.S. EPA 1995). TTHM concentration was defined as the sum of chloroform, BDCM, dibromochloromethane, and bromoform. Dibromochloromethane and bromoform rarely exceeded the detection limit in these sampled communities, so we restricted the data analysis to chloroform, BDCM, and TTHM.

HAA samples were collected by 17 towns on a weekly to quarterly basis from 1997 to 1998 and were analyzed using gas chromatography (U.S. EPA method 552; U.S. EPA 1995).

Total HAAs included monochloroacetic, dichloroacetic, trichloroacetic, monobromoacetic, and dibromoacetic acids. Monochloroacetic acid, monobromoacetic acid, and dibromoacetic acid rarely exceeded the detection limit in these sampled communities, so we restricted the data analysis to dichloroacetic acid, trichloroacetic acid, and total HAAs.

We previously measured MX and mutagenic activity in Massachusetts' surface water systems described in detail elsewhere (Wright et al. 2002). Briefly, we collected 88 tap water samples from 36 towns during the fall and spring of 1997 and 1998. The tap water samples were collected in 4-L bottles, extracted, and evaporated to 1 mL ethyl acetate. The extracts were analyzed at the Laboratory of Chemistry of the National Public Health Institute in Kuopio, Finland. MX concentrations were measured using gas chromatography/mass spectrometry (Fawell and Horth 1990). Mutagenicity, measured as the number of net revertants (rev) per liter, was determined by the plate incorporation method of Maron and Ames (1983). The Ames test was conducted on *Salmonella typhimurium* tester strain TA100, which has been shown to be the most sensitive strain for detecting mutagenicity caused by MX (Daniel et al. 1991). MX is a direct-acting mutagen, so no metabolic activation was required. After linkage with the birth certificate data, MX and mutagenicity measurements for 34 towns were available for use in the present study.

Exposure assessment. Maternal ZIP code and infant month of birth were used to assign third-trimester town-specific DBP and mutagenicity data. Quarterly town averages were calculated from all available samples for the different sampling locations. Towns with annual THM measurements were assigned the same concentration for each quarter. To estimate third-trimester exposures, each mother with an infant born in the second or third month of a quarter was assigned the mean quarterly value for her town of residence. For infants born in the first month of a quarter, the third-trimester exposure was determined from the previous quarterly average concentration. Mothers delivering before 29 gestational weeks were not assigned a third-trimester value. We divided maternal exposures into approximately the lowest 50th percentile (reference), 50th–90th percentile, and $>$ the 90th percentile. We also examined exposure–response gradients based on equal increments of THM concentration.

Statistical methods. Statistical Analysis Systems software (SAS, version 6.11; SAS Institute, Inc., Cary, NC) was used for the statistical analyses. We used linear regression to estimate changes in birth weight and gestational age associated with exposure to DBPs and mutagenic activity. We used logistic regression to estimate ORs for preterm delivery and SGA

infancy. To indicate the precision of the effect estimates, 95% CIs were calculated. Pearson correlation coefficients were used to examine the relation between the town-specific exposure metrics. We included the categorical THM variables as continuous regressors in the final models as a test of trend for the exposure–response analyses.

The regression models were adjusted for the following dichotomous maternal risk factors: diabetes, lung disease, renal disease, chronic hypertension, marital status, previous preterm delivery, and previous birth to an infant weighing $> 4,000$ g. We also included categorical variables for maternal education, parity, prenatal care, and the number of cigarettes smoked per day based on a previous analysis of nonparametric smooth functions (Hattis D. et al., unpublished data). The adequacy of prenatal care classification (no care, inadequate care, intermediate care, and adequate) was based on the Kessner index, which incorporates gestational age, timing of the first prenatal visit, and total number of prenatal visits (Alexander and Kotelchuck 1996). A quadratic polynomial for maternal age and categorical variables for maternal race (Caucasian, African American, Asian, Native American, and other) were included in all of the regression models. Except for the SGA analyses, all of the regression models were adjusted for infant sex. Median household incomes specific to ZIP code obtained from 1990 U.S. Census data (Geolytics, Inc., East Brunswick, NJ) and weight gain during pregnancy were included as continuous variables. Weight gain during pregnancy and marital status were not available on birth certificates before 1997, so we could not adjust for these covariates in the THM analyses.

Results

As shown in Table 1, the study population included Massachusetts residents with singleton infants 22–45 gestational weeks and ≥ 200 g ($n = 196,000$). Of the 194,827 births with recorded gestational age and THM measurements, 11,580 (6%) were classified as preterm deliveries (< 37 gestational weeks). Among the 183,247 term births, 17,359 (9%) were classified as SGA. Prenatal care and maternal smoking were the strongest risk factors for the three outcomes. Mothers without prenatal care had infants that weighed an average of 250 g less than those with adequate prenatal care. Similar reductions in infant birth weight were observed among mothers smoking > 10 cigarettes per day compared with nonsmokers. Third-trimester TTHM exposure was weakly associated with mean birth weight and SGA infancy in these unadjusted analyses.

Table 2 shows the distribution of third-trimester DBP and mutagenic activity exposure for residents of towns with populations

> 10,000. The average third-trimester TTHM exposure was 38 µg/L, with 7% of the maternal exposures exceeding 80 µg/L. The maximum total HAA concentration was 58 µg/L, and the average maternal exposure was 31

µg/L. The average third-trimester exposure was 25 ng/L for MX and 1,400 rev/L for mutagenicity.

Birth weight. Reductions in mean birth weight were observed for individual THMs,

MX, and mutagenic activity (Table 3). Compared with TTHM levels < 50th percentile (≤ 33 µg/L), exposures in the 50th–90th percentiles (> 33 to 74 µg/L) and those > 90th percentile (> 74 µg/L) were associated with 12-g (95% CI, –16 to –7) and 18-g (95% CI, –26 to –10) reductions in birth weight, respectively. Similar associations were observed for chloroform, whereas smaller effects were observed for BDCM. Statistically significant tests for trend ($p < 0.001$) were detected suggesting an exposure–response relationship between birth weight and THM exposures. Although a monotonic gradient was not evident for any of the THM exposure metrics (Figure 1), reductions in mean birth weight were observed for chloroform concentrations > 20 µg/L and TTHM exposures > 40 µg/L.

The number of towns with MX, mutagenicity, and HAA data was limited. Nevertheless, exposure to high MX concentrations resulted in mean birth weight reductions similar to those observed for THMs (Table 3). Elevated mutagenicity (> 2,250 rev/L) was associated with a 27-g (95% CI, –54 to –1) reduction compared with the reference population ($\leq 1,250$ rev/L). No associations were detected for high third-trimester HAA exposures, but birth weight increases > 20 g were observed for intermediate total haloacetic and trichloroacetic acids.

Gestational age. We detected an association between mean gestational age and exposure to THMs and mutagenicity (Table 3). Mothers exposed to high THM concentrations had slightly longer gestational periods (0.4–0.5 days) than did those with lower exposures. Mutagenicity > 2,250 rev/L was associated with longer gestation (1.1 days; 95% CI, 0.4 to 1.7) compared with $\leq 1,250$ rev/L. Trichloroacetic acid > 27 µg/L was associated with shorter gestational duration (–0.9 days; 95% CI, –1.7 to –0.1) compared with ≤ 18 µg/L.

SGA births. Statistically significant tests for trend ($p \leq 0.002$) suggested an exposure–response relationship between SGA and categorical THM exposures. We detected a monotonic increase in risk of SGA for chloroform exposures > 20 µg/L (Figure 2). A monotonic gradient was not evident between SGA and BDCM, but associations were detected for exposures > 5 µg/L (ORs = 1.09–1.23). We found similar ORs (1.05–1.15) for intermediate and high THM exposures based on the 50th and 90th percentile cut points (Table 4). Relative risks similar in magnitude were observed for elevated exposures to MX (OR = 1.14; 95% CI, 0.95 to 1.37) and mutagenic activity (OR = 1.25; 95% CI, 1.04 to 1.51). We did not detect an increased risk of SGA infancy for high HAA exposures, but inverse associations were detected for intermediate trichloroacetic and dichloroacetic acid exposures.

Table 1. Characteristics of singleton infants born 1995–1998 in Massachusetts towns with populations > 10,000 with TTHM data available.

Characteristics	Study population [no. (%)]	Mean birth weight (g) ^a	SGA (%) ^{a,b}	Preterm delivery (%) ^c
Total births (no.)	196,000	3,463	17,359 ^d	11,580 ^d
Maternal race				
Caucasian	138,381 (70.8)	3,509	8.5	5.5
African American	19,213 (9.8)	3,346	9.8	11.0
Other	27,106 (13.9)	3,370	12.6	8.7
Asian	10,357 (5.3)	3,283	15.4	7.1
American Indian	360 (0.2)	3,434	10.6	9.0
Maternal age [years]				
12–20	24,794 (12.7)	3,322	14.2	9.1
21–25	36,093 (18.4)	3,409	11.2	6.8
26–30	56,799 (29.0)	3,481	8.7	5.9
31–35	54,094 (27.6)	3,520	7.6	5.7
36–40	21,234 (10.8)	3,514	8.2	6.8
41–53	2,984 (1.5)	3,484	10.5	8.3
Maternal education				
\leq 9th grade	14,743 (7.6)	3,329	14.8	9.8
10th grade	9,192 (4.7)	3,333	14.0	8.8
11th grade	10,536 (5.4)	3,345	13.7	8.8
High school graduate	160,649 (82.3)	3,489	8.5	6.0
Maternal smoking (cigarettes/day)				
0	168,463 (86.3)	3,491	8.2	6.1
1–5	8,711 (4.5)	3,323	15.1	8.7
6–10	10,134 (5.2)	3,271	17.9	9.1
> 10	7,888 (4.0)	3,238	20.7	10.2
Prenatal care (Kessner index)				
No prenatal care	464 (0.2)	3,233	19.9	25.1
Inadequate	6,582 (3.4)	3,333	14.1	10.6
Intermediate	33,860 (17.5)	3,399	11.5	9.1
Adequate	152,305 (78.8)	3,483	8.8	5.7
No. of previous births				
0	87,278 (44.5)	3,412	11.6	7.3
1	64,149 (32.7)	3,508	7.5	5.3
2 or 3	38,878 (19.8)	3,502	8.2	6.4
≥ 4	5,636 (2.9)	3,450	10.1	10.1
Infant sex				
Male	100,428 (51.2)	3,525	9.3	6.9
Female	95,572 (48.8)	3,398	9.7	6.2
Third-trimester TTHM (µg/L)				
0–20	63,138 (32.2)	3,484	8.6	6.7
> 20–40	48,623 (24.8)	3,468	9.3	6.5
> 40–60	44,218 (22.6)	3,442	10.3	6.6
> 60–80	25,562 (13.0)	3,440	10.2	6.6
> 80–163	14,459 (7.4)	3,454	10.5	5.8

^aInfants 22–45 gestational weeks and ≥ 200 g. ^bSGA defined as lowest 10% of birth weight per gestational age, sex, and race. ^cInfants < 37 gestational weeks and ≥ 200 g. ^dAmong 194,827 infants with recorded clinical estimates of gestational age.

Table 2. Maternal third-trimester exposure to DBPs and mutagenic activity for residents of Massachusetts towns with populations > 10,000 during 1995–1998.

	No. of towns	No. of births	10th ^a	Median	90th ^a	Maximum	Mean \pm SD
THMs (µg/L) ^b							
TTHM	109	196,000	8	33	74	163	38.2 \pm 27.0
Chloroform	109	195,506	4	25	63	135	31.0 \pm 23.6
BDCM	109	195,506	1	4	12	46	5.7 \pm 5.1
HAAs (µg/L) ^c							
Total HAAs	17	18,750	13	30	49	58	31.4 \pm 13.6
Trichloroacetic acid	15	14,151	9	19	28	37	16.9 \pm 7.5
Dichloroacetic acid	15	14,151	8	15	24	24	15.3 \pm 5.7
MX (ng/L) ^c	34	16,378	13	20	45	80	24.6 \pm 12.8
Mutagenicity (rev/L) ^c	34	16,378	820	1,260	2,040	5,710	1,410 \pm 700

^aPercentile. ^b1995–1998 data. ^c1997–1998 data.

Preterm delivery. The risk of preterm delivery (< 37 gestational weeks) was significantly lower for mothers with intermediate and high THM exposures (ORs = 0.88–0.95; Table 4). Elevated levels of HAAs, MX, and mutagenicity were not associated with preterm delivery. No associations were detected between very preterm infants (< 34 gestational weeks) and THMs, MX, mutagenicity, or dichloroacetic acid (data not shown), but an increased risk was observed for high trichloroacetic (OR = 1.33; 95% CI, 0.77 to 2.30) and total HAAs (OR = 1.48; 95% CI, 0.84 to 2.61).

Discussion

Low birth weight and preterm delivery are strongly associated with infant morbidity and mortality (Branum and Schoendorf 2002;

Infant Health and Development Program 1990; McCormick 1985), especially in the United States, where infant mortality rates are largely attributable to preterm delivery (Wilcox et al. 1995). Although many important risk factors have been identified, the underlying etiology of approximately 60% of preterm deliveries and 40% of low-birth-weight infants remains unclear (Wollmann 1998). There is increasing interest in the role of environmental exposures, including ambient air pollution (Bobak 2000; Maisonet et al. 2001; Ritz and Yu 1999; Rogers et al. 2000; Wang et al. 1997) and DBPs in drinking water (Graves et al. 2001; Nieuwenhuijsen et al. 2000; Reif et al. 1996).

Consistent with previous term birth analyses (Bove et al. 1995), we found associations

between TTHM exposures > 40 µg/L and mean birth weight. Reductions in birth weight were also observed for low third-trimester chloroform (> 20 µg/L) and BDCM (> 5 µg/L) concentrations. Exposure to high levels of mutagenic activity resulted in the largest reduction in birth weight (–27 g; 95% CI, –54 to –1). The reductions in mean birth weight associated with DBPs and mutagenicity were an order of magnitude less than those observed for maternal smoking and other risk factors.

We evaluated SGA infancy as a measure of fetal growth restriction, because birth weight is a function of gestational duration and rate of fetal growth. We found evidence of exposure–response effects of THMs on SGA and a monotonic increase in risk for chloroform. Increased risks of SGA were observed for TTHM > 40 µg/L, chloroform > 20 µg/L, BDCM > 5 µg/L, and mutagenic activity

Table 3. The effect of third-trimester DBP and mutagenicity exposure on mean birth weight among term births and gestational age among all births.^a

Exposure	No. of births ^b	Birth weight		No. of births	Gestational age	
		Δ Birth weight (g) ^b	95% CI		Δ Gestational age (days)	95% CI
THMs (µg/L)						
TTHM						
0–33	89,881	Reference		95,630	Reference	
> 33–74	70,567	–12	–16 to –7	74,956	0.0	–0.1 to 0.1
> 74–163	16,729	–18	–26 to –10	17,627	0.5	0.3 to 0.7
Per 66 µg/L		–18	–23 to –13		0.3	0.1 to 0.4
Chloroform						
0–26	91,277	Reference		97,040	Reference	
> 26–63	69,285	–14	–19 to –9	73,637	0.0	–0.2 to 0.1
> 63–135	16,153	–18	–26 to –10	17,054	0.4	0.2 to 0.6
Per 59 µg/L		–19	–25 to –14		0.1	0.0 to 0.3
BDCM						
0–5	101,564	Reference		108,457	Reference	
> 5–13	60,873	–12	–17 to –8	64,215	0.6	0.5 to 0.7
> 13–46	14,278	–12	–20 to –3	15,059	0.5	0.3 to 0.8
Per 11 µg/L		–9	–13 to –4		0.5	0.4 to 0.6
HAAs (µg/L)^c						
Total HAA						
4–30	7,853	Reference		8,360	Reference	
> 30–49	6,599	25	9 to 40	7,005	0.1	–0.3 to 0.5
> 49–58	881	7	–25 to 39	934	0.7	–1.5 to 0.1
Per 36 µg/L		25	6 to 45		0.2	–0.2 to 0.6
Trichloroacetic acid						
0–18	5,175	Reference		5,494	Reference	
> 18–27	4,953	21	3 to 39	5,264	0.2	–0.3 to 0.6
> 27–37	1,031	–4	–35 to 27	1,093	–0.9	–1.7 to –0.1
Per 19 µg/L		16	–9 to 40		0.1	–0.6 to 0.8
Dichloroacetic acid						
2–15	5,135	Reference		5,457	Reference	
> 15–22	4,346	15	–4 to 34	4,587	0.0	–0.5 to 0.5
> 22–24	1,678	12	–14 to 38	1,807	–0.3	–0.9 to 0.4
Per 16 µg/L		29	4 to 55		0.1	–0.4 to 0.6
MX (ng/L)^c						
4–20	7,368	Reference		7,804	Reference	
> 20–46	5,542	–2	–17 to 14	5,879	–0.4	–0.8 to 0.0
> 46–80	1,484	–18	–44 to 8	1,552	0.1	–0.5 to 0.8
Per 32 ng/L		–14	–33 to 5		0.2	–0.3 to 0.7
Mutagenicity (rev/L)^c						
330–1,250	6,414	Reference		6,763	Reference	
> 1,250–2,250	6,476	–19	–35 to –2	6,909	–0.5	–0.9 to 0.0
> 2,250–5,710	1,504	–27	–54 to –1	1,563	1.1	0.4 to 1.7
Per 1,450 rev/L		–16	–32 to –1		0.5	0.1 to 0.9

^aRegression coefficients adjusted for median household income, infant sex, adequacy of prenatal care, maternal race, maternal education, maternal cigarette consumption, maternal age, parity, previous infant weighing ≥ 4,000 g, previous preterm delivery, and maternal medical history (diabetes, chronic hypertension, lung disease, and renal disease). ^bAmong term births only. ^c1997–1998 analyses included adjustment for marital status and weight gain during pregnancy.

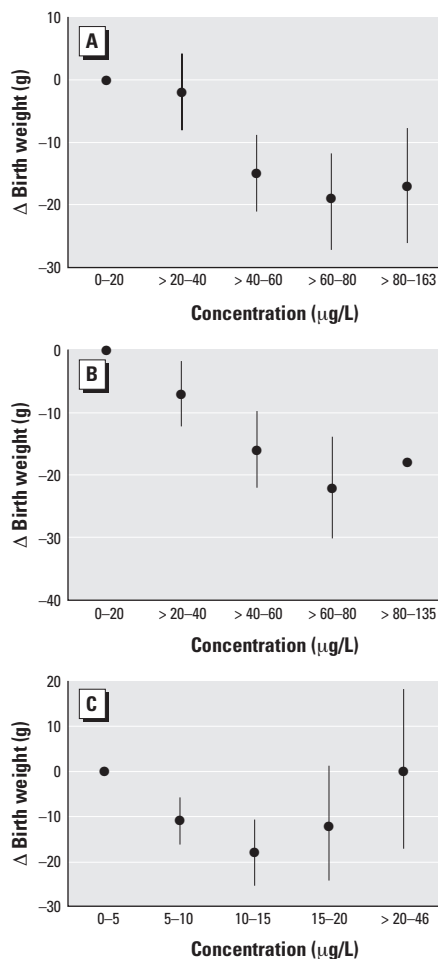


Figure 1. Change in mean birth weight and 95% CIs for third-trimester THM exposures: regression coefficients for (A) TTHM, (B) chloroform, and (C) BDCM adjusted for median household income, infant sex, adequacy of prenatal care, maternal race, maternal education, maternal cigarette consumption, maternal age, parity, previous infant weighing ≥ 4,000 g, previous preterm delivery, and maternal medical history (diabetes, chronic hypertension, lung disease, and renal disease).

> 2,250 rev/L. The effects of DBPs and mutagenicity on SGA and birth weight were smaller than previously reported for THMs.

Elevated THM and chloroform exposures were associated with a reduced risk of preterm delivery (< 37 gestational weeks). We found similar reductions in the risk of very preterm delivery (< 34 gestational weeks), although an increased risk was detected for total HAAs and trichloroacetic acid. It is unclear whether these differences are due to less misclassification among very preterm infants than among preterm infants or result from inaccurate gestational age estimates. We confirmed previous findings of associations between high THM exposures and increases in mean gestational age (Wright et al. 2003), but we are cautious in our interpretation given the likelihood of errors in gestational age estimates (David 1980; Gjessing et al. 1999). Although the clinical significance of small changes in gestational duration and

birth weight is unclear, the potential public health impact is considerable given widespread exposure to DBPs.

The modest effects that were detected reinforce the need for adequate control of confounding in environmental epidemiologic studies. Because of the comprehensive birth certificate data in Massachusetts, we were able to adjust for many potential confounders previously not considered. Moreover, nonparametric smoothing of confounders allowed for better control of established maternal risk factors for fetal growth retardation. Gestational age was a strong predictor of birth weight, but it is unclear whether gestational age is an intermediate in the causal pathway of DBPs and birth weight. Because bias may be introduced by adjusting for a causal intermediate (Rothman and Greenland 1998), we did not include gestational age in the final regression models. We had similar concerns regarding several maternal medical conditions including eclampsia, hydramnios, hypertension during pregnancy, and uterine bleeding, despite their being strong risk factors for infant birth

weight. Adjustment for these covariates had minimal effect on the results, so they were not included in the final regression models.

The main limitation of our study is the potential for exposure misclassification, because we relied on town average data to estimate individual exposures. Although we were unable to assess within-town variability because of the use of the aggregate exposure measures, between-town variability accounts for most of the total variation in DBP concentrations (Keegan et al. 2001). Interindividual variability in water use (e.g., showering, water consumption) is an important determinant of overall DBP exposure. Incorporating individual information such as water consumption rates should limit the amount of exposure misclassification, but previous studies have reported equivocal findings compared with the use of town average exposure measures (Klotz and Pyrch 1999; Savitz et al. 1995; Waller et al. 1998). The lack of information on maternal water use limited our ability to assess the impact of specific routes of exposure. Although inhalation and dermal absorption

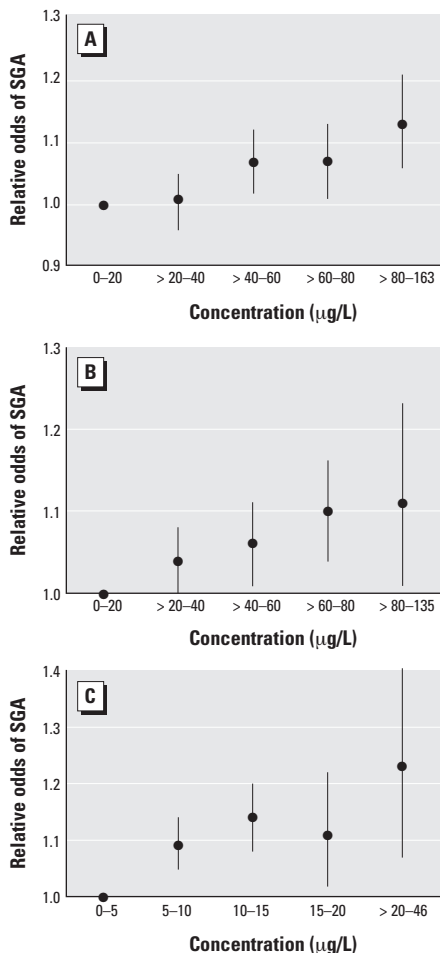


Figure 2. ORs and 95% CIs for SGA infancy and third-trimester THM exposures: ORs for (A) TTHM, (B) chloroform, and (C) BDCM adjusted for median household income, adequacy of prenatal care, maternal race, maternal education, maternal smoking, maternal age, parity, previous infant weighing \geq 4,000 g, previous preterm delivery, and maternal medical history (diabetes, chronic hypertension, lung disease, and renal disease).

Table 4. Adjusted ORs and 95% CIs for SGA and preterm delivery by third-trimester DBP and mutagenicity exposure.^a

Exposure	SGA ^{b,c}	Preterm delivery ^d
	OR (95% CI)	OR (95% CI)
THMs (µg/L)		
TTHM		
0-33	1.0	1.0
> 33-74	1.06 (1.02 to 1.10)	0.95 (0.91 to 0.99)
> 74-163	1.13 (1.07 to 1.20)	0.88 (0.81 to 0.94)
Chloroform		
0-26	1.0	1.0
> 26-63	1.05 (1.02 to 1.09)	0.95 (0.91 to 0.99)
> 63-135	1.11 (1.04 to 1.17)	0.90 (0.84 to 0.97)
BDCM		
0-5	1.0	1.0
> 5-13	1.1 (1.07 to 1.14)	0.89 (0.85 to 0.93)
> 13-46	1.15 (1.08 to 1.22)	0.92 (0.85 to 0.99)
HAAs (µg/L)^e		
Total HAAs		
4-30	1.0	1.0
> 30-49	0.90 (0.81 to 1.01)	0.95 (0.83 to 1.10)
> 49-58	0.97 (0.77 to 1.23)	1.03 (0.77 to 1.39)
Trichloroacetic acid		
0-18	1.0	1.0
> 18-27	0.87 (0.76 to 0.99)	0.91 (0.77 to 1.07)
> 27-37	0.95 (0.76 to 1.19)	1.07 (0.81 to 1.42)
Dichloroacetic acid		
2-15	1.0	1.0
> 15-22	0.86 (0.75 to 0.99)	0.85 (0.71 to 1.01)
> 22-24	0.90 (0.75 to 1.09)	0.99 (0.79 to 1.23)
MX (ng/L)^e		
4-20	1.0	1.0
> 20-46	0.97 (0.86 to 1.09)	1.03 (0.89 to 1.19)
> 46-80	1.14 (0.95 to 1.37)	0.87 (0.66 to 1.14)
Mutagenicity (rev/L)^e		
330-1,250	1.0	1.0
> 1,250-2,250	0.98 (0.87 to 1.11)	1.09 (0.94 to 1.27)
> 2,250-5,710	1.25 (1.04 to 1.51)	0.79 (0.59 to 1.05)

^aORs adjusted for median household income, adequacy of prenatal care, maternal race, maternal education, maternal smoking, maternal age, parity, previous infant weighing \geq 4,000 g, previous preterm delivery, and maternal medical history (diabetes, chronic hypertension, lung disease, and renal disease). ^bSGA defined as lowest 10% of birth weight per gestational age, sex, and race. ^cAmong term births only. ^dPreterm (< 37 gestational weeks) analyses adjusted for infant sex. ^e1997-1998 analyses adjusted for marital status and weight gain during pregnancy.

are important determinants of exposure to volatile DBPs such as THMs (Weisel and Jo 1996), mothers exposed to high THM levels via drinking water also likely receive high exposures from other routes. The contribution of dermal and inhalation exposures to overall dose is considered minimal for nonvolatile DBPs such as HAAs and MX (Xu et al. 2002).

Residential mobility can lead to additional misclassification of exposures that are based on maternal ZIP codes at time of birth. Although an estimated 20–25% of women move during pregnancy (Khoury et al. 1988; Shaw and Malcoe 1992; Speare et al. 1976), only 8% of mothers of infants with birth defects reported moving to a different county during pregnancy (Khoury et al. 1988). Klotz and Pynch (1999) conducted a sensitivity analysis addressing the impact of residential mobility on risk of neural tube defects for DBP exposures during the first month of pregnancy. Slightly stronger associations were detected among mothers with known residences at conception compared with those with confirmed and unconfirmed residences. The impact of mobility may depend on the critical period of exposure, because women may be less likely to move late in pregnancy. Among women who moved during pregnancy, Schulman et al. (1993) reported that 40% chose to move during the first trimester. This suggests that misclassification due to residential mobility is less likely to influence third-trimester exposure estimates. Although exposure misclassification is present to some degree in our study, these errors are unlikely to be associated with the birth outcomes. Random exposure misclassification will typically bias effect estimates toward the null and may explain the modest effects that we observed.

THM concentration may be of limited value as a surrogate of DBP exposure because the degree of correlation with individual THMs and nonvolatile DBPs can vary dramatically by water system (King et al. 2000; Whitaker et al. 2003; Wright et al. 2002). We observed effects similar in magnitude for individual THMs such as chloroform and BDCM, although most of the water systems in our study had low levels of brominated THMs. The associations that we detected between mutagenicity with birth weight and risk of small for gestational age infancy suggest an effect of mutagenic compounds on fetal development. These associations are not likely attributable to HAAs or THMs, because these DBPs are not considered strong mutagens (Daniel et al. 1993; Rosenthal 1987). MX was strongly correlated with mutagenic activity ($r = 0.86$) in drinking water samples from Massachusetts (Wright et al. 2002), but adjustment for MX in the regression models did not substantially alter the effect of mutagenic activity on mean birth weight (data not shown). Mutagenicity may be a better indicator of the complex mixture of mutagenic

compounds present in drinking water than are traditional DBP surrogates, but additional research is needed to determine the correlation between mutagenicity and individual DBP concentrations.

REFERENCES

- Alexander GR, Kotelchuck M. 1996. Quantifying the adequacy of prenatal care: a comparison of indices. *Public Health Rep* 111(5):408–418.
- Bobak M. 2000. Outdoor air pollution, low birth weight and prematurity. *Environ Health Perspect* 108:173–176.
- Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. 1995. Public drinking water contamination and birth outcomes. *Am J Epidemiol* 141(9):850–862.
- Branum AM, Schoendorf KC. 2002. Changing patterns of low birthweight and preterm birth in the United States, 1981–98. *Paediatr Perinat Epidemiol* 16(1):8–15.
- Daniel FB, Meier JR, Deangelo AB. 1993. Advances in research on carcinogenic and genotoxic by-products of chlorine disinfection: chlorinated hydroxyfuranones and chlorinated acetic acids. *Ann Ist Super Sanita* 29(2):279–291.
- Daniel FB, Olson GR, Stober JA. 1991. Induction of gastrointestinal tract nuclear anomalies in B6C3F1 mice by 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-furanone and 3,4-(dichloro)-5-hydroxy-2[5H]-furanone, mutagenic byproducts of chlorine disinfection. *Environ Mol Mutagen* 17(1):32–39.
- David RJ. 1980. The quality and completeness of birthweight and gestational age data in computerized birth files. *Am J Public Health* 70(9):964–972.
- Dodds L, King W, Woolcott C, Pole J. 1999. Trihalomethanes in public water supplies and adverse birth outcomes. *Epidemiology* 10(3):233–237.
- Epstein DL, Nolen GA, Randall JL, Christ SA, Read EJ, Stober JA, et al. 1992. Cardiopathic effects of dichloroacetate in the fetal Long-Evans rat. *Teratology* 46(3):225–235.
- Fawell JK, Horth H. 1990. Assessment and identification of genotoxic compounds in water. In: *Genetic Toxicology of Complex Mixtures* (Waters MD, ed). New York:Plenum Press, 197–214.
- Gallagher MD, Nuckols JR, Stallones L, Savitz DA. 1998. Exposure to trihalomethanes and adverse pregnancy outcomes. *Epidemiology* 9(5):484–489.
- Gjessing HK, Skjaerven R, Wilcox AJ. 1999. Errors in gestational age: evidence of bleeding early in pregnancy. *Am J Public Health* 89(2):213–218.
- Graves CG, Matanoski GM, Tardiff RG. 2001. Weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by products: a critical review. *Regul Toxicol Pharmacol* 34(2):103–124.
- Infant Health and Development Program. 1990. Enhancing the outcomes of low-birth-weight, premature infants. *JAMA* 263(22):3035–3042.
- Keegan T, Whitaker H, Nieuwenhuijsen MJ, Toledano MB, Elliott P, Fawell J, et al. 2001. Use of routinely collected data on trihalomethane in drinking water for epidemiological purposes. *Occup Environ Med* 58(7):447–452.
- Khoury MJ, Stewart W, Weinstein A, Panny S, Lindsay P, Eisenberg M. 1988. Residential mobility during pregnancy: implications for environmental teratogenesis. *J Clin Epidemiol* 41(1):15–20.
- King WD, Dodds L, Allen AC. 2000. Relation between stillbirth and specific chlorination by-products in public water supplies. *Environ Health Perspect* 108:883–886.
- Klotz JB, Pynch LA. 1999. Neural tube defects and drinking water disinfection by-products. *Epidemiology* 10(4):383–390.
- Kramer M, Lynch C, Isacson P, Hanson JW. 1992. The association of waterborne chloroform with intrauterine growth retardation. *Epidemiology* 3(5):407–413.
- Maisonnet M, Bush TJ, Correa A, Jaakkola JJK. 2001. Relation between ambient air pollution and low birth weight in the northeastern United States. *Environ Health Perspect* 109(suppl 3):351–356.
- Maron DM, Ames BN. 1983. Revised methods for the *Salmonella* mutagenicity test. *Mutat Res* 113(3–4):173–215.
- McCormick MC. 1985. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med* 312(2):82–90.
- Murray FJ, Schwetz BA, McBride JG, Staples RE. 1979. Toxicity of inhaled chloroform in pregnant mice and their offspring. *Toxicol Appl Pharmacol* 50:515–522.
- Nieuwenhuijsen MJ, Toledano MR, Eaton NE, Fawell J, Elliott P. 2000. Chlorination disinfection by-products in water and their association with adverse reproductive outcomes: a review. *Occup Environ Med* 57(2):73–85.
- Reif JS, Hatch MC, Bracken M, Holmes LB, Schwetz BA, Singer PC. 1996. Reproductive and developmental effects of disinfection by-products in drinking water. *Environ Health Perspect* 104:1056–1061.
- Ritz B, Yu F. 1999. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. *Environ Health Perspect* 107:17–25.
- Rogers JF, Thompson SJ, Addy CL, McKeown RE, Cowen DJ, Decoufle P. 2000. Association of very low birth weight with exposures to environmental sulfur dioxide and total suspended particulates. *Am J Epidemiol* 151(6):602–613.
- Rosenthal SL. 1987. A review of the mutagenicity of chloroform. *Environ Mol Mutagen* 10:211–226.
- Rothman KJ, Greenland S. 1998. *Modern Epidemiology*. 2nd ed. Philadelphia:Lippincott-Raven.
- Ruddick JA, Villeneuve DC, Chu I. 1983. A teratological assessment of four trihalomethanes in the rat. *J Environ Sci Health B* 18:333–349.
- Savitz DA, Andrews KW, Pastore LM. 1995. Drinking water and pregnancy outcome in central North Carolina: source, amount, and trihalomethane levels. *Environ Health Perspect* 103:592–596.
- Schulman J, Selvin S, Shaw GM, Malcoe LH. 1993. Exposure misclassification due to residential mobility during pregnancy in epidemiologic investigations of congenital malformations. *Arch Environ Health* 48(2):114–119.
- Schwetz BA, Leong BKJ, Gehring PJ. 1974. Embryo- and fetotoxicity of inhaled chloroform in rats. *Toxicol Appl Pharmacol* 28:442–451.
- Shaw GW, Malcoe LH. 1992. Residential mobility during pregnancy for mothers of infants with or without congenital cardiac anomalies: a reprint. *Arch Environ Health* 47:236–238.
- Smith MK, George EL, Zenick H, Manson JM, Stober JA. 1987. Developmental toxicity of halogenated acetonitriles: drinking water by-products of chlorine disinfection. *Toxicology* 46(1):83–93.
- Smith MK, Randall JL, Read EJ, Stober JA. 1989a. Teratogenic activity of trichloroacetic acid in the rat. *Teratology* 40(5):445–451.
- Smith MK, Randall JL, Read EJ, Stober JA. 1989b. Developmental toxicity of dichloroacetonitrile: a by-product of drinking water disinfection. *Fund Appl Toxicol* 12(4):765–772.
- Smith MK, Randall JL, Read EJ, Stober JA. 1992. Developmental toxicity of dichloroacetate in the rat. *Teratology* 46(3):217–223.
- Smith MK, Randall JL, Tocco DR, York RG, Stober JA, Read EJ. 1988. Teratogenic effects of trichloroacetonitrile in the Long-Evans rat. *Teratology* 38(2):113–120.
- Speare A, Goldstein S, Frey WH. 1976. *Residential Mobility, Migration and Metropolitan Change*. Cambridge, MA:Ballinger Publishing Co., 127–162.
- Teramoto S, Takahashi K, Kikuta M, Kobayashi H. 1998. Potential teratogenicity of 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-furanone (MX) in micromass *in-vitro* test. *J Toxicol Environ Health* 53(8):607–614.
- Thompson DJ, Warner SD, Robinson VB. 1974. Teratology studies on orally administered chloroform in the rat and the rabbit. *Toxicol Appl Pharmacol* 29:348–357.
- U.S. EPA. 1995. *Methods for the Determination of Organic Compounds in Drinking Water*. Supplement III. EPA/600/R-95/131. Washington, DC:U.S. Environmental Protection Agency.
- Waller K, Swan SH, DeLorenze G, Hopkins B. 1998. Trihalomethanes in drinking water and spontaneous abortion. *Epidemiology* 9(2):134–140.
- Wang X, Ding H, Ryan L, Xu X. 1997. Association between air pollution and low birth weight: a community-based study. *Environ Health Perspect* 105:514–520.
- Weisel CP, Jo WK. 1996. Ingestion, inhalation and dermal exposures to chloroform and trichloroethane from tap water. *Environ Health Perspect* 104:48–51.
- Whitaker H, Nieuwenhuijsen MJ, Best N, Fawell J, Gowers A, Elliott P. 2003. Description of trihalomethane levels in three UK water suppliers. *J Expo Anal Environ Epidemiol* 13(1):17–23.
- Wilcox A, Skjaerven R, Buekens P, Kiely J. 1995. Birth weight and perinatal mortality: a comparison of the United States and Norway. *JAMA* 273(9):709–711.
- Wollmann HA. 1998. Intrauterine growth restriction: definition and etiology. *Horm Res* 49(suppl 2):1–6.
- Wright JM, Schwartz J, Dockery DW. 2003. Effect of trihalomethane exposure on fetal development. *Occup Environ Med* 60(3):173–180.
- Wright JM, Schwartz J, Vartiainen T, Mäki-Paakkanen J, Altshul L, Harrington JJ, et al. 2002. 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-furanone (MX) and mutagenic activity in Massachusetts drinking water. *Environ Health Perspect* 110:157–164.
- Xu X, Mariano TM, Laskin JD, Weisel CP. 2002. Percutaneous absorption of trihalomethanes, haloacetic acids, and haloalkenes. *Toxicol Appl Pharmacol* 84(1):19–26.