Drinking Water Contaminants and Adverse Pregnancy Outcomes: A Review

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Concern for exposures to drinking water contaminants and their effects on adverse birth outcomes has prompted several studies evaluating chlorination disinfection by-products and chlorinated solvents. Some of these contaminants are found to be teratogenic in animal studies. This review evaluates 14 studies on chlorination disinfection by-products such as trihalomethanes (THMs) and five studies on chlorinated solvents such as trichloroethylene (TCE). The adverse birth outcomes discussed in this review include small for gestational age (SGA), low birth weight, preterm birth, birth defects, spontaneous abortions, and fetal deaths. Because of heterogeneities across the studies in the characterization of birth outcomes, the assessment and categorization of exposures, and the levels and mixtures of contaminants, a qualitative review was conducted. Generally, the chief bias in these studies was exposure misclassification that most likely underestimated the risk, as well as distorted exposure–response relationships. The general lack of confounding bias by risk factors resulted from these factors not being associated with drinking water exposures. The studies of THMs and adverse birth outcomes provide moderate evidence for associations with SGA, neural tube defects (NTDs), and spontaneous abortions. Because fewer studies have been conducted for the chlorinated solvents than for THMs, the evidence for associations is less clear. Nevertheless, the findings of excess NTDs, oral clefts, cardiac defects, and choanal atresia in studies that evaluated TCE-contaminated drinking water deserve follow-up. ***Key words:*** **birth defects, drinking water, low birth weight, pregnancy outcomes, trichloroethylene, trihalomethanes.** ***Environ Health Perspect*** **110(suppl 1):61–74 (2002).**
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Considerable public concern exists regarding the effects of exposures to contaminants in drinking water on the health of infants and children. Animal studies have indicated that some of these contaminants are teratogens (*1,2*). Yet, research on the potential causal relationships between adverse birth outcomes and maternal exposures to chemical contaminants in drinking water is at a very early stage. In this article we review the strengths and weaknesses of the current epidemiologic evidence for causal relationships between adverse birth outcomes and exposures to drinking water contaminated with chlorination disinfection by-products (DBPs) and chlorinated solvents (e.g., trichloroethylene).

Evaluating links between drinking water contamination and adverse birth outcomes is feasible because most U.S. states maintain databases of tap water samples conducted by water utilities in compliance with federal and state drinking water regulations. In addition, every state maintains a birth certificate database containing information on gestational age, birth weight, other characteristics of the birth, and parental risk factors. Similar data are also available from fetal (>20 weeks gestation) death certificates. From these data, outcomes such as low birth weight, preterm birth, small for gestational age (SGA), and fetal death can be evaluated. However, these data are not sufficient for the study of birth defects, even those that should be apparent at birth, such as spina bifida and oral clefts (*3*). Studies of birth defects require a review of medical records or the availability of data from a population-based birth defects registry. Birth defects registries exist in more than half the states, but many have been in operation for a relatively short period (*4,5*).

The major difficulty in conducting a study of drinking water and adverse birth outcomes is the exposure. Available data usually consist of a small number of tap water samples taken each year at a few points in a town's distribution system. Therefore, extrapolations over distance and time are necessary to link tap sample data to maternal residence during pregnancy and the time period of the pregnancy. Some investigators have conducted space–time extrapolations by modeling water system characteristics and tap sample data (*6–8*). At least one state has developed a water quality database that links data from tap water samples to maps of the public water distribution systems (*9*). This allows identification of smaller subsystems with relatively homogeneous water quality.

Additional difficulties involved in assessing exposure include determining the mother's residential history during the pregnancy, the source of drinking water (private well or public system) for each residence, and the mother's water usage and routes of exposure (e.g., ingestion of glasses per day of tap water, consumption of bottled water, inhalation and dermal exposure from showering and dishwashing, and water usage outside the home). Although some studies conducted maternal interviews to obtain this information, most studies based exposure assessments on the maternal address at delivery from the fetal death or birth certificate. The latter studies assumed that mothers did not change their residences during pregnancy, a problematic assumption, especially in the study of birth defects, because 20–25% of mothers change their residences during pregnancy (*10,11*). In virtually all the studies, the study areas were served mostly or entirely by public water systems for which data on water quality were available. (These data are usually not routinely available for private wells.) However, the studies in which maternal interviews were not conducted could not include maternal consumption habits, especially bottled water usage, during pregnancy. On the other hand, case–control studies in which maternal interviews were conducted faced the problem of recall errors, because interviews occurred several months or even years after the child's birth. Only one prospective cohort study has been conducted that obtained information on maternal water consumption habits in real time during the first trimester (*12*). Difficulties in assessing exposure may result in exposure misclassification biases that would most likely produce substantial underestimates of risk as well as distorted or attenuated exposure–response trends.

Statistical power and the precision of risk estimates tend to be quite limited in studies of relatively rare outcomes such as neural tube defects (NTDs) and oral clefts. Because the number of exposed cases of a particular defect usually are quite small, even risk estimates that indicate a relatively strong effect have wide confidence intervals and are frequently not statistically significant at the $p < 0.05$ level. In an attempt to increase statistical power, some studies combine etiologically heterogeneous birth defects by organ system (e.g., "all heart defects") and into one overall group (i.e., "all defects"). Unfortunately, grouping birth defects that have different causes can introduce disease misclassification bias that might lead to substantial underestimation of risk.

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Summarizing the epidemiologic evidence for causal relationships between drinking water contaminants and adverse birth outcomes is difficult because of methodological differences across studies. For example, some studies evaluate low birth weight, whereas others evaluate SGA, itself defined as low birth weight among term births or the fifth (or 10th) percentile weight by gestational week at birth. Groupings of birth defects sometimes differ across studies. Exposure assessment methodologies, the amount of available drinking water sample data, the levels of contaminants in drinking water, and the mixtures of contaminants found in the drinking water also differ considerably across studies. Because of these methodologic differences across studies, a quantitative meta-analysis seemed inappropriate. Therefore, we undertook a qualitative review *a*) to assess each study's methods, strength of associations (i.e., the odds ratios, relative risks, and mean differences), and exposure–response relationships; *b*) to describe the heterogeneities and consistencies across studies; and *c*) to provide a summary of the epidemiologic evidence linking the drinking water contaminants to adverse birth outcomes.

Methods

In this review we evaluate epidemiologic studies of adverse birth outcomes and either DBPs or chlorinated solvents in drinking water. A MEDLINE search of publications in English from 1966 through September 2001 identified 19 publications that provided the findings from 16 studies (*13*). Key words and phrases used to search the database included chlorine disinfection by-products, trihalomethanes, trichloroethylene, tetrachloroethylene, drinking water, birth defects, and low birth weight. This review also includes reports of two studies funded by the Agency for Toxic Substances and Disease Registry (ATSDR) that were peer-reviewed but not indexed in MEDLINE.

For each study, we present the adjusted results as reported, unless the study reported only unadjusted results. We present confidence intervals to one decimal point. However, when we identified major problems with the adjusted results (e.g., missing data problems or unstable models because of sparse data), we present the unadjusted results as well. Virtually all the studies reviewed here show minor (i.e., <10%) or no differences between unadjusted and adjusted results, indicating that there was little or no confounding by risk factors for which information was available either from the birth or fetal death certificate, or from maternal interviews. For example, smoking, alcohol consumption, maternal illnesses, and socioeconomic and demographic factors were not confounders in the vast majority of these studies, most likely because they were not associated with drinking water exposures. For some studies, the authors did not present odds ratios when data were sparse. In these instances, we calculated the odds ratios if the studies provided sufficient information.

We emphasize that difficulties in estimating and categorizing drinking water exposures will likely result in attenuated and distorted exposure–response relationships. Therefore, to present a stronger case for an association between a drinking water exposure and an adverse birth outcome, we sometimes explored an alternative exposure–response relationship. When a study provided sufficient information, we recategorized the exposure and calculated odds ratios. Prior to presenting an alternative exposure–response relationship, we reported the original findings of the study.

Epidemiologic Studies

Chlorination Disinfection By-products

Over 86 million households (84%) in the United States receive their water from public water systems, according to the 1990 census (*14*). Most of these public drinking water systems use chlorine for disinfection (*15*). When chlorine is added to drinking water, it reacts with any residual organic matter in the water (e.g., from the decomposition of leaves and other vegetation in surface waters) to form unwanted by-products. Chief among these by-products are the trihalomethanes (THMs), particularly, chloroform. A variety of other by-products also are produced, including haloacetic acids that have been shown to be teratogenic in animal studies (*1*) and a substance known as MX [3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone], which is highly mutagenic (*16*).

When chlorine has more time to react with organic matter in the water, levels of THMs and other chlorination DBPs increase. For this reason, areas in the distribution system farther from the treatment plant tend to have higher levels of THMs than areas closer to the treatment plant. In addition, in areas where there is a low use of water or a "deadend" in the system, or where the system consists of small-diameter pipes, the water tends to move very slowly and the chlorine has more time to react with any organic matter in the water to produce more THMs and other DBPs. As a result, residences in different areas of a town's water system can have very different levels of THMs in their drinking water. THM levels also vary by season because the amount of organic matter in surface waters tends to be greater in the summer and fall than in the winter or spring. Other factors that affect THM levels include water temperature, pH, the type and reactivity of organic matter in the water, the amount and type of disinfection used, and the point in the water purification process at which the disinfectant is added. In addition, the levels of brominated DBPs will be affected by the presence and amount of bromide in the water. Water systems supplied by groundwater will usually have very low amounts of THMs (e.g., <10 ppb) and other DBPs because groundwater contains much less organic matter. Water systems supplied by surface waters (e.g., rivers, reservoirs, lakes) will have much higher levels of THMs (30–150 ppb and possibly higher) and other DBPs.

In 1979, a maximum contaminant level (MCL) for total trihalomethanes (TTHMs) was set in the United States at an annual average of 100 ppb (*17*). Large water systems serving more than 10,000 people were required to report quarterly samples of TTHMs to state environmental agencies and the U.S. Environmental Protection Agency. In 1999, the MCL for TTHMs was reduced to 80 ppb (*18*), and further reductions in the MCL are planned. Eight studies discussed in this review used THM monitoring data. The median TTHM levels in these studies tended to be in the 30–50 ppb range. Only the study in Denver, Colorado, had a maximum level of TTHMs below 100 ppb (*6*).

Table 1 summarizes the characteristics of the eight DBP studies that based their exposure assessments on measurements of THMs in tap water supplies (*6,12,19–26*). Seven of these studies used THM monitoring data concurrent with the time of pregnancy, and one study used THM monitoring data occurring several years before the study period (*19*). Table 2 summarizes the six DBP studies that based their exposure assessments on the type of water disinfection treatment (*27–33*). One of these six studies also used water color measurements (*29,30*).

Four studies identified the maternal address during the first trimester (*12,25, 26,32*). Three case–control studies (*21,25,26*) and one prospective cohort study (*12*) conducted maternal interviews to determine water consumption habits during pregnancy. Table 3 presents risk estimates (relative risk or odds ratio) for DBPs and the various adverse reproductive outcomes for those studies utilizing THM monitoring data. Table 4 presents results for those studies that did not use THM monitoring data.

Small for gestational age. Nine studies evaluated adverse birth outcomes focusing on SGA, low birth weight, and preterm birth. Two of these studies also evaluated body length and cranial circumference.

The Iowa study defined SGA as the fifth percentile weight by gestational week of birth (*19*). Cases and controls were sampled from singleton births occurring from January 1989 through June 1990 in small towns (population size, 1,000–5,000) served entirely by public water systems. Each town was assigned levels of THMs based on tap sample data from a 1-year program conducted statewide in 1986 and 1987 more than 1 year prior to the actual study period. The mother's town of residence at delivery ascertained from the birth certificate was used to assign exposure to each case and control. Odds ratios were adjusted for marital status, maternal age, parity, appropriate number of prenatal visits, maternal smoking, and education.

For SGA, odds ratios of 1.8 (95% confidence interval [CI]: 1.1, 2.9) and 1.7 (95% CI: 0.9, 2.9) were found for chloroform and bromodichloromethane at levels ≥10 ppb when compared with levels <1 ppb. An odds ratio of 1.1 (95% CI: 0.7, 1.6) was found for SGA and bromoform levels above the detection limit. For low birth weight, the odds ratio for chloroform at levels ≥10 ppb was 1.3 (95% CI: 0.8, 2.2). For preterm birth, the odds ratios for chloroform, dibromochloromethane, and bromoform were all 1.1, with 95% confidence intervals that ranged between 0.7 and 1.6.

A study of 80,938 singleton live births during 1985–1988 was conducted in 75 towns in northern New Jersey primarily served by public water systems (*20*). As in the Iowa study, SGA was defined as the fifth percentile weight by gestational week. In addition, average birth weight and low birth weight among term births were evaluated. The exposure assessment was based on the averaging of quarterly tap samples concurrent with each birth's gestational period for the public water system serving the mother's town of residence at delivery. No confounding by maternal age, race, education, prenatal care, parity, or previous stillbirth or miscarriage was observed; therefore, the study reported only unadjusted results. The odds ratios for SGA and term low birth weight were 1.5 (90% CI: 1.2, 1.9) and 1.4 (90% CI: 1.0, 2.0), respectively, for TTHM levels of >100 ppb compared with levels of ≥20 ppb. A mean birth weight deficit of 70.4 g (90% CI: –40.6, –100.2) was found for term births assigned exposures of >100 ppb TTHMs compared with levels of ≥20 ppb. No association was found for preterm birth.

A study of three counties in central North Carolina identified 586 preterm births and 464 low-birth-weight births during September 1988 through August 1989 (extended to April 1991 in one county) (*21*).

Table 1. Description of studies that use tap sample data to estimate levels of chlorine disinfection by-products.

Study site and period	Outcome	No. of subjects	Exposure
California, 1981–1983 (*26*)	Cardiac defects	138 cases, 168 controls	Estimated THM levels and address during first trimester; interview data on water consumption collected 3–7 years after birth
Iowa, 1989–1990 (*19*)	SGA Low birth weight Preterm delivery	187 cases, 935 controls 159 cases, 795 controls 342 cases, 1,710 controls	1987 data from water survey, and address at delivery
Northern New Jersey, 1985–1988 (*20*)	SGA Preterm delivery Specific birth defects Still births	80,938 live births and 594 fetal deaths	Estimated monthly THM levels, and address at delivery
Central North Carolina, 1988–1991 (*21*)	Spontaneous abortion Low birth weight Preterm delivery	126 cases, 122 controls 178 cases, 333 controls 244 cases, 333 controls	Estimated monthly THM levels; interview data on water consumption; address at delivery
Denver, CO, area, 1990–1993 (*6*)	Term low birth weight (SGA) Low birth weight Preterm delivery	1,224 births with exposure data	Modeling the distribution system to estimate third trimester THM levels at census block group areas; and address at delivery
California, 1989–1991 (*12*)	Spontaneous abortion	4,622 pregnancies w/THM data, 442 SAs; 5,109 pregnancies ("personal exposure"), 493 SAs	Estimated THM levels and address during first trimester; interview data on water usage at 8 weeks gestation
New Jersey, 1993–1994 (*25*)	NTDs	90 cases and 183 controls with known residence at conception	Estimated THM levels and address during first trimester; interview data on water consumption
Nova Scotia, 1988–1995 (*22–24*)	SGA Low birth weight Preterm delivery Specific birth defects Stillbirths	49,842 births 49,756 births for stillbirths	Estimated average monthly THM levels, and address at delivery

SA, spontaneous abortion.

Table 2. Description of studies that evaluate water source and water chlorination disinfection treatment.

Study site and period	Outcome	No. of subjects	Exposure
Massachusetts, 1976–1978 (*33*)	SA	286 cases, 1391 controls	Drinking water source; surface water treatment; address at delivery
Massachusetts, 1977–1980 (*32*)	Specific birth defects Stillbirths	1,039 cases 77 cases, 1177 controls	Drinking water source; surface water treatment; and address during first trimester
Italy, 1988–1989 (*28*)	SGA (cranial circumference and body length) Low birth weight Preterm delivery	548 exposed births and 128 unexposed births	Water treatment (chlorine dioxide, sodium hypochlorite); address at delivery
Norway, 1993–1995 (*30,31*)	SGA Low birth weight Preterm delivery	137, 145 births without a birth defect and with data on birth weight	1994 data on water treatment and color; ecologic exposure variables (e.g., % served by chlorinated supplies); address at delivery
	Specific birth defects	141,077 births (2,608 birth defects)	
Sweden, 1985–1994 (*29,35*)	SGA Low birth weight Preterm delivery Specific birth defects	78,237 unexposed singleton or multiple deliveries; 15,761 chlorine dioxide singleton or multiple deliveries; 41,076 sodium hypochlorite singleton or multiple deliveries	Drinking water source and surface water treatment for 1985, 1989, and 1994; address at delivery
Taiwan, 1994–1996 (*27*)	Term low birth weight (SGA) Preterm delivery	18,025 births	Drinking water source and treatment; address at delivery

Table 3. Summary of results of studies that use tap sample data to estimate levels of chlorine disinfection by-products.

Study site	SGA	Low birth weight	Preterm birth	Neural tube defects	Oral clefts	Heart defects	Other defects	Fetal deaths	Spontaneous abortion
California (*26*)									
Chlorinated water	—	—	—	—	—	1.1[a]	—	—	—
Iowa (*19*)									
Chloroform	1.8	1.3	1.1	—	—	—	—	—	—
Bromodichloromethane	1.7	1.0	1.0	—	—	—	—	—	—
Northern New Jersey (*20*)									
Total trihalomethanes	1.5	—	<1.0	3.0	3.2	1.8	—	<1.0	—
Central North Carolina (*21*)									
Total trihalomethanes	—	1.3	0.9	—	—	—	—	—	1.2
And maternal water usage	—	0.8	0.9	—	—	—	—	—	0.6
Denver area, Colorado (*6*)									
Total trihalomethanes	5.9	2.1	1.0	—	—	—	—	—	—
California (*12*)									
Total trihalomethanes	—	—	—	—	—	—	—	—	1.8
Bromodichloromethane	—	—	—	—	—	—	—	—	3.0
New Jersey (*25*)									
Total trihalomethanes	—	—	—	2.1[b]	—	—	—	—	—
Nova Scotia (*22–24*)									
Total trihalomethanes	1.08	1.04	0.97	1.18	1.01	0.77	1.38[c]	1.66, 4.57[d]	—
Chloroform	—	—	—	1.2	1.5	0.7	1.4[c]	1.56, 3.15[d]	—
Bromodichloromethane	—	—	—	2.5	0.6	0.3	0.9[c]	1.98, 1.75[d]	—

[a]Conotruncal heart defects. [b]Result is for isolated NTDs. [c]Chromosomal anomalies. [d]Asphyxia as cause of death.

Table 4. Summary of results of studies that evaluate water source and water chlorination disinfection treatment.

Study site	SGA	Low birth weight	Preterm birth	Neural tube defects	Oral clefts	Heart defects	Other defects	Fetal deaths	Spontaneous abortion
Massachusetts (*33*)									
Surface vs. groundwater	—	—	—	—	—	—	—	—	2.2
Chlorinated surface water	—	—	—	—	—	—	—	—	0.9
Massachusetts (*32*)									
Surface vs. groundwater	—	—	—	—	—	—	1.0[a]	1.0	—
Chlorinated surface water	—	—	—	—	—	—	1.5[a], 2.6	—	—
	—	—	—	—	—	—	3.2[b], 4.1[c]	—	—
Italy (*28*)									
Chlorine dioxide	2.2[c]	5.9	1.8	—	—	—	—	—	—
	2.0[d]	—	—	—	—	—	—	—	—
Sodium hypochlorite	3.5[c]	6.0	1.1	—	—	—	—	—	—
	2.3[d]	—	—	—	—	—	—	—	—
Norway (*30,31*)									
Water color and chlorination	1.00	0.97	0.91	1.26	0.94	1.05	1.07[b]	—	—
	—	—	—	—	—	—	1.99[c]	—	—
Sweden (*29*)									
Chlorine dioxide	1.29[d], 0.91[e]	0.93	0.96	**1.0**	0.9	0.9	0.9[c]	—	—
Sodium hypochlorite	1.46[d], 1.97[e]	1.15	1.09	**1.0**, 1.4[f]	1.1	1.1	1.4[c]	—	—
Taiwan (*27*)									
Surface water	0.90	—	1.3	—	—	—	—	—	—

Bolded results were calculated by the reviewing authors. [a]All major congenital anomalies. [b]Respiratory defect. [c]Urinary tract defect. [d]Small cranial circumference (an indicator of intrauterine growth retardation). [e]Small body length (an indicator of intrauterine growth retardation). [f]Spina bifida.

A sample of 782 term, normal-weight live births, matched to the cases on race, date of birth, and hospital of birth, constituted the control group. Data from concurrent THM samples from the water system serving the mother's address were combined with information on water consumption habits from maternal interviews in order to estimate exposures. Information on maternal water consumption habits could not be obtained for about one third of the cases and controls, so these were excluded from the study. In addition, cases and controls were excluded if their source of water was bottled water or a private well, if the mother reported that she consumed no water, or if quarterly THM data corresponding to the 28th week of pregnancy were missing. Approximately 40% of the identified cases and controls were included in the study: 178 low-birth-weight cases, 244 preterm birth cases, and 333 controls. Maternal risk factors such as age, education, race, smoking, and income were evaluated as potential confounders but generally were not found to be strongly associated with THM exposure.

An odds ratio of 1.3 (95% CI: 0.8, 2.1) was found for low birth weight among those exposed to TTHM levels of >82.7 ppb compared with the reference group range of 40.8–63.3 ppb. However, when water consumption was taken into account, this association disappeared. No associations were found for preterm birth. A major limitation of this study was the large number of case and control exclusions, which was a likely source of selection bias. In addition, the reference exposure level of 40.8–63.3 ppb was very high and might include those at increased risk of low birth weight or preterm birth.

A study conducted in the Denver area applied a hydraulic model (EPANET) to the pipe networks of two surface water municipal systems to identify census block group areas that were hydraulically similar to the TTHM quarterly tap sample locations of the two systems (*6*). Of 86 census block groups,

28 were found to be hydraulically similar to a TTHM sample location over the study period 1990–1993. A birth occurring during the study period was included in the study if the maternal residence at delivery was in one of these 28 census block groups and if a tap sample was taken during the child's third trimester at a location hydraulically similar to the mother's block group of residence. A total of 1,244 births met these requirements. Exposure assignment was based on the third-trimester samples. About 6% of the births were assigned exposures of >60 ppb TTHM, and none were exposed to levels of ≥100 ppb. The reference exposure level was ≥20 ppb TTHM. SGA was defined as low birth weight among term births. Potential confounders evaluated included maternal age, education, smoking, parity, prenatal care, and marital status.

An unadjusted odds ratio of 5.0 (95% CI: 1.7, 13.9) was found for SGA at TTHM levels of >60 ppb. After adjustment by maternal education and prenatal care, the odds ratio increased to 5.9 (95% CI: 2.0, 17.0). This increase may have had less to do with confounding bias than with the impact of small numbers of SGA cases (e.g., six cases were exposed at levels >60 ppb) on an unconditional logistic regression model. As in previous studies, no association was found for preterm birth. For low birth weight among all births (i.e., term and preterm), no adjustment of the odds ratio was necessary because the maternal risk factors were not confounders, and the unadjusted odds ratio was 2.1 (95% CI: 1.0, 4.8) at TTHM levels of >60 ppb.

A study was conducted of 49,842 singleton births to mothers residing at delivery in an area served by a municipal surface water system in Nova Scotia during the study period 1988 through 1995 (*22*). A linear regression model was used to predict the third-trimester exposure to TTHMs based on all the samples taken during the study period by the municipal system serving the mother's town and postal code of residence at delivery. SGA was defined as the 10th percentile by gestational week. Prevalence relative risks were calculated using Poisson regression. Risk factors such as neighborhood family income and maternal age, smoking, parity, prepregnancy weight, and attendance at prenatal classes were evaluated as potential confounders. However, none of these risk factors was observed to change the unadjusted results by more than 5%.

Preterm birth was not associated with TTHMs. The relative risk for SGA was 1.08 (95% CI: 1.0, 1.2) for TTHM levels of ≥100 ppb compared with levels of <50 ppb. A similar relative risk of 1.04 for low birth weight among all births was observed (95% CI: 0.9, 1.2). A limitation of the study was the use of a reference exposure category of "0–49 ppb." Because over 90% of the births in this reference category were assigned exposures between 25 and 49 ppb, the reference group did not represent a population minimally exposed to TTHMs. Furthermore, exposures in the range between 20 and 50 ppb may be associated with increased risk of SGA. This was the case in the New Jersey and Denver studies, where odds ratios for SGA between 1.2 and 1.3 occurred when exposures between 20 and 49 ppb were compared with exposures of <20 ppb. Another limitation might have been the use of the 10th percentile weight as the definition for SGA. This cutoff might be too high and include term births with weights between 6.5 and 7 pounds that do not have a serious adverse birth outcome (*34*).

A study conducted in Taiwan evaluated SGA (defined as term low birth weight) and preterm delivery and included first-parity, singleton births born during 1994–1996 in 14 chlorinated municipalities (n = 10,007) served primarily by surface water supplies and 14 nonchlorinating municipalities (n = 8,018) served primarily by groundwater supplies (*27*). Municipalities were matched based on their urbanization level. Odds ratios were adjusted for maternal age, martial status, maternal education, and sex of the infant, which were obtained from the birth certificates. Births exposed to chlorinated supplies had a higher rate of preterm birth (odds ratio [OR] = 1.34, 95% CI: 1.1, 1.6) but a lower rate for SGA (OR = 0.90, 95% CI: 0.7, 1.1). The authors of the study note that because these municipalities were rural, it was unlikely that women drank bottled water or any water from sources other than the home.

A study conducted in Italy of 548 births in Genoa and 128 births in Chiavari during 1988 and 1989 used medical records to evaluate low birth weight, preterm birth, small body length, and cranial circumference (*27*). Genoa was served by a municipal system with two treatment plants, one using the disinfectant chlorine dioxide and the other using sodium hypochlorite. Chiavari's births constituted the reference population because the town was served by a groundwater system that did not apply disinfectants. The study focused on the DBPs of chlorine dioxide, in particular, chlorites and chlorates. The levels of TTHMs were extremely low, ranging from <4 ppb in water disinfected with chlorine dioxide to 8–16 ppb in water disinfected with sodium hypochlorite. The exposure assessment was based not on contaminant measurements but on the type of disinfectant used in the water serving the mother's residence at delivery.

The study did not state how many births were excluded because of missing information on the type of disinfectant used in the water serving the mother's residence. However, given the population sizes of Genoa (640,000) and Chiavara (35,000), it appeared that a large majority of births occurring in these two cities during 1988 and 1989 were not included. In addition, the prevalence of low birth weight was extremely low in the reference population (i.e., 1 in 128 births in Chiavara). Risk factors evaluated as potential confounders included maternal age, education, income, and smoking. However, in most instances, the unadjusted and adjusted results did not differ by more than 10%.

The odds ratios for low birth weight and water disinfected with both chlorine dioxide and sodium hypochlorite and with chlorine dioxide alone were 6.6 (95% CI: 0.9, 14.6) and 5.9 (95% CI: 0.8, 14.9), respectively. The unadjusted odds ratio of 2.9 for sodium hypochlorite and low birth weight increased drastically to 6.0 (95% CI: 0.6, 12.6) after adjustment, but this result was likely due to the impact of small numbers of low-birth-weight cases (n exposed = 2, n unexposed = 1) on the unconditional logistic regression model.

The odds ratios for preterm birth and water disinfected with both chlorine dioxide and sodium hypochlorite, chlorine dioxide alone, and sodium hypochlorite alone were 1.8 (95% CI: 0.6, 5.0), 1.8 (95% CI: 0.7, 4.7), and 1.1 (95% CI: 0.3, 3.7), respectively. For cranial circumference, the odds ratios were 2.4 (95% CI: 1.6, 5.3), 2.2 (95% CI: 1.4, 3.9), and 3.5 (95% CI: 2.1, 8.5) for chlorine dioxide and sodium hypochlorite, chlorine dioxide alone, and sodium hypochlorite alone, respectively. For small body length, the odds ratios were 1.4 (95% CI: 0.8, 2.5), 2.0 (95% CI: 1.2, 3.3), and 2.3 (95% CI: 1.3, 4.2) for chlorine dioxide and sodium hypochlorite, chlorine dioxide alone, and sodium hypochlorite alone, respectively.

A study in Sweden evaluated 132,001 singleton births (*35*) from 1989 to 1995 to women residing at the time of birth in the central portions of municipalities for which disinfection treatment could be determined from data supplied by the water companies in 1985, 1989, and 1994 (*29*). Some of the municipalities included in the study were served by more than one water source. But in these cases, all sources serving the municipality received the same type of disinfection.

About 65% of the births occurred in municipalities that did not disinfect the drinking water. These water supplies were mostly (>90%) groundwater sources. About 22% of the births occurred in municipalities

served by drinking water disinfected with sodium hypochlorite, and 13.5% of the births were exposed to drinking water disinfected with chlorine dioxide. About half the supplies treated with sodium hypochlorite and 63% of supplies disinfected with chlorine dioxide were from surface water sources. It was not known what the levels of DBPs were in Sweden during the study period, but it would be expected that appreciable amounts of DBPs would occur only from the disinfection of surface water supplies. The levels of DBPs in this study may have been as low as in the Italian study. SGA, specific for parity and infant sex, was determined by applying the coefficients of variation corresponding to the –2 and –3 standard deviations (SD) from the mean weight at gestational age 40 weeks to the mode weights at other gestational ages (*36*). Maternal risk factors evaluated as potential confounders included age, education, parity, and smoking.

For both chlorine dioxide and sodium hypochlorite, the odds ratios for SGA at less than –2 SD and less than –3 SD hovered minimally above and below 1.0. The odds ratios for low birth weight were 0.93 (95% CI: 0.8, 1.0) and 1.15 (95% CI: 1.0, 1.3) for chlorine dioxide and sodium hypochlorite, respectively. For small head circumference (<31 cm), the odds ratios were 1.29 (95% CI: 0.9, 1.8) and 1.46 (95% CI: 1.1, 2.0) for chlorine dioxide and sodium hypochlorite, respectively. The odds ratio for sodium hypochlorite and short body length (<43 cm) was 1.97 (95% CI: 1.3, 3.0), but no association was found for chlorine dioxide. An odds ratio of 1.22 (95% CI: 1.0, 1.5) was observed between sodium hypochlorite and gestational age less than 32 weeks, but for preterm birth (i.e., <37 weeks gestation) the odds ratio dropped to 1.09 (95% CI: 1.0, 1.2). No association was found for chlorine dioxide and preterm birth.

A study conducted in Norway evaluated live births from 1993 to 1996 in 366 municipalities with information on water treatment and water color (*30*). After excluding birth defects, 137,145 live births with information on birth weight were evaluated for low birth weight, and 123,747 live births with information on birth weight and gestational age were evaluated for preterm birth and SGA (defined as the 10th percentile weight by 10-day intervals of gestational age). Exposures were assigned to each birth based on the municipality of maternal residence at the time of delivery. Exposures were based not on DBP levels but on whether a public waterworks facility chlorinated its drinking water, and the "color" of its water reported in 1994. Color was correlated with the amount of dissolved organic matter in drinking water.

Most municipalities (72%) were served by more than one waterwork facility, and nearly half were served by three or more waterworks facilities. Therefore, two ecologic variables for exposure were calculated for each municipality: the percentage of the population served by chlorinated supplies ("chlorination proportion") and the average color weighted by the percentage of the population served by each waterwork supplying the municipality ("weighted mean color"). These variables were then dichotomized (low/high color, and 0/>0 chlorination proportion) and assigned to each municipality.

After adjustment for maternal age, parity, whether the birth occurred in a university clinic, and ecologic factors associated with the municipality of birth (i.e., population density, urbanicity, and types of industries), the odds ratios for SGA, low birth weight, and preterm birth were ≥1.0. Taking into account the water color measurement appeared to have no impact on the findings.

SUMMARY OF THE SGA STUDIES. The studies that evaluated SGA and related outcomes had several limitations. First, exposure estimates were assigned to the mother's residence at time of delivery, which could differ from the mother's residence during the relevant period of the pregnancy. Second, except for the central North Carolina study (*21*), which suffered from a poor participation rate, no interviews were conducted to obtain maternal water consumption habits. This might not be a critical problem if the causative agents were volatile (e.g., THMs), because inhalation exposures from hot water uses and showering would be at least as important as water ingestion. However, if the causative agents were not volatile (e.g., the haloacetic acids), then a failure to take into account water ingestion likely would introduce substantial exposure misclassification.

Studies in the Denver area (*6*), northern New Jersey (*20*), central North Carolina (*21*), and Nova Scotia (*22*) based their exposure estimates on tap samples of THMs taken concurrently with the pregnancy period. However, only the Denver area study (*6*) went beyond averaging all the samples in a town and attempted to account for the within-town variability of THM levels by modeling the water distribution systems and matching the residence at the block level with the appropriate sample location(s). Modeling the distribution system characteristics was an important advance in exposure assessment methodology that likely minimized exposure misclassification and might have been responsible, to some extent, for the stronger relationship found in this study between TTHMs and SGA.

The Iowa (*19*), northern New Jersey (*20*), and Denver area (*6*) studies provided moderate evidence for a causal relationship between a narrow definition of SGA (as either the fifth percentile weight by gestational week, or as low birth weight among term births) and TTHM levels that could be found currently in some U.S. public water systems. Of particular importance was the fact that the strongest association (OR = 5.9) was observed in the Denver area study, the only one that modeled the distribution system and presumably had the best exposure assessment. Maternal risk factors (e.g., smoking, socioeconomic factors) derived from the birth certificate were not observed to confound the relationship between SGA and THM levels. In general, only weak effects were found when SGA was more broadly defined (i.e., 10th percentile weight by gestational week) or when low birth weight among all births was evaluated. No appreciable effects were found for preterm birth. One question left unanswered by these studies was whether accounting for maternal water consumption habits would strengthen the relationship between SGA and THM levels. Although the central North Carolina study evaluated maternal water consumption habits, SGA was not evaluated and the findings for the other adverse birth outcomes could have been biased by the high number of excluded cases and controls.

Birth defects. Seven studies (*20,22, 24–26,29,31,32*) evaluated birth defects; in particular, NTDs, oral clefts, and cardiac defects. Four of the seven studies based their exposure assessments on concurrent THM sample data (*20,22,24–26*). Only three of the seven studies determined the maternal address during the first trimester (*25,26,32*).

The previously mentioned northern New Jersey study evaluated central nervous system (CNS) defects, oral cleft defects, and major cardiac defects occurring in 80,938 live births and 594 fetal deaths (*20*). Birth defects up to 1 year after birth were ascertained by the New Jersey Birth Defects Registry, a population-based, statewide registry. Fetal death certificates were also reviewed to ascertain birth defects. Estimates of first trimester exposure were based on quarterly TTHM samples and maternal address at delivery. Unadjusted results were presented in the study because adjustment for maternal risk factors derived from the birth certificate did not change the unadjusted results by more than 15%. TTHM levels above 80 ppb were associated with CNS defects (OR = 2.6; 90% CI: 1.5, 4.3), NTDs (OR = 3.0; 90% CI: 1.3, 6.6), oral clefts (OR = 1.7; 90% CI: 1.0, 3.1), and major cardiac defects (OR = 1.8; 90% CI: 1.0, 3.3). Above 100 ppb, a stronger relationship was found for oral clefts (OR = 3.2;

90% CI: 1.2, 7.3). The outcome "major cardiac defects" included common truncus, transposition of great vessels, tetralogy of Fallot, anomalies of the pulmonary valve, tricuspid atresia and stenosis, aortic valve stenosis and insufficiency, hypoplastic left heart, coarctation of aorta, and anomalies of the pulmonary artery.

A statewide New Jersey study was conducted to follow-up the NTD findings in the northern New Jersey study. The statewide study used the New Jersey Birth Defects Registry and fetal death records to ascertain 112 NTDs occurring during 1993 and 1994 (*25*). Controls consisted of 248 live births randomly sampled from all births in New Jersey during 1993 and 1994, excluding term births of low birth weight and births with anomalies registered by the birth defects registry. Through interviews, the mother's residence and water consumption habits during the first trimester were determined for 90 of the NTDs and for 183 of the controls.

The study used concurrent quarterly tap sample data on THMs from public water systems to determine first-trimester exposures. The maximum level of exposure to TTHMs was 135 ppb, consisting mostly of chloroform (maximum = 122 ppb). First-trimester TTHM exposure levels were categorized in tertiles (<5 ppb, 5 to <40 ppb, and ≥40 ppb) and by quintiles (<20 ppb, 20 to <40 ppb, 40 to <60 ppb, 60 to <80 ppb, and ≥80 ppb). Unadjusted results were presented in the study because adjustment for maternal risk factors and demographics changed the unadjusted results by <10%.

When exposure was categorized by tertile and all NTD cases were included, an odds ratio of 1.6 (95% CI: 0.9, 2.7) was observed at TTHM levels of ≥40 ppb compared with <5 ppb. Limiting the comparison to cases and controls whose first-trimester residence was known, an odds ratio of 1.7 (95% CI: 1.0, 3.1) was observed, which increased to 2.1 (95% CI: 1.1, 4.0) when only isolated NTDs were evaluated.

An alternative exposure categorization would be to dichotomize at 40 ppb because the odds ratio found for the 5 to <40 ppb level was <1.0 and the odds ratios for the three higher levels (40 to <60 ppb, 60 to <80 ppb, and ≥80 ppb) were similar. Comparing TTHM levels of ≥40 ppb and <40 ppb and limiting the analyses to those whose first-trimester residences were known, the odds ratios for all NTDs and for isolated NTDs are 2.0 and 2.2, respectively.

Excesses in NTDs were seen for each THM except bromoform; however, the exposure level of bromoform was <1 ppb for most of the cases and controls. The study also evaluated the efficacy of conducting tap samples at the first-trimester residence approximately 1 year after the first trimester of the case or control, in order to take into account the seasonality of THM levels. However, no advantage was found using this approach because the findings were similar to those obtained using concurrent quarterly data from the water companies.

The Nova Scotia study mentioned above evaluated NTDs, clefts, major cardiac defects, and chromosomal defects among 49,842 singleton births to mothers residing at delivery in an area served by a municipal surface water system from 1988 to 1995 (*22*). Birth defects were ascertained from a perinatal database that provided information on diagnoses determined prior to hospital discharge after birth. In addition, a fetal anomaly database containing pregnancies terminated because of a diagnosis of a birth defect was also used to ascertain birth defects. The study did not provide a list of diagnoses included in the category "major cardiac defects." Maternal residence at delivery was used to estimate TTHM exposures. Estimated TTHM exposures during the first 2 months of pregnancy were used in the analyses of clefts and major cardiac defects, whereas exposures estimated for the month before and month after conception were used for the analysis of NTDs. Maternal risk factors and neighborhood family income were evaluated as potential confounders. Prevalence relative risks were calculated using Poisson regression.

When comparing exposures of 100 ppb or more with the reference level of <50 ppb, elevations in the relative risks were found for NTDs (1.18; 95% CI: 0.7, 2.1) and chromosomal anomalies (1.38; 95% CI: 0.7, 2.6). No elevations were found for clefts and major cardiac defects. In the NTD analysis, the prevalence of NTDs was considerably higher in the reference exposure category than in the middle exposure categories. Even after adjustment for income at the neighborhood level, the relative risks for exposure levels of 50–74 ppb and 75–99 ppb were 0.67 and 0.42, respectively. These unusual findings could be because of confounding bias from unmeasured risk factors or to exposure misclassification. Using the data provided in the study, we compared the prevalence of NTDs in the ≥100 ppb range with a prevalence that we estimated over the entire 0–99 ppb range and obtained a relative risk of approximately 1.85.

For all the adverse outcomes evaluated in this study, the only adjusted relative risk that differed by ≥10% from the unadjusted relative risk was observed for NTD at TTHM levels of ≥100 ppb. After adjustment for neighborhood family income level (based on census enumeration area representing 125–375 households), the relative risk for NTD at ≥100 ppb dropped from 1.32 to 1.18 when compared with the reference group of <50 ppb. This observation might be because of a selection bias introduced by removing births with missing data on income. In the reference group, 1.6% of the births were excluded for missing data on income, whereas in the ≥100 ppb group, 4.2% of the births were excluded.

A more recent report (*24*) presents the birth defect findings for chloroform and bromodichloromethane (BDCM). Given the high correlation between chloroform and TTHM (Pearson correlation coefficient, r = 0.98), the results for chloroform were only minimally different from those for TTHM for NTD, cardiac defects, and chromosomal defects. However, for oral clefts, the relative risk at chloroform levels of ≥100 ppb was 1.5 (95% CI: 0.8, 2.8) compared with levels of <50 ppb. The relative risks for oral clefts and chloroform levels between 50 and 99 ppb hovered around 1.0.

BDCM was not highly correlated with either TTHM or chloroform (Pearson correlation coefficients, r = 0.44 and r = 0.26, respectively). The relative risks for NTD and BDCM levels of 5–9 ppb, 10–19 ppb, and ≥20 ppb, were 1.4 (95% CI: 0.8, 2.3), 0.6 (95% CI: 0.2, 1.5), and 2.5 (95% CI: 1.2, 5.1), respectively. The authors noted that there was no apparent exposure–response trend between NTD and BDCM using this exposure categorization. However, we observed an exposure–response trend for NTD and BDCM after we combined the two middle exposure categories (relative risk = 1.25 for BDCM levels of 5–19 ppb). BDCM was not associated with oral clefts, cardiac defects, or chromosomal defects.

A case–control study of congenital cardiac anomalies was conducted in Santa Clara County, California, as reported in a letter to the editor (*26*). Cases diagnosed within the first year after birth for those born between 1981 and 1983 were ascertained by the California Birth Defects Monitoring Program. Maternal interviews conducted 3–7 years after birth of the 138 cases and 168 controls obtained information on first-trimester address and water consumption habits. First-trimester exposures to TTHMs were estimated from the water company's quarterly sample data. The average level of TTHMs in the drinking water serving all the cardiac defect cases (64 ppb) was lower than the level among the controls (74.2 ppb). Comparing residences receiving chlorinated water with residences that did not receive chlorinated water, the authors reported unadjusted odds ratios of 1.0 (95% CI: 0.7, 1.6) and 1.1 (95% CI: 0.6, 2.1) for all cardiac defects and for conotruncal heart

defects (a pathogenetically related subgroup of heart defects), respectively. The authors stated that these odds ratios did not change substantially when water consumption habits or maternal risk factors (i.e., age, education, race) were taken into account.

The previously mentioned Swedish study evaluated major groups of birth defects among 135,074 singleton and multiple births (*29*). No associations with oral clefts or cardiac defects were found for exposure to water treated with chlorine dioxide or sodium hypochlorite. The authors did not present findings for NTDs, but we calculated odds ratios of 1.0 for both chlorine dioxide and sodium hypochlorite. An odds ratio of 1.4 (95% CI: 0.7, 1.4) was found for spina bifida and sodium hypochlorite. Other elevated odds ratios for sodium hypochlorite included 1.8 (95% CI: 0.7, 4.3) for anal atresia, 1.6 (95% CI: 0.9, 3.0) for limb reductions, 1.4 (95% CI: 0.7, 3.0) for severe kidney malformation, 3.2 (95% CI: 1.0, 10.0) for spine malformation, 2.0 (95% CI: 0.8, 5.1) for diaphragmatic hernia, and 1.3 (95% CI: 0.4, 4.4) for abdominal wall hernia. Odds ratios of 1.5 (95% CI: 0.3, 7.3) and 1.5 (95% CI: 0.6, 3.6) were found for chlorine dioxide and hydrocephaly and anal atresia, respectively.

The previously mentioned study conducted in Norway evaluated birth defects diagnosed during the first week after birth among 141,077 live births to residents in 366 municipalities during 1993–1995 (*30*). Exposures were assigned to each birth based on the municipality of maternal residence at the time of delivery. The exposure assessment was based on type of treatment (chlorination vs. none) and the water color measurement. Color was correlated with the amount of dissolved organic matter in drinking water.

Because most municipalities (72%) were served by more than one waterwork facility, two ecologic variables were calculated for each municipality: the percentage of the population served by chlorinated supplies ("chlorination proportion"), and the average color weighted by the percentage of the population served by each waterwork supplying the municipality ("weighted mean color"). These variables were then dichotomized (low/high color, and 0/>0 chlorination proportion) and assigned to each municipality. The study did not take into account the season in which the first-trimester occurred. Odds ratios were adjusted by maternal age, parity, whether the birth occurred in a university clinic, and by factors associated with the municipality of birth (i.e., population density, urbanicity, and types of industry).

When births assigned a high color and >0 chlorination proportion were compared with the reference level of a zero chlorination proportion and low color, the odds ratio for the outcome "all birth defects" was 1.14 (95% CI: 1.0, 1.3). Odds ratios of 1.26 (95% CI: 0.6, 2.6), 0.94 (95% CI: 0.6, 1.4), 1.05 (95% CI: 0.8, 1.5), 1.07 (95% CI: 0.5, 2.2), and 1.99 (95% CI: 1.1, 3.6) were also observed for NTD, oral cleft, cardiac, respiratory, and urinary defects, respectively.

As with the analyses of SGA and preterm birth (*30*), the use of the color measurement appeared to add little to the study. For example, from the data provided in the study, we calculated an unadjusted odds ratio of 1.15 for "all birth defects," comparing the chlorination proportions 0 and 100% without accounting for water color. This odds ratio was very close to the unadjusted (OR = 1.18) and adjusted (OR = 1.14) findings when both chlorination proportion and color level were taken into account.

This study suffered from a number of weaknesses. First, no details were provided on the timing and frequency of color testing. Even though the color level (and DBP levels) will vary considerably by season, only one color value was used to characterize each municipality over the entire 3-year study period. Considerable exposure misclassification would be likely, given the study's failure to account both for the seasonality of color levels and the season in which the first trimester occurred.

Second, the study provided no information on how well the color level in a chlorinated supply correlated with THMs or other DBPs. Third, ecologic biases were possible because the study used two ecologic exposure variables, "chlorination proportion" and "weighted mean color." For a municipality served by both chlorinated and unchlorinated supplies, averaging the color level across waterworks made little sense because, in unchlorinated supplies, the color measurement would likely not be correlated with DBP levels. Ecologic biases could have been avoided if only municipalities served exclusively by either chlorinated or unchlorinated supplies were included (n = 82,540 births) and if the within-municipality color levels did not vary appreciably.

A study conducted at Brigham and Women's Hospital in Boston, Massachusetts, enrolled 14,130 obstetric patients delivering live births or fetal deaths of at least 20 weeks gestation between August 1977 and March 1980 (*32*). Because of lack of personnel and refusals, the study could not enroll about 3,000 obstetric patients delivering during this period. All congenital anomalies diagnosed at birth or at discharge by pediatric resident examinations were eligible for the study. Controls were randomly sampled from deliveries alive at discharge without congenital anomalies. About 21% of the identified cases and sampled controls were excluded from the study because of "lost" medical records or maternal illnesses during pregnancy or because the mother's first-trimester address was out of state or not served by a public water system. Although maternal interviews were conducted, no information on water consumption habits was obtained. Maternal risk factors (age, race, alcohol consumption, previous birth defect, and having no insurance) were evaluated as potential confounders.

When all anomalies were grouped together, an odds ratio of 1.5 (95% CI: 0.7, 2.1) was obtained comparing those served by chlorinated surface water supplies to those served by chloraminated surface water supplies. Chloraminated supplies typically have much lower TTHM levels than chlorinated supplies. The excess in total anomalies was primarily due to excesses in respiratory defects (OR = 3.2; 95% CI: 1.1, 9.0) and urinary tract defects (OR = 4.1; 95% CI: 1.2, 14.1). No confounding by maternal risk factors was observed for these findings. The study did not report the disinfection treatment results for NTDs, clefts, or cardiac defects.

SUMMARY OF THE BIRTH DEFECT STUDIES. Summarizing the results for each birth defect grouping, there was some consistency in the findings for NTDs and oral cleft defects but not for cardiac defects. Associations were found for NTDs in all three studies (northern New Jersey, Nova Scotia, and statewide New Jersey) that evaluated levels of THMs (*20,22,24,25*). In the two studies that evaluated NTD and individual THMs, one obtained similar findings for both chloroform and BDCM (*25*), whereas the other study found a much stronger association with BDCM (*24*). Of the two studies that evaluated oral cleft defects and levels of THMs, one found an association with TTHM (*20*) and the other found an association with chloroform but not TTHM (*24*).

Although the northern New Jersey study (*20*) found an association between cardiac defects and TTHM, the Nova Scotia (*22,24*) and Santa Clara County, California (*26*), studies did not confirm this finding. Finally, urinary tract defects were evaluated in the three studies that defined exposure by type of treatment (*29,31,32*). In each study, an association was found between urinary tract defects and chlorination. Although this exposure definition was admittedly crude, these defects should be evaluated in future studies.

Spontaneous abortions and fetal deaths. Three studies evaluated spontaneous abortions (*12,21,33*), and three studies evaluated fetal deaths (>20 weeks gestation) or stillbirths (*20,22,23,32*). The first studies of spontaneous abortion and stillbirths

occurred in Boston, Massachusetts (*32,33*). These studies evaluated sources of drinking water (surface water vs. groundwater) and type of disinfection (chlorination vs. chloramination). Chlorinated surface water generally has higher levels of DBPs, such as THMs, than does chloraminated surface water. The spontaneous abortion study identified and interviewed a sample of mothers with pathological evidence of a pregnancy loss through 27 weeks gestational age who were treated at Brigham and Women's Hospital, in Boston, from July 1976 to February 1978 (*33*). Controls were selected from among mothers who delivered term births with no birth defects at the hospital within 1 week of a pregnancy loss. Cases and controls were excluded if the mothers refused to be interviewed, used an IUD at the time of conception, had diabetes or cervical incompetence, or did not live in a town with a public water system during the pregnancy. If a mother had more than one pregnancy during the study period, only the first pregnancy was included. A total of 286 spontaneous abortions and 1,391 controls were analyzed in the study. Comparing surface water source to groundwater source, the odds ratio was 2.2 (95% CI: 1.3, 3.6) after adjustment for water quality variables (e.g., inorganics, pH) and maternal age, education, and history of spontaneous abortion. However, an odds ratio of <1.0 was found when comparing chlorinated versus chloraminated surface water supplies.

In the stillbirth study, cases were restricted to those born without birth defects from August 1977 to March 1980 at Brigham and Women's Hospital in Boston, whose mothers lived in towns served by public water systems during their pregnancies and did not have diabetes or epilepsy (*32*). Similar restrictions applied to the controls, who were sampled from among live births without birth defects that delivered at the hospital over the same period. About 28% of the sampled cases and 14% of the sampled controls were excluded because their medical records were "lost," which occurred most frequently among African American mothers and among young mothers receiving welfare benefits. A total of 77 stillbirths and 1,177 controls were included in the study. Maternal risk factors (age, race, alcohol consumption, previous birth defect, and having no insurance) were evaluated as potential confounders. Surface water source was not associated with stillbirths. However, chlorinated surface water was associated with stillbirths (OR = 2.6; 95% CI: 0.9, 7.5) when compared with chloraminated surface water.

The study of three counties in central North Carolina mentioned above evaluated the effects of TTHMs on spontaneous abortions (*21*). A total of 418 spontaneous abortions were identified through medical care provider records from September 1988 through August 1991. A sample of 341 controls (term, normal-weight live births) matched to the cases on date, hospital of birth, and maternal race was obtained. Data from concurrent THM samples from the water system serving the mother's address were combined with information on water consumption habits from maternal interviews in order to estimate exposures. Information on maternal water consumption habits could not be obtained for about one third of the cases and controls, so these were excluded from the study. In addition, cases and controls were excluded if their source of water was bottled water or private well, if the mother reported that she consumed no water, or if quarterly THM data corresponding to the fourth week of pregnancy were missing. About one third of the identified cases and controls were included in the study: 126 cases and 122 controls. Maternal risk factors such as age, education, race, smoking, and income were evaluated as potential confounders

In the highest exposure range, 81.1–168.8 ppb TTHMs, the odds ratio was 1.2 (95% CI: 0.6, 2.4), but the risk varied greatly within this exposure range, from an odds ratio of 2.8 at the higher portion of the range to an odds ratio of 0.2 at the lower portion of the range. Despite the wide heterogeneity in effect within the highest exposure range, and the lack of an effect in the 60–81 ppb exposure range, a change in the odds ratio of 1.7 (95% CI: 1.1, 2.7) was found per 50 ppb increment in TTHMs. However, when the daily amount of water consumed was taken into account, no dose–response trend was found. The study did not distinguish cold tap water consumption and hot tap water consumption.

A prospective cohort study of spontaneous abortions of ≥20 weeks gestation was conducted in three regions of California (*12*). Pregnancies identified at the time the mothers scheduled their first prenatal care visit at Kaiser Permanente from January 1990 through September 1991 were potentially eligible for inclusion in the cohort. After excluding an unspecified number of ineligible pregnancies (i.e., maternal age <18 years old, pregnancy identified at >13 weeks gestational age, or mother did not speak English or Spanish), the mothers of 5,342 pregnancies completed interviews. Although not reported in the study, the percentage of those eligible who completed interviews was probably around 75%. After exclusions due to loss to follow-up (1%), molar and ectopic pregnancies, and elective terminations, the pregnancies of 5,144 women remained in the cohort. Most spontaneous abortions were confirmed by medical records with a small percentage (<8%) ascertained through maternal interviews conducted by the study physician.

Telephone interviews were conducted to determine the woman's address, water usage, tobacco consumption, alcohol consumption, caffeine consumption, and employment status at week 8 of gestational age. The median gestational age at interview was 8 weeks. Because the interviews were conducted prior to the occurrence of a spontaneous abortion or live birth, bias in the recall of water consumption habits was minimized.

THM data from the water utilities serving the regions were available to estimate exposures for almost 90% of the cohort (n = 4,622), including 442 spontaneous abortions. For about 86% of these pregnancies, first-trimester exposures to THMs were based on distribution samples taken by the water utilities during the first trimester. For 4% of these pregnancies, first-trimester exposure to THMs was based on distribution samples taken no more than 30 days before or after the first trimester. For the remaining 10%, the yearly average level of THMs was used to estimate first-trimester exposure to THMs. Maternal risk factors (e.g., smoking, history of pregnancy loss, race, age, and employment) were evaluated as potential confounders.

An odds ratio of 1.2 (95% CI: 1.0, 1.5) was obtained when TTHM levels of ≥75 ppb were compared with levels of <75 ppb. However, when we recategorized exposure using data presented in the study and defining the reference group as TTHM < 30 ppb, an exposure–response trend was evident: 30–74 ppb (OR = 1.2), 75–104 ppb (OR = 1.4), and >104 ppb (OR = 1.7). For women consuming less than five glasses per day of cold tap water, the study found an odds ratio of 1.1 (95% CI: 0.9, 1.4) at TTHM levels of ≥75 ppb compared with levels of <75 ppb. However, for women consuming five or more glasses per day, the odds ratio at TTHM levels of ≥75 ppb was 2.0 (95% CI: 1.1, 3.6). Comparing women exposed to ≥75 ppb TTHMs who consumed five or more glasses per day of cold tap water ("high personal TTHM exposure," n = 121 pregnancies) with a reference group of women who either were *a*) exposed to <75 ppb, *b*) were served by utilities that used groundwater sources for ≥95% of their supply, or *c*) consumed fewer than five glasses per day ("low personal TTHM exposure," n = 4,988 pregnancies), the study obtained an odds ratio of 1.8 (95% CI: 1.1, 3.0). A letter to the editor critical of this comparison pointed out that a woman consuming four glasses of water with TTHM levels of >100 ppb would be considered in the reference group (*37*).

The letter also recommended that inhalation and dermal exposures in addition to ingestion exposures should be included in the estimation of TTHM exposure. In response, Waller and Swan (*38*) calculated an oral daily dose (glasses/day × TTHM level), but the cutoff they used (90 µg/day) still permitted a woman exposed to 90 ppb TTHMs who drank four glasses per day to be in the reference group. The odds ratio comparing oral doses ≥90 µg/day to <90 µg/day was 1.6 (95% CI: 1.1, 2.3). They also calculated a "total" TTHM dose that included estimates of inhalation and dermal exposures using a number of assumptions that they acknowledged were problematic. Again, dichotomizing "total" TTHM exposure in an analysis similar to their analyses of "personal TTHM exposure" and "oral daily dose," they obtained an odds ratio of 1.1 (95% CI: 0.7, 1.7). In our opinion, instead of dichotomizing exposures, a better approach might have been to characterize exposures using several levels, including a reference level consisting of those exposed to low levels of TTHMs (e.g., <20 ppb) whose water usage (e.g., glasses per day, minutes of showering) was also low.

This study provided conflicting evidence as to whether the DBPs associated with spontaneous abortions were volatile or nonvolatile chemicals. For example, the lack of associations with showering and swimming suggested that the inhalation of volatile DBPs was not an important route of exposure and that the effect was due to ingestion of nonvolatile DBPs. On the other hand, women in the high personal TTHM group who let tap water sit before drinking it (and presumably ingested less DBPs because the volatile DBPs were allowed to escape from the water) had a lower risk of spontaneous abortion than those who did not—a result favoring volatile DBP agents. The conflicting findings might arise because information obtained through interview on water consumption habits may lack sufficient accuracy.

This study also evaluated individual THM data that were available for 61% of the cohort. When all four THMs were included in a model adjusting for other risk factors, only high personal exposure to BDCM had an elevated risk for spontaneous abortion (OR = 3.0; 95% CI: 1.4, 6.6). Of the three regions, region 1 (Santa Clara County) had the highest spontaneous abortion risk among those with high personal TTHM exposure (OR = 4.3; 95% CI: 1.8, 10.6). The surface water sources for this region had higher bromine content than those of region 2 (region 3 was served entirely by groundwater sources). The study also attempted to evaluate the extent of exposure misclassification that occurred because of water consumption outside the home at the workplace. Among those not employed, the odds ratio for high personal TTHM exposure was 3.0 (95% CI: 1.2, 7.9), whereas the odds ratio among those employed outside the home was 1.5 (95% CI: 0.8, 2.8).

In the northern New Jersey study, no excess of fetal deaths was found with increasing levels of TTHM (*20*).

In the Nova Scotia study, an adjusted odds ratio of 1.66 (95% CI: 1.1, 2.5) was found for stillbirths when TTHM levels of ≥100 ppb were compared with levels of <50 ppb (*22*). In subsequent analyses (*23*), a stronger relationship was found for BDCM when levels of ≥20 ppb were compared with levels of <5 ppb (OR = 1.98; 95% CI: 1.2, 3.5) than was found for chloroform when levels of ≥100 ppb were compared with levels of <50 ppb (OR = 1.56; 95% CI: 1.0, 2.3).

Of the 214 stillbirths, the cause of death was "unexplained" for 39% (n = 84) and asphyxia for 34% (n = 72). Other causes of death individually accounted for ≥10% of the stillbirths and were not evaluated in the analyses. For the unexplained cause of death, odds ratios of 1.07 (95% CI: 0.5, 2.2) and 1.35 (95% CI: 0.6, 3.2) were obtained for TTHMs and BDCM, respectively, and an odds ratio of <1.0 was obtained for chloroform. Much higher odds ratios were obtained for stillbirths caused by asphyxia, indicating that failure to stratify on cause of stillbirth could mask an effect. For TTHMs, chloroform, and BDCM, the odds ratios were 4.57 (95% CI: 1.9, 10.8), 3.15 (95% CI: 1.6, 6.0), and 1.75 (95% CI: 0.7, 4.2), respectively.

SUMMARY OF THE SPONTANEOUS ABORTION AND FETAL DEATH STUDIES. In summary, the best conducted study of spontaneous abortions and THMs, the California prospective cohort study (*12*), found a strong association, especially for BDCM. The central North Carolina study (*21*) also found an excess of spontaneous abortion when TTHM levels were evaluated, but the excess disappeared when water consumption habits were taken into account. However, this study suffered from exclusions and low participation rates and because maternal interviews were conducted some time (not stated in the study) after the spontaneous abortion occurred, there was the possibility of errors in the recall of water consumption habits during pregnancy. The Massachusetts study (*33*) defined exposure by type of treatment and water source. No excess for spontaneous abortion was found by type of treatment (chlorination vs. chloramination), but an effect was seen by water source (surface water vs. groundwater). Given its conflicting findings and crudeness of exposure definition, this study does not provide evidence for or against an association.

The two studies that evaluated fetal deaths and THM levels had very different results. The Nova Scotia study (*24*) found a strong association especially with BDCM levels. This association was strengthened when cause of death (asphyxia) was evaluated. On the other hand, the northern New Jersey study (*20*) could not evaluate the individual THM levels or the cause of death information. Therefore, its finding of no excess could be the result of misclassification biases due to the failure to evaluate individual THMs and specific causes of death. The Massachusetts study (*32*) found an association between stillbirths and chlorinated surface water when compared with chloraminated surface water.

Solvents

Table 5 summarizes the characteristics and results of the five studies of chlorinated solvents and adverse birth outcomes (*7,8,20,39,40*). Three studies focused primarily on trichloroethylene (TCE) contamination in drinking water. Two of these studies were conducted in Tucson, Arizona (*7,39*), and one study was conducted in Woburn, Massachusetts (*8*). Two studies evaluated other solvents in addition to TCE: a study at the U.S. Marine base Camp LeJeune in North Carolina (*40*) focused on tetrachloroethylene (PCE), and the previously mentioned northern New Jersey study (*20*) evaluated several solvents, including PCE, carbon tetrachloride, the dichloroethylenes, 1,2-dichloroethane, 1,1,1-trichloroethane, and benzene.

Trichloroethylene. A case–control study conducted in Tucson, Arizona, evaluated the association between TCE and congenital heart defects in babies born during 1969–1987 (*39*). In 1973, clinicians noticed that a considerable number (about one third) of cardiac defect cases in the town came from an area defined by two ZIP codes in the southwestern portion of town near the airport. In 1981 this area was found to be served by public wells contaminated by TCE used to degrease missile and aircraft parts. The maximum level of TCE found in a public well was 239 ppb. Exposure was defined as parental residence in the contaminated water area for at least 1 month before and during the first trimester of the affected pregnancy. Detailed interviews also collected data on residential address, employment history, family history of congenital heart disease, birth weight, parents' ages, education, occupation, ethnicity, and mother's history of rubella during pregnancy.

This review focuses only on data from this study for the years 1969–1981, when the contaminated wells were in operation. There were 365 cases of congenital heart defects (excluding syndromes, preterm births

Table 5. Summary of studies that evaluated exposures to trichloroethylene and tetrachloroethylene.

Study site and period	Outcome	No. of subjects	Exposure	Results (OR)
Arizona, 1969–1981 (*39*)	Cardiac defects	365 cases	First trimester residence (or employment) in area of TCE contamination	Prevalence ratio = 2.58
Woburn, MA, 1975–1979 (*8*)	SGA Preterm birth Birth defects Fetal deaths	2,211 births, 19 fetal deaths	Modeled distribution system to estimate monthly exposures; address at delivery	SGA = 1.55; LBW = 0.9; preterm birth ≤1.0; **fetal death = 2.57; NTD = 2.21; cleft lip = 2.21; cleft palate = 0.0; heart = 0.40; eye = 4.41;** cluster of choanal atresia
1969–1979	LBW	5,347 births		
Northern New Jersey, 1985–1988 (*20*)	SGA Preterm birth Birth defects Fetal death	80,938 live births, 594 fetal deaths	Estimated average monthly levels of solvents based on tap water sample data and address at delivery	TCE: SGA ≤1.0; preterm birth = 1.02; NTDs = 2.53; oral clefts = 2.24; heart defects = 1.24; fetal death ≤1.0 PCE: SGA ≤1.0; preterm birth ≤1.0; NTDs = 1.16; oral clefts = 3.54; heart defects = 1.13; fetal death ≤1.0
Camp LeJeune, NC, 1968–1985 (*40*)	MBW SGA Preterm birth	31 births exposed to TCE, 997 unexposed; 6,117 births exposed to PCE, 5,681 women unexposed	Residence in a base housing area known to have received contaminated water	TCE: SGA = 1.5; MBWD = –139 g; preterm birth = 0.0; males: SGA = 3.9; MBWD = –312 g PCE: SGA = 1.2; MBWD = –24 g; preterm birth = 1.0; >35 yr: SGA = 4.0; MBWD = –205 g; women with ≥2 fetal losses: SGA = 2.5
Arizona, 1979–1981 (high exposure) and 1983–1985 (post-exposure) (*7*)	LBW VLBW Full-term LBW	1,099 exposed births, 877 unexposed births	Maternal residence in target or comparison census tracts at delivery; GIS modeling of groundwater plume	LBW = 0.90; VLBW = 3.30; full-term LBW = 0.81

Results set in bold type indicate those that were calculated by the reviewing authors. Abbreviations: LBW, low birth weight; MBWD, mean birth weight difference; VLBW, very low birth weight.

with patent ductus arteriosis, and minor anomalies) whose first trimester occurred when the contaminated wells were in operation. Of these 365 cases, 143 had parents who lived and/or worked in the areas served by the contaminated wells during their first trimester. Of the 143 cases with potential first-trimester exposure, 74 had mothers who resided in the contaminated area. The prevalence ratio of cardiac defects among residents of the contaminated area with first-trimester exposure (6.8/1,000 live births) compared with residents in uncontaminated areas (2.7/1,000 live births) was 2.58 (95% CI: 2.0, 3.4, calculated for this review using Poisson regression).

The study obtained two control groups by conducting random samples of households in Tucson. All members of a sampled household, regardless of age or gender, were asked if they worked or resided in the contaminated area. These control groups were inappropriate because they did not provide estimates of the exposure prevalence in the birth population that gave rise to the cardiac defect cases. Instead, the control groups provided estimates of the proportion of households in Tucson that had at least one member who worked or resided in the contaminated area. The estimated proportion ranged between 10% and 11%. The exposure prevalence among cardiac defect cases with first-trimester exposures prior to the well closures was 39.2% (mother or father worked or lived in the contaminated area) or 20.3% (mother resided in the contaminated area). Therefore, the exposure prevalence among the cases was between two and four times higher than the estimated exposure prevalence among households in Tucson obtained from the two control groups.

Maternal interviews could not be conducted for 172 cardiac defect cases whose first trimesters occurred prior to the well closures. Assuming that the noninterviewed cases had the same exposure prevalence as the interviewed cases, we estimated that the prevalence of cardiac defects in the exposed areas would be about 2.3 times that in the uncontaminated areas. Alternatively, assuming that the noninterviewed cases had an exposure prevalence similar to the exposure prevalence among all births in Tucson, we estimated that the prevalence of cardiac defects in the exposed area would be about two times that in the uncontaminated areas.

This study had several weaknesses including the use of inappropriate control groups and the failure to delineate precisely the exact boundaries of the contaminated area. Nevertheless, it seems reasonable to conclude from all the results found in the Tucson study that the risk of cardiac defects among those exposed to TCE-contaminated drinking water was between two and three times the risk of those in the uncontaminated areas of the city.

A second study in Tucson evaluated the association between TCE and low birth weight, very low birth weight, and term low birth weight (*7*). The study used the state's birth certificate database, which unconventionally categorized "term" (>35 weeks gestation), "low birth weight" (<2,501 g), and "very low birth weight" (<1,501 g). In contrast to the previous Tucson study, a geographic information system (GIS) was used to define more precisely the areas served by the contaminated public wells. Although exposures may have occurred before 1979, the study's exposure period was from 1979 through 1981 and included 1,099 births from three census tracts served by the contaminated water, and 877 births from other census tracts not served by the contaminated water but similar in demographics to the exposed census tracts. The mother's address from the birth certificate was used to assign the census tract. The estimated concentration of TCE during this period ranged from <5 to 107 ppb. In addition, births occurring in these same areas 2–4 years after the well closures (i.e., 1983–1985) also were analyzed to determine if any observed association during the exposure period might be the result of some risk factor other than TCE. Maternal race/ethnicity, education, pregnancy complications, and whether the child had a congenital anomaly as reported on the birth certificate were evaluated as potential confounders.

No associations were found during the exposure period for full-term low birth weight or low birth weight among all births. The study's unconventionally wide definition of "term" may have biased the result for full-term low birth weight. The odds ratios for very low birth weight during the exposure period was 3.30 (95% CI: 0.5, 20.6). During the postexposure period, the odds ratio was 1.68 (95% CI: 0.4, 6.8). From information provided in the article, we calculated unadjusted odds ratios for very low birth weight during the exposure and postexposure periods. For the exposure period, an unadjusted odds ratio of 2.61 was obtained, somewhat lower than the adjusted

result of 3.30. The difference may be due to the effect of small numbers of very low birth weight infants (e.g., $n = 4$ in the unexposed group) on the unconditional logistic regression model. For the postexposure period, an unadjusted odds ratio of 0.76 was obtained, considerably different from the adjusted result of 1.68. This difference might have been due to the inclusion of a variable in the logistic model for congenital anomalies as reported on the birth certificate (OR = 61.9) that may simply have been an indicator for very low birth weight (e.g., "respiratory defect" might be checked on the birth certificate if the very low birth weight infant had respiratory distress).

A study at Camp LeJeune evaluated SGA and mean birth weight difference among births occurring at base housing from 1968 through 1985 (*40*). Base housing records and mother's address at time of birth on the birth certificate were used to determine mother's residence during pregnancy. The Hospital Point housing area received water from a well system that had TCE levels as high as 1,400 ppb during sampling from 1982 through 1985. It was not known how long the contamination existed, but the industrial activities that might have contributed to the contamination were in operation since the 1940s. Over the study period, 31 births occurred among residents of the Hospital Point. A total of 5,681 births occurred during the study period among residents of base housing that did not receive contaminated water. Paternal (age, education) and maternal (age, education, race, parity, prenatal care, marital status, history of fetal death) risk factors were evaluated as potential confounders.

SGA (defined as the 10th percentile weight by gestational week) and mean birth weight difference were associated with TCE exposure. The odds ratio was 1.5 (90% CI: 0.5, 3.8), and the mean birth weight difference was –139 g (90% CI: –277, –1). However, these adverse effects were found only for male births exposed to TCE. The odds ratio for SGA among male births exposed to TCE was 3.9 (90% CI: 1.1, 11.9), and the mean birth weight difference was –312 g (90% CI: –540, –85). Preterm delivery was not associated with TCE exposure. The study was limited by the small number of exposed births.

A study conducted at Woburn, Massachusetts, examined the impact of TCE-contaminated water and various adverse reproductive outcomes, including SGA and birth defects (*8*). Two public drinking wells, wells "G" and "H," serving most of the eastern portion of the city were found to be contaminated with TCE at up to 267 ppb and PCE at up to 21 ppb. Among other contaminants found at much lower levels were 1,1,1-trichloroethane and 1,2-dichloroethylene. The drinking water system was extensively modeled and monthly exposures, based on the amount of water received weekly from wells G and H at the maternal address at time of birth, were assigned to each live birth and fetal death. Exposures were categorized initially as ever/never and then subsequently as high (at or above the 90th percentile mean weekly exposure score), moderate, and none. Exposures were assessed for the entire pregnancy period and for the first and third trimesters. Although the study period was extended for 9 years after the wells were closed in May 1979, this review focuses only on that part of the study that examined births from 1969 through the end of 1979. Birth weight data were available for the entire study period, but outcomes such as preterm birth, SGA (race and sex specific, 10th percentile weight by gestational week), fetal death, and birth defects were evaluated from 1975 to 1979 because of financial constraints and the lack of gestational age data on the birth certificates prior to 1975. Maternal risk factors (age, education, race, prenatal care, parity) were evaluated as potential confounders.

From 1969 to 1979, drinking water exposures could be determined for 5,347 live births in Woburn. From 1975 to 1979, drinking water exposures could be determined for 2,211 live births and 19 fetal deaths in Woburn. Low birth weight and preterm birth were not associated with exposures to wells G and H. Stronger effects on SGA were found when third-trimester exposures were evaluated rather than exposure over the entire pregnancy. Comparing the ever exposed during the third trimester to the never exposed, the odds ratios for SGA were 1.21 (95% CI: 0.9, 1.6) for Woburn as a whole and 1.50 (95% CI: 1.0, 2.3) when only births in the eastern portion of Woburn were analyzed. When we compared the high exposure group during the third trimester with the never exposed, the unadjusted odds ratio for SGA for Woburn as a whole was 1.55 (95% CI: 1.0, 2.4). The adjusted model included an interaction term for maternal age and high exposure, and the reported adjusted odds ratio of 1.39 (95% CI: 0.9, 2.2) was for women 20–34 years of age in the high-exposure group. For east Woburn, the unadjusted odds ratio for SGA in the high-exposure group was 1.85 (95% CI: 1.1, 3.1). In the adjusted model, an interaction term for maternal age and high exposure was included, and the reported adjusted odds ratio for women 20–34 years of age in the high-exposure group was 1.57 (95% CI: 0.9, 2.8).

Because of sparse data due to the relatively short period of evaluation (i.e., 1975–1979), the study often did not present odds ratios for individual birth defects or for some of the analyses of fetal deaths. When odds ratios were not presented, we calculated them. When we compared high exposure during the entire pregnancy to never exposed, the odds ratio for fetal deaths in Woburn as a whole was 2.57 (95% CI: 0.7, 8.9). For east Woburn, there were no fetal deaths that were never exposed over the entire pregnancy, so the odds ratio was infinity. Considering only third-trimester exposures, we obtained an odds ratio of 3.33 (95% CI: 0.3, 98.5).

For the birth defects analyses, the data were too sparse for us to evaluate east Woburn separately or to compare high, moderate, and no exposures. Comparing ever exposed during the first trimester with never exposed in Woburn as a whole, we found no associations for the following defects grouped by organ system: CNS, oral clefts, cardiac defects, musculoskeletal defects, urinary system defects, gastrointestinal defects, and skin defects. The odds ratio for genital defects was reported as 1.10 (95% CI: 0.5, 2.6). We obtained odds ratios of 1.10 (95% CI: 0.3, 4.4) and 1.10 (95% CI: 0.3, 3.8) for respiratory defects and ear defects, respectively. For eye defects, we obtained an odds ratio of 4.41 (95% CI: 0.5, 39.6). For NTDs and for cleft lip, there were two exposed and one unexposed, and the calculated odds ratios were both 2.21 (95% CI: 0.2, 24.4). No cleft palate cases were ever exposed. There were six exposed and four unexposed hypospadias cases, and the calculated odds ratio was 1.66 (95% CI: 0.5, 5.9).

A striking finding was an excess of choanal atresia, with three exposed cases constituting a prevalence of about 2.94 per 1,000 live births, which is over 20 times the prevalence found in the Metropolitan Atlanta Congenital Defects Program (0.14 per 1,000). There were no unexposed cases of choanal atresia. Choanal atresia is a nasal defect (blockage of the nasal airway by bony or membranous tissue) that is etiologically similar to conotruncal heart defects and other defects that arise from abnormal development and/or migration of the neural crest cells during embryogenesis.

In summary, the Woburn study found associations between exposures to wells G and H contaminated primarily with TCE and SGA, fetal deaths, eye defects, choanal atresia, NTDs, cleft lip, and hypospadias. Because of the short study period for these outcomes (i.e., 1975–1979), the odds ratios for birth defects and fetal deaths were based on a small number of cases.

The study conducted in 75 towns in northern New Jersey also examined the relationship between TCE and SGA, birth defects, and fetal death (*20*). (The methods are described in the section on chlorination disinfection by-products, above.) When term births only were evaluated, an association with low birth weight was found for TCE (OR = 1.23), but this association disappeared when carbon tetrachloride was added to the model. No associations were found for SGA (defined as the fifth percentile weight by gestational week), preterm delivery, very low birth weight, or fetal death. Associations with TCE were found for CNS defects (OR = 1.68; 90% CI: 0.8, 3.5), NTDs (OR = 2.53; 90% CI: 0.9, 6.4), oral clefts (OR = 1.3; 90% CI: 0.4, 3.7), and major cardiac defects (OR = 1.24; 90% CI: 0.5, 2.9) at levels above 10 ppb. A stronger association between TCE and oral clefts was reported in the study (OR = 2.24; 90% CI: 1.2, 4.2) when exposures above 5 ppb were grouped together.

SUMMARY OF THE TRICHLOROETHYLENE STUDIES. The Camp LeJeune (*40*) and Woburn (*8*) studies found increased risks of SGA ranging from 1.5 to 1.9. No association was found in the northern New Jersey study (*20*), but this may be due to the relatively lower levels of contamination in that study. Only the Camp LeJeune study evaluated exposure interactions with other risk factors and found that the increased risk was entirely among the male births. The Tucson study (*7*) found an association with very low birth weight, which conflicts with the findings in the northern New Jersey and Woburn studies. TCE was not associated with preterm delivery in any of the studies. An association with fetal death was found in the Woburn study but not in the northern New Jersey study, again possibly because of the lower levels of contamination in the latter study.

The Tucson study (*39*) found an association with cardiac defects, but this finding conflicted with the findings in the Woburn and northern New Jersey studies. However, the Woburn study did find a cluster of choanal atresia, a defect related to conotruncal heart defects. The Woburn and northern New Jersey studies found similar associations with NTDs and cleft lip. In addition, the Woburn study found an association with eye defects.

Tetrachloroethylene. Two studies evaluated the effects of PCE-contaminated drinking water and SGA. In the northern New Jersey study (*20*), PCE was not associated with SGA. In the Camp LeJeune study (*40*), PCE exposure was associated with SGA and mean birth weight difference. The odds ratio for SGA was 1.2 (90% CI: 1.0, 1.3), and the mean difference was –24 g (90% CI: –41.0, –7.0). Most of the effect occurred among mothers 35 years old or older who were exposed to PCE, with an odds ratio for SGA of 4.0 (90% CI: 1.6, 10.2) and a mean birth weight difference of –205 g (90% CI: –333.0, –78.0). In addition, among mothers with 2 or more prior fetal losses who were exposed to PCE, the odds ratio for SGA was 2.5 (90% CI: 1.5, 4.6). Only the northern New Jersey study evaluated birth defects and fetal deaths (*20*). For NTDs and major heart defects, only one case was exposed to >10 ppb. The odds ratios for NTDs and major heart defects exposed to >5 ppb were 1.16 (90% CI: 0.5, 2.6) and 1.13 (90% CI: 0.6, 2.1), respectively. For oral clefts exposed to >10 ppb, the odds ratio was 3.54 (90% CI: 1.3, 8.8). No association was found for fetal deaths.

Other solvents. The northern New Jersey study (*20*) evaluated several other solvents in drinking water: the dichloroethylenes, 1,1,1-trichloroethane, carbon tetrachloride, 1,2-dichloroethane, and benzene. The strongest associations were found for carbon tetrachloride. The odds ratios for SGA, term low birth weight, NTDs, and oral clefts were 1.75 (90% CI: 1.3, 2.3), 2.26 (90% CI: 1.5, 3.4), 5.39 (90% CI: 1.1, 19.0), and 3.60 (90% CI: 0.8, 12.5), respectively. Carbon tetrachloride was also associated with fetal deaths (OR = 1.35; 90% CI: 0.5, 3.5) but not with cardiac defects. The dichloroethylenes were associated with NTDs (OR = 2.60; 90% CI: 0.9, 6.5) and oral clefts (OR = 1.71; 90% CI: 0.6, 4.2), and benzene was associated with NTD (OR = 2.05; 90% CI: 0.6, 5.8) and cardiac defects (OR = 1.75; 90% CI: 0.7, 3.9). 1,2-Dichloroethane was also associated with cardiac defects (OR = 2.11; 90% CI: 0.8, 5.2). All of the associations between these solvents and birth defects were based on small numbers of exposed cases.

Conclusions

The studies of THMs and adverse birth outcomes provide moderate evidence for associations with SGA, NTDs, and spontaneous abortions. Because fewer studies have been conducted for the solvents than for THMs, the evidence for associations is weaker. Nevertheless, the findings of excess NTDs and clefts in the northern New Jersey (*20*) and Woburn studies (*8*) should be followed up in future studies. The finding of excess choanal atresia in the Woburn study and the finding of an excess of cardiac defects in the Tucson study (*39*) warrant follow-up as well, because some of the cardiac defects are etiologically related to choanal atresia.

States with population-based birth defects registries should be encouraged to conduct studies of public drinking water contamination. Although there are limitations to studies that base exposure assessments only on concurrent water utility monitoring data and the maternal address at time of birth, these studies nonetheless can provide timely and cost-efficient information that can supplement the growing evidence on the adverse effects of drinking water contaminants. To enhance these studies, the distribution systems could be modeled following the examples of the Denver area study (*6*), the Tucson study (*7*), and the Woburn study (*8*).

Ongoing, case–control sampling and interviewing of birth defect cases are being conducted by states with birth defects registries (*41*). These studies are including questions on the maternal interview concerning water consumption habits at home and at the workplace and linking water utility monitoring data to maternal address during the first trimester. An important limitation to these studies is the length of time, usually several months, between the child's birth and the maternal interview. Prospective cohort studies similar to the California prospective study of spontaneous abortions (*12*) do not have this limitation. However, because birth defects are rare events, prospective cohort studies are not feasible for individual states to conduct. Discussion is currently underway to conduct a large-scale, national longitudinal study enrolling children prenatally during the first trimester and following them through adolescence. Such a study should have drinking water exposures and adverse birth outcomes as an important component.

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