Please review and let me know about problem areas or potential problems that could arise from this study. 0477

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY
ATLANTA, GEORGIA

VOLATILE ORGANIC COMPOUNDS IN DRINKING WATER AND ADVERSE PREGNANCY OUTCOMES

INTERIM REPORT

UNITED STATES MARINE CORPS BASE CAMP LEJEUNE, NORTH CAROLINA

JANUARY 1997

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ABSTRACT

The potential relationship between environmental exposure to volatile organic compounds (VOCs) in drinking water and adverse pregnancy outcomes is one that warrants exploration. In 1995, data collection was begun for a retrospective cohort study of exposure to VOCs in drinking water and a variety of adverse pregnancy outcomes at the U.S. Marine Corps Base at Camp LeJeune, Onslow County, North Carolina. This interim report discusses the influence of VOC-contaminated drinking water on mean birth weight (MBW) and the outcome small for gestational age (SGA) among residents of base family housing at Camp LeJeune. These study results are based on analysis of live births to women residing in base family housing when they delivered during the period January 1, 1968 through December 31, 1985; birth certificates were studied from 6,131 tetrachloroethylene-exposed women (PCE-exposed), 141 short-term trichloroethylene-exposed women (TCE-exposed), 31 long-term TCE-exposed women and 5,681 unexposed women. The following potential confounders and effect modifiers were evaluated: sex of infant, maternal and paternal age, maternal race, maternal and paternal education, military paygrade, maternal parity, adequacy of prenatal care, marital status, and year of birth. The influence of timing and duration of exposure on potential effects was also explored by linking family base housing records to birth certificate data.

For most live births, including all births to women younger than 35 years of age with no prior fetal deaths, there was no association between PCE-contaminated drinking water and MBW or SGA. For the group as a whole, infants whose mothers resided in PCE-exposed areas were an average of 24 grams (g) lighter at birth than infants whose mothers lived in unexposed housing. This difference was too small to be biologically meaningful. After controlling for potential confounders, the overall odds ratio (OR) for PCE and SGA was 1.2 (90% confidence interval [CI]: 1.0, 1.3). These results provide reasonable assurance that PCE-contaminated drinking water did not affect the birth weight of infants of mothers who were younger than 35 years of age and had no medical history of fetal death; this accounts for most base residents exposed to PCE.

Associations between PCE and the study outcomes were observed in two potentially susceptible subgroups: infants of mothers 35 years of age and older and infants whose mothers had histories of fetal deaths. For older mothers, the adjusted difference in MBW between PCE-exposed and unexposed births was -207 g (90% CI: -334, -79), and the adjusted odds ratio was 3.9 (90% CI: 1.6, 9.8) for PCE exposure and SGA. Among mothers with histories of fetal deaths, the difference in MBW between PCE-exposed and unexposed births was -51 g (90% CI: -97, -5), and the adjusted odds ratio for PCE and SGA was 1.6 (90% CI: 1.3, 2.1). Because associations in these subgroups were not anticipated, these results should be considered to be exploratory. They are, however, biologically plausible and deserving of followup.

The TCE-exposed groups were both very small. The difference in adjusted MBW between the long-term TCE-exposed group and the unexposed comparison group was -139 g (90% CI: -277, -1); the odds ratio was 1.5 (90% CI: 0.5, 3.8) for SGA and this exposure. This

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increase was entirely attributable to differences in male infants within the long-term TCE-exposed group. Among males alone, the odds ratio for SGA was 3.9 (90% CI: 1.1, 11.9) and the difference in MBW was -312 g (90% CI: -540, -85). The short-term TCE-exposed group had a lower prevalence of SGA births and MBW was slightly higher overall in this group compared with the unexposed group.

The finding and magnitude of reduced birth weight and increased SGA in males within the long-term TCE-exposed group is potentially important. However, the sample size was small and weakens the evidence for a causal association considerably. Although it is possible to speculate on mechanisms by which such a sex-based difference might arise, this difference was unexpected and is not explained by currently described mechanisms of TCE toxicity. These findings warrant followup in a larger TCE-exposed population.

The following projects are ongoing and will be reported at a later date: analyses of preterm delivery and fetal death, analysis of a study designed to assess the feasibility and utility of reviewing medical records for this cohort, and an evaluation of the quality and completeness of the study's measures of duration of exposure.

INTRODUCTION

The Agency for Toxic Substances and Disease Registry (ATSDR) is an agency of the Public Health Service. ATSDR has a broadly defined legislative mandate to prevent or mitigate adverse human health effects and diminished quality of life resulting from exposure to hazardous substances in the environment. Population-based research conducted to identify links between exposures and specific adverse health effects is a necessary part of this mandate. One exposure-disease relationship that warrants further exploration is that between volatile organic compounds (VOCs) in drinking water and adverse pregnancy outcomes. Adverse pregnancy outcomes are of particular concern to populations residing on military bases because such populations have a high proportion of individuals of reproductive age, and are a priority for ATSDR.

In 1995, data collection was begun for a retrospective cohort study of exposure to VOCs in drinking water and a variety of adverse pregnancy outcomes at the U.S. Marine Corps Base at Camp LeJeune, Onslow County, North Carolina. This interim report discusses the influence of VOC-contaminated drinking water on mean birth weight (MBW) and the outcome small for gestational age (SGA) among residents of base family housing at Camp LeJeune; there is documented past exposure to tetrachloroethylene (PCE), trichloroethylene (TCE), and 1,2-dichloroethylene (1,2-DCE) in drinking water supplies at the base. Analyses of other pregnancy outcomes, such as preterm delivery and fetal death, exploratory analyses of birth defects and medical complications reported on birth certificates, results of the medical record pilot study, and an evaluation of the data quality of housing records will be presented in a subsequent report.

OBJECTIVES

The primary objective of this project was to describe the association between VOC-contaminated drinking water and mean birth weight (MBW) and the outcome small for gestational age (SGA) among residents of base family housing at Camp LeJeune; there was documented past exposure to tetrachloroethylene (PCE), trichloroethylene (TCE), and 1,2-dichloroethylene (1,2-DCE) in drinking water supplies at the base. A secondary objective was to explore the influence of timing and duration of exposure on associations between exposure and outcome.

BACKGROUND

Environmental exposure to hazardous substances and the adverse health effects that result are a public health issue that is growing in importance. In 1981, the U.S. Environmental Protection Agency (EPA) estimated that 264 million metric tons of hazardous wastes were

produced. By 1988, this figure had risen to 5.5 billion *(1)*. In 1990, an estimated 4 million people in the United States lived within 1 mile of one or more of the 1135 hazardous waste sites then on the National Priorities List (NPL) *(1)*. Today, there are more than 1,400 sites on the NPL *(2)*. These sites represent a small fraction of the estimated 439,000 hazardous waste sites that might be present in the United States *(1)*. There are no reliable estimates of the number of people actually exposed to toxic substances either at NPL sites or at hazardous waste sites in general.

ATSDR is required by law to conduct a public health assessment at each of the sites on the NPL. The aim of each assessment is to determine whether the population residing around a particular site might have been exposed to any toxic substances and also to assess whether any adverse health effects have resulted from the exposure. Known health effects are documented in these assessments and public health recommendations are made accordingly. Potential health effects are also identified and referred to ATSDR scientists for additional investigation. As part of the public health assessment process at Camp LeJeune, exposure to TCE, PCE, and 1,2-DCE was documented in two sources of drinking water at the base over a period of 34 months. Included in the population that used this water were slightly more than half of all residents in family base housing. Residents of base family housing are almost always married and move frequently. It is believed that few residents would have experienced more than a few years of exposure. For women of reproductive age, or women who were pregnant during their residence on base, a few years could amount to a significant exposure. Hence, concern was expressed about the potential health effects on fetuses exposed to toxic substances in utero.

Site Description and Exposure History

Camp LeJeune is a military base that comprises approximately 233 square miles in Onslow County on the coast of North Carolina. It is one of 123 federal facilities on the NPL because of the presence of contaminants in the environment originating at the facility. The base consists of six Marine Corps commands and two Navy commands. Almost 130,000 people have access to the base. The population includes active military personnel (43,000) and their dependents (52,000). Base housing for enlisted personnel, officers, and their families is located in 15 different areas on the base. An average of 8.3 million gallons of water is distributed daily at Camp LeJeune. More than 100 wells have been drilled to supply this water. Almost all of these wells use a tertiary sand aquifer that is permeable to contamination.

The first VOC contamination at Camp LeJeune was detected in drinking water in April 1982. This coincided with a change in the laboratory that conducted routine water quality testing, and was unlikely to have been related to the onset of first exposure. On the basis of anomalous readings in the April samples, water samples were collected in May and July and analyzed for a limited number of VOCs. PCE and TCE were found in two drinking water systems: the Tarawa Terrace system and the Hadnot Point system. However, the source of the contamination was not identified. Although the base contacted the state for advice, no further action was taken because there were no water quality standards for the detected VOCs in 1982.

In July 1984, Camp LeJeune began sampling wells in the Hadnot Point area as part of the base Superfund program. Seven contaminated wells were closed in November and December 1984. Tap water sampling conducted in December after the closure of these seven wells showed no additional evidence of contamination. However, on January 27, 1985, a fuel pump broke at the Holcomb Boulevard water system. Water from Hadnot Point was supplied to the Holcomb Boulevard service area while repairs were conducted at Holcomb Boulevard. Tap water samples taken from buildings temporarily supplied by Hadnot Point contained high levels of TCE. This prompted additional sampling of tap and finished water for VOCs at Hadnot Point and Tarawa Terrace. Contaminated wells in both water systems were closed soon after they were identified in January and February 1985, and a routine sampling program was implemented at all distribution systems on the base. Notable contamination has not been detected in Camp LeJeune's drinking water systems since February 1985.

The Hadnot Point system has been primarily for industrial purposes, but the Hospital Point housing area also receives water from the Hadnot Point system. This small housing area was populated by hospital personnel and their families until 1983 when the area became housing for a more diverse group of officers' families. It is not known when the Hadnot Point supply wells first became contaminated, but VOCs were present for at least two and a half years. Industrial activity on the base began in the 1940s. No records indicate when the various VOC plumes now contaminating supply wells in the Hadnot Point System may have originated. However, the contaminated supply wells were shut down in 1984 and 1985. A chronology of these events is included in Table 1.

At Tarawa Terrace, the highest concentrations of contaminants measured in tap water samples were 215 parts per billion (ppb) PCE, 8 ppb TCE, and 12 ppb 1,2-DCE. This distribution system continued to serve base family housing until 1986. The highest contaminant levels taken from tap water samples at Hadnot Point were 1400 ppb TCE and 407 ppb 1,2—DCE.

Contamination at Tarawa Terrace is thought to have occurred considerably before it was first documented in 1982. The source of the PCE at Tarawa Terrace was the ABC One-Hour Cleaners (ABC), a dry-cleaning establishment near Tarawa Terrace *(3)*. PCE leaked into the groundwater from ABC's septic system. According to EPA records, ABC's septic system was in operation from 1954 through 1985. In 1958, the base dug a supply well for the Tarawa Terrace system approximately 900 feet from the drycleaners. Because this supply well was so close to the contaminated septic system, because there were few changes in the dry-cleaning operation after 1960 *(4)*, and because of the very permeable aquifer at Camp LeJeune, it is likely that the Tarawa Terrace well was contaminated soon after it was built, and that human exposure to PCE and other contaminants through this well could have occurred for as long as 27 years.

A list of the housing areas that received contaminated water, a list of contaminants, and contaminant levels are summarized in Table 2. Each of the affected housing areas received water containing a mixture of many contaminants, a phenomenon common to almost every population exposed to contaminants released from hazardous waste sites. For the sake of simplicity, each

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group of exposed housing areas is referred to by the predominant contaminant in the mixture. Residents of Tarawa Terrace are referred to as the PCE-exposed group and residents of Hospital Point are referred to as the long-term TCE-exposed group. The short-term TCE-exposed group refers to residents of Berkeley Manor, Midway Park, Paradise Point, and Watkins Village during the 12-day period from January 27, 1985, through February 7, 1985, when these residents received water from the same supply as Hospital Point residents.

The exposure data, summarized in Tables 3 and 4, are limited. Samples were collected at three different points in time. However, the May 1982 samples were preserved for several months before they were analyzed, which might have decreased the concentration of VOCs observed in the analysis. Moreover, the 1985 sampling at Hadnot Point was conducted after seven of eight contaminated wells were closed. Hence, before 1985, contamination levels in the Hadnot Point distribution system would be expected to have been higher than the concentrations measured in 1985. In addition, one supply well for the Hadnot Point distribution system contained concentrations of benzene as high as 700 ppb. Because the 1982 analyses were limited to TCE and PCE, and because the well containing benzene was shutoff before the distribution system was sampled again, benzene was never detected in Hadnot Point tap water. Nonetheless, low-level exposure estimated at around 35 ppb would have been expected among women receiving Hadnot Point water before December 1984.

An important feature of the exposure at Camp LeJeune was its intermittent nature. Each of the contaminated systems had more wells than were necessary to supply water on any given day. Contaminant levels varied with the supply wells in service. The process by which a particular well was selected for use on any given day was essentially random, but all wells were assumed to have been used in any given month unless they were taken out of service for mechanical failure or contamination. Daily or monthly well usage logs were not available to evaluate this assumption. Despite these variations, on any given day, the concentrations of VOCs were likely to have been distributed fairly uniformly to all residential units because the water from all wells was mixed before its treatment and distribution. The similarity in concentrations can be observed in the data from several different buildings where tap water was sampled on January 31, 1985 (Table 4).

Human Health Effects of Concern

Experience with environmental and pharmacologic agents has shown that human gestation is a time of great vulnerability. Environmental exposure to mercury has been shown to cause adverse effects *in utero* even when the pregnant woman remains unaffected *(5)*. Of the many possible pregnancy outcomes that might be studied, SGA and MBW are two related outcomes *(6)*. These outcomes are important because of their contribution to perinatal and infant mortality. Moreover, they are among the most practical outcomes to study near hazardous waste sites because they are common, well-ascertained, reported in a standardized fashion on birth records, and computerized *(7)*. Birth records also include information on maternal residence. These practical aspects of the study outcomes are quite important in an exposure

setting such as that at Camp LeJeune: exposure ceased almost 10 years before the study and most of the exposed population had moved during the intervening period.

SGA and preterm delivery are separate entities with distinct pathogeneses that are commonly grouped together and measured as low birth weight. In 1989, 7.0% of infants were designated as low birth weight, weighing less than 2500 grams (g) at birth *(8)*. Low birth weight is the third most important predictor of infant mortality in the United States and the most important predictor of infant mortality among blacks in the United States *(9)*. In 1980, the risk of infant mortality for singleton, very low birth weight infants (weighing under 1,500 g at birth) was 94 times higher than for infants of normal birth weight (more than 2,500 g at birth) *(10)*. Low birth weight and very low birth weight infants are also at greater risk of having neurodevelopmental handicaps such as cerebral palsy and seizure disorders, developing lower respiratory tract conditions, and experiencing complications from neonatal care *(11)*.

Distinguishing between SGA and preterm infants is often difficult because the growth and maturity of an infant is highly dependent on its gestational age. Infants who are born small because they are born before 37 weeks completed gestation are considered to be preterm. Infants who have sufficient time to grow and mature, but are nonetheless small, are also often less viable because of intrauterine processes that have delayed their growth. In general, whether preterm or full-term, growth-retarded infants are at greater risk of antenatal and neonatal mortality than infants whose weights fall within the average range for their gestational age *(12,13)*. SGA infants are within the bottom tenth percentile of the birth weight distribution at any given gestational age. As with any population-based measure, some SGA infants are simply substantially smaller than average, but many are growth retarded. Currently, SGA is the only marker for intrauterine growth retardation that is readily available for population-based studies.

As reported by Kline et al. *(12)*, biological factors reducing growth include maternal parity, young maternal age, low maternal pre-pregnant weight, insufficient maternal weight gain during pregnancy, and anoxia resulting from cigarette smoking and altitude. Maternal medical complications such as hypertension can also produce anoxic conditions resulting in SGA infants *(14)*. Plurality and gender also influence birth weight. Important social determinants of SGA in the United States are maternal race, education, socioeconomic status, and adequacy of prenatal care.

Toxicologic Literature

Whether PCE, TCE, and 1,2-DCE affect birth weight in the offspring of exposed women is not known. In a study conducted by Schwetz et al. *(15)*, pregnant mice exposed to 300 ppm PCE delivered litters that were on average 9% lighter at birth and twice as likely to have subcutaneous edema than unexposed mice. A statistically significant increase in the number of litters with delayed ossification of skull bones was also observed. There was a 60% increase in the number of mice that were runts (defined as weighing less than three standard deviations below average) among exposed litters, but this was not statistically significant. Fetal rats exposed

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to the same regimen did not experience lower birth weights or excessive delays in ossification. However, there was a greater proportion of fetal resorptions in exposed rats than in unexposed rats. This effect was not observed in mice. Maternal toxicity resulting from PCE exposure was manifested by decreased maternal weight gain and increased maternal liver weight in rats and mice, respectively. However, it seems unlikely that the developmental effects of PCE were the result of maternal toxicity because rodents exposed to other solvents in the study experienced similar maternal toxicity but their litters were unaffected.

TCE has not been associated with decreased birth weight except in cases of severe maternal toxicity. However, behavioral effects and cardiac birth defects have been noted in rodents exposed to TCE *(15-18)*.

The toxicologic literature on the late reproductive effects of 1,2-DCE consists of a single study *(19,20)*. This study revealed maternotoxic effects at 1/6 of the levels required to detect fetotoxic effects *(19)*, suggesting that the fetal rat is not particularly sensitive to 1,2-DCE.

Toxicological studies are useful in generating hypotheses regarding the developmental hazards of specific contaminants. However, using toxicological studies to assess hazards in humans is complicated by the need to extrapolate from animal species to humans and from the high doses used in laboratory experiments to the low doses generally experienced from environmental exposures. In addition, laboratory studies do not adequately capture the complex personal and environmental context in which human exposures to VOCs occur *(21)*.

Epidemiologic Literature

Several studies have examined SGA or decreased MBW and occupations in which women might have been exposed to VOCs *(22-32)*. However, few of these studies have examined exposure to specific chemicals or chemical classes. Two studies of maternal occupational exposure to solvents *(24)* and degreasing agents *(28)* noted small decreases in birth weight (-41 g $\pm$ 124 and -16 g $\pm$ 75, respectively), but neither approached statistical significance. A small case-control study (26 cases) of birth outcomes among female workers in Sweden, Finland, and Norway, found no association between low birth weight (defined as $<$1,500 g), congenital malformations, or stillbirths and working in the dry-cleaning or laundry industry *(33)*. However, in addition to studying a very small number of cases, these authors combined all three outcomes into a single case-definition; because stillbirths and low birth weight are both generally assumed to be late pregnancy events, while congenital malformations are formed early in pregnancy, this grouping is especially inappropriate. Two studies attempted to examine associations between SGA and occupational exposure to specific chemical classes: Savitz et al. *(30)* noted no association between the halogenated hydrocarbons and SGA (OR: 0.6 [95% CI: 0.2, 1.4]) and Windham et al. *(31)* noted no association between SGA and maternal exposure to halogenated solvents in the first 20 weeks of pregnancy (OR: 1.1 [95% CI: 0.4, 2.9]). However, fetal growth is generally thought to be most vulnerable to environmental insults in the third trimester of pregnancy. Therefore, the Windham study might have been insensitive to late pregnancy effects such as SGA.

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Limitations common to many of these occupational studies included indirect assignment of exposure based on job title rather than on measuring exposure in the work place, small numbers in specific exposure categories, and differential participation and recall by underlying maternal risk. In addition, because exposure to many different substances occurs in the same workplace *(34)*, the relevant hazards could be difficult to identify. Many of these factors are more likely to prevent the observation of real health hazards than to introduce spurious associations where none exist; however, spurious associations could be introduced by differential participation or recall.

Compared with occupational settings, environmental exposures to toxic substances occur at lower concentrations. Moreover, environmental exposures often occur through contaminated drinking water, while occupational exposures usually occur through inhalation or skin contact. Environmental exposures are not limited to the 40-hour work week. In addition, environmental exposures can occur in populations not represented in the work force, such as women who cannot find work, women who stopped working after previous children were born, and those without economic incentive to work *(35)*. Therefore, one can make only limited generalizations about populations exposured to environmental contaminants from studying occupational populations.

The earliest suggestion of a relationship between environmental exposure to VOCs and decreased birth weight in humans was reported at Love Canal, a former dump site where 248 different chemicals were identified, in Niagara Falls, New York. The prevalence of low birth weight was elevated in two different studies of area residents *(36,37)*. Home ownership among white residents of Love Canal, where contaminants seeped into the basements of several homes, was associated with a 60% increase in low birth weight compared with the rate of low birth weight in white residents of upstate New York (OR: 1.6 [95% CI: 1.0, 2.3]). The low birth weight rate observed in Love Canal homeowners was also higher than the low birth weight rate observed in homeowners in neighboring areas of Niagara Falls (OR: 3.1 [95% CI: 1.3, 7.1]). However, no increase in low birth weight (OR: 1.1 [95% CI: 0.5, 2.3]) was observed in renters at Love Canal when compared with low birth weight rates in renters in neighboring areas.

More recently, an increased prevalence of term low birth weight (a correlate of SGA) was found in residents living near Lipari Landfill in Gloucester County, New Jersey. During the years when odors were greatest at the site, the odds ratio and 90% confidence interval were 5.1 and 2.5-10.6, respectively *(38)*. Moreover, a strong correlation was observed between 3-year weighted averages of excess term low birth weight around the landfill and the timing of dumping and odors throughout the 25-year study period. A cohort study conducted near the Stringfellow hazardous waste site in Riverside County, California *(39)*, and an ecologic study conducted of hazardous waste sites in five counties in the San Francisco Bay area, California *(40)*, reported no association between proximity to hazardous waste site and low birth weight (OR: 0.9 [95% CI: 0.3-2.7]) or MBW ($^{-}$.6 g $\pm$12.3).

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Each of the studies of birth weight around hazardous waste sites (summarized in Table 5A), had methodologic limitations. At Love Canal, families living closest to the site were relocated before the study was conducted *(36)*. The remaining families were evacuated selectively, beginning with families with pregnant women and young children *(36,41)*. Hence, selective migration could have introduced bias into the association between exposure and outcome. Selective migration is likely to be a problem at other hazardous waste sites as well, especially when strong odors reduce the quality of life in a neighborhood. In these situations, it might be expected that those with the highest incomes (who would be at the lowest risk *(10)*) and those who were most sensitive to the exposures would be the most likely to leave. It is not sensible to predict how selective migration might operate at hazardous waste sites in general. However, in the case of Love Canal, it seems likely that bias would have been towards the null because the women who were most likely to have been exposed had already been evacuated and therefore were not included in the study.

The conflation of the outcomes preterm delivery and SGA in all but two of the studies likely reduced observed effect measures. Failure to account for such etiologic heterogeneity has been discussed in detail elsewhere *(42)*. The study conducted at the Lipari Landfill, in Gloucester County, New Jersey, demonstrates this issue clearly; the association observed between residence near Lipari Landfill and term low birth weight was stronger than the association observed between residence near Lipari landfill and low birth weight among term and pre-term infants combined *(38)*.

Small numbers were also a problem, limiting the precision of the observed effect estimates. However, in most cases it would not have been appropriate to increase the sample size because that would have created a more heterogeneous exposure and diluted the observed association between exposure and outcome. Control for most major risk factors was addressed in the studies summarized in Table 5A, except for smoking, which was not measured in the San Francisco, California *(40)*, or Gloucester County, New Jersey, studies *(38)*. However, both the San Francisco and Gloucester County studies controlled for demographic variables that would have minimized bias related to smoking.

The most important limitation of the studies summarized in Table 5A was misclassification of exposure. In all of the studies, proximity to site was the primary method of exposure classification. There was some evidence of exposure to VOCs based on reports of odors and, at Love Canal and Lipari, very limited air measurements were taken. However, overall, it was difficult to determine if the populations in the studies were exposed, as well as to which substances and at what concentrations. Because both the probability of exposure and the chemical mixture at each site was different, it would have been difficult to evaluate the hypothesis that hazardous waste reduces birth weight on the basis of consistency across these studies. However, in general, it seems reasonable to infer that, at some sites, environmental exposure to some compounds or combinations of compounds found at hazardous waste sites might decrease birth weight.

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Studies of populations consuming contaminated drinking water, although still imprecise, are a substantial improvement over studies based on proximity to site. Even when there are limited exposure data and multiple contaminants in the same system, drinking water studies provide a well-defined route of exposure along the water distribution system, leaving less guess work as to whether there is an exposed population, how large it is, what chemicals are present, and at what concentrations exposures are occurring or have occurred in the past. Moreover, exposure is defined in a manner that can be directly compared to other studies. Only three analytic studies have investigated the relationship between TCE, PCE, or DCE in drinking water and late pregnancy outcomes *(43-45)*. As shown in Table 5B, contaminant levels measured in the studies were comparable to or lower than those observed at Camp LeJeune *(43-45)*.

Two studies were conducted in Woburn, Massachusetts, where two town wells were found to be contaminated with TCE, PCE, and chloroform. In the first of the Woburn studies *(43)*, self-reported outcomes were examined for 4,396 pregnancies between 1960 and 1982. An important feature of the study is that the investigators characterized exposure using information about the municipal use of supply wells in different areas of Woburn. No association was noted between exposure to contaminated well water and low birth weight, but birth weight was not adjusted for gestational age. Moreover, low birth weight was reported by each mother and a non-standard definition of low birth weight was used. Other limitations of the study included the sample selection process, which was based upon residence in Woburn at the time the study began. Although the selection process was convenient, as discussed previously, it might have introduced selection bias.

The second study conducted at Woburn addressed a number of the methodologic limitations raised in the first study by examining birth weight based on birth certificates for Woburn residents during the time of exposure *(44)*. The most relevant comparisons made in this study of SGA were the comparisons made between live births to residents of East Woburn exposed to high or moderate levels of contaminants during the period 1975 through 1979 and live births to East Woburn residents who were not exposed to contaminants. For the approximately 3,000 live births studied in these comparisons, SGA was not elevated in infants who were highly exposed in utero (OR: 1.1 95% CI:0.5-2.4) or moderately exposed (OR: 0.7 95% CI: 0.4-1.4) when exposure was classified based on the experience of the entire pregnancy. However, when the exposure classification was restricted to the third trimester, the odds ratios were 1.6 (95% CI: 0.9-2.8) and 1.3 (95% CI: 0.8-2.1) for highly and moderately exposed births, respectively. Despite the authors conclusions that the study "was unable to detect an adverse effect of exposure to Wells G and H on the reproductive health of exposed subgroups of Woburn residents," the specificity of these findings, that is, increasing odds ratios with more refined classification of exposure and outcome provides some evidence for a causal association between TCE exposure and SGA.

The relationship between exposure to TCE, PCE, and DCE[1] in drinking water and late pregnancy outcomes was also examined by Bove et al. *(45)* for the entire state of New Jersey. Birth certificates and fetal death certificates were the source population for the investigation. Exposure was assigned based on semi-annual, quarterly, or monthly monitoring of drinking water. Maternal residence indicated on the birth certificate was used to assign exposure and was assumed to be the residence throughout pregnancy. Although no associations were found between TCE, PCE, and DCE exposure and SGA, the median exposures studied were 200 to 1,000 times lower than the exposures examined in this study.

Overall, direct evidence of the potential relationship between PCE, TCE, and 1,2-DCE exposure and SGA and MBW is extremely limited. A few important results suggest that environmental exposure to VOCs can cause adverse late pregnancy outcomes, but the literature is very small and equivocal. Maternal occupational exposure to solvents and other VOCs has been associated with decreases in birth weight *(29)*. However, two occupational studies that looked specifically at halogenated hydrocarbons reported no association between these exposures and birth weight *(30,31)*. Low birth weight has also been associated with residence near two different hazardous waste sites containing large quantities of VOCs and other chemicals *(36-38)*, but the exposures were too poorly defined and too complex to permit generalizations from these hazardous waste sites to others. Only one study, in Woburn, Massachusetts, examined the relationship between SGA and a chemical exposure at concentrations similar to those at Camp LeJeune. That study found a moderate excess rate of SGA when exposure was classified according to the third trimester experience, but it was based on small numbers.

In addition to this direct, albeit limited, evidence supporting the hypothesis that one or more of the solvents studied are associated with adverse late pregnancy outcome, two studies have noted associations between term low birth weight and SGA and exposure to carbon tetrachloride *(45)* and trihalomethanes (THMs), including chlorinated compounds of similar chemical structure *(45,46)*. There are also suggestions that occupational or environmental exposures to solvents in general, and to TCE or PCE in particular, can cause other adverse pregnancy outcomes such as stillbirths, spontaneous abortion, cardiac anomalies, oral clefts, and neural tube defects *(31,43,45,47-49)*. A comprehensive review of this larger literature is beyond the scope of this report.

Finally, there is evidence to support an association between solvent exposure and maternal complications of pregnancy. In a small prospective study of women occupationally exposed to solvents, Eskenazi et al. *(24)* found increased rates of pre-eclampsia (OR: 3.9 [2.4-5.4]) and hypertension (OR: 3.0 [0.9-9.9]). Moreover, these complications were restricted to women who worked through their second trimester of pregnancy. In a very small, nested case-control study of 130 pregnant residents of an industrial area of Bulgaria, Tabacova et al. *(50)* found substantially increased odds of exposure to styrene among pregnant women with anemia (OR: 2.4 [0.5-13.8]), proteinuria (OR: 7.4 [1.7-37.2]), hyperemesis (OR: 13.1 [1.4-165.9]),

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[1] Both 1,1-DCE and 1,2-DCE were included in the same exposure category.

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arterial hypertension (26.4 [2.2-1266.8]), and nephropathy (30.8 [2.6-1448.0]). However, as can be assumed from the wide range in confidence intervals[2], this study was extremely small. Although the literature tying VOC exposure to medical complications of pregnancy is only suggestive, it provides a biologically plausible mechanism through which exposure to VOCs might influence fetal growth.

In summary, the existing literature on the relationship between exposure to organic solvents such as PCE, TCE, and 1,2-DCE in drinking water and late pregnancy outcomes is quite sparse. Given the level of public concern about toxic substances, and the frequency with which PCE, TCE, and 1,2-DCE occur in the environment, there are too many indirect suggestions to ignore. However, the potential relationship has not been looked at systematically. Only three studies have directly examined the relationship between PCE, TCE, or 1,2-DCE in drinking water and late adverse pregnancy outcomes. Only two of those studies, both analyzing data from the same city, investigated exposures of concentrations similar to the exposures at Camp LeJeune. Almost any well-designed study on this subject would be useful. This study should add to the existing body of knowledge, providing more information on a topic of great public health concern.

METHODS

RATIONALE AND HYPOTHESES

Drinking water at Camp LeJeune was recently found to be contaminated with VOCs. Because a sizeable population of young married women was exposed, concern has been raised about adverse pregnancy outcomes. The health significance of VOC contamination in drinking water is of particular interest at Camp LeJeune because the base's aquifer is quite permeable and therefore vulnerable to future contamination. An association between VOC contaminated drinking water and adverse pregnancy outcomes is plausible, but further study is necessary to fill in the many data gaps in the existing literature. This cohort study examined the relationship between VOC exposure and SGA and MBW in three groups with different exposures to contaminated drinking water and in an unexposed comparison population. These related outcomes are markers of delayed fetal growth; both can be studied even in an extremely mobile population of moderate size.

The primary objective of this interim report is to evaluate the hypothesis that maternal residence in each of the exposed housing areas was associated with SGA, decreased MBW or both.

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[2]Odds ratios were not reported by the authors in the study. For the purposes of this discussion, odds ratios and exact confidence limits were computed using Epi Info. For computational purposes, one count was added to each cell for arterial hypertension and nephropathy because there were no unexposed cases in either of the groups. CLW

The primary source of data was birth certificates filed with the North Carolina Vital Statistics office. For each of the three categories of exposed births defined previously, MBW and prevalence of SGA among singleton live births were compared with MBW and prevalence of SGA in unexposed births. In addition, the effects of timing and duration of exposure were examined by linking data from family base housing with the birth certificate data.

Study Population

The study population consisted of all singleton live births of 20 weeks or more completed gestation that were delivered from January 1, 1968, through December 31, 1985 to families residing in base family housing at Camp LeJeune.

Approximately one-third of women who seek prenatal care at the Navy Regional Medical Center (NRMC) at Camp LeJeune move or are transferred before they can deliver (personal communication: Commander James McGinnis, Camp LeJeune). These individuals could not be identified, but there was no reason to believe that their exclusion would introduce selection bias because rates of mobility would not be expected to be associated either with being exposed to VOCs or with having an adverse pregnancy outcome.

North Carolina Vital Statistics Data Files

The state of North Carolina has maintained computerized databases of all live births and fetal deaths of more than 20 weeks gestation since 1968. Two versions of the birth certificate have been used during the period from 1968 through 1985, and three versions of the database file format have been used. The smallest recognizable unit for which birth records can be selected from these data files or hard copies is the county of residence; information on mother's zip code and residence on base was not available for any of the years under study. Therefore, eligible births were identified by searching all records for Onslow County residents for the time period of interest. For the years 1975 through 1985, this search was conducted on computerized records for eligible street addresses. For the years 1968 through 1974, the mother's street address and city of residence were not computerized. In addition, other critically important fields such as exact birth weight in pounds and ounces were included on the hard-copy certificate, but not in the computerized file. Therefore, hard copies of records for Onslow County residents were searched by hand for addresses with eligible street names. The relevant data for each record containing an eligible street name was then entered into a database using a 100% re-key procedure. Some of the housing units on eligible streets were not, in fact, eligible. For example, units 2000 through 2999 Onslow Drive are base family housing units, but housing units on Onslow Drive with numbers of 3,000 or higher are privately owned. Requiring data entry personnel to look for a unique combination of street unit number and name before determining eligibility might result in the exclusion of eligible births. Therefore, after addresses for all eligible street names were computerized, a second electronic search was completed to remove addresses with an eligible street name, but an ineligible housing unit number.

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Base Family Housing Records

For each base family housing unit, Camp LeJeune maintains the following records on an index card: (1) the first and last names and middle initial of the active duty person to whom the housing unit is assigned; (2) the rank (such as seaman first class, captain, etc.) of the person to whom the housing unit is assigned; and (3) the first and last dates of occupancy by the active duty person to whom the unit is assigned. For purposes of this study, approximately 8,000 names and addresses were entered into a database from the housing cards with 10% rekey verification. Birth certificate data were then matched to housing record data on the basis of the address listed on the birth certificate and the name of the father. For a match to be considered acceptable, the birth date was required to be during the period between the first and last dates of occupancy. Because it was possible that the father's name was spelled slightly differently in the birth and housing records, when no match was found for a particular birth certificate, a manual search was conducted comparing the father's last name from the birth certificate to alphabetized lists of names from the housing record. When the father's name did not match either by a computerized or a hand search, then a match was attempted on the mother's name. For the few parents who were dependents, matches were made by address and last name of the father or the maiden name of the mother, and a notation was made that the parents were dependents in another household.

DEFINITION OF DISEASE

The outcomes MBW and SGA were studied. Birth weight in pounds and ounces was obtained from the birth certificate and converted to weight in grams. SGA was defined as a singleton live birth weighing less than the 10th percentile based on published sex-specific growth curves. The standard published by Williams et al. *(51)* for whites in the state of California was selected because it (1) was derived from birth certificates; (2) was based on a large group of live births occurring during the mid-years of the study period; (3) was published in a reputable journal and in an easily read format; and (4) categorized approximately 10% of the unexposed population as SGA. No other published standard met these criteria.

Although the standard published by Williams was for white infants only, in this study, the Williams standard was applied to white infants as well as to African-American infants and to infants of other races. This standard was used for non-white births because better published standard was not available. However, some of the data were reanalyzed using an unpublished, race-specific standard developed by the state of New Jersey for white and African-American births occurring during the years 1985 through 1988. Because there was essentially no difference in the associations observed using the New Jersey race-specific standard and the associations observed using the Williams standard, only results based on the Williams standard are presented. Nevertheless, the New Jersey standard provided reassurance that the data on African-American births were analyzed in a reasonable manner.

Gestational age was calculated based on the last menstrual period (LMP). For observations with a valid month and year of LMP, but a missing day, the day was interpolated

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to the value of 15. LMPs with a valid month and day but no year were assigned to the year that would yield the most biologically plausible gestational age. LMPs for which the month of the last period was not reported were excluded. The effects of missing gestational age were explored by comparing birth weight distributions and demographic information between births with missing gestational age data and births for which gestational age data were available.

Definition of Exposure

Infants identified from birth certificates were divided into three distinct exposed groups (summarized in Table 2). These groups were (1) PCE-exposed; (2) long-term TCE-exposed; and (3) short-term TCE-exposed. The mothers of PCE-exposed infants resided at Tarawa Terrace for at least one week before the birth occurred. Mothers of long-term TCE-exposed infants resided at Hospital Point for at least one week before the children were born, between the years 1968 and 1985. The housing units that were supplied with TCE on a short-term basis were Berkeley Manor, Midway Park, Paradise Point, and Watkins Village. Requirements for inclusion of births in the short-term TCE-exposed group were these: (1) the mother resided in Berkeley Manor, Midway Park, Paradise Point, or Watkins Village at the time of her child's birth and for a minimum of 1 week between January 27 and February 7 1985; (2) the mother's last menstrual period was on or before January 31, 1985; and (3) the birth date was after February 2, 1985. These dates were selected to ensure a minimum of 1 week of exposure to TCE during pregnancy. Infants born to the remaining residents of base family housing during the specified period were considered unexposed. This group consisted of all residents of the Marine Corps Air Station, Rifle Range, and Courthouse Bay housing areas, as well as residents of Berkeley Manor, Midway Park, Paradise Point, and Watkins Village who were not in the short-term TCE-exposed group.

Several groups of residents whose status regarding exposure to PCE or TCE on a short-term basis was not known were excluded from the study. These residents included infants whose fathers experienced short-term exposure during spermatogenesis (based on mother's LMP), infants whose mothers resided in any of the exposed housing areas for less than 1 week while pregnant, and infants whose parents first moved into Berkeley Manor, Midway Park, Paradise Point, or Watkins Village between February 8, 1985, and February 21, 1985. Although all of the contaminated wells were closed on or before February 7, 1985, the first documentation that water samples were entirely free of contamination was on February 21, 1985. Therefore, residents who did not experience exposure during a known period of contamination but who lived in the affected housing units during this ambiguous exposure period were excluded.

Analyses

Separate analyses were conducted for each of the six exposure-outcome combinations defined previously. For SGA, odds ratios were computed relating exposure to outcome *(52)*. MBW was computed using the SAS software package. The main criteria for identifying elevations in SGA and decreases in MBW were the size and the plausibility of the association. The degree of variability in the data was examined by computing 90% confidence intervals

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(CIs). 90% CIs also correspond to one-tailed t-statistics with an alpha of .05. One-tailed tests were appropriate because improvements in birth weight outcome (increased MBW or decreased SGA) following exposure were not considered to be relevant. For most analyses, 90% CIs were computed using the logit estimators produced by the SAS statistical package *(53, 54)*. However, when the number of either the exposed or unexposed cases fell below 10, odds ratios and CIs were recomputed using the exact method. Exact computations were conducted using the StatXact software package. The mid-P approximation for CIs was reported *(55)*.

The following characteristics from the birth certificate were evaluated for their potential as confounders or effect modifiers: gestational age, maternal race, sex of infant, year of birth, mother's age, mother's education level, father's age, father's education level, parity, adequacy of prenatal care, maternal history of fetal death, and mother's marital status. In addition, military ranks obtained from the housing records were standardized into nine enlisted paygrades (E1 through E9), four warrant officer paygrades (WO1 through WO4), and six officer paygrades (O1 through O6). Paygrade is an accurate measure of income for the active duty member of the household, although no information was available about the occupation or income of the parent not listed on the housing card.

Each potential confounder or effect modifier was examined separately through stratified analysis. Potential confounders were those variables that met all of the following conditions: (1) they were distributed differently in the exposed and unexposed groups; (2) they were risk factors for or protective against decreased MBW or increased SGA; and (3) adjusting for the potential confounder changed the parameter estimate for the association between exposure and outcome variables. The variables maternal age, maternal and paternal education levels, parity, year of birth, gestational age, and military paygrade were collapsed to a minimal number of categories for stratified analyses, and in some cases for multiple regression (linear and logistic) analyses. Cut points for these variables were selected on the basis of their distribution and on their relevant social or biological meaning. Graphical methods employed to examine the distribution of these variables were histograms, scatter plots, and plots of means at different levels of each factor.

The potential for effect modification consisted of a simple inspection of odds ratios in different strata, and a Breslow-Day test for homogeneity *(56)*. Ideally, one would identify effect modifiers a priori *(57)*, but the current state of the literature is too undeveloped to anticipate which risk factors might act as effect modifiers. In the absence of a well-developed literature, the potential biological and sociological relevance of each potential effect modifier were considered.

Each variable that was either an effect modifier or a confounder based on stratified analysis was retained in analyses for multiple logistic regression and linear regression modeling, and was eliminated in a backwards fashion. For SGA, potential confounders were eliminated from a model if their removal did not change the odds ratio relating exposure and outcome (or the odds ratios for different exposure-covariate combinations if interaction terms are used) by more than 10%. For MBW, potential confounders were eliminated from a linear regression

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model if their removal did not change the effect estimate by a minimum of 20 g or 10% of the effect estimate, whichever was larger. Variables that indicated effect modification (also known as interaction terms), were included in regression models if they were biologically plausible, described heterogeneous groups in which the odds ratios differed by more than 25%, and had p values less than .20. A less stringent p value for effect modifiers was used because of the low statistical power available to detect them *(58)*. The selection of a 25% change was arbitrary, but provided an effective decision-rule for screening potential effect modifiers.

Years of Exposure

Although exposure to VOCs probably occurred throughout the study period in the PCE-exposed and long-term TCE-exposed groups, exposure before 1982 could not be documented. Because the PCE-exposed group was large enough, separate analyses were conducted for births occurring in the years 1982 through 1985 in this group. The number of births in the years 1982 and 1985 in the long-term TCE-exposed group was too small to complete separate analyses.

Timing and Duration of Exposure

The third trimester of pregnancy is usually regarded as the most important for fetal growth and most significant in terms of toxicity resulting in late pregnancy outcomes *(12)*. However, Dejmek et al. recently observed an association between SGA and air pollutants that was greatest when exposure occurred during the second and third months of pregnancy *(59)*. A cumulative effect of exposure might also be possible *(60)*, and many questions remain about the way in which timing of exposure may influence pregnancy outcome *(61)*. The population at Camp LeJeune has always been unusually mobile. Approximately one-third of women receiving prenatal care at the NRMC, move to another base or into civilian life between the time of their first prenatal care visit and the time of their delivery. If exposure must occur in the early part of the pregnancy or during spermatogenesis to cause an adverse outcome, then use of maternal residence at time of birth would reduce or obscure an important association because individuals would be included who were not exposed at these critical times.

To address these issues, the dates of base family housing occupancy for each household in the study were examined to determine whether and when each family moved over the course of the pregnancy. This information was used to explore the influence of the timing and duration of exposure on each study outcome. Within the PCE-exposed and long-term TCE-exposed groups, length of residence in the housing unit listed on the birth certificate was used as a surrogate for length of exposure. From discussions with Camp LeJeune personnel, it was determined that once a pregnant woman moved into base family housing, she generally remained in the same housing unit until after she gave birth. Therefore, it was assumed that each family resided in only one base housing unit during the pregnancy, an assumption that will be evaluated in a later report. Therefore, except for births occurring after exposure ceased, length of exposure indicates the number of consecutive weeks before birth that the mother lived in exposed housing. For example, a 10-week exposure occurred during the last 10 weeks of the pregnancy, and not the first 10 weeks. Among births in 1985, the year that the contamination ceased, timing of

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exposure was more heterogeneous. To maintain consistency regarding the meaning of the duration of exposure variable, births that occurred after the contamination ended were excluded from analyses by duration of exposure.

Births were divided into the following categories: births to mothers exposed for 1 to 3 weeks, births to mothers exposed for 4 to 10 weeks, births to mothers exposed for 11 to 20 weeks, births to mothers exposed for 21 to 45 weeks, births to mothers exposed before conception and throughout pregnancy, and births to mothers exposed for 1 or more years before conception and throughout pregnancy. A number of duration-response relationships were considered to be biologically plausible. Because weight gain occurs most rapidly at the end of pregnancy, it was considered plausible that the last weeks of pregnancy would be most important; in this case, birth outcome would not differ by the length of exposure. It was also considered to be biologically plausible that the effect measures would increase with duration during the last 20 weeks of pregnancy, when most weight gain occurs, or throughout the pregnancy. Other biologically plausible scenarios were that an association would be observed only in births to mothers that were exposed during the entire first trimester, or only in births to mothers who were exposed before conception and throughout pregnancy. Finally, because of the possibility of selective survival, it was considered plausible that no effect or a very limited effect would be observed among births to mothers who were exposed during the first 12 weeks of pregnancy, when spontaneous abortion rates are highest, and that a duration-response relationship would be observed thereafter. A number of scenarios that were considered to be implausible. For example, unless if the pattern of effects was consistent with selective survival early in pregnancy, it would be implausible to observe less of an effect among individuals who were exposed the longest compared with individuals exposed for shorter periods. Because length of residence during pregnancy was a function of length of gestation, the part of the pregnancy during which exposure occurred and the gestational age at first entry into the exposed area were also examined.

To examine the influence of timing of exposure in the short-term TCE-exposed group, the week of gestation at time of exposure and the number of weeks between exposure and birth were examined.

Data Quality

In total, 12,509 live births that met the study selection criteria were identified. Forty-four of these births were deleted from analyses because the mother was exposed for less than 1 week during pregnancy or only during spermatogenesis. Of the remaining 12,465 live births, 481 (3.9%) were eliminated from all analyses because of missing or biologically implausible data for gestational age, or because exposure status could not be ascertained with certainty. The distribution of births in each exposure group and the distribution of observations eliminated from each group because of poor data quality are presented in Table 6. Some observations were eliminated for more than one reason, for example, an infant reportedly weighing less than 350 grams and for which no data were available on the mother's last menstrual period. To provide a better sense of overall data quality for each critical field, observations that were eliminated are

listed for each category. Therefore, the percentages in Table 6 do not add up to 100%. The gestational age standard by which SGA was calculated was available only for births of 22 weeks or more of gestation. Table 6 also includes the total number of observations used for SGA analyses within each exposure group.

In addition to observations that were entirely excluded from this analysis, there were a number of observations with questionable values for gestational age. It is well recognized that in most populations, a disproportionate number of births are classified as very pre-term that are heavier than would be expected for their gestational ages; the majority of these heavy, so-called "very pre-term" births are actually births of later gestational age for which the gestational ages have been misclassified *(62)*. To determine if the gestational ages for births classified as being very preterm were more commonly misclassified, the distribution of birth weights among these births was compared to the 90th percentile for birth weight at each gestational age reported for a standard population *(51)*. Among live births less than 28 weeks of gestation, 17% of the values in the study population fell above the 90th percentile reported for the standard population; only 10% would have been expected. These data values were marked as unlikely, but were not excluded from the analyses because (1) although at a population level it was possible to determine that most of these values were misclassified, it was not possible to distinguish which individual observations were misclassified and which were correct, but outlying; and (2) these observations account for a large proportion of early pre-term births, but only 1% of all live births. Other questionable gestational ages were those that were estimated because the date of the mother's last menstrual period was missing from the birth certificate. These represented about 2.7% of the data. The final models were analyzed two ways: including observations with unlikely or interpolated gestational ages and excluding them. Unless specifically discussed, re-analyses without these data points had negligible impact on study results.

RESULTS

PCE Analyses

The distribution of demographic characteristics in the unexposed and PCE-exposed groups is presented in Table 7. PCE-exposed mothers were less likely to live in officers' housing (18% unexposed, 8% exposed), less likely to be college-educated (11% unexposed, 5% exposed), and less likely to have a college educated partner (18% unexposed, 7% exposed). Table 8 contains results of the analyses of birth outcomes comparing PCE-exposed and unexposed residents. The difference in MBW between the PCE-exposed and unexposed groups was -24 g (90% CI: −42, −7). The OR for PCE exposure and SGA was 1.2 (90% CI: 1.0, 1.3). Adjustment for differences in demographic characteristics between the two groups did not substantially influence the effect estimates.

Year of Birth

When the analyses were restricted to the years 1982 through 1985, the effect estimates changed only slightly. The difference in MBW between PCE-exposed and unexposed births for these years; was -12 g (90% CI: -44, 21) the OR for PCE and SGA adjusted for father's education and military paygrade was 1.3 (90% CI: 1.0, 1.7).

Duration of Exposure

Table 9 presents analyses based on duration of exposure to PCE. Differences in MBW ranged from -30 g to +18 g for the various exposure categories. The ORs for SGA ranged from 0.9 to 1.2 for the various exposure categories.

Potential Interactions Between PCE and Demographic Characteristics

PCE exposure appeared to be associated with reductions in MBW and increased odds of SGA in two potentially susceptible subgroups. These groups were (1) births to mothers who had previously had a fetal death and (2) births to mothers 35 years of age or older. When these groups were excluded from the main analyses, the OR for PCE and SGA dropped to 1.0 (90% CI: 0.9, 1.2) and the difference in MBW between PCE-exposed and unexposed births was reduced to -13 g (-32, +5). Additional analyses were conducted separately for each of the two subgroups.

Age of Mother—Mothers aged 35 years or older who were exposed to PCE were at higher risk for having infants who were SGA; overall, their infants had a lower MBW than unexposed mothers within the same age category (Table 10). However, the exposed and unexposed groups in this age range were quite different demographically. In particular, members of the PCE-exposed group were substantially less likely to live in officers' households (3%) than the unexposed group (28%), and a substantially higher proportion of exposed mothers were neither white nor African-American (26%) compared with mothers in the unexposed group (10%). Reflecting these demographic differences, mothers aged 35 years or older in the unexposed group had a lower prevalence of SGA compared with mothers in all of the younger age groups, while mothers aged 35 or older in the exposed group had higher rates than mothers in every other age group. However, after adjusting for gestational age and mother's race, the difference in MBW between PCE-exposed and unexposed births in this age group was -207 g (90% CI: -334.4, -79.4), which was very similar to the crude mean difference of -212 g. Moreover, the odds ratio for PCE-exposure and SGA increased slightly from 3.5 (90% CI: 1.6, 8.0) in unadjusted analysis, to 3.9 (90% CI: 1.6, 10.0) after adjusting for residence in an officer's household because of a very strong association between exposure and outcome among older mothers living in an officer's household. The effect of length of exposure to PCE was not examined in mothers aged 35 or older because there were too few cases to meaningfully stratify on this variable.

Mothers with Histories of Fetal Deaths—Table 11 presents analyses of the association between PCE exposure and outcome among mothers with histories of fetal deaths. The difference in MBW was -51 g (90% CI: -96, -5). The OR for SGA was 1.6 (90% CI: 1.3, 2.1) after adjustment for living in an officer's or warrant officer's household. The influence of length of exposure in the unexposed and PCE-exposed groups was also explored (Table 12). Differences in MBW ranged from -121 g to +5 g, and ORs for SGA varied from 1.4 to 2.1. These effect estimates did not follow a pattern of increasing effect with increasing duration. However, the confidence intervals were sufficiently wide that it was difficult to conclude whether any real differences were present across the duration of exposure categories.

Long-term TCE Exposure

The demographic characteristics for the long-term TCE-exposed group and an unexposed comparison group are described in Table 13. Because the housing area where long-term exposure to TCE occurred was for officers' families, a comparison group consisting of births among residents of unexposed officers' housing was used in all analyses of this group. It was felt that this restriction would make the exposed and unexposed groups more comparable in terms of demographic characteristics. Some differences between the two groups remained for sex of infant, mother's age, military paygrade, parity, father's education level, and self-reported maternal history of fetal death.

Unadjusted measures of association between exposure and outcome are presented in Table 14. A -108 g (90% CI: -230, -13) difference in MBW and an OR of 1.5 for SGA (90% CI: 0.5, 3.8) were observed in the exposed group compared with the unexposed group. After adjustment for gestational age, the difference in MBW was -139 g (90% CI: -277, -1) in the TCE-exposed group. Because there were only three exposed births that were SGA, it was not possible to assess confounding for this outcome using multiple regression models. However, in simple stratified analysis, none of the covariates influenced the odds ratio by more than 10%.

Interaction Between Long-term TCE Exposure and Sex of Infant

Because there were so few infants with long-term TCE exposure, no attempt was made to address the issue of interaction for most of the covariates. The interaction between long-term TCE exposure and sex of infant was examined because it was so large that it was observed by simple inspection of the data. Adjusted models for the association between TCE and MBW are presented by sex in Table 15. For females, there was no difference in MBW between the exposed and the unexposed infants. However, in exposed males, the difference in MBW was −312 g (90% CI: -632, -102) compared with their unexposed counterparts. Table 15 also examines the influence of duration of exposure on MBW. In models restricted to the infants of mothers who resided in family base housing for 20 or more weeks during pregnancy, the difference in MBW was very similar to the group overall, but the number of exposed individuals made this difficult to examine.

Interaction between sex and long-term TCE exposure was also present in the SGA analysis. All three SGA births were males. The OR for long-term TCE exposure in male infants was 3.9 (90% CI: 1.1-11.8). Among females, there were no SGA births; 1 birth was expected based on the prevalence of SGA in the unexposed group. The mothers of each of the 3 SGA infants in the long-term TCE-exposed group resided in the exposed housing area for their entire pregnancies.

SHORT-TERM TCE EXPOSURE

Demographic characteristics for short-term TCE-exposed and unexposed residents are compared in Table 16. By definition, all the residents in the short-term TCE-exposed group were born in 1985. Because a trend of increasing birth weight with later year of birth was observed in this data set, only births between 1983 and 1985 were included in the unexposed group. Except for slight differences in parity and maternal education, the exposed and unexposed groups were quite comparable demographically.

Table 17 presents crude analyses of birth outcome among unexposed residents and short-term TCE-exposed residents. MBW was slightly higher in the exposed group for both sexes combined. There was no difference in MBW in analyses restricted to males only. The prevalence of SGA was lower in this group than in the unexposed group. Adjustment for potential confounders did not eliminate the differences between exposed and unexposed groups.

Within the course of each pregnancy, the timing of the short-term TCE exposure varied from the 1st week of gestation to the 40th. It was anticipated that the effect of exposure might be limited to a particular time in gestation, that is, during some critical period of organogenesis. Alternatively, the possibility was considered that the weeks closest to birth would be most relevant, because weight gain is greatest at the end of gestation and there would be limited time for catch-up growth. Examination of MBW based upon both (1) weeks elapsed between exposure and birth, and (2) gestational age at time of exposure revealed no pattern of decrement with exposure (see Figures 1-2). However, the number of observations within each time frame of exposure was quite small. The five SGA infants did not share any distinct characteristics with regard to timing of exposure.

DISCUSSION

The main findings of this study were (1) no association between PCE exposure and decreased MBW or increased SGA among most births, although associations between PCE exposure and both study outcomes were observed among the infants of mothers who were 35 years of age or older and among the infants of mothers with histories of fetal deaths; (2) a pronounced association between long-term TCE exposure in male infants and decreased MBW and increased SGA with no association observed in female infants; and (3) no association between short-term exposure to TCE and MBW or SGA.

PCE EXPOSURE

In the analyses of PCE exposure, a slight statistically significant difference in MBW between the exposed and comparison groups was observed. However, the mean difference was so small as to be clinically negligible. One reason that small differences in mean values are sometimes important is that the mean difference may reflect a downward shift of the entire birth weight distribution. The most serious consequence of such a downward shift is an increase in the number of low birth weight or SGA infants. However, SGA was not associated with PCE exposure among most residents at Camp LeJeune. This would seem to confirm that the difference in MBW was not large enough to be biologically important.

Given the lack of association between PCE exposure and birth weight in the study population overall and given the large number of subjects studied, it is unlikely that maternal exposure to the unique combination of contaminants in the Tarawa Terrace water system had much of an effect on birth weight, except perhaps on births to older women and births to women with histories of fetal deaths. Sources of uncertainty remained for the subgroups in which elevations were found and some important confounders, such as maternal smoking habits, and maternal height, were not controlled for. It seems unlikely that these factors could have totally obscured a strong effect, especially in a population as homogeneous as the one studied. Further pursuit of this issue is planned if review of medical records is feasible.

Misclassification of both exposure and outcome are problematic in almost every epidemiologic study. In this study, information on exposure was limited to water quality measurements taken over a 3-year period; the study examined 28 years of birth weight data. It is therefore conceivable that no PCE effect was observed because the study population was primarily unexposed. However, this seems unlikely, both because the activities resulting in the PCE contamination occurred throughout the study period, and because there were not large differences in the study findings for PCE exposure when the sample was restricted to years of known exposure. In addition, concern that an association between PCE and birth weight outcomes might have been obscured by studying births exposed during the wrong time window was addressed. Across a variety of exposure categories, at most a very weak association was observed among the births exposed for the longest duration.

Other sources of misclassification might have been more relevant. Even during the known exposure period, exposure occurred intermittently because different wells were used on different days. However, although the exposure occurred intermittently, it probably occurred at least for some days during every month of the study period. Misclassification of gestational age is also quite likely, especially among the pre-term births. These factors may be quite relevant to the PCE findings because it would be expected that these sources of misclassification would reduce the ability to detect exposure-related effects.

In addition, exposure to PCE probably did not occur consistently across the different individuals studied because different pregnant women would have ingested different quantities of water and would have spent variable amounts of time showering. Lack of information on the

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variation in the personal habits of individual women means that the exposure dose that each woman received could not be quantified. Such precise dose information is helpful in risk assessment, but given how little is known about PCE exposure and birth weight at this time, such information would not necessarily improve scientific understanding.

Groups Potentially Susceptible to PCE Exposure

Despite the overall finding of no association between PCE and birth weight outcomes, there were two clinically distinct subgroups: (1) mothers 35 years of age or older, and (2) mothers with histories of fetal deaths, in which PCE exposure was associated with birth weight outcomes. There are several reasons to question the meaning of the associations observed in these groups. Among mothers 35 years of age or older, the number of women studied was relatively small. This is reflected in the wide confidence intervals, suggesting a variety of values that would be consistent with the observed data. Second, the exposed and unexposed women of older ages were not comparable in terms of important demographic characteristics. Given these important differences, there might have been some residual confounding, even after adjustment for measured risk factors. However, adjustment for residence in an officer's household did not affect MBW and adjustment for mother's race had a only a minor effect on MBW. For SGA, adjustment for mother's race produced negligible changes and adjustment for residence in an officer's household actually increased the odds ratio. The negligible impact of adjustment for these confounders suggests that residual confounding by socioeconomic factors was unlikely.

The finding in older mothers was unanticipated, and no mechanism exists to explain it. Nonetheless, the association between PCE exposure and adverse outcome among mothers aged 35 years or older was sizeable and is biologically plausible. As a general rule, mothers 35 years of age or older are considered to be at higher risk for adverse reproductive outcomes, especially infertility, miscarriage and birth defects *(12)*, but also for factors that have a clear role in reduced birth weight, such as pregnancy-induced hypertension *(63)*. Moreover, the effects of maternal smoking on birth weight have been observed by several authors to increase profoundly with age *(64-67)*.

The second potentially susceptible subgroup for which an association was observed between PCE-exposure and birth weight was the group of women with histories of fetal deaths. As with older mothers, women with histories of fetal deaths might represent a physiologically susceptible subgroup with poorer pregnancy outcomes, including low birth weight, than women without such histories *(68)*. Unlike the older mothers, mothers with histories of fetal deaths composed a fairly large group, so that the effect estimates were statistically stable.

Heterogeneity and data quality are concerns for reported history of fetal death. Each birth certificate contained information on previous fetal deaths at any gestational age. However, fetal deaths occurring at early gestational ages (miscarriages) have a different etiology than fetal deaths occurring at late gestational ages (stillbirths). Moreover, it is not clear whether fetal deaths at these different gestational ages were reported more or less completely. Differences in reporting of fetal deaths based on socioeconomic status might have occurred as well.

Analyses by length of exposure within this group provided no insight into the importance of the associations observed. A strict duration-response relationship would have reinforced concern about this association, while a duration-response in which the most exposed people had the smallest (or no effect) would have lessened concern about this association. However, neither one of these patterns was detected, and a variety of other models would have been consistent with an effect of PCE on fetal weight gain. Moreover, the effect estimates within specific exposure-duration categories were based on relatively small numbers and hence would have fluctuated randomly. Currently, more sophisticated statistical modelling techniques are being explored that might provide us with greater insight into the duration-response relationship.

One mechanism that has been hypothesized for the reproductive effects of PCE is central nervous system depression of the hypothalamus or pituitary glands resulting in hormonal changes in the mother or the fetus or both *(69-71)*. However, an actual link between hormonal changes and mothers 35 years of age or older and mothers with histories of fetal deaths would be difficult to make. Patterns of hormonal function and activity among women in their 30s have not been well studied, although hormonal changes associated with the onset of menopause occur primarily in women in their 40s rather than in their late 30s *(72)*. Nevertheless, it is possible that the concentrations of PCE in the drinking water at Camp LeJeune were too low to influence birth weight within the population as a whole, but that among groups that are known to have more reproductive problems, the minor stress resulting from PCE exposure was sufficient to disturb the developmental environment of the fetus.

The finding of associations in these two potentially susceptible subgroups must be interpreted cautiously. Nonetheless, this suggests an important area for future research because exposure to PCE is common. In addition, if these associations bear out under further scrutiny, they could influence general thinking about the groups that are especially vulnerable to toxic substances. As discussed previously, data quality for the reporting of previous fetal deaths is of considerable concern. Information regarding maternal medical conditions such as diabetes and hypertension, maternal weight gain, and smoking would also greatly enrich the existing data on this study population. A feasibility study is now being conducted to determine whether medical records might be obtained for a sample of women in these susceptible subpopulations.

TCE Exposure

Strong associations between long-term TCE exposure and birth weight were observed in males, but not in females. Both the decrement in MBW and the increase in SGA among males exposed to TCE compared with unexposed males were quite large, about the magnitude of the effect of maternal cigarette smoking in the general literature. Overall, the long-term TCE-exposed group was very small, and there was not a great deal of variation in the length of exposure during pregnancy. Therefore, it is not of great concern that no meaningful differences were observed when the possible influence of duration of exposure was explored by restricting the dataset to infants exposed for at least 20 weeks of pregnancy.

The finding of an association in males but not in females was unexpected and reduces the plausibility of the findings. In studies of male-female differences in TCE metabolism, adult females were found to absorb TCE better than adult males, and to metabolize TCE more slowly. The slower metabolism of TCE in females is due largely to the higher proportion of bodyweight contributed by fat in adult females. TCE, a fat-loving molecule, is better diluted in females, and hence in females a greater proportion of the body's TCE is stored in fat where it is not metabolized *(17)*. Male-female differences in body fat concentration are already present at birth *(73)*. These are factors that one might anticipate would make female infants more susceptible to TCE, not less.

Solvents in general, and TCE in particular, are known to interfere with lipid metabolism in the liver, and to affect lipid composition in the liver and brain *(74,75)*. One might speculate that the mechanisms that promote fat accumulation in female fetuses are sufficient to overcome small changes in lipid metabolism and composition, while male fetuses, lacking the same fat-accumulating hormones, do not have the capacity to overcome such small changes. In addition, it is possible that males, who have a higher mortality rate at birth and throughout infancy *(76)*, are slightly more susceptible to toxic insult, and might respond to lower doses than females.

Other studies of environmental exposure to toxic substances and birth weight have observed more pronounced effects in males than in females *(38,77,78)*. The chemicals studied in two of these studies *(77,78)* were polycyclic aromatic compounds such as polychlorinated biphenyls (PCBs) and dioxins; in the third study *(38)*, the responsible compound(s) were not identified. In other studies of polycyclic aromatic compounds, sex-specific interactions involving similar exposures have not been observed *(79)*, or were not evaluated *(80)*. The differences between the sexes observed by Rylander et al. *(78)* were not nearly as profound as the differences observed in this study. In addition, polycyclic aromatic compounds might be expected to have more sex-specific effects because they bind to estrogen receptors *(81)*. While also metabolized by the P-450 enzyme system in the liver *(17)*, TCE has a chemical structure very different from these other compounds.

Given the small numbers of long-term TCE-exposed births, it is also possible that the observed associations arose in this group by chance or bias. One potential source of confounding was that the long-term TCE-exposed group was a very select subpopulation. Unlike the rest of the housing areas, whose inhabitants had diverse occupations, residents of Hospital Point were primarily hospital workers. Therefore, the observed effect might have been related to the presence of characteristics unique to health care personnel or their wives. Although possible, this seems unlikely because the effects of behavioral factors such as smoking and patterns of use of medical care on birth weight have been studied much more frequently than the effects of TCE on birth weight. Smoking and access to medical care have not been observed to have sex-specific effects. Contaminants other than TCE that the active duty parents (in all of these cases, fathers) might have been exposed to at work were also plausible sources of confounding. However, these contaminants would not necessarily have been more likely to have a sex-specific effect than TCE.

The study's failure to find any association between short-term exposure to TCE and birth outcomes was not inconsistent with findings in the long-term TCE-exposed group. One would expect that a 12-day exposure would have less of an effect than a 40-week exposure. However, the short-term exposure findings also lend no support to the long-term exposure findings. The timing of the exposure was heterogeneous. One particularly relevant timeframe is very early in gestation during embryonic development because cell death that occurs at this time may affect the development of entire organs. Another very relevant timeframe is shortly before delivery, because any effect of exposure earlier in pregnancy might be obscured by catch-up growth. However, the small number of short-term TCE-exposed births occurring within either of these two relevant time windows would make it difficult to rule out the possibility of an effect specific to one or both of these particular times.

In short, the lack of additional studies to either support or refute the findings and the limitations in the size of the exposed population prevented stronger conclusions from being reached regarding the potential effects of long-term TCE exposure. Moreover, the male-only effect greatly weakened the biological plausibility of the long-term TCE findings. However, it should be noted that many factors that adversely affect health have been identified and confirmed through epidemiologic analysis without a clear explanation as to the mechanism of action. TCE is an extremely common exposure at hazardous waste sites, and pregnancy outcomes are near or at the top of the list of community concerns when such exposures occur. Given these factors and the magnitude of the association observed, the potential effects of exposure to TCE during pregnancy deserve further study. The best way to obtain more conclusive information on the effects of TCE exposure on birth weight is to repeat a similar analysis in a larger population of TCE-exposed pregnancies, in which the TCE concentrations occur at similar or higher levels. In the meantime, it is far from certain that the long-term TCE exposure was actually responsible for the decreased MBW and increased SGA observed in male infants at Camp LeJeune. Still, prudence would dictate that the associations between TCE exposure and birth weight observed at Camp LeJeune be seriously considered both when identifying new avenues for research, and when assessing the health impact of TCE exposure at hazardous waste sites.

CURRENT STATUS OF ATSDR RESEARCH AT CAMP LEJEUNE

This document reflects the current status of research into the effects of VOCs on pregnancy outcomes at Camp LeJeune. Because of strong public interest in the health effects of VOCs, it was decided to provide timely feedback through this interim report. However, several activities within the original protocol have not yet been completed. These include analysis of exposure to VOCs in relation to the outcomes preterm delivery and fetal death, and evaluation of the completeness of the housing record data used to measure duration of exposure. As base efforts to better define and remediate the TCE plumes progress, it might also be possible to better estimate when exposure to TCE first began. There are also plans to address many of the data quality issues raised in this discussion by reviewing medical records for a sample of pregnancies within this cohort. Data collection for a pilot study that evaluates the feasibility and usefulness of such medical records is currently underway. The results of this feasibility study

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will also be made available with the final report. The study protocol included plans to evaluate the associations between exposure to VOCs and maternal medical complications and birth defects, using data obtained from the birth certificate. However, the data were not of sufficient quality to make these analyses worthwhile.

Interim Conclusions

Based on the analysis of birth weight and gestational age data for residents of base family housing at Camp LeJeune, the following interim conclusions were made.

1. No association was observed between MBW or SGA and exposure to PCE in the range of 80 to 200 ppb among the offspring of mothers younger than 35 who had no medical history of fetal death. Most of the PCE-exposed infants studied were included in this group.

2. Decreased MBW and increased SGA were associated with exposure to PCE among the offspring of mothers 35 years of age or older. Smaller decreases in MBW and increases in SGA were associated with exposure to PCE among the offspring of mothers with histories of fetal deaths. While these finding have some biological plausibility, they were not anticipated and require further evaluation.

3. No association was observed between MBW or SGA and exposure to 1 ppm TCE for 7 to 12 days. However, it was not possible to evaluate whether short-term TCE exposure might be associated with MBW or SGA at particularly critical times during pregnancy.

4. Strong associations were observed between long-term exposure to TCE in the range of 1 ppm and decreased MBW and increased SGA in male infants. No associations were observed for female infants for these study outcomes. These results should be interpreted cautiously because the sample size was very small, which increases the likelihood that the association was a chance occurrence. In addition, an effect on males and not on females was not anticipated. Nonetheless, study of birth weight in the offspring of a larger population of pregnant women exposed to TCE is recommended.

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TABLES

Table 1.—Summary of contamination history at Camp LeJeune, 1940-1985.

1940s	Base operations begin. Degreasing solvents are used and stored in underground storage tanks at Hadnot Point.
1954	Dry-cleaning operation near base.
1958	Base digs supply well for family housing at Tarawa Terrace near dry-cleaner's septic system.
1982	
April	New laboratory begins analyzing water for disinfection by-products. Unidentified contaminants interfere with analysis.
July	Contaminants detected and identified in two systems.
	Tarawa Terrace 102 ppb PCE Hadnot Point 1400 ppb TCE 15 ppb PCE
1984	
July	Navy samples supply wells located near underground storage tanks.
Nov	Navy notified that a supply well at Hadnot Point is contaminated with benzene.
Dec	Wells in Hadnot Point system sampled. Water drawn only from wells pumping on sampling date. Contaminated wells are taken off line. No contaminants detected in tap water.
1985	
January	
27	Accident at Holcomb Boulevard system.
29	Sampled tap water coming from Hadnot Point being supplied to Holcomb Boulevard.
31	Results of January 29 sampling received. Hadnot Point contamination similar to 1982 levels.
February	
4	Additional contaminated supply wells identified at Hadnot Point.
7	Contaminated wells at Hadnot Point and Tarawa Terrace shut off.
12	Water from Tarawa Terrace determined to contain no VOCs.
22	Water from Hadnot Point determined to contain no VOCs.

Table 2.—Summary of exposure groups and the estimated concentrations of volatile organic compounds in drinking water.

Exposure Group	Water Distribution System	Housing Area Served	Contaminants	Estimated Contaminant Levels	Period of Exposure
PCE-exposed	Tarawa Terrace	Tarawa Terrace	Tetrachloroethylene Trichloroethylene 1,2-Dichloroethylene	215 ppb 8 ppb 12 ppb	1958-Feb 1985
Long-term TCE-exposed	Hadnot Point	Hospital Point	Trichloroethylene Dichloroethylene Benzene Methylene chloride Vinyl chloride	900-1400 ppb 321-407 ppb 35 ppb* 54 ppb 3 ppb†	? - Feb 1985 (Activities began in 1940s)
Short-term TCE-exposed	Hadnot Point	Midway Park, Berkeley Manor, Paradise Point, Watkins Village	Trichloroethylene Dichloroethylene	900-1148 ppb 321-407 ppb	Jan 27-Feb 7, 1985

* Estimated assuming a dilution factor of 20 from sampling data for well 602.
† Detection limit was 10 ppb.

Table 3.—Concentrations of VOCs in finished water samples from Tarawa Terrace distribution system.

Sampling Date	Tetrachloroethylene (in ppb)	Trichloroethylene (in ppb)	1,2-Dichloroethylenne (in ppb)
5/27/82	80	ND	NA
7/27/82	76	ND	NA
7/27/82	82	ND	NA
7/28/82	104	ND	NA
2/5/85	215	8.1*	12*
2/12/85†	ND*	ND*	ND*
2/19/85†	ND*	ND*	ND*

* Detection limit was 10 ppb.
† This sample was collected after the contaminated well was taken off line.

Table 4.—Concentrations of VOCs in finished water samples from Hadnot Point distribution.

Sample Date	Sample Source	1,2-DCE (ppb)	PCE (ppb)	TCE (ppb)	Other
5/27/82	Hadnot Point Water System	NA	15	1400	NA
7/27/82	Hadnot Point Water Treatment Plant	NA	< 1	19	NA
7/27/82	Hadnot Point Water Treatment Plant	NA	< 1	21	NA
7/28/82	Hadnot Point Water System	NA	1.0	ND*	NA
12/4/84	Hadnot Point Water Treatment Plant	83	3.9	200	ND*
12/10/84	Hadnot Point Water Treatment Plant	2.3	ND*	2.3	ND*
12/13/84	Hadnot Point Water Treatment Plant	ND*	ND*	ND*	Methylene chloride 54 ppb
12/14/84 -12/19/84	Hadnot Point Water Treatment Plant	ND*	ND*	ND*	ND *
12/19/84	French Creek Building 540	ND*	ND*	1.2	ND *
1/29/85	Holcomb Blvd Water Treatment Plant†	ND*	ND*	339.8	ND*
1/29/85	Married Officers Quarters Bldg 2212†	ND*	ND*	1,040.9	ND*
1/31/85	Hadnot Point Water Treatment Plant	321	ND*	900	ND*
1/31/85	Berkeley Manor Housing Unit 5531†	335	ND*	905	ND*
1/31/85	Berkeley Manor Housing Unit 5677†	368.7	ND*	981	ND*

* Detection limit = 10 ppb.
† Normally supplied by Holcomb Boulevard; received Hadnot Point water during an emergency.
NA = Not analyzed
ND = Not detected

Table 4.—Continued.

Sample Date	Sample Source	1,2-DCE (ppb)	PCE (ppb)	TCE (ppb)	Other
1/31/85	Paradise Point Officers Club†	332.4	ND*	890.1	ND*
1/31/85	Berkeley Manor Elementary School†	406.6	ND*	1148.4	ND*
1/31/85	Holcomb Blvd Water Treatment Plant†	7.6	ND*	26.8	ND*
2/5/85§	Hadnot Point Water Treatment Plant	150	7.5	429	vinyl chloride 2.9
2/7/85§	Hadnot Point Water Treatment Plant†	5.3	ND*	16.8	ND*
2/7/85§	Holcomb Blvd Water Treatment Plant†	< 2.0	ND*	< 2.0	ND*
2/7/85§	Berkeley Manor School†	44.8	ND*	135.1	ND*
2/7/85§	Married Officers Quarters 2204†	9	ND*	32.4	ND*
2/21/85§	Hadnot Point Water Treatment Plant	ND*	ND*	ND*	ND*
2/21/85§	Holcomb Boulevard Water Treatment Plant	ND*	ND*	ND*	ND*
4/22/85§	Hadnot Point Water Treatment Plant	ND*	ND*	ND*	ND*

* Detection limit = 10 ppb.
† Normally supplied by Holcomb Blvd; received Hadnot Point water during an emergency.
§ All contaminated wells closed by 2/4/85.
NA = Not Analyzed
ND = Not Detected

Table 5A.—Studies of late pregnancy outcomes conducted around hazardous waste sites; exposure defined based on proximity to sites.

Hazardous Waste Site	Sampling Frame and Exposure Ascertainment (Reference)	Confounders Measured	Outcome Studied (Outcome Definition)	Odds Ratio (95% CI) (# Exposed Cases)
Love Canal site Niagara Falls, NY Active dumping: 1920s-1953 Odors: through 1978	Birth records were sampled of white residents of Love Canal homeowners 1940-1978 for at least 9 months prior to birth compared to standard population (upstate New York infants). Exposed areas defined by proximity to site and to swale (37).	Maternal age, medical history, smoking, alcohol, education, occupation	Low birth weight (weight on birth certificate <2,500g)	Swale area: 1.6 (1.0-2.3) (21)* Near canal: 0.8 (0.4-1.6) (8)*
	Telephone logs and census were used to sample Love Canal households 1980 (homeowners and renters) compared to residents other parts of Niagara Falls. All pregnancies examined 1965-1977 (36).	Race, income, education, previous adverse pregnancy, medical history, alcohol, smoking	Low birth weight parental interview (<2,500 g)	Homeowners: 3.1 (1.3-7.1) (14) Renters: 1.1 (0.5-2.3) (13)
Lipari landfill, Gloucester County, NJ Heaviest dumping: 1967-1969 Earliest odor complaints: 1970	Birth certificates of Mantua, Pitman, Glasboro, and Harrison, New Jersey, residents were reviewed for the years 1961-1985. Residents in the neighborhood adjacent to Lipari landfill compared to residents within the study area who lived >1 km from the landfill (38).	Maternal age, education, race, parity, previous stillbirths, prenatal care, pregnancy complications, child's sex	Low birth weight birth certificate (<2,500g) Term low birth weight birth certificate (<2,500 g, ≥37 weeks)	1971-1975: 2.9 (1.5-5.3) (9) 1971-1975: 5.1 (2.5-10.6) (7)
Stringfellow landfill Riverside County, CA Active dumping odors	Residents since 1980 near Pyrite Channel compared to controls from Rubidoux. Identified through tax rolls, telephone books, etc. All pregnancies from 1955-1980 studied (39).	Age, ethnicity, income, education, occupation, smoking	Low birth weight (<2,500 g as reported by family member)	High: 0.9 (0.3-2.7) (5) Low: 0.8 (0.2-3.9) (2)
Facilities in San Francisco area with evidence of off-site exposure.	Ecologic study. Mean birth weight per census tract analyzed. Singleton live births from birth records in San Francisco Bay area 1983-1985 (40).	Maternal age, race, parity, education, income, child's sex	Mean birth weight (>28 weeks from birth certificate)	-.6 gram difference (-12.9-11.5) (6590)

* Crude risk ratios and 95% confidence intervals were computed based on numbers provided in text.
CI = Confidence Interval

Table 5B.—Studies examining late pregnancy outcomes among women exposed to TCE, PCE, or 1,2-DCE in drinking water.

Exposure and Concentration (ppb)	Sampling Frame and Exposure Ascertainment (Reference)	Confounders Measured	Outcome Studied (and Definition)	Odds Ratio (95% Confidence Interval) (# Exposed Cases)
TCE (6-267)* PCE (21)* Chloroform (12)*	Birth certificates were obtained for the years 1975-1979 among Woburn, Massachusetts, residents. Street address on the birth certificate was used to assign residence. Within East Woburn, a water distribution model was used to determine usage areas in which a high, moderate, or no proportion of water was supplied by contaminated wells during pregnancy.	Mother's age, education, and race and sex of infant	SGA (<10th percentile for gestational age specific weight; determined from birth certificate)	High 3rd trimester exposure: 1.6 (0.9-2.8) (28) Moderate 3rd trimester exposure: 1.3 (0.8-2.1) (64)
TCE (6-267)* PCE (21)* Chloroform (12)*	Pregnancies 1960-1980 in Woburn, Massachusetts, identified by 1982 telephone census. Exposure measurements for supply wells for a single year combined with well usage logs for 30 years. Analysis by continuous estimate of dose in Woburn (43).	Maternal age, smoking, SES defined by census tract	Low birth weight (maternal report less than 6 pounds)	1.0 (0.6-1.8)† (16)
TCE (1.0)§ PCE (0.8)§ DCE (0.2)§	Singleton births and fetal deaths 1985-1988 in New Jersey towns identified by birth records. Monthly, quarterly, or semi-annual exposure measurements made of municipal systems. Maternal exposure based on residence shown on birth certificate (45).	Maternal age, race, education, parity, previous stillbirth or miscarriage, prenatal care, plurality	SGA (< 5th percentile for gestational age specific weight; determined from birth certificate)	TCE 1.0 (0.9-1.1) (396) PCE 1.0 (0.9-1.1) (419) DCE 1.1 (0.9-1.3) (168)

* Maximum values measured in supply wells.
† Crude risk ratios and 95% confidence intervals were computed based on numbers provided in text.
§ Mean values measured in tap water.
CI=Confidence Interval

Table 6.—Frequency of live births in each exposure group included in and eliminated from analyses.*

Table 6.—Frequency of live births in each exposure group included in and eliminated from analyses.*

Characteristic	# (%) Unexposed	# (%) PCE-Exposed	# (%) Long-Term TCE-Exposed	# (%) Short-Term TCE-Exposed
Total live births	5,890	6,372	32	171
OBSERVATIONS ELIMINATED BECAUSE OF POOR DATA QUALITY				
Moved in/conceived when exposure was undefined	0 (0.0)	6 (0.1)	0 (0.0)	23 (13.5)
Exposure unknown because residential history missing during critical time†	0 (0.0)	4 (0.1)	0 (0.0)	3 (1.8)
Live birth weighing <350 g	22 (0.4)	22 (0.3)	0 (0.0)	0 (0.0)
Last menstrual period missing	55 (0.9)	56 (0.9)	0 (0.0)	3 (1.8)
Gestational age >45 weeks	151 (2.6)	172 (2.7)	1 (3.1)	1 (0.6)
Total N used in MBW analyses	5,681 (96.5)	6,131 (96.2)	31 (96.9)	141 (82.5)
Gestational age <22 weeks§	2 (0.0)	8 (0.1)	0 (0.0)	0 (0.0)
Total N used in SGA analyses	5,679 (96.4)	6,123 (96.1)	31 (96.9)	141 (82.5)

* Individual observations might fall into more than one category.
† Contamination was last observed on February 7, 1985. For births occurring after February 7, 1985, residence at time of birth could not be used to assume imply residence for 1 week or more during exposure.
§ Excluded from SGA analyses.

Table 7.—Distribution of demographic characteristics among live births to PCE-exposure and unexposed residents.

Characteristic	PCE-Exposed # (%)	Unexposed # (%)
N	6,131	5,681
Mother's Race		
White	4,349 (70.9)	4,487 (79.0)
Black	1,419 (23.1)	1,006 (17.7)
Other	363 (5.9)	188 (3.3)
Sex		
Female	3,062 (49.9)	2,778 (48.9)
Male	3,069 (50.1)	2,903 (51.1)
Year of Birth		
1968-1970	1,047 (17.1)	1,000 (17.6)
1971-1974	1,556 (25.4)	1,507 (26.5)
1975-1980	1,865 (30.4)	1,639 (28.9)
1981-1985	1,663 (27.1)	1,535 (27.0)
Rank and Paygrade		
No Card/Unknown	92 (1.5)	136 (2.4)
E1-E3	633 (10.3)	1,408 (24.7)
E4-E5	3,882 (63.3)	1,896 (33.4)
E6-E9	1,017 (16.6)	1,177 (20.7)
WO	25 (0.4)	67 (1.2)
O1-O3	482 (7.9)	793 (14.0)
O4 or higher	0 (0.0)	204 (3.6)
Parity		
1	1,864 (30.4)	2,223 (39.1)
2 or greater	4,262 (69.5)	3,454 (60.8)
Missing	5 (0.1)	4 (0.1)
Mother's Age (years)		
<20	761 (12.4)	1,235 (21.7)
20-24	3,483 (56.8)	2,406 (42.4)
25-29	1,449 (23.6)	1,349 (23.7)
30-34	366 (6.0)	527 (9.3)
35 +	72 (1.2)	164 (2.9)

Table 7.—Continued.

Characteristic	PCE exposed # (%)	Unexposed # (%)
N	6,131	5,681
Gestational Age		
20-23 weeks	11 (0.2)	10 (0.2)
24-27 weeks	18 (0.3)	19 (0.3)
28-32 weeks	102 (1.7)	78 (1.4)
33-36 weeks	382 (6.2)	348 (6.1)
37-40 weeks	3,526 (57.5)	3,310 (58.3)
41-42 weeks	1,610 (26.3)	1,528 (26.9)
43-45 weeks	482 (7.9)	388 (6.8)
Prenatal Care		
Inadequate	2,070 (33.8)	1,868 (32.9)
Intermediate	2,165 (35.3)	1,863 (32.8)
Adequate	1,228 (20.0)	1,313 (23.1)
Superadequate	285 (4.7)	268 (4.7)
Missing	383 (6.3)	369 (6.5)
Past Fetal Deaths*		
2 or more	254 (4.1)	210 (3.7)
1 or more	1,069 (17.4)	866 (15.2)
None	5,059 (82.5)	4,810 (84.7)
Not reported	3 (0.0)	5 (0.1)
Mother's Education		
0-8 years	168 (2.7)	133 (2.3)
9-11 years	1,333 (21.7)	1,221 (21.5)
12 years	3,327 (54.3)	2,770 (48.8)
13-15 years	979 (16.1)	955 (16.8)
16 or more years	321 (5.2)	600 (10.6)
Unknown	3 (0.0)	2 (0.0)
Father's Education		
0-8 years	57 (0.9)	41 (0.7)
9-11 years	671 (10.9)	702 (12.4)
12 years	4,291 (70.0)	3,342 (58.8)
13-15 years	657 (10.7)	593 (10.5)
16 or more years	448 (7.3)	997 (17.5)
Unknown	7 (0.1)	6 (0.1)

Table 8.—Distribution of pregnancy outcomes among residents of PCE-exposed and unexposed housing.

Variable	PCE-Exposed	Unexposed	Mean Difference or Odds Ratio and 90% Confidence Interval
Birth weight in grams Mean (St Err)	n = 6,131 3,326 (7.2)	n = 5,681 3,351 (7.4)	-24 (-42, -7)
Frequency SGA/all births ≥23 weeks (%)	624/6,123 (10.2)	509/5,679 (9.0)	1.2 (1.0, 1.3)

Table 9.—Association between duration of exposure to PCE and birth outcome.

Duration of Exposure*	N	MBW (St Err) in Grams	Mean Difference† (90% Confidence Interval)	Frequency SGA Births/All Births ≥22 Wks (%)	Odds Ratio (90% Confidence Interval)
Never exposed	5344	3352 (7.5)	0.0	488/5337 (9.1)	1.0
1-3 weeks	189	3346 (37.4)	18 (-40, 76)	15/189 (7.9)	0.9 (0.5, 1.3)
4-10 weeks	598	3293 (24.5)	-16 (-50, 18)	60/596 (10.1)	1.1 (0.9, 1.4)
11-20 weeks	917	3301 (18.8)	-30 (-58, -2)	84/914 (9.2)	1.0 (0.8, 1.2)
21-45 weeks	1555	3350 (13.8)	-29 (-51, -6)	168/1554 (10.8)	1.2 (1.0, 1.4)
Entire pregnancy and <1 yr before LMP	1996	3326 (12.5)	-15 (-36, 6)	208/1994 (10.4)	1.2 (1.0, 1.3)
Entire pregnancy and ≥1 yr before LMP	608	3350 (21.7)	-18 (-52, 16)	61/608 (10.0)	1.1 (0.9, 1.4)

* Unless otherwise noted, duration of exposure is expressed in consecutive weeks before birth.
† Adjusted for gestational age.
MBW = mean birth weight
LMP = last menstrual period
St Err= standard error

Table 10.—Distribution of pregnancy outcomes among mothers aged 35 years or older residing in PCE-exposed and unexposed housing.

Variable	PCE-Exposed	Unexposed	Mean Difference or Odds Ratio and 90% Confidence Interval
Birth weight in grams Mean (St Err)	n = 72 3,286 (72.0)	n = 164 3,497 (44.0)	-207 (-334, -79)*
Frequency (%) SGA/ all births ≥22 weeks	11/72 (15.3)	8/164 (4.9)	3.9 (1.6, 9.8)†

* Adjusted for gestational age and mother's race other than white or African-American.
† Adjusted for officer or warrant officer household; 2 observations were deleted due to missing values regarding officer's household.
St Err = standard error
SGA = small for gestational age.

Table 11.—Distribution of birth outcomes to mothers with histories of fetal deaths residing in PCE-exposed and unexposed housing.

Variable	PCE-Exposed	Unexposed	Mean Difference or Odds Ratio and 90% Confidence Interval
Birth weight in grams Mean (St Err)	n = 1,069 3,284 (24.4)	n = 866 3,335 (18.7)	-51.1 (-96.8,-5.4)
Frequency SGA/ all births ≥22 weeks (%)	148/1,067 (13.9)	70/866 (8.1)	1.6 (1.3, 2.1)*

*Adjusted for officer's or warrant officer's household. 11 observations deleted because of missing information regarding officer's household.
St Err = standard error
SGA = small for gestational age

Table 12.—Association between duration of exposure to PCE and birth outcome among births to mothers with histories of fetal deaths.

Duration of Exposure*	N	MBW (St Err) in Grams	Mean Difference† (90% Confidence Interval)	Frequency SGA Births/ All Births ≥22 wks (%)	Odds Ratio (90% Confidence Interval)§
Never exposed	818	3,332 (21.3)	0	69/818 (8.4)	1.0
1-3 weeks	24	3,277 (123.9)	5 (-162, +173)	4/24 (16.7)	1.9 (0.8, 4.8)
4-10 weeks	73	3,183 (81.2)	-110 (-209, +12)	13/73 (17.8)	2.1 (1.2, 3.7)
11-20 weeks	131	3,318 (53.6)	2 (-74, +78)	19/130 (14.6)	1.7 (1.1, 2.7)
21-45 weeks	287	3,318 (32.6)	- 73 (-128, -17)	36/287 (12.5)	1.4 (1.0, 2.0)
Entire pregnancy and <1 yr before LMP	366	3,269 (33.8)	- 55 (-106, - 5)	48/368 (12.9)	1.4 (1.0, 2.0)
Entire pregnancy and ≥1 yr before LMP	136	3,236 (52.4)	-121 (-196, +46)	23/136 (16.9)	2.0 (1.3, 3.1)

* Unless otherwise noted, duration of exposure is expressed in consecutive weeks before birth.
† Adjusted for gestational age.
§ Adjusted for officer or warrant officers household. One observations deleted because of missing values for officer or warrant officer's household.
MBW = mean birth weight
St Err = standard error
SGA = small for gestational age
LMP = last menstrual period

Table 13.—Distribution of demographic characteristics among residents of long-term TCE-exposed and unexposed officers' housing.

Characteristic	Long-Term TCE-Exposed	Unexposed # (%)
N	31	997
Mother's Race		
White	29 (93.5)	960 (96.3)
Black	0 (0.0)	23 (2.3)
Other	2 (6.5)	14 (1.4)
Sex		
Female	19 (61.3)	500 (50.2)
Male	12 (38.7)	497 (49.8)
Year of Birth		
1968-1970	8 (25.8)	211 (21.2)
1971-1974	6 (19.4)	252 (25.3)
1975-1980	7 (22.6)	279 (28.0)
1981-1985	0 (32.3)	255 (25.6)
Rank and Paygrade		
Unknown	3 (9.7)	0
O1-O3	11 (35.5)	793 (79.5)
O4 or higher	17 (54.8)	203 (20.5)
Parity		
1	7 (22.6)	344 (34.6)
2 or greater	24 (77.4)	653 (65.5)
Mother's Age (years)		
< 20	0	2 (0.2)
20-24	3 (9.7)	275 (27.6)
25-29	18 (58.1)	512 (51.4)
30-34	10 (32.3)	160 (16.0)
35 +	0	48 (4.8)
Gestational Age		
20-23 weeks	0	1 (0.1)
24-27 weeks	0	2 (0.2)
28-32 weeks	0	7 (0.7)
33-36 weeks	0	32 (3.2)
37-40 weeks	23 (74.2)	613 (61.5)
41-42 weeks	7 (22.6)	305 (30.6)
43-45 weeks	1 (3.2)	37 (3.7)

Table 13.—Continued.

Characteristic	Long-Term TCE Exposed	Unexposed # (%)
N	31	997
Prenatal Care		
Inadequate	8 (25.9)	197 (19.8)
Intermediate	12 (38.7)	359 (36.1)
Adequate	10 (32.3)	298 (29.9)
Superadequate	1 (3.2)	51 (5.1)
Missing	0	92 (9.3)
Past Fetal Deaths*		
2 or more	2 (6.5)	44 (4.4)
1 or more	7 (22.6)	157 (15.7)
None	24 (77.4)	840 (84.3)
Mother's Education		
0-8 years		1 (0.1)
9-11 years		11 (1.1)
12 years	7 (21.9)	200 (20.1)
13-15 years	13 (40.6)	303 (30.4)
16 or more years	11 (35.5)	481 (48.2)
Unknown		1 (0.1)
Father's Education		
0-8 years	0	1 (0.1)
12 years	0	22 (2.2)
13-15 years	0	58 (5.8)
16 or more years	31 (100.0)	915 (91.8)
Unknown	0	1 (0.1)

Table 14.—Distribution of pregnancy outcomes among residents of long-term TCE-exposed and unexposed officer's housing.

Variable	Long-Term TCE-Exposed	Unexposed	Mean Difference or Odds Ratio and 90% Confidence Interval
Birth weight in grams Mean (St Err)	n = 31 3,361 (71.8)	n = 997 3,469 (16.9)	-108 (-230, 13)
Frequency SGA/ all births ≥22 weeks (%)	3/31 (9.7)	68/997 (6.8)	1.5 (0.5, 3.8)

St Err = standard error
SGA = small for gestational age

Table 15.—Analysis of long-term TCE exposure and MBW by sex of infant and duration of residence in base housing.

	N	MBW (St Err)	Mean Difference (90% Confidence Interval)	One-Tailed p-Value
All Live Births				
Exposed	31	3,361 (71.8)	-139* (-277, -1)	.05
Unexposed	997	3,469 (16.9)		
All Males				
Exposed	12	3,213 (113.3)	-312* (-540, -85)	.01
Unexposed	497	3,527 (25.2)		
All Females				
Exposed	19	3,454 (88.3)	-4† (-171, +163)	.48
Unexposed	500	3,412 (22.3)		
Mothers lived on base ≥20 weeks before birth				
Both Sexes				
Exposed	21	3,352 (95.3)	-144§ (-486, +27)	.08
Unexposed	742	3,473 (19.8)		
Males				.01
Exposed	9	3,207 (143.6)	-367* (-632, -102)	
Unexposed	368	3,525 (30.3)		
Females				1.0
Exposed	12	3,461 (122.9)	+26† (+196, +248)	
Unexposed	374	3,423 (25.5)		

* Final model after adjustment for gestational age.
† Final model after adjustment for gestational age and military paygrade.
§ Final model after adjustment for gestational age, military paygrade, mothers 35 years or older, and year of birth.
MBW = mean birth weight
St Err = standard error

Table 16.—Distribution of demographic characteristics among live births of residents of short-term TCE--exposed and unexposed housing.

Characteristic	Short-Term TCE-Exposed # (%)	Unexposed # (%)
N	141	868
Mother's Race		
White	107 (75.9)	647 (74.5)
Black	31 (22.0)	193 (22.2)
Other	3 (2.1)	28 (3.2)
Sex		
Female	69 (48.9)	447 (51.5)
Male	72 (51.1)	421 (48.5)
Rank and Paygrade		
No Card/Unknown	2 (1.4)	21 (2.4)
E1-E3	50 (35.5)	344 (39.6)
E4-E5	28 (19.9)	165 (19.0)
E6-E9	35 (24.8)	184 (21.2)
WO	2 (1.4)	10 (1.2)
O1-O3	23 (16.3)	130 (15.0)
O4 or higher	1 (0.7)	14 (1.6)
Parity		
1	36 (25.5)	293 (33.4)
2 or greater	105 (74.5)	575 (66.2)
Mother's Age (years)		
< 20	16 (11.3)	114 (13.1)
20-24	61 (43.3)	419 (47.9)
25-29	41 (29.1)	223 (25.7)
30-34	19 (13.5)	93 (10.7)
35 +	4 (2.8)	19 (2.2)

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Table 16.—Continued.

Characteristic	Short-Term TCE-Exposed # (%)	Unexposed # (%)
N	141	868
Gestational Age		
20-23 weeks	0	2 (0.2)
24-27 weeks	0	3 (0.3)
28-32 weeks	2 (1.4)	13 (1.5)
33-36 weeks	9 (6.4)	58 (6.7)
37-40 weeks	91 (64.5)	532 (61.3)
41-42 weeks	28 (19.9)	203 (23.4)
43-45 weeks	11 (7.8)	57 (6.6)
Prenatal Care		
Inadequate	27 (19.2)	148 (17.1)
Intermediate	33 (23.4)	231 (26.6)
Adequate	60 (42.6)	380 (43.7)
Superadequate	21 (14.9)	108 (12.4)
Missing		1 (0.1)
Past Fetal Deaths*		
2 or more	8 (5.7)	46 (5.3)
1 or more	25 (17.7)	163 (18.8)
None	116 (82.3)	705 (81.2)
Mother's Education		
0-8 years		16 (1.8)
9-11 years	15 (10.6)	134 (15.4)
12 years	75 (53.2)	446 (51.4)
13-15 years	33 (23.4)	192 (22.1)
16 or more years	18 (12.8)	80 (9.2)
Father's Education		
0-8 years	0	1 (0.1)
9-11 years	5 (3.5)	46 (5.3)
12 years	90 (63.8)	568 (65.4)
13-15 years	22 (15.6)	102 (11.8)
16 or more years	24 (17.0)	151 (17.2)
Unknown	0	1 (0.1)

Table 17.—Distribution of pregnancy outcomes among residents of short-term TCE-exposed and unexposed housing.

Variable	Short-Term TCE-Exposed		Unexposed		Mean Difference or Odds Ratio and 90% Confidence Interval
Birth weight in grams Mean (St Err)	N= 141 3,455	(41.7)	N= 868 3,385	(19.7)	+70 (-6, +146)
Frequency SGA/ all births ≥22 weeks (%)	5/141	(3.6)	58/868	(6.7)	1.1 (0.2, 1.1)

St Err = standard error
SGA = small for gestational age

FIGURES

Figure 1. Time elapsed between short-term exposure to TCE and birth weight among term live births.

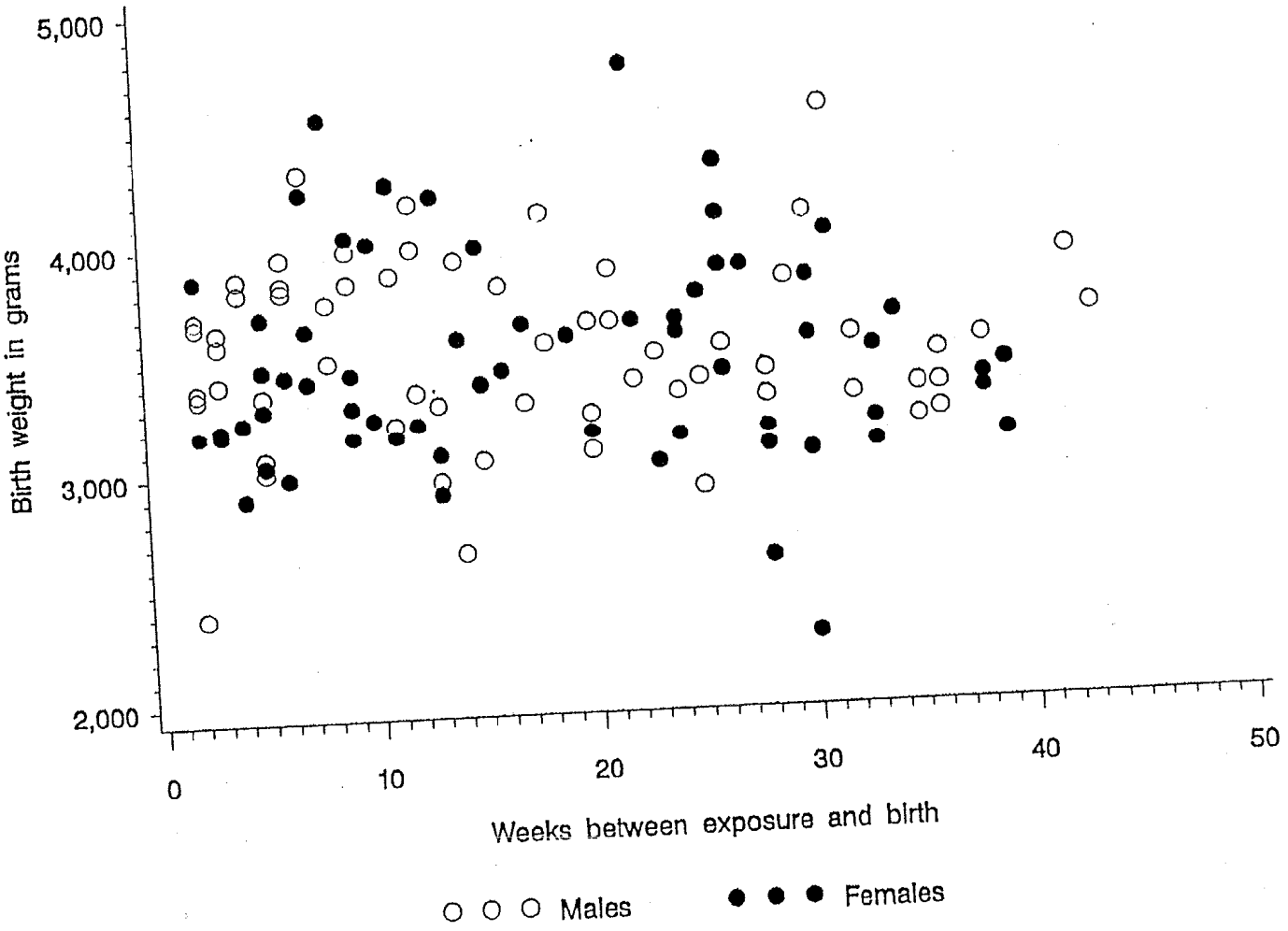

Figure 2. Gestational age at time of short-term exposure to TCE and birth weight among term live births.