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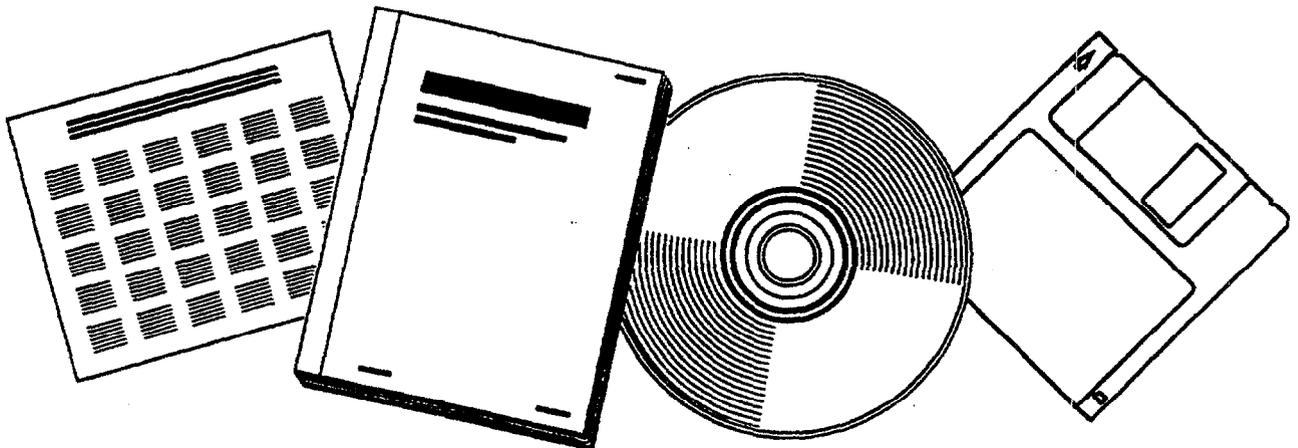
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**VOLATILE ORGANIC COMPOUNDS IN DRINKING
WATER AND ADVERSE PREGNANCY OUTCOMES,
UNITED STATES MARINE CORPS BASE, CAMP
LEJEUNE, NORTH CAROLINA**

(U.S.) AGENCY FOR TOXIC SUBSTANCES AND
DISEASE REGISTRY, ATLANTA, GA. DIV. OF
HEALTH STUDIES

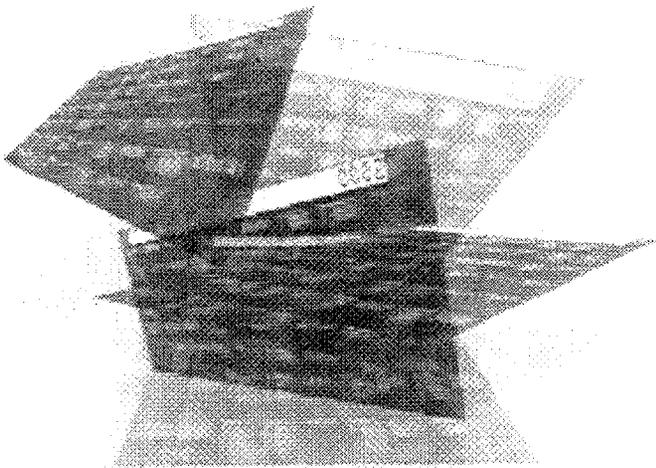
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Agency for Toxic Substances and Disease Registry

Division of Health Studies

VOLATILE ORGANIC COMPOUNDS IN DRINKING WATER AND ADVERSE PREGNANCY OUTCOMES

UNITED STATES MARINE CORPS BASE

CAMP LEJEUNE, NORTH CAROLINA

August 1998



**U.S. DEPARTMENT OF HEALTH
& HUMAN SERVICES**

Agency for Toxic Substances
and Disease Registry
Atlanta, Georgia 30333

In 1980, Congress created the Agency for Toxic Substances and Disease Registry (ATSDR) to implement health-related sections of laws that protect the public from hazardous wastes and environmental spills of hazardous substances. The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), commonly known as the "Superfund" Act, designated ATSDR as the lead agency within the Public Health Service to help prevent or reduce further exposure to hazardous substances and the adverse health effects that result from such exposures, and also to expand the knowledge base about such effects.

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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**

**UNITED STATES MARINE CORPS BASE
CAMP LEJEUNE, NORTH CAROLINA**

August 1998

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LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
CI	confidence interval
CL	confidence limit
DCE	dichloroethylene
g	grams
LMP	last menstrual period
MBW	mean birth weight
NPL	National Priorities List
OR	odds ratio
PCE	tetrachloroethylene
ppb	parts per billion
ppm	parts per million
SGA	small for gestational age
Std Err	standard error
TCA	trichloroacetic acid
TCE	trichloroethylene
VOC	volatile organic compound

ABSTRACT

In 1995, the Agency for Toxic Substances and Disease Registry (ATSDR) began data collection for a study of environmental exposure to volatile organic compounds (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 study was undertaken following documentation that environmental exposure to VOCs in drinking water had occurred in the past. At that time, there was no evidence of an increased rate of adverse pregnancy outcomes at Camp Lejeune. However, because fetuses tend to be more sensitive to toxic chemical exposures and many pregnant women had resided in housing areas supplied with contaminated water, it appeared prudent to research the topic. This report describes a study of past exposure to VOC-contaminated drinking water and mean birth weight (MBW), small for gestational age (SGA), and preterm birth in residents of base family housing at Camp Lejeune. The results were 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 6,117 tetrachloroethylene (PCE)-exposed women, 141 short-term trichloroethylene (TCE)-exposed women, 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 ages, maternal race, maternal and paternal education, military pay grade, 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.

Preterm delivery was not associated with VOC-exposure in any category. 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 weighed an average of 24 grams (g) less 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 limits [CL]: 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 accounted 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 or 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 -205 g (90% CL: -333, -78), and the adjusted OR was 4.0 (90% CL: 1.6, 10.2) for PCE exposure and SGA. In mothers who had previously had one or more fetal deaths, the adjusted OR for PCE and SGA was 1.6 (90% CL: 1.2, 2.1). In mothers who had previously had two or more fetal deaths, the differences in MBW and SGA between PCE-exposed and unexposed mothers were much larger, but the number of births to women in

this group was fairly small. Because associations in these subgroups were not anticipated, these results should be considered exploratory. They are, however, biologically plausible and deserving of followup.

The TCE-exposed groups were both small in number. The difference in adjusted MBW between the long-term TCE-exposed group and the unexposed comparison group was -139 g (90% CL: -277, -1); the OR was 1.5 (90% CL: 0.5, 3.8) for SGA and long-term TCE exposure. This increase was entirely attributable to differences in male infants within the long-term TCE-exposed group. Among males alone, the OR for SGA was 3.9 (90% CL: 1.1, 11.9) and the difference in MBW was -312 g (90% CL: -540, -85). The short-term TCE-exposed group had a lower prevalence of SGA infants, 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 small sample size considerably weakened the evidence for a causal association. Although it is possible to speculate on mechanisms by which such a sex-based difference might arise, this difference was unexpected and could not be explained by known mechanisms of TCE toxicity. These findings warrant followup in a larger TCE-exposed population.

ATSDR had intended to analyze fetal death data, but existing records were too incomplete to be useful. In addition to the main analyses, several substudies were conducted and are presented in Appendices A and B. Important conclusions from these substudies are (1) the housing record data were complete and should have provided reasonable information regarding length of exposure during pregnancy; (2) abstracting medical records is feasible and might enrich the data quality for the subgroups of study participants for which associations between VOC-exposure and MBW and SGA were noted; (3) a limited amount of birth defects data was available from the birth certificate. These data were inadequate for a formal evaluation of associations between VOC exposure and birth defects. Alternative approaches are recommended to study VOC exposure and birth defects if the question remains an issue of public health interest.

VOLATILE ORGANIC COMPOUNDS IN DRINKING WATER AND ADVERSE PREGNANCY OUTCOMES

INTRODUCTION

The Agency for Toxic Substances and Disease Registry (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 investigation is the association between volatile organic compounds (VOCs) in drinking water and adverse pregnancy outcomes. Pregnancy outcomes are of particular importance to populations residing on military bases because such populations include a high proportion of reproductive-aged individuals.

OBJECTIVES

The primary objective of this retrospective study was to explore potential associations between previous exposure to VOCs in drinking water and three adverse pregnancy outcomes at the U.S. Marine Corps Base at Camp Lejeune, Onslow County, North Carolina, where tetrachloroethylene (PCE), trichloroethylene (TCE), and 1,2-dichloroethylene (1,2-DCE) were found in drinking water supplies in the 1980s. The three pregnancy outcomes were (1) reduced fetal growth, measured as decreased mean birth weight (MBW) and small for gestational age (SGA); (2) preterm birth; and (3) late fetal deaths. However, because of incomplete data, this third outcome could not be determined.

Three secondary objectives of the study were (1) to validate the quality of housing record information as it was used to assign exposure and duration of exposure (see Appendix A); (2) to evaluate the feasibility and utility of reviewing medical records to enhance the study's inferences (see Appendix B); and (3) to gather existing information on birth defects (see Appendix B). It was understood from the outset that the third and final objective would be difficult to achieve because of the limited information regarding birth defects available from birth certificates. Nonetheless, the potential relationship between VOCs and birth defects is of such strong public health concern that an attempt was made to evaluate all existing data.

BACKGROUND

Environmental exposure to hazardous substances and the adverse health effects that can result are increasing in public health importance. In 1981, the U.S. Environmental Protection Agency (EPA) estimated that 264 million metric tons of hazardous wastes were produced. By 1988, this estimate 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 1,135 hazardous waste sites then on the National Priorities List (NPL) (1). By 1994, there were more than 1,400 sites on the NPL (2). These sites represented a small fraction of the estimated 439,000 hazardous waste sites that might be present in the United States (1). The number of people actually exposed to toxic substances either at NPL sites or at hazardous waste sites in general cannot be estimated accurately.

ATSDR is required by law to conduct a public health assessment at each NPL site. 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 to assess whether adverse health effects possibly resulted from this 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 this health assessment process, Camp Lejeune personnel provided ATSDR with drinking water monitoring records indicating that two drinking water supplies at Camp Lejeune were contaminated over a period of 34 months. Included in the population supplied with this water were slightly more than half of all residents in family base housing. Because this population consisted of a large proportion of young married women, concern was raised about 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, and it is included because of the presence of contaminants in the environment originating at the facility. The military 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 are 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 sand aquifer that is permeable to contamination (3).

Personnel at Camp Lejeune first detected VOC contamination 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. Because test results of water samples obtained in April were anomalous, 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 officials at the base contacted the state for advice, no further action was taken because water quality standards had not been established for these VOCs in 1982.

In July 1984, Camp Lejeune began sampling wells in the Hadnot Point area as part of the base's environmental restoration program. As a result of this sampling, 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. Tap water samples taken from buildings temporarily supplied by Hadnot Point contained high levels of TCE, which prompted additional tap and finished water sampling 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 routine sampling 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 used 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 2½ years. Industrial activity on the base began in the 1940s. No records indicate when the VOC plumes that contaminated supply wells in the Hadnot Point system originated. 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 measured in tap water samples from Hadnot Point were 1,400 ppb TCE and 407 ppb 1,2-DCE.

Contamination at Tarawa Terrace probably occurred many years before it was first documented in 1982. The source of the PCE at Tarawa Terrace was the ABC One-Hour Cleaners, a dry-cleaning establishment near Tarawa Terrace (3). PCE leaked into the groundwater from the company's septic system. According to EPA records, the septic system was in operation from 1954 through 1985. In 1958, military personnel dug a supply well for the Tarawa Terrace system approximately 900 feet from the dry cleaners. Because this supply well was near the contaminated septic system, because few changes were made in the dry-cleaning operation after 1960 (4), and because of the very permeable aquifer at Camp Lejeune, the Tarawa Terrace well probably was contaminated soon after it was built. Human exposure to PCE and other contaminants through this well could have occurred for as long as 30 years (3).

The housing areas that received contaminated water in each exposure group, the contaminants, and the estimated contaminant levels are summarized in Table 2. Each of the affected housing areas received water containing a mixture of many contaminants, a phenomenon noted with almost every population exposed to contaminants released from hazardous waste sites. For simplicity, each 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 comprises residents of Berkeley Manor, Midway Park, Paradise Point, and Watkins Village during the 12-day period from January 27 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. Water samples were collected on three different dates; the May 1982 samples, however, were preserved for several months before they were analyzed, which might have decreased the observed concentration of VOCs. Moreover, the 1985 sampling at Hadnot Point was conducted after seven of eight contaminated wells were closed. Hence, the expected contamination levels in the Hadnot Point distribution system before 1985 would 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 shut off before the distribution system was sampled again, benzene was never detected in Hadnot Point tap water. Nonetheless, low-level exposure (an estimated 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 one day. Contaminant levels have been noted to differ with the supply wells in service. The process by which a particular well was selected for use was essentially random, but all wells presumably were used in a given month unless they were out of service for mechanical failure or contamination. Daily or monthly well-usage logs were not available for evaluation. Despite these variations, on any specified day, VOC concentrations were probably distributed uniformly to all residential units because the water from all wells was mixed before treatment and distribution. For example, on January 31, 1985, VOC concentrations were similar in tap water samples obtained from several different buildings (Table 4).

HUMAN HEALTH EFFECTS OF CONCERN

Human gestation is a time of great vulnerability to environmental and pharmacologic agents. Environmental exposure to mercury has been shown to cause adverse effects in utero even though the pregnant woman is unaffected (5). The outcomes evaluated (i.e., decreased MBW, SGA, and preterm delivery) are several of the many possible adverse pregnancy outcomes that might be associated with exposure to environmental toxins (6). These outcomes are important because of their contribution to infant mortality and morbidity; moreover, they are among the most practical outcomes to study near hazardous waste sites because they are common, well-ascertained, and reported in a standardized fashion on birth records (7). Birth records also include information on maternal residence. These practical aspects of the study outcomes are important in situations, such as that at Camp Lejeune, in which exposure ceased almost 10 years before the study and most of the exposed population had moved in the intervening period.

Intrauterine growth retardation (measured as decreased MBW and SGA) and preterm delivery are two conditions with distinct pathogeneses that are usually grouped together and measured as low birth weight. In 1989, 7.0% of infants had low birth weight, weighing <2,500 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 for infant mortality for singleton infants with very low birth weight (i.e., <1,500 g at birth) was 94 times higher than for infants of normal birth weight (>2,500 g at birth) (10). Low birth weight and very low birth weight infants are also at greater risk for neurodevelopmental handicaps (e.g., cerebral palsy and seizure disorder), lower respiratory tract conditions, and complications from neonatal care (11).

Distinguishing between effects on fetal growth and effects on gestational age at delivery is often difficult because growth and maturity of an infant are both highly dependent on gestational age. Infants who are born small because they are born at <37 weeks of gestation are considered to be preterm. Approximately 10% of all infants born during 1988 in the United States were preterm (12). Approximately 40% of these preterm infants weighed <2,500 g (12). Such infants are clearly at higher risk for morbidity and mortality. The risk for fetal death is three times higher for infants surviving to 26 weeks than for infants surviving to 40 weeks (13). Factors predictive of preterm delivery include maternal socioeconomic status, race-ethnicity, cigarette smoking, stress, nutrition, past pregnancy history, access to prenatal care, and medical complications such as sexually transmitted diseases, infection, hypertension, and preeclampsia (14).

Infants who have sufficient time to grow and mature but have low birth weight often are less viable because of intrauterine processes that delayed their growth. In general, whether preterm or full-term, growth-retarded infants are at greater risk for antenatal and neonatal mortality than full-term infants who are at the appropriate weight for their gestational age (14, 15). SGA infants are those within the bottom tenth percentile of the birth weight distribution at any given gestational age. As with other population-based measures, some SGA infants will be healthy and simply smaller than average, but many will be growth retarded. At present, SGA is the only marker for intrauterine growth retardation that is readily available for population-based studies.

Biologic factors reducing growth include young maternal age, low maternal prepregnant weight, short maternal height, insufficient maternal weight gain during pregnancy, maternal alcohol consumption, and anoxia resulting from cigarette smoking and altitude (14,16). Maternal medical complications, such as hypertension, can also produce anoxic conditions resulting in SGA infants (17). Plurality, the sex of the infant, and maternal parity also influence birth weight. Important social determinants of SGA infants in the United States are maternal race, education, socioeconomic status, and utilization of prenatal care (14).

Late fetal deaths (i.e., stillbirths) occur more rarely than preterm birth and SGA but account for a greater proportion of perinatal mortality. Late fetal deaths, defined as fetal deaths occurring after 20 weeks of gestation, account for approximately 80% of all perinatal deaths.

In 1989, the fetal death rate after 20 weeks of gestation was 7.5 deaths per 1,000 births, with a rate of 6.4 per 1,000 births in whites and 13.1 per 1,000 births in nonwhites (18). These rates probably underestimate the actual numbers of fetal deaths because of underreporting (7,19). Despite the importance of late fetal death, the causes of fetal death have not been widely studied. Important maternal risk factors for fetal death are maternal age, race, education, parity, body mass, cigarette smoking, hypertension and hypertensive disorders, diabetes, and previous adverse pregnancy outcome. Risk factors inherent to the specific infant or pregnancy include sex, congenital anomalies, plurality, and cord and placental complications (15,20,21).

ROUTES OF TCE AND PCE EXPOSURE AND METABOLISM

PCE and TCE, the predominant contaminants in the chemical mixtures studied, are structurally similar chemicals with many common toxicologic properties. Both compounds are lipophilic (22,23) and readily cross the placenta (24-26). Compared with other solvents, both TCE and PCE have relatively long half-lives in the human body (27). PCE is retained in the body three to four times longer than TCE, and females retain both compounds longer than males (27). A number of models have been developed to estimate the distribution of PCE and TCE within the human body after exposure to contaminated air or groundwater (28-30). In general, ingesting contaminated drinking water is not an efficient way to deliver these toxic chemicals to the fetus (26). Activities that cause VOCs in household water supplies to evaporate include bathing; showering; cooking; and operating toilets, washing machines, and dishwashers (29-31). Inhalation of TCE and PCE that have evaporated from household water is likely to result in higher exposures than ingesting water from the same water supply (29). Larger fractions of PCE and TCE are metabolised after ingestion than after inhalation (26). Moreover, trichloroacetic acid (TCA), a biologically active metabolite of PCE and TCE, has been observed to persist in the rat fetus after exposure to either PCE or TCE has stopped; TCA can cycle from the fetus into the amniotic fluid and back into the fetus (25). Therefore, the relative contributions of inhalation and ingestion of PCE and TCE depend on whether the primary toxicants are the chemical(s) or the chemical metabolites.

One potential mechanism for reproductive toxicity of PCE is a generalized central nervous system depression that suppresses the hypothalamus and pituitary in the mother, the fetus, or both (32). A similar mechanism might operate for TCE because it has similar chemical properties. Although this hypothesis remains untested, central nervous system depression after PCE and TCE exposure is well-established (22,23), fatty acid composition changes in the brains of fetal guinea pigs have been observed after in utero exposure to PCE (33), and suppression of the fetal hypothalamus would affect fetal growth (34-35). Suppression of the maternal hypothalamus probably does not affect fetal growth (34), but the interactions between the maternal hormonal environment, the placental hormonal environment, and the fetal hormonal environment are complex.

Metabolites of TCE are possibly responsible for the developmental defects observed in laboratory animals exposed to TCE in drinking water (36-38). Infants with birth defects are often SGA. An association between SGA or reduced MBW and exposure to PCE or TCE might also

be a marker for birth defects. However, SGA is only a weak surrogate for birth defects (39). Therefore, an association between exposure and birth defects would have to be very strong to be detected in this study of SGA. It is not known whether metabolites of TCE or PCE might affect fetal growth through a mechanism independent of birth defects.

TOXICOLOGIC LITERATURE

The association between low level environmental exposure to PCE or TCE and adverse pregnancy outcomes has not been determined. In one controlled clinical trial (40), pregnant mice exposed to 300 parts per million (ppm) PCE delivered litters that had an average birth weight that was 9% lower than the normal average; these litters also were twice as likely to have subcutaneous edema than unexposed mice, and the increase in the number of litters with delayed ossification of skull bones was statistically significant. There was a 60% increase in the number of mice that were runts (defined as weighing less than three standard deviations below average) among the exposed litters, but this difference was not statistically significant. Fetal rats exposed to the same regimen did not have lower birth weight or excessive delays in ossification. However, there were a greater proportion of fetal resorptions among exposed rats than among unexposed rats. This effect was not observed among 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 pregnant rodents exposed to other solvents in this investigation experienced similar toxicity but their litters were unaffected.

TCE exposure has not been associated with measured adverse pregnancy outcomes in the late stages of gestation except with severe maternal toxicity (40). However, both developmental and behavioral effects in laboratory animals after exposure to TCE have been noted (38,41,42). The timing of the development of human and rat brains is different. Neonatal development of the rat brain corresponds to development of the human brain during the third trimester of pregnancy (43); therefore, behavioral effects observed in neonatal rats might be of significance to the developing human fetus.

Although useful in generating hypotheses regarding the developmental hazards of specific contaminants, toxicologic studies are complicated by the need to extrapolate from animal species and high doses. In addition, laboratory studies do not adequately capture the complex personal and environmental contexts in which human exposures to VOCs occur (44).

EPIDEMIOLOGIC LITERATURE

Several studies have examined the issue of late pregnancy outcomes and occupations in which women might have been exposed to VOCs (45-57). However, fewer of these studies have examined exposure to specific chemicals or chemical classes. Two studies of maternal occupational exposure to solvents (47) and degreasing agents (52) noted small decreases in birth weight ($-41 \text{ g} \pm 124 \text{ g}$ and $-16 \text{ g} \pm 75 \text{ g}$, respectively), but these decreases were not statistically significant. A small case-control study (26 cases) of birth outcomes among female workers in

Sweden, Finland, and Norway found no association between very low birth weight, congenital malformations, or stillbirths and working in the dry-cleaning or laundry industry (58). However, in addition to the limited number of cases, all three outcomes were combined into a single case definition; this categorization did not account for the different times at which developing organisms are vulnerable to stillbirth or very low birth weight and when they are vulnerable to congenital malformations.

Only two studies have evaluated the possible association between halogenated hydrocarbons and late pregnancy outcomes. Savitz et al. (54) noted no association between exposure to halogenated hydrocarbons and SGA (OR: 0.6 [95% CL: 0.2, 1.4]), preterm delivery (OR: 1.1 [95% CL: 0.5, 2.4]), and stillbirth (OR: 1.0 [95% CL: 0.7, 1.5]). Windham et al. (55) noted no association between SGA and maternal exposure to halogenated solvents during the first 20 weeks of pregnancy (OR: 1.1 [95% CL: 0.4, 2.9]); however, fetal growth is considered most vulnerable to environmental insults during the third trimester of pregnancy. Therefore, this latter study might have focused on exposures that occurred at a time when the fetus was relatively invulnerable to effects on birth weight.

Limitations common to many of these occupational studies included: indirect estimates of exposure derived from job titles rather than measured exposure in the work place, the small numbers of women 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 work place (59), the relevant hazards could be difficult to identify. Many of these factors are more likely to introduce bias toward the null hypotheses than they are to introduce associations where none exist, although an upward bias could be introduced by differential participation or recall.

Environmental exposures to toxic substances occur at lower concentrations relative to the occupational setting. However, environmental exposures often occur through contaminated drinking water, while occupational exposures usually occur through inhalation or skin contact. As discussed previously (see "Routes of TCE and PCE Exposure and Metabolism"), PCE and TCE metabolism differ depending on whether these compounds are inhaled or ingested. Environmental exposures are not limited to the 40-hour work week and can occur in populations that are not represented in the work force. Women who are less likely to work include those who cannot find work, those who already have children, and those without economic incentive to work (60). In addition, women who are at high risk for adverse pregnancy outcomes might be instructed by their physicians to cease work during pregnancy (60). These factors all limit the generalizations that can be made from studies of occupational populations to residential populations exposed to environmental contaminants.

The earliest report of a relationship between environmental exposure to toxic substances at hazardous waste sites and late pregnancy outcomes was based on an investigation at Love Canal in Niagara Falls, New York, a former dump site where 248 different chemicals were identified. The prevalence of low birth weight was elevated in two different studies of area residents (61,62). Home ownership among whites in the area of Love Canal where contaminants

had seeped into the basements of several homes was associated with a 60% increase in low birth weight compared with all white residents of upstate New York (OR: 1.6 [95% CL: 1.0, 2.3]). Both the rate of low birth weight and the rate of prematurity were higher among Love Canal homeowners compared with rates among homeowners in neighboring areas of Niagara Falls (low birth weight OR: 3.1 [95% CL: 1.3, 7.1], prematurity OR: 1.4 [95% CL: 0.8, 3.5]). However, no increases in low birth weight (OR: 1.1 [95% CL: 0.5, 2.3]) or preterm delivery (OR: 1.1 [95% CL: 0.6, 2.2]) were observed among renters at Love Canal when compared with rates among renters in neighboring areas.

More recently, an increased prevalence of term low birth weight (another index of intrauterine growth retardation) was found among residents near Lipari landfill in Gloucester County, New Jersey. During the years when odors were greatest at the site, the OR was 5.1 (90% CL: 2.5, 10.6) (63). 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 (64), and an ecologic study conducted of hazardous waste sites in five counties in the San Francisco Bay area of California (65) reported no associations between proximity to site and low birth weight (OR: 0.9 [95% CL: 0.3, 2.7]) or MBW (-0.6 g \pm 12.3).

Each of the studies of birth weight around hazardous waste sites, summarized in Table 5, had methodologic problems. One problem faced at Love Canal was that the families living closest to Love Canal were relocated before the study was conducted (61), and the remaining families were evacuated selectively, beginning with those families with pregnant women and young children (61,66). Hence, selective migration could have introduced bias in the association between exposure and outcome. Selective migration also is likely to be a problem at other hazardous waste sites, especially when strong odors reduce the quality of life in a neighborhood. In such a situation, residents with the highest incomes (who would be at the lowest risk (10)) and residents who were most sensitive to the exposures would be most likely to leave the vicinity. Although the effects that selective migration had on the results cannot be predicted, it seems reasonable that the results of the Love Canal evaluation might have been biased toward the null hypothesis. The women who were most likely to have been exposed had already been evacuated and were not included in the study.

The conflation of preterm delivery and SGA births in all but two of the studies probably reduced the observed effect measures. Failure to account for such etiologic heterogeneity has been discussed in detail elsewhere (67). The study conducted at Lipari landfill demonstrates this problem: the association found between residence near the landfill and low birth weight in full-term infants was stronger than the association found between residence near the landfill and low birth weight in all infants (63).

Small numbers were also a problem, especially at the Stringfellow site (64), limiting the precision of the observed effect estimates. In most cases however, it would not have been appropriate to increase the sample size because this would have created a more heterogeneous

exposure and, therefore, would have diluted the observed association between exposure and outcome. Control for most major risk factors was addressed in the studies summarized in Table 5, except for smoking, which was not measured in the studies in San Francisco, California (65), or Gloucester County, New Jersey (63). However, both the San Francisco and Gloucester County studies controlled for demographic variables that would have minimized bias from smoking.

The most important limitation to the studies summarized in Table 5 was misclassification of exposure. In all these studies, proximity to the hazardous waste site was the primary classification of exposure. Although there was some evidence of population exposure to VOCs based on reports of odors, and at both Love Canal and Lipari minimal air measurements were taken, it was difficult to determine if the persons included in the studies had been exposed and, if so, to which substances and at what concentrations. Because both the probability of exposure and the chemical mixture at each site differ, it was difficult to evaluate, on the basis of consistency across these studies, whether exposure to hazardous waste reduces birth weight. However, in general, it seems reasonable to infer that environmental exposure to some compounds or combinations of compounds found at hazardous waste sites might decrease birth weight at least at some sites.

Studies of populations consuming contaminated drinking water, although still imprecise, are a substantial improvement over studies based on proximity to site. Even when exposure data are limited and multiple contaminants are detected in the same water distribution system, studies that focus on drinking water provide a well-defined route of exposure, leaving less uncertainty as to whether there is an exposed population, how many persons might be exposed, which 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 with exposure in other studies. Only three analytic studies have investigated the relationship between TCE, PCE, or DCE in drinking water and late pregnancy outcomes (68-70). As summarized in Table 6, contaminant levels measured in these studies were comparable to, or lower than, those observed at Camp Lejeune (68-70).

Two studies were conducted in Woburn, Massachusetts, where two wells that supplied the town were found to be contaminated with TCE, PCE, and chloroform. In the first of the Woburn studies (68), self-reported outcomes were examined for 4,396 pregnancies from 1960 through 1982. An important feature of the study was that the investigators used information about the municipal use of supply wells in different areas of Woburn to characterize exposure. Based on a logistic regression model that examined exposure as a continuous variable, women who received 100% of their water from contaminated wells had a tenfold increase in risk for perinatal mortality relative to women who received no water from contaminated wells. Although this risk estimate is impressive, it was based on small numbers (four exposed cases). Furthermore, only two women whose infants died could have received 100% of their water supply from contaminated wells. This effect was noted only among pregnancies occurring after 1970, with no increase in perinatal mortality noted among women exposed during the first 10 years of the study. Because exposure was not measured before 1979 (i.e., when tests first

became available) it is possible that there was less or no contamination during the earlier study period. Despite the magnitude of the observed association, the small number of exposed cases and inconsistency across time periods raises the possibility that this finding was artifactual (i.e., arising through chance or confounding). 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 nonstandard definition of low birth weight was used. Other limitations included the sample selection process, which was based on residence in Woburn at the time the study began, and the convenient selection process which could have resulted in selection bias.

The second study conducted at Woburn addressed a number of the methodologic limitations of the first study by examining birth weight as recorded on birth certificates of infants born to residents of Woburn during the time of exposure (69). The most relevant comparisons in this study of SGA were those between birth weights of live-born infants of East Woburn residents who were exposed to high or moderate levels of contaminants during 1975 through 1979 and live-born infants of East Woburn residents who were not exposed to contaminants. For the approximately 3,000 live births, the prevalence of SGA was not elevated among live-born infants of women who were highly exposed (OR: 1.1; 95% CL: 0.5, 2.4) or moderately exposed (OR: 0.7; 95% CL: 0.4, 1.4) when exposure was classified on the basis of the entire pregnancy. However, when the exposure classification was restricted to the third trimester, the ORs were 1.6 (95% CL: 0.9, 2.8) and 1.3 (95% CL: 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," (69) the specificity of these findings—that is, increasing ORs with more refined classification of exposure and outcome—provides some evidence for an association between TCE exposure and SGA.

The relationship between exposure to TCE, PCE, and DCE¹ and late pregnancy outcomes in drinking water was also examined for the entire state of New Jersey (70). Information was obtained from birth certificates and fetal death certificates; exposure levels were based on semiannual, quarterly, or monthly monitoring of drinking water. Maternal residence 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, or DCE exposure and SGA, preterm birth, or fetal death, the median exposures evaluated were 200–1,000 times lower than the exposures evaluated in this study.

Overall, knowledge about the potential relationship between PCE, TCE, and 1,2-DCE exposure and late pregnancy outcome is limited; although the results of several studies indicate that environmental exposure to these VOCs might affect late pregnancy outcomes, literature on this topic is limited and equivocal. Maternal occupational exposure to solvents and other VOCs has been associated with increases in stillbirths (51,53,54) and decreases in birth weight (53).

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

However, two occupational studies that focused specifically on halogenated hydrocarbons reported no associations between these exposures and stillbirths, preterm deliveries, or birth weight (54,55). Low birth weight has also been associated with residence near two different hazardous waste sites containing large quantities of VOCs and other chemicals (61-63), but the exposures were too poorly defined and too complex to permit generalizations from these hazardous waste sites to others. Only the investigations (69,70) conducted in Woburn, Massachusetts, examined the relationship between perinatal mortality and SGA and a chemical exposure at concentrations similar to those at Camp Lejeune. These investigations found increased rates of perinatal mortality and moderate excesses in SGA, but both associations were based on small numbers.

In addition to this direct, albeit limited, evidence that one or more of the solvents studied are associated with adverse late pregnancy outcomes, two studies have noted associations between term low birth weight and SGA and exposure to carbon tetrachloride (70) and trihalomethanes, including chlorinated compounds of similar chemical structure (70,71). Other reports suggest that occupational or environmental exposures to solvents in general, and to TCE or PCE in particular, can cause other adverse pregnancy outcomes, such as spontaneous abortion, cardiac anomalies, oral clefts, and neural tube defects (42,55,70,72,73).

Finally, there may be an association between solvent exposure and maternal complications of pregnancy. In a small prospective study of women occupationally exposed to solvents, Eskenazi et al. found increased rates of preeclampsia (OR: 3.9; 95% CL: 2.4, 5.4) and hypertension (OR: 3.0; 95% CL: 0.9, 9.9) (47). Moreover, these complications were restricted to women who worked during their second trimester of pregnancy. In a small case-control study of 130 pregnant residents of an industrial area of Bulgaria, Tabacova et al. (74) found substantially increased odds of exposure to styrene among pregnant women with anemia (OR: 2.4; 95% CL: 0.5, 13.8), proteinuria (OR: 7.4; 95% CL: 1.7, 37.2), hyperemesis (OR: 13.1; 95% CL: 1.4, 165.9), arterial hypertension (OR: 26.4; 95% CL: 2.2, 1266.8), and nephropathy (OR: 30.8; 95% CL: 2.6, 1448.0). However, as one might gather from the wide confidence intervals², that study was extremely small. Although the literature relating VOC exposure to medical complications of pregnancy is only suggestive, it provides a biologically plausible mechanism by which exposure to VOCs might affect fetal growth.

In summary, information is sparse regarding the relationship between exposure to organic solvents, such as PCE and TCE in drinking water, and late pregnancy outcomes; and PCE and TCE frequently occur in the environment. Only three studies have examined directly the relationship between PCE or TCE in drinking water and late adverse pregnancy outcomes. Only two of those studies, both analyzing data from the same city, observed exposures of similar

²Odds 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 EpiInfo. For computational purposes, one count was added to each cell for arterial hypertension and nephropathy because there were no nonexposed cases in either of these groups.

concentration to the exposures experienced at Camp Lejeune. This study at Camp Lejeune 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 contaminated with VOCs until the mid-1980s. Because a sizable population of young, married women were supplied with this water in their homes, concern has been raised about the potential adverse effects of VOCs on pregnancy outcomes. An association between VOC-contaminated drinking water and adverse late pregnancy outcomes is plausible, but further investigation is needed. The health significance of VOC contamination in drinking water is of particular interest at Camp Lejeune because some of the site's VOC plumes are still unremediated and might contaminate other supply wells in the future. Although Camp Lejeune supply wells are monitored on an annual or semi-annual basis as a protective public health measure, this action may not protect all segments of the population. Fetal development can be disrupted by toxic chemical exposures in less time than the 6-month intervals at which the wells are being monitored. Hence, additional knowledge of the risks presented by these plumes might be useful in managing the potential risks from the unremediated plumes.

This cohort study examined the relationship between VOC exposure and fetal growth retardation (measured as SGA and decreased MBW) and preterm delivery in three groups with different exposures to contaminated drinking water and in an unexposed comparison population. The primary objectives of this investigation were to evaluate the following three hypotheses:

1. Residence in each of the exposed housing areas was associated with fetal growth retardation, measured as SGA and decreased MBW.
2. Residence in each of the exposed housing areas was associated with preterm birth.
3. Residence in each of the exposed housing areas was associated with late fetal death. This third hypothesis could not be tested because of poor data quality (see Data Quality).

The primary sources of data were birth and fetal death certificates at the North Carolina Vital Statistics Office. For each of the three categories of exposed births defined later, MBW, the prevalence of SGA and preterm births, and the ratio of fetal deaths per singleton live births were compared with these outcomes in unexposed births. In addition, the effects of timing and duration of exposure were examined by linking data from family base housing with birth and

fetal death certificate data. The rationale and methods employed to complete three secondary objectives previously described (see Objectives) are included in Appendices A and B of this document.

STUDY POPULATION

The study population consisted of all singleton live-born and stillborn infants delivered at ≥ 20 weeks of gestation during 1968–1985 to families residing in base family housing units at Camp Lejeune. Residents of Camp Geiger and Knox Trailer Parks were excluded because of incomplete housing records and ambiguity regarding their drinking water source. Approximately one-third of the women who sought prenatal care at the Navy Regional Medical Center at Camp Lejeune moved or were transferred before they delivered (CDR J. McGinnis, Camp Lejeune, personal communication). These women could not be identified; however, their exclusion from this analysis probably did not introduce selection bias because rates of mobility were not expected to be associated with being exposed to VOCs.

North Carolina Vital Statistics Data Files

Since 1968, the state of North Carolina has maintained computerized databases of live births and fetal deaths occurring at > 20 weeks. During 1968–1985, the state used two versions each of the birth and fetal death certificates and three versions of the database file format.

The smallest recognizable unit for which birth and fetal death records could be selected from the data files was county of residence; information about the mother's ZIP code and residence on base was not available for the study period. Eligible births and fetal deaths, therefore, were identified by searching all records for Onslow County residents. For live births during 1975–1985, computerized records were searched for eligible street addresses. For the years 1968–1974, the mother's street address and city of residence were not included in computerized birth certificate files. In addition, other important information (e.g., exact birth weight in pounds and ounces) was 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. Relevant information from records containing eligible street names was then entered into a computer file.

Some housing units on eligible streets were not eligible for inclusion in the study. For example, units 2000 through 2999 Onslow Drive were base family housing units, but housing units with numbers of 3000 or higher were privately owned. 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.

The mother's street address was not available in databases containing fetal death records. For fetal deaths occurring from 1968 through 1977, the mother's address was computerized from hard-copy records, and eligible records were identified in a process similar to that described for live births. Fetal death certificates for 1980–1985 were destroyed in accordance with North

Carolina state law. Therefore, the housing record database was searched for matches with the father's name from the fetal death certificate, and eligibility was based on the housing records.

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 (e.g., seaman first class or captain) of the person to whom the housing unit is assigned; (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 88,000 names and addresses were identified. 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 pregnancy interval had to have occurred 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 records. When the father's name did not match either by a computerized or a manual search, then a match was attempted on the mother's name. For the few parents who were dependents, matches were made by address and the 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.

If a birth or fetal death record contained no address information, the housing record database was searched for matches with the father's name from the birth or fetal death record. A match was considered acceptable if the father's name on the housing record and the birth or fetal death record were the same, if the dates of occupancy for the housing record coincided with the time of the live birth or fetal death, and if no more than two other persons with the same first, last, and middle initial were identified in the housing record. Different persons with the same name were distinguished by comparing multiple housing records for dates of occupancy. In general, the dates of occupancy were contiguous for individuals who had more than one housing record. When the dates of occupancy were overlapping or separated by long time periods, it was assumed that different individuals with the same name had been identified. Although occurrences of several people with exactly the same first and last names and middle initials in the housing records were rare, excluding such person from the analysis minimized the possibility that fetal death records were randomly matched with a housing record coincidentally containing the same name as the death record.

DEFINITION OF STUDY OUTCOMES

The outcomes that were studied are MBW, SGA, and preterm birth. All data regarding these outcomes were obtained from North Carolina birth records.

Live births occurring at less than 37 weeks of gestation were defined as premature. Gestational age was based on the date of the last menstrual period. For observations with a valid

month and year of last menstrual period, but a missing day, the day was interpolated to the value of 15. Last menstrual periods with a valid month and day but no year were assigned to the year that would yield the most biologically plausible gestational age. Last menstrual periods in which the month of the last period was not reported were excluded. The effects of missing gestational age were evaluated by comparing birth weight distributions and demographic information between births with missing and nonmissing gestational age data.

Birth weight in pounds and ounces was obtained from the birth certificate and converted to weight in grams. An SGA birth was defined as a singleton live-born infant weighing less than the 10th percentile based on published sex-specific growth curves. The standard published by Williams et al. (75) for whites in the state of California was selected because it (1) was derived from birth certificate, (2) was based on a large group of live births occurring during the midyears of the study period, (3) was published in a reputable journal and in an easily read format, and (4) categorized approximately 10% of unexposed births as SGA. No other published standard met these criteria.

Although Williams published a standard for whites only, this standard was applied to births among women of all races. This decision was made because published race-specific standards were not readily available during the time period under investigation. Analyses were stratified on this variable to ensure that race did not confound the association. To provide further reassurance that use of the Williams data set for births to black women did not bias the results, some of the data were reanalyzed using an unpublished race-specific standard developed by the state of New Jersey for white and black births that occurred during 1985–1988. 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.

An attempt was also made to study late fetal deaths. A late fetal death was defined as any fetal death occurring at 20 or more weeks of gestation for which a North Carolina fetal death certificate was filed. Fetal deaths were not studied because of incomplete data (see Data Quality).

DEFINITION OF EXPOSURE

Infants identified from birth and fetal death certificates were divided into three distinct exposed groups, which are summarized in Table 2. These groups are referred to as (1) PCE exposed; (2) long-term TCE exposed; and (3) short-term TCE exposed. The mothers of PCE-exposed children resided at Tarawa Terrace for at least 1 week before birth occurred. Mothers of long-term TCE-exposed infants resided at Hospital Point during 1968–1985 for at least 1 week before the children were born. 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 (1) the mother resided in Berkeley Manor, Midway Park, Paradise Point, or Watkins Village at the time of birth and for a minimum of 1 week during January 27 through February 7, 1985; (2) the

mother's last menstrual period was on or before January 31, 1985; and (3) the birth occurred after February 2, 1985. These dates were selected to ensure a minimum of 1 week of exposure to TCE during pregnancy. Births to the remaining residents of base family housing were considered unexposed. The unexposed 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 infants whose exposure to PCE or to TCE on a short-term basis was unknown were excluded from the study. These included infants whose fathers had short-term exposure during spermatogenesis (i.e., based on the mother's last menstrual period); 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 during February 8–21, 1985. Although all of the contaminated wells were closed on or before February 7, 1985, the first day that water samples were entirely free of contamination was February 21, 1985. Therefore, residents who were not exposed during a known period of contamination, but who lived in the affected housing units during this ambiguous exposure period, were excluded.

Membership in each of these exposure groups was based on residence in a housing area known to have received contaminated water. Within each housing area receiving contaminated water, every housing unit probably received similar concentrations of contaminants; however, information regarding tap water concentrations in each housing unit was unavailable. Information about behavioral risk factors that would have affected exposure levels, such as showering and drinking water patterns, also was unavailable.

ANALYSES

Separate analyses were conducted for each of the exposure-outcome combinations defined previously. For dichotomous outcomes (SGA and preterm delivery), odds ratios (ORs) were computed relating exposure to outcome using the SAS software package (76). MBW was also computed using the SAS software package. The two main criteria for identifying elevations in the dichotomous outcomes and decreases in MBW were the size and the plausibility of the association. The degree of variability in the data was examined by computing the 90% confidence interval (CI). For most analyses, 90% CIs were computed using the logit estimators produced by the SAS statistical package (77,78). However, when the number of either exposed or unexposed cases was fewer than 10, ORs 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 (79).

The following characteristics from the birth certificates 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 educational level, father's age, father's educational level, parity, adequacy of prenatal care, maternal history of fetal deaths, and mother's marital status. In

addition, military ranks obtained from housing records were standardized into nine enlisted pay grades (E1-E9), four warrant officer pay grades (WO1-WO4), and six officer pay grades (O1-O6). Pay grade is an accurate measure of income for the active duty member of the household, although information was unavailable about the occupation and income of the parent not listed on the housing card.

Each possible confounder or effect modifier was evaluated separately by using 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 factors against the study outcome, and (3) the association between exposure and outcome variables that was stratified on the potential confounder differed from the association between exposure and outcome variables that was not stratified on the potential confounder. The variables, maternal age, maternal and paternal educational levels, parity, year of birth, gestational age, and military pay grade, were collapsed to a minimal number of categories for the purposes of stratified analyses and, in some cases, for multiple regression (linear and logistic) analyses. Cut-off points for these variables were selected on the basis of both their distribution and their relevant social or biologic meaning. Histograms, scatter plots, and plots of means at different levels of each factor were employed to examine the distributions of these variables.

The potential for effect modification consisted of a simple inspection of ORs, or means in different strata, and a Breslow-Day test for homogeneity (80). Ideally, effect modifiers would be identified *a priori* (81), but current information is insufficient to determine which risk factors might act as effect modifiers. In the absence of a well-developed literature, the potential biologic and sociological relevance of each potential effect modifier were considered.

Each variable that was either an effect modifier or a confounder (i.e., based on the results of stratified analysis) was retained in analyses for multiple logistic regression or linear regression modeling, and was eliminated in a backwards fashion. For SGA and preterm births, potential confounders were eliminated from a model if their removal did not change the ORs relating exposure and outcome (or the ORs for different exposure-covariate combinations if interaction terms were used) by more than 10%. For MBW, potential confounders were eliminated from a linear regression model if their removal did not change the effect estimate by either a minimum of 20 g or 10% of the effect estimate, whichever was greater. For analyses of dichotomous outcomes, variables that indicated effect modification (also known as interaction terms), were included in logistic regression models if they were biologically plausible, described heterogeneous groups in which the ORs differed by more than 25%, and had P values less than 0.20. A less stringent P value for effect modifiers was used because of the low statistical power available to detect them (82). The choice of a 25% change was arbitrary, but provided an effective decision rule for screening potential effect modifiers. For MBW, covariates for which at least one stratum-specific estimate showed a mean difference between PCE-exposed and PCE-unexposed births of -50 g or less were examined more closely for effect modification. Statistical significance was not helpful in identifying effect modifiers for MBW because the statistical power was so great overall that almost every parameter estimate was statistically significant.

Years of Exposure

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

Timing and Duration of Exposure

The third trimester of pregnancy is usually regarded as the most important for fetal growth and toxicity resulting in delayed fetal growth (83). 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 (84). A cumulative effect of exposure might also be possible (85), and the influence of the exposure of timing on pregnancy outcome has not been fully determined (86). In addition, the population at Camp Lejeune has always been unusually mobile. Approximately one-third of women receiving prenatal care at the Navy Regional Medical Center move to another base or into civilian life between the first prenatal care visit and delivery. If exposure is necessary in the early part of the pregnancy or during spermatogenesis to observe an outcome, then use of maternal residence at time of birth can, by including persons who were not exposed at these critical times, reduce or obscure an important association.

To address these concerns, the dates of occupancy for each household were examined to determine whether and when each family moved during 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. Based on discussions with Camp Lejeune personnel, it was determined that most women who had given birth while living at Camp Lejeune had remained in the same housing unit until after the delivery. Therefore, it was assumed that each family resided in only one base housing unit during the pregnancy, an assumption that was evaluated and is presented in a later section. Therefore, except for births occurring after the exposure ceased, length of exposure indicates the number of consecutive weeks before delivery that the mother lived in exposed housing. For example, a woman residing in exposed housing for 10 weeks during pregnancy was exposed 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 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 of duration of exposure.

Births were categorized in the following groups depending on length of exposure: births to mothers exposed for 1–3 weeks, for 4–10 weeks, for 11–20 weeks, for 21–45 weeks, before conception and throughout pregnancy, and 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 the most important; in this case, birth outcome would not differ by exposure category. 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 that effects would increase with duration throughout pregnancy. Other biologically plausible scenarios were that an association would be observed only in infants born to mothers who were exposed during the entire first trimester or in infants of 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 infants born to mothers who were exposed during the first 12 weeks of pregnancy when spontaneous abortion rates are highest, and then a duration-response relationship would be observed thereafter. There were also scenarios that were considered to be implausible. For example, it would be implausible to observe less of an effect among the women who were exposed for the longest time periods relative to women exposed for shorter periods, except where the pattern was consistent with selective survival. Because length of residence during pregnancy was a function of length of gestation, the percentage 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, both week of gestation at time of exposure and weeks elapsed between exposure and birth were examined.

DATA QUALITY

A total of 12,493 live births and 83 fetal deaths that met the study selection criteria were identified. Figure 1 shows fetal death ratios for Camp Lejeune by race and year of birth compared with overall fetal death ratios for the United States (87). Because of the small numbers of fetal deaths within some racial groups each year, 5-year averages were computed for each 5-year period starting with 1968 through 1972 (midpoint was 1970) and ending with 1981 through 1985. As illustrated in Figure 1, the fetal death ratio for whites in Camp Lejeune was about half of that expected for most of the study period; the fetal death ratio for nonwhites was close to that expected until 1972, but was approximately five times less than expected by 1982. In addition, less than half of the fetal death certificates listed a cause of fetal death. Given the low likelihood that these rates were accurate, and the expectation that all causes of fetal death would not be uniformly associated with VOC-exposure, no further analyses were conducted for the fetal death outcome.

Table 7 contains the distribution of live births in each exposure group. Forty-four births were deleted from analyses because the mothers were exposed for less than 1 week during pregnancy or only during spermatogenesis. Of the remaining 12,449 births, 479 (3.9%) were eliminated from all analyses because of poor data quality. The total numbers of observations included in or excluded from each analysis are presented by exposure group in Table 7. Some observations were eliminated for more than one reason, such as an infant who reportedly weighed less than 350 g and who had no data 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 in each category into which they fell. Therefore, the numbers in Table 7 do not add up to 100%.

Live births at less than 22 weeks of gestation were eliminated only from the SGA analyses. These births were not eliminated because of poor data quality, but because the population standard selected to compute SGA began at 22 weeks. The number of births eliminated for this reason was less than 0.1%.

In addition to observations that were entirely excluded from MBW and SGA analyses, there were a number of observations with questionable values for gestational age. It is well recognized that, in most populations, there are a disproportionate number of infants who are classified as very preterm that are heavier than would be expected for their gestational ages; most of these heavy, very preterm infants are actually infants born at later gestational ages than indicated in the birth certificates (88). To determine if the gestational ages for infants classified as very preterm were more commonly misclassified, the distribution of birth weights among these infants was compared with the standard birth weight distribution at each gestational age (75). Of live births at less than 28 weeks of gestation, 17% were above the 90th percentile reported for the standard population, although only 10% would have been expected. These data values were marked as unlikely but were not excluded from the MBW and SGA 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 represented a large proportion of early preterm births, but only 1% of all live births. Another set of questionable gestational ages were those that were estimated because the day of the last menstrual period was missing from the birth certificate (i.e., approximately 2.7% of the data). The final models for SGA and MBW were analysed by both including observations with unlikely or interpolated gestational ages and excluding them. Unless explicitly discussed, reanalyses without these data points had negligible impact on study results.

Preterm live-born infants that weighed more than the 90th percentile for birth weight at 36 weeks of gestation were excluded from the preterm birth analyses. Inclusion of these heavy, preterm infants substantially affected the total number of preterm infants in each exposure category.

RESULTS

PCE EXPOSURE

The distribution of demographic characteristics in the unexposed and PCE-exposed groups is presented in Table 8. PCE-exposed mothers were less likely to live in officer's 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 9 contains results of the analyses of birth outcomes comparing PCE-exposed and PCE-unexposed residents. The difference in mean birth weight between the PCE-exposed and PCE-unexposed groups was -24 g (90% CL: -41, -7). The OR for PCE exposure and SGA was 1.2 (90% CL: 1.0, 1.3). The OR for PCE exposure and preterm birth was 1.0 (90% CL: 0.9, 1.2). None of the demographic characteristics examined met the criteria for confounding; therefore, adjusted estimates are not presented.

Year of Birth

When the analyses were restricted to data for 1982-1985, the effect estimates changed only slightly and without any pattern. The difference in MBW adjusted for residence in an officer's household was +5 g (90% CL: -34, +44) between PCE-exposed and PCE-unexposed births for these years, and the OR for PCE and SGA adjusted for father's level of education and military pay grade was 1.3 (90% CL: 1.0, 1.8). The OR for PCE and preterm birth was 0.7 (90% CL: 0.6, 0.9) adjusted for father's level of education and mother's race.

Duration of Exposure

Tables 10 and 11 present analyses based on the duration of exposure to PCE. Differences in MBW ranged from -31 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. For preterm births, the ORs ranged from 0.8 to 1.3 and did not follow any clear pattern with duration of exposure.

Potential Interactions Between PCE and Demographic Characteristics

Crude stratum-specific estimates of the differences in MBW for PCE-exposed and PCE-unexposed infants were computed for each covariate of interest. For mother's race, military pay grade, mother's age, mother's history of fetal death, and father's level of education, at least one crude stratum-specific estimate had a mean difference of >50 g between PCE-exposed and PCE-unexposed infants. Table 12 contains adjusted stratum-specific estimates of the difference in MBW between exposed and unexposed infants for these potential effect modifiers. After adjustment for other covariates, only mother's age clearly modified the association between PCE exposure and MBW. In mothers younger than 35 years of age, the adjusted difference in MBW between PCE-exposed and PCE-unexposed mothers was -9 g (90% CL: -23, +6). The adjusted difference in MBW between infants of PCE-exposed and unexposed mothers 35 years of age or older was -205 g (90% CL: -333, -78). A much weaker effect modification was observed between PCE exposure and mother's history of fetal death. The adjusted difference in MBW between infants of PCE-exposed and PCE-unexposed mothers who had no history of fetal death was -21 g (90% CL: -40, +3). A similar estimate of -28 g (90% CL: -79, +24) was seen for PCE-exposed and PCE-unexposed infants born to mothers with one previous fetal death. The adjusted difference in MBW in PCE-exposed and PCE-unexposed infants born to mothers with two or more fetal deaths was -91 g (90% CL: -190, +8).

Crude stratum-specific estimates of the association between PCE exposure and SGA births were computed for each covariate of interest. In crude analyses, military pay grade, mother's age, and mother's history of fetal deaths contained at least one stratum that differed from the overall effect estimate by more than 25%. Table 13 contains adjusted stratum-specific estimates for these covariates. After adjustment for other confounders, mother's age and mother's history of fetal death were both effect modifiers of the association between PCE exposure and SGA. In infants born to mothers less than 35 years of age, the adjusted OR for the association between PCE exposure and SGA was 1.1 (90% CL: 1.0, 1.2). In infants born to mothers 35 years of age or older, the association between PCE exposure and SGA was 4.0 (90% CL: 1.6, 10.2). In infants born to mothers with histories of two or more fetal deaths, the OR for PCE exposure and SGA was 2.5 (90% CL: 1.5, 4.6). For infants born to mothers with one previous fetal death, the OR for PCE exposure and SGA was 1.4 (1.0, 1.9). In infants born to mothers with no history of fetal deaths, the OR was 1.0 (90% CL: 0.9, 1.1). The slightly lower prevalence of SGA in mothers with one fetal death compared with mothers with no fetal deaths reflected the greater parity of these mothers.³ Because (1) the baseline rate of SGA in the group of unexposed infants of mothers who had had two or more fetal deaths was slightly lower than the prevalence of SGA among infants of mothers who had no histories of fetal deaths, (2) the total number of births to mothers who had two or more fetal deaths was small, and (3) because there was some evidence of effect modification even among mothers with only one previous fetal death, the categories for one previous fetal death and two or more previous fetal deaths were collapsed. The adjusted OR for PCE exposure and SGA among mothers with a history of one or more fetal deaths was 1.6 (90% CL: 1.2, 2.1).

Duration of Exposure to PCE in Mothers With Histories of Fetal Deaths

The influence of duration of exposure in the PCE-exposed and PCE-unexposed groups was explored for mothers with histories of one or more fetal deaths (Tables 14 and 15). Differences in MBW ranged from -121 g to +5 g, and ORs for SGA ranged from 1.4 to 2.1. These effect estimates did not follow a pattern of increasing effect with increasing duration. However, the CIs were sufficiently wide that it was difficult to conclude whether any real differences were present across the duration of exposure categories. There were too few mothers aged 35 years or older to permit analysis of duration of exposure in this group.

LONG-TERM TCE EXPOSURE

The demographic characteristics for the long-term TCE-exposed group and an unexposed comparison group are described in Table 16. Because the housing area where long-term exposure to TCE occurred was for officers' families, a comparison group consisting of infants born to

³The baseline SGA rate in unexposed mothers who had no history of fetal death but had previously had a pregnancy was 7.8%, which was much closer to the rates of 8.5 for unexposed mothers with one previous fetal death and 6.7 for unexposed mothers with two or more previous fetal deaths.

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 the distribution of sex of infant, mother's age, military pay grade, 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 17. A -108 g (90% CL: -230, -13) difference in MBW and an OR of 1.5 for SGA (90% CL: 0.5, 3.8) were observed in the exposed group compare with the unexposed group. There were no preterm births in the long-term TCE-exposed group. After adjustment for gestational age, the difference in MBW was -139 g (90% CL: -277, -1) in the TCE-exposed group. Because there were only three TCE-exposed infants 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 OR by more than 10%.

Interaction Between Long-Term TCE Exposure and Sex of Infant

Because there were so few observations in this category, 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 this interaction was so large that it was observed by simple inspection of the data. Adjusted models for the association between TCE exposure and MBW are presented by sex in Table 18. For females, there was almost no difference in MBW between the exposed and the unexposed groups. In exposed males, however, the difference in MBW was -312 g (90% CL: -632, -102) compared with their unexposed counterparts. Table 18 also examines the influence of duration of exposure on MBW. In models restricted to infants of mothers who resided in family base housing for 20 or more weeks during pregnancy, the difference in MBW between the exposed and unexposed groups was similar to that observed for the entire data set. However, the small number of exposed women residing in base housing for 20 weeks or more made this difficult to examine.

Interaction between sex and long-term TCE exposure was also present in the SGA analysis (Table 19). All three infants who were SGA were males. The OR for long-term TCE exposure among male infants was 3.9 (90% CL: 1.1, 11.8). No females in the TCE-exposed group were SGA, compared with 1.1 expected based on the prevalence of SGA in the unexposed group. The mothers of each of the three SGA infants in the long-term TCE-exposed group resided in an TCE-exposed housing area during the entire pregnancy.

SHORT-TERM TCE EXPOSURE

The distributions of demographic characteristics between short-term TCE-exposed and unexposed residents are compared in Table 20. By definition, all of 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 infants born during 1983-1985 were

included in the unexposed group. Except for slight differences in parity and maternal education level, the exposed and unexposed groups were comparable demographically.

Table 21 presents crude analyses of birth outcomes among residents of unexposed and short-term TCE-exposed housing. MBW was slightly higher in the exposed group for both sexes combined. There were no differences in MBW in analyses restricted to males only. The prevalence of SGA was lower in this group compared with 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 first week of gestation to the fortieth week. 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 2 and 3). However, the number of observations within each time frame of exposure was quite small. The five SGA infants in the short-term TCE-exposed group did not share any distinct characteristics with regard to timing of exposure.

DISCUSSION

The main findings of this study were as follows:

1. No association was observed between PCE exposure and MBW, and a weak association was observed between PCE exposure and SGA infants, overall. Much stronger associations were observed between PCE exposure and both birth weight outcomes among the infants of mothers who were 35 years of age or older and among the infants of mothers who had histories of fetal deaths, especially mothers who had had two or more fetal deaths.
2. A modest association was observed between long-term TCE exposure and decreased MBW and increased SGA births, overall. In male infants, the association between long-term TCE exposure and these study outcomes was much more pronounced. No association was observed between long-term TCE exposure and decreased MBW and increased SGA births among female infants.
3. No association was observed between short-term exposure to TCE and MBW or SGA births.
4. No association was observed between any exposure group and preterm delivery.
5. Fetal death reporting was not complete enough to include in the analyses.

PCE EXPOSURE

In the analyses of PCE exposure, a slight but statistically significant difference in MBW was observed between the exposed and comparison groups. However, the mean difference was so small as to be clinically negligible.

Given the lack of an association between PCE exposure and birth weight in the overall study population, and given the large number of persons in the study, 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 in some small subgroups. Sources of uncertainty remained, not only for the subgroups in which elevations were found, but also because some potentially important confounders (e.g., maternal smoking, alcohol consumption, and height) were not controlled for in the analysis. It seems unlikely that these factors could have totally obscured a strong effect, especially in a population as homogeneous as the one studied.

Misclassification of both exposure and outcome is a problem in almost every epidemiologic study. In this study, information on exposure was limited to water quality measurements taken over a 3-year period, while the study examined 28 years of birth weight data. It is, therefore, conceivable that no overall PCE effect was observed because the study population was primarily unexposed. However, this seems unlikely, because the activities that resulted in the PCE contamination occurred throughout the study period, and no large differences existed in the study findings for PCE exposure when the sample was restricted to years of known exposure. In addition, a variety of exposure categories were examined and at most a very weak association was observed among the births in which exposure occurred 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 was intermittent, it probably occurred at least for some days over every month of the study period. Misclassification of gestational age was also possible, especially among the preterm births. These factors could be 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 among the pregnant women included in the study because they would have drunk different quantities of water and would have spent variable amounts of time showering. Lack of information on the variation in the personal habits of individual women precluded quantification of the exposure dose each woman received. Such precise dose information is helpful in risk assessment; however, little is currently known about PCE exposure and birth weight, and such information is not necessary to advance 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 in which PCE exposure was associated with birth weight outcomes—mothers 35 years of age or older and mothers with a history of fetal deaths. There are several reasons to question the meaning of the associations observed in these two subgroups. Of the mothers aged 35 years and older, the number of women studied was relatively small. This is reflected in the wide CIs, 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 by socioeconomic status, even after adjustment for measured risk factors. In addition, because many other maternal risk factors for SGA such as cigarette smoking and alcohol consumption are related to social factors, lack of comparability on demographic characteristics also may have introduced confounding by behavioral characteristics. However, adjustment for residence in an officer's household did not affect MBW, while adjustment for mother's race had a only a minor effect on MBW. For SGA, adjustment for mother's race produced negligible differences, while adjustment for residence in an officer's household actually increased the OR. The negligible impact of adjustment for these confounders suggests that residual confounding by socioeconomic factors or their behavioral correlates was unlikely.

The finding among mothers aged 35 years and older was unanticipated and not explainable. Nonetheless, the association between PCE exposure and adverse birth outcomes among mothers in this age group was sizeable and biologically plausible. As a general rule, older mothers are considered to be at higher risk for adverse reproductive outcomes, especially infertility, miscarriage, and chromosomal anomalies (89). Older maternal age is not always associated with decreased MBW and increased SGA births (90), but factors that have a clear role in reduced birth weight (e.g., pregnancy-induced hypertension) are associated with maternal age (91,92). Moreover, previously published reports indicate that the effects of maternal smoking on birth weight increase profoundly with age (93-96).

The second potentially susceptible subgroup in which an association was observed between PCE exposure and birth weight was the group of women with a history of fetal deaths. This group included women who had had either early or late fetal deaths. As with older mothers, women with a history of fetal deaths might represent a more physiologically susceptible subgroup of women with poorer pregnancy outcomes, including low birth weight (97). Unlike the older mothers, mothers with a history of fetal deaths composed a fairly large group, so that the effect estimates were statistically stable. In addition, there were differences in the strength of the association between PCE exposure and SGA among infants born to mothers who had had only one previous fetal death and to mothers with two or more previous fetal deaths. To the extent that the association increased with the severity of the medical history, it seemed less likely that this association occurred by chance.

Heterogeneity and data quality were a concern for reported history of fetal deaths. 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 unclear whether fetal deaths at these different gestational ages were reported completely. In addition, differences in reporting of fetal deaths based on socioeconomic status might have occurred.

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 persons 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.

One hypothesized mechanism 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 (98-100). An actual link between hormonal changes and older maternal age and mothers with a history of fetal deaths would be difficult to determine. Patterns of hormonal function and activity among women in their thirties have not been well studied. Hormonal changes associated with the onset of menopause occur primarily in women in their forties rather than in their late thirties (101). However, an increase in chromosomally normal spontaneous abortions has been noted among women aged 37 years or older—an effect that could be associated with a decline in uterine function (102). In the study population, older women and women with a history of fetal deaths were distinct groups, but it does seem plausible that changing uterine function could play a role in both risk groups.

Concentrations of PCE in the drinking water at Camp Lejeune might have been too low to influence birth weight within the overall study population, but the minor stress resulting from PCE exposure among groups that are known to have more reproductive problems could have been sufficient to disturb the developmental environment of the fetus. However, given that other known maternal risk factors for reduced MBW and SGA (i.e., young maternal age or maternal race) were not effect modifiers, mere vulnerability does not appear sufficient to result in an association between PCE exposure and delayed fetal growth.

The observed associations in these two potentially susceptible subgroups must be interpreted cautiously. Nonetheless, these findings suggest an important area for future research either at Camp Lejeune or in another PCE-exposed population. 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, and prepregnancy maternal weight would also greatly enrich existing data on this study population.

The pilot study summarized in Appendix B of this document indicates that it would be feasible to obtain medical record information for a sample of women in these susceptible subpopulations. However, it would not address concerns regarding maternal smoking and drinking habits.

TCE EXPOSURE

Strong associations between long-term TCE exposure and birth weight were observed in male, but not female infants. Both the decrement in MBW and the increase in SGA among male infants exposed to TCE compared with unexposed male infants were large and were on the same magnitude of the effect of maternal cigarette smoking reported in the general literature.

The finding of an association in male infants was unexpected, and it reduced the plausibility of a causal association. In studies of male-female differences in TCE metabolism, adult females were found to absorb TCE more completely 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 lipophilic molecule, is more greatly diluted in females, and hence in females a greater proportion of the body's TCE is stored in fat and is not metabolized (23). Male-female differences in body fat concentration are already present at birth (103). These are factors that would be expected to make female infants more—and not less—susceptible to TCE.

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 (104,105). It is possible to 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 (106), are slightly more susceptible to toxic insult, and they might respond to lower doses than females. Males also grow faster late in pregnancy compared with females; this higher growth rate might make them more vulnerable to interference.

In a study of occupational exposure to anesthetic gases and miscarriage, Askrog and Harvald reported a higher than expected proportion of female infants, suggesting a male-specific embryo lethality (107). In a similar study, Cohen et al. (108) did not determine a sex-specific association between anesthetic gas exposure and miscarriage. However, there are a variety of different anesthetic gases, and Cohen et al. (108) did not study TCE. The English summary of the Askrog and Harvald study (107) did not indicate which anesthetic gases were evaluated.

Other studies of environmental exposure to toxic substances and birth weight have observed more pronounced effects in males than in females (63,109,110). The chemicals examined in two of these studies (109,110) were polycyclic aromatic compounds such as polychlorinated biphenyls and dioxins; in the third study (63), the responsible compounds were not identified. In other studies of polycyclic aromatic compounds, sex-specific interactions

involving similar exposures either have not been observed (111) or were not evaluated (112). The differences reported by Rylander et al. (110) between the sexes 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 (113). TCE has a very different chemical structure from these other compounds.

Given the small numbers of long-term TCE-exposed infants, it is also possible that the observed associations in this group occurred by chance or reflected bias. One potential source of confounding was that the long-term TCE-exposed group was a 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 associated with the presence of characteristics unique to health-care personnel or their spouses. Although possible, this seems unlikely because the effects of behavioral factors such as smoking, alcohol consumption, and patterns of use of medical care on birth weight have been studied much more frequently than the effects of TCE on birth weight. These factors have not been observed to have sex-specific effects. Contaminants other than TCE that the active-duty parents (which in all of these cases were the fathers) might have been exposed to at work were also possible sources of confounding. However, these contaminants would not necessarily have been more likely to have a sex-specific effect than TCE.

Chance might also have played a role in the sex specificity of the effects results of this analysis. Because there were only three SGA infants, the fact that they were all male could have been completely accidental. Arguing against this possibility is the generally decreased birth weight of all 12 TCE-exposed infants, none of whom had a birth weight above the average weight for their gestational age, and seven of whom fell below the 25th percentile in birth weight.

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. It might be expected 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 gestational time period is very early in gestation, during embryonic development, because cell death that occurs at this time can affect the development of entire organs. Another relevant gestational time period 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 periods would make it difficult to exclude 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 biologic 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 TCE concentrations occurred 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 Camp Lejeune and other hazardous waste sites.

CONCLUSIONS

Based on the analysis of birth weight and gestational age among residents of base family housing at Camp Lejeune, the following conclusions were made:

1. No association was observed between MBW and SGA and exposure to PCE in the range of 80 to 200 ppb among infants born to mothers who were <35 years of age and had no history of fetal death.
2. Decreased MBW and increased SGA in infants born to women aged ≥ 35 years were associated with exposure to PCE. Smaller decreases in MBW and increases in SGA were associated with exposure to PCE among infants born to women who had a history of fetal death. These findings were not anticipated and should be interpreted with caution. However, they are interesting because they have some biologic plausibility, and they require additional evaluation either at Camp Lejeune or in another PCE-exposed population.
3. No association was found between MBW or SGA and exposure to 1 ppm TCE for 7–12 days. However, whether short-term TCE exposure might be associated with MBW or SGA at particularly critical times during pregnancy could not be evaluated.
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 of the small sample size, which increases the likelihood that the association occurred by chance. In addition, an effect on males and not on females was not anticipated. Nonetheless, study of TCE exposure in a larger population of pregnant women is recommended.
5. No exposure groups were significantly associated with preterm birth.

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TABLES

Table 1.—Summary of contamination history at Camp Lejeune, 1940–1985.

1940s	Base operations began. Degreasing solvents were used and stored in underground storage tanks at Hadnot Point.
1954	Dry-cleaning operation began near the base.
1958	Base dug a supply well for family housing at Tarawa Terrace near dry cleaner's septic system.
1982	
April	New laboratory began analyzing water for disinfection by-products. Unidentified contaminants interfered with analysis.
July	Contaminants detected and identified in two systems.
	Tarawa Terrace 102 ppb PCE Hadnot Point 1,400 ppb TCE 15 ppb PCE
1984	
July	Navy sampled supply wells located near underground storage tanks.
Nov.	Navy notified that a supply well at Hadnot Point was contaminated with benzene.
Dec.	Wells in Hadnot Point system sampled. Water drawn only from wells pumping on the sampling date. Contaminated wells were 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 were shut off.
12	Water from Tarawa Terrace determined to contain no VOCs.
22	Water from Hadnot Point determined to contain no VOCs.

ppb – parts per billion.

VOC – volatile organic compound.

PCE – tetrachloroethylene.

TCE – trichloroethylene.

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

Exposure Group	Water Distribution System	Housing Area Served	Contaminants	Estimated Contaminant Levels ¹	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	900–1,400 ppb 321–407 ppb 35 ppb ² 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	900–1,148 ppb 321–407 ppb	Jan 27–Feb 7, 1985

PCE – Tetrachloroethylene.

TCE – Trichloroethylene.

¹Detection limit was 10 ppb.

²Estimated assuming a dilution factor of 20 from sampling data for well 602.

Table 3.—Concentrations of volatile organic compounds in finished water samples from the Tarawa Terrace distribution system.

Sampling Date	Tetrachloroethylene (in ppb)	Trichloroethylene (in ppb)	1,2-Dichloroethylene (in ppb)
05/27/82	80	ND	NA
07/27/82	76	ND	NA
07/27/82	82	ND	NA
07/28/82	104	ND	NA
02/05/85	215	8.1 ¹	12 ¹
02/12/85 ²	ND ¹	ND ¹	ND ¹
02/19/85 ²	ND ¹	ND ¹	ND ¹

NA - Not analyzed

ND - Not detected

¹Detection limit was 10 ppb.

²The sample was collected after all contaminated wells were taken off line.

Table 4.—Concentrations of volatile organic compounds in finished water samples from Hadnot Point distribution.

Sample Date	Sample Source	1,2-DCE (ppb)	PCE (ppb)	TCE (ppb)	Other (ppb)
05/27/82	Hadnot Point Water System	NA	15.0 ¹	1,400.0	NA
07/27/82	Hadnot Point Water Treatment Plant	NA	< 1.0 ¹	19.0 ¹	NA
07/27/82	Hadnot Point Water Treatment Plant	NA	< 1.0 ¹	21.0 ¹	NA
07/28/82	Hadnot Point Water System	NA	1.0 ¹	ND ¹	NA
12/04/84	Hadnot Point Water Treatment Plant	83.0	3.9 ¹	200.0	ND ¹
12/10/84	Hadnot Point Water Treatment Plant	2.3 ¹	ND ¹	2.3	ND ¹
12/13/84	Hadnot Point Water Treatment Plant	ND ¹	ND ¹	ND ¹	Methylene chloride 54
12/14/84 -12/19/84	Hadnot Point Water Treatment Plant	ND ¹	ND ¹	ND ¹	ND ¹
12/19/84	French Creek Building 540	ND ¹	ND ¹	1.2	ND ¹
01/29/85	Holcomb Blvd. Water Treatment Plant ²	ND ¹	ND ¹	339.8	ND ¹
01/29/85	Married Officers Quarters Bldg 2212 ²	ND ¹	ND ¹	1,040.9	ND ¹
01/31/85	Hadnot Point Water Treatment Plant	321.0	ND ¹	900.0	ND ¹
01/31/85	Berkeley Manor Housing Unit 5531 ²	335.0	ND ¹	905.0	ND ¹

Table 4.—Continued.

Sample Date	Sample Source	1,2-DCE (ppb)	PCE (ppb)	TCE (ppb)	Other (ppb)
01/31/85	Berkeley Manor Housing Unit 5677 ²	368.7	ND ¹	981.0	ND ¹
01/31/85	Paradise Point Officers Club ²	332.4	ND ¹	890.1	ND ¹
01/31/85	Berkeley Manor Elementary School ²	406.6	ND ¹	1,148.4	ND ¹
01/31/85	Holcomb Blvd Water Treatment Plant ²	7.6	ND ¹	26.8	ND ¹
02/05/85 ³	Hadnot Point Water Treatment Plant	150.0	7.5	429.0	vinyl chloride 2.9
02/07/85 ³	Hadnot Point Water Treatment Plant	5.3	ND ¹	16.8	ND ¹
02/07/85 ³	Holcomb Blvd Water Treatment Plant ²	< 2.0	ND ¹	< 2.0	ND ¹
02/07/85 ³	Berkeley Manor School ²	44.8	ND ¹	135.1	ND ¹
02/07/85 ³	Married Officers Quarters 2204 ²	9.0	ND ¹	32.4	ND ¹
02/21/85 ³	Hadnot Point Water Treatment Plant	ND ¹	ND ¹	ND ¹	ND ¹
02/21/85 ³	Holcomb Blvd Water Treatment Plant	ND ¹	ND ¹	ND ¹	ND ¹
04/22/85 ³	Hadnot Point Water Treatment Plant	ND ¹	ND ¹	ND ¹	ND ¹

NA - Not analyzed.

DCE - 1,2-Dichloroethylene.

TCE - Trichloroethylene.

ND - Not detected.

PCE - Tetrachloroethylene.

¹Detection limit = 10 ppb.

²Supplied by Hadnot Point system temporarily after a pump broke in the Holcomb Boulevard system.

³All contaminated wells taken off line by 02/04/85.

Table 5.—Studies of late pregnancy outcomes conducted in areas around hazardous waste sites. ¹

Hazardous Waste Site	Sampling Frame and Exposure Ascertainment (Reference)	Confounders Measured	Outcome Studied (Outcome Definition)	Odds Ratio (95% CI) ² (# Exposed Cases)
Love Canal, NY Active dumping: 1920s–1953 Odors: through 1978	Birth records were sampled of white Love Canal homeowners 1940–1978 for at least 9 months before birth compared with all upstate New York infants. Exposed areas defined by proximity to site and to swale (38).	Maternal age, medical history, smoking, alcohol, education, occupation	Low birth weight (<2,500 g), obtained from weight on birth certificate	Swale area: 1.6 (1.0–2.3) (21) ² Near canal: 0.8 (0.4–1.6) (8) ²
	Telephone logs and census records were used to sample Love Canal homeowners and renters and compare other Niagara Falls residents. All pregnancies examined 1965–1977 (37).	Race, income, education, previous adverse pregnancy, medical history, alcohol, smoking	Low birth weight (<2,500 g), obtained from parental interview	Homeowners: 3.1 (1.3–7.1) (14) Renters: 1.1 (0.5–2.3) (13)
Lipari landfill, NJ Heaviest dumping: 1967–1969 Earliest odor complaints: 1970	Birth certificates of Gloucester County, New Jersey residents were reviewed for the years 1961–1985. Residents in the neighborhood adjacent to Lipari landfill were compared with residents within the study area who lived > 1 km from the landfill (39).	Maternal age, education, race, parity, previous stillbirths, prenatal care, pregnancy complications, and sex of infant	Low birth weight (<2,500 g), obtained from birth certificate Term low birth weight (<2,500 g, ≥37 weeks), obtained from birth certificate	1971–1975: 2.9 (1.5–5.3) (9) 1971–1975: 5.1 (2.5–10.6) (7)
Stringfellow landfill, CA Active dumping odors	Residents since 1980 near Pyrite Channel compared with control residents from Rubidoux. Identified through tax rolls, telephone directories, etc. Pregnancies during 1955–1980 studied (40).	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 for 1983–1985 (41).	Maternal age, race, parity, education, income, and sex of infant	Mean birth weight (>28 weeks), obtained from birth certificate	-0.6 g difference (-12.9–11.5) (6,590)

¹Exposure defined on the basis of proximity to sites.

²Crude risk ratios and 95% confidence intervals were based on numbers reported in text.

Table 6.—Studies examining late pregnancy outcomes among women exposed to trichloroethylene (TCE), tetrachloroethylene (PCE), or 1,2-dichloroethylene (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) ¹ PCE (21) ¹ Chloroform (12) ¹	Birth certificates were obtained for 1975–1979 among residents of Woburn, Massachusetts. 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 (68).	Mother's age, education, and race, and sex of infant	Small for gestational age (< 10% percentile for gestational age-specific weight), obtained 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) ¹ PCE (21) ¹ Chloroform (12) ¹	Pregnancies during 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 (69).	Maternal age, smoking, and socio economic status defined by census tract	Low birth weight (< 6 pounds) obtained from maternal report	1.0 (0.6–1.8) ² (16)
TCE (1.0) ³ PCE (0.8) ³ DCE (0.2) ³	Singleton births and fetal deaths during 1985–1988 identified by birth records in New Jersey towns. Monthly, quarterly, or semiannual exposure measurements made of municipal systems. Maternal exposure based on residence shown on birth certificate (70).	Maternal age, race, education, parity, previous stillbirth or miscarriage, prenatal care, and plurality	Small for gestational age (< 5% percentile for gestational age-specific weight), obtained 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)

¹Maximum values measured in supply wells.

²Crude risk ratios and 95% confidence intervals were based on numbers provided in text.

³Mean values measured in tap water.

Table 7.—Frequency of live births in each exposure group included in and eliminated from analyses.¹

Characteristic	# (%) Unexposed	# (%) PCE Exposed	# (%) Long-Term TCE Exposed	# (%) Short-Term TCE Exposed
Total Number of Live-born Infants	5,890	6,356	32	171
<u>Eliminated from all analyses because of poor data quality</u>				
Moved in/conceived when exposure was undefined	0 (0.0)	6 (0.1)	0 (0.0)	21 (12.3)
Exposure unknown because residential history during a critical time was missing	0 (0.0)	4 (0.1)	0 (0.0)	6 (3.5)
Live-born infant weighing <350 grams	2 (0.0)	3 (0.0)	0 (0.0)	0 (0.0)
Birth weight missing	20 (0.3)	19 (0.3)	0 (0.0)	3 (1.8)
Last menstrual period missing	55 (0.9)	55 (0.9)	1 (3.1)	1 (0.6)
Gestational age >45 weeks	151 (2.6)	171 (2.7)	0 (0.0)	0 (0.0)
Total Number of Live-born Infants Used in Mean Birth Weight Analyses	5,681 (96.5)	6,117 (96.2)	31 (96.9)	141 (82.5)
<u>Eliminated from small for gestational age analyses only</u>				
Gestational age <22 weeks	2 (0.0)	6 (0.1)	0 (0.0)	0 (0.0)
Total Number of Live-born Infants Used in Small for Gestational Age Analyses	5,679 (96.4)	6,111 (96.1)	31 (96.9)	141 (82.5)
<u>Eliminated from preterm analyses only</u>				
Heavy preterm births	42 (0.7)	56 (0.9)	0 (0.0)	3 (1.8)
Total Number of Live-born Infants Used in Preterm Analyses	5,639 (95.7)	6,061 (95.4)	31 (96.9)	138 (80.7)

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¹Individual observations might fall into more than one category.

Table 8.—Distribution of demographic characteristics among live births to residents of PCE-exposed and PCE-unexposed housing.

Characteristic	PCE Exposed # (%)	PCE Unexposed # (%)
Number	6,117	5,681
Mother's Race		
White	4,339 (70.9)	4,487 (79.0)
Black	1,415 (23.1)	1,006 (17.7)
Other	363 (5.9)	188 (3.3)
Sex		
Female	3,057 (50.0)	2,778 (48.9)
Male	3,060 (50.0)	2,903 (51.1)
Year of Birth		
1968-1970	1,046 (17.1)	1,000 (17.6)
1971-1974	1,556 (25.4)	1,507 (26.5)
1975-1980	1,859 (30.4)	1,639 (28.9)
1981-1985	1,656 (27.1)	1,535 (27.0)
Rank and Pay Grade		
No Card/Unknown	91 (1.5)	136 (2.4)
E1-E3	633 (10.3)	1,408 (24.7)
E4-E5	3,875 (63.3)	1,896 (33.4)
E6-E9	1,011 (16.5)	1,177 (20.7)
WO	25 (0.4)	67 (1.2)
O1-O3	482 (7.9)	793 (14.0)
≥ O4	0 (0.0)	204 (3.6)
Parity		
1	1,861 (30.4)	2,223 (39.1)
≥ 2	4,251 (69.5)	3,454 (60.8)
Missing	5 (0.1)	4 (0.1)
Mother's Age (years)		
< 20	759 (12.4)	1,235 (21.7)
20-24	3,480 (56.9)	2,406 (42.4)
25-29	1,443 (23.6)	1,349 (23.7)
30-34	363 (5.9)	527 (9.3)
≥ 35	72 (1.2)	164 (2.9)

Table 8.—Continued.

Characteristic	PCE Exposed # (%)	PCE Unexposed # (%)
Number	6,117	5,681
Gestational Age (weeks)		
20-23	11 (0.2)	10 (0.2)
24-27	18 (0.3)	19 (0.3)
28-32	101 (1.7)	78 (1.4)
33-36	381 (6.2)	348 (6.1)
37-40	3,517 (57.5)	3,310 (58.3)
41-42	1,607 (26.3)	1,528 (26.9)
43-45	482 (7.9)	388 (6.8)
Less than adequate	3,846 (62.9)	3,731 (65.6)
Adequate or better	1,888 (30.9)	1,581 (27.8)
Missing	383 (6.3)	369 (6.5)
Past Fetal Deaths		
≥ 2	250 (4.1)	210 (3.7)
1	815 (13.3)	656 (11.5)
None	5,049 (82.5)	4,810 (84.7)
Not reported	3 (0.0)	5 (0.1)
Mother's Education (years)		
0-8	168 (2.7)	133 (2.3)
9-11	1,331 (21.8)	1,221 (21.5)
12	3,319 (54.3)	2,770 (48.8)
13-15	977 (16.0)	955 (16.8)
≥ 16	319 (5.2)	600 (10.6)
Unknown	3 (0.0)	2 (0.0)
Father's Education (years)		
0-8	57 (0.9)	41 (0.7)
9-11	669 (10.9)	702 (12.4)
12	4,282 (70.0)	3,342 (58.8)
13-15	655 (10.7)	593 (10.4)
≥ 16	447 (7.3)	997 (17.5)
Unknown	7 (0.1)	6 (0.1)

PCE - tetrachloroethylene.

Table 9.—Distribution of pregnancy outcomes in residents of PCE-exposed and PCE-unexposed housing.

Variable	PCE Exposed	PCE Unexposed	Mean Difference or Odds Ratio and 90% Confidence Interval
Frequency	6,117	5,681	
Mean birth weight in grams (Standard error)	3,327 (7.2)	3,351 (7.4)	-24.0 (-41.0, -7.0)
Frequency small for gestational age/ all births at ≥ 22 weeks of gestation (%)	622/6,111 (10.2)	509/5,679 (9.0)	1.2 (1.0, 1.3)
Frequency preterm births/ all births (%)	455/6,061 (7.5)	413/5,639 (7.3)	1.0 (0.9, 1.2)

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PCE - tetrachloroethylene.

Table 10.—Association between duration of exposure to PCE and mean birth weight.

Duration of Exposure ¹	Number	Mean birth weight (g) (SE)	Mean Difference ² (90% Confidence Interval)
Never exposed	5,344	3,348 (7.7)	0
1-3 weeks	189	3,345 (38.5)	18 (-40, 76)
4-10 weeks	597	3,291 (25.3)	-17 (-51, 17)
11-20 weeks	915	3,298 (19.2)	-31 (-59, -3)
21-45 weeks	1,551	3,351 (13.9)	-28 (-50, -5)
Entire pregnancy and < 1 year before LMP	1,994	3,323 (12.8)	-15 (-35, 5)
Entire pregnancy and ≥ 1 year before LMP	605	3,349 (22.3)	-18 (-51, 16)

LMP - last menstrual period.

PCE - tetrachloroethylene.

SE - Standard error.

¹Unless otherwise noted, duration of exposure is expressed in consecutive weeks before birth.

²Adjusted for gestational age.

Table 11.—Association between duration of exposure to PCE and small for gestational age.

Duration of Exposure ¹	Number	Frequency (%) small for gestational age births	Odds Ratio (90% Confidence Interval)
Never exposed	5,344	488 (9.1)	1.0
1-3 weeks	189	15 (7.9)	0.9 (0.5, 1.3)
4-10 weeks	597	60 (10.1)	1.1 (0.9, 1.4)
11-20 weeks	915	84 (9.2)	1.0 (0.8, 1.2)
21-45 weeks	1,551	16 (10.8)	1.2 (1.0, 1.4)
Entire pregnancy and <1 year before LMP	1,994	207 (10.4)	1.2 (1.0, 1.3)
Entire pregnancy and ≥1 year before LMP	605	61 (10.1)	1.1 (0.9, 1.4)

LMP - last menstrual period.
PCE - tetrachloroethylene.

¹Unless otherwise noted, duration of exposure is expressed in consecutive weeks before birth.

Table 12.—Adjusted stratum-specific estimates for the difference in mean birth weight for PCE-exposed and unexposed births for risk factors where effect modification appeared possible.

Characteristic	PCE Exposed Mean Birth Weight (SE)	Unexposed Mean Birth Weight (SE)	Mean Difference (90% Confidence Interval)
Mother's Race			
White or Black	3,333 (7.4)	3,352 (7.5)	-5 (-22, 13) ^{1,2}
Other	3,217 (30.3)	3,298 (42.7)	-24 (-112, 64) ^{1,3}
Rank and Paygrade			
E1-E5	3,316 (8.4)	3,286 (9.8)	+30 (+8, 51) ⁴
≥E6	3,364 (14.6)	3,349 (11.5)	-38 (-70, 17) ⁴
Mother's Age (years)			
< 35	3,327 (7.3)	3,346 (7.5)	-9 (-23, 6) ⁵
≥ 35	3,286 (72.0)	3,497 (49.0)	-205 (-333, -78) ⁵
Past Fetal Deaths			
None	3,336 (7.8)	3,354 (7.8)	-21 (-40, -3) ⁶
1	3,305 (20.8)	3,335 (23.5)	-28 (-79, 24) ⁶
≥ 2	3,331 (7.3)	3,335 (41.4)	-91 (-190, 8) ⁶
Father's Education (years)			
< 16	3,321 (7.6)	3,326 (8.2)	-5 (-23, 14) ⁷
≥ 16	3,398 (23.6)	3,466 (16.9)	-30 (-82, 22) ⁷

SE - Standard error.

¹Adjusted for year of birth and officer or warrant officer's household.

²214 observations deleted because of missing values for officer or warrant officer's household.

³7 observations deleted because of missing values for officer or warrant officer's household.

⁴Adjusted for year of birth and mother's race.

⁵Adjusted for gestational age and mother's race.

⁶Adjusted for mother's age.

⁷Adjusted for year of birth.

Table 13.—Adjusted stratum-specific estimates for the association between PCE exposure and small for gestational age among covariates identified as potential effect modifiers.

Characteristic	PCE exposed Frequency (%) SGA/ Frequency all births	Unexposed Frequency (%) SGA/ Frequency all births	Odds Ratio (90% Confidence Interval)
Rank and Paygrade			
E1-E5	456/4,505 (10.1)	342/3,302 (10.4)	1.0 (0.9, 1.2) ¹
≥E6	151/1,516 (10.0)	158/2,241 (7.1)	1.2 (0.9, 1.4) ¹
Mother's Age (years)			
<35	622/6,111 (10.2)	509/5,679 (9.0)	1.1 (1.0, 1.2) ²
≥35	11/72 (15.3)	8/164 (5.0)	4.0 (1.6, 10.2) ²
Past Fetal Deaths			
None	475/5,045 (9.4)	438/4,808 (9.1)	1.0 (0.9, 1.1) ^{2,3}
1	104/815 (12.8)	56/656 (8.5)	1.4 (1.0, 1.9) ^{2,4}
≥2	43/248 (17.3)	14/210 (6.7)	2.5 (1.5, 4.6) ^{2,5}
Past Fetal Deaths			
None	475/5,045 (9.4)	438/4,808 (9.1)	1.0 (0.9, 1.1) ^{2,6}
≥1	147/1,063 (13.8)	70/866 (8.1)	1.6 (1.2, 2.1) ^{2,7}

¹ Adjusted for year of birth and exact pay grade.

² Adjusted for officer or warrant officer's household.

³ 77 observations deleted because officer or warrant officer missing.

⁴ 11 observations deleted because officer or warrant officer missing.

⁵ One observation deleted because officer or warrant officer missing.

⁶ 77 observations deleted because officer or warrant officer missing.

⁷ 12 observations deleted because officer or warrant officer missing.

Table 14.—Association between duration of exposure to PCE and mean birth weight in births to mothers with history of one or more fetal deaths.

Duration of Exposure ¹	Number	Mean Birth Weight (SE) in Grams	Mean Difference ² (90% Confidence Interval)
Never exposed	818	3,332 (21.3)	0
1-3 weeks	24	3,277 (123.9)	5 (-162, 173)
4-10 weeks	73	3,183 (81.2)	-110 (-209, 12)
11-20 weeks	130	3,313 (53.8)	-1 (-77, 75)
21-45 weeks	287	3,318 (32.6)	-73 (-128, -17)
Entire pregnancy and <1 year before LMP	365	3,271 (33.8)	-53 (-104, -2)
Entire pregnancy and ≥1 year before LMP	134	3,235 (53.1)	-121 (-196, 46)

LMP - last menstrual period.

¹Unless otherwise noted, duration of exposure is expressed in consecutive weeks before birth.

²Adjusted for gestational age.

Table 15.—Association between duration of exposure to PCE and small for gestational age in births to mothers with history of one or more fetal deaths.

Duration of Exposure ¹	Number	Frequency (%) Small for Gestational Age	Odds Ratio (90% Confidence Interval) ²
Never exposed	818	69 (8.4)	1.0
1-3 weeks	24	4 (16.7)	1.9 (0.8, 4.8)
4-10 weeks	73	13 (17.8)	2.1 (1.2, 3.7)
11-20 weeks	130	19 (14.6)	1.7 (1.1, 2.7)
21-45 weeks	287	36 (12.5)	1.4 (1.0, 2.0)
Entire pregnancy and < 1 year before LMP	365	46 (12.6)	1.4 (1.0, 2.0)
Entire pregnancy and ≥ 1 year before LMP	134	23 (17.2)	2.0 (1.3, 3.2)

LMP - last menstrual period.

¹Unless otherwise noted, duration of exposure is expressed in consecutive weeks before birth.

²Adjusted for officer or warrant officers household. One observation deleted because of missing values for officer or warrant officer's household.

Table 16.—Distribution of demographic characteristics among residents of long-term TCE-exposed and unexposed officer's housing.

Characteristic	Long-Term TCE Exposed	Unexposed # (%)
Number	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 Pay grade		
Unknown	3 (9.7)	0
O1-O3	11 (35.5)	793 (79.5)
≥ O4	17 (54.8)	203 (20.5)
Parity		
1	7 (22.6)	344 (34.6)
≥ 2	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 (weeks)		
20-23	0	1 (0.1)
24-27	0	2 (0.2)
28-32	0	7 (0.7)
33-36	0	32 (3.2)
37-40	23 (74.2)	613 (61.5)
41-42	7 (22.6)	305 (30.6)
43-45	1 (3.2)	37 (3.7)

Table 16.—Continued.

Characteristic	Long-Term TCE Exposed	Unexposed # (%)
Number	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 ¹		
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 (years)		
0-8		1 (0.1)
9-11		11 (1.1)
12	7 (21.9)	200 (20.1)
13-15	13 (40.6)	303 (30.4)
≥ 16	11 (35.5)	481 (48.2)
Unknown		1 (0.1)
Father's Education (years)		
0-8	0	1 (0.1)
12	0	22 (2.2)
13-15	0	58 (5.8)
≥ 16	31 (100.0)	915 (91.8)
Unknown	0	1 (0.1)

¹Observations might be included in more than one category.

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

Variable	Long-Term TCE Exposed	Unexposed	Mean Difference or Odds Ratio and 90% Confidence Interval
Frequency	31	997	
Mean birth weight in grams (SE)	3,361 (71.8)	3,469 (16.9)	-108 (-230, 13)
Frequency small for gestational age/ all births ≥ 22 weeks (%)	3/31 (9.7)	68/997 (6.8)	1.5 (0.5, 3.8)
Frequency preterm/all births (%)	0/31 (0.0)	35/990 (3.5)	0.0 (0.0, 1.5)

Table 18.—Analysis of long-term TCE-exposure and mean birth weight by sex of infant and duration of residence in base housing.

Category	Number	Mean birth weight (SE)	Mean Difference (90% Confidence Interval)	One-Tailed P Value
All Live Births				
Exposed	31	3,361 (71.8)	-139 ¹ (-277, -1)	0.05
Unexposed	997	3,469 (16.9)		
All Males				
Exposed	12	3,213.3)	-312 ¹ (-540, -85)	0.01
Unexposed	497	3,527 (25.2)		
All Females				
Exposed	19	3,454 (88.3)	-4 ² (-171, 163)	0.48
Unexposed	500	3,412 (22.3)		
Mothers lived on base \geq 20 weeks before birth				
Both Sexes				
Exposed	21	3,352 (95.3)	-144 ³ (-486, 27)	0.08
Unexposed	742	3,473 (19.8)		
Males				
Exposed	9	3,207 (143.6)	-367 ¹ (-632, -102)	0.01
Unexposed	368	3,525 (30.3)		
Females				
Exposed	12	3,461 (122.9)	+26 ² (+196, 248)	1.0
Unexposed	374	3,423 (25.5)		

SE - standard error.

¹Adjusted for gestational age.

²Final model after adjustment for gestational age and military pay grade.

³Final model after adjustment for gestational age, military pay grade, mothers aged \geq 35 years, and year of birth.

Table 19.—Analysis of long-term TCE-exposure and small for gestational age birth by sex of infant.

	Number	Frequency small for gestational age (%)	Odds Ratio (90% Confidence Interval)
All Live Births			
Exposed	31	3/31 (9.7)	1.5 (0.5, 3.8)
Unexposed	997	68/997 (6.8)	
All Males			
Exposed	12	3/12 (25.0)	3.9 (1.1, 11.9)
Unexposed	497	39/497 (7.9)	
All Females			
Exposed	19	0/19 (0.0)	0.0 (0.0, 1.5)
Unexposed	500	29/500 (5.8)	

Table 20.—Distribution of demographic characteristics among live births of residents of short-term TCE-exposed and unexposed housing.

Characteristic	Short-Term TCE Exposed # (%)	Unexposed # (%)
Number	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	1 (0.7)	14 (1.6)
Parity		
1	36 (25.5)	293 (33.4)
≥ 2	105 (74.5)	575 (66.2)
Gestational Age (weeks)		
20-23	0	2 (0.2)
24-27	0	3 (0.3)
28-32	2 (1.4)	13 (1.5)
33-36	9 (6.4)	58 (6.7)
37-40	91 (64.5)	532 (61.3)
41-42	28 (19.9)	203 (23.4)
43-45	11 (7.8)	57 (6.6)
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)

Table 20.—Continued.

Characteristic	Short-Term TCE Exposed # (%)	Unexposed # (%)
Number	141	868
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 ¹		
≥2	8 (5.7)	46 (5.3)
≥1	25 (17.7)	163 (18.8)
None	116 (82.3)	705 (81.2)
Mother's Education (years)		
0-8		16 (1.8)
9-11	15 (10.6)	134 (15.4)
12	75 (53.2)	446 (51.4)
13-15	33 (23.4)	192 (22.1)
≥16	18 (12.8)	80 (9.2)
Father's Education (years)		
0-8	0	1 (0.1)
9-11	5 (3.5)	46 (5.3)
12	90 (63.8)	568 (65.4)
13-15	22 (15.6)	102 (11.8)
≥16	24 (17.0)	151 (17.2)
Unknown	0	1 (0.1)

¹Observations might be included in more than one category.

Table 21.—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
Frequency	141	868	
Mean birth weight in grams (SE)	3,455 (41.7)	3,385 (19.7)	+70 (-6, 146)
Frequency small for gestational age /all births at ≥ 22 weeks (%)	5/141 (3.6)	58/868 (6.7)	1.1 (0.2, 1.1)
Frequency preterm births/all births (%)	8/138 (5.8)	75/867 (8.7)	0.7 (0.3, 1.2)

FIGURES

Figure 1.—Fetal death ratio per 100 live births by year of birth
 (Camp LeJeune ratios are computed as 5-year averages with midpoints shown)

LL

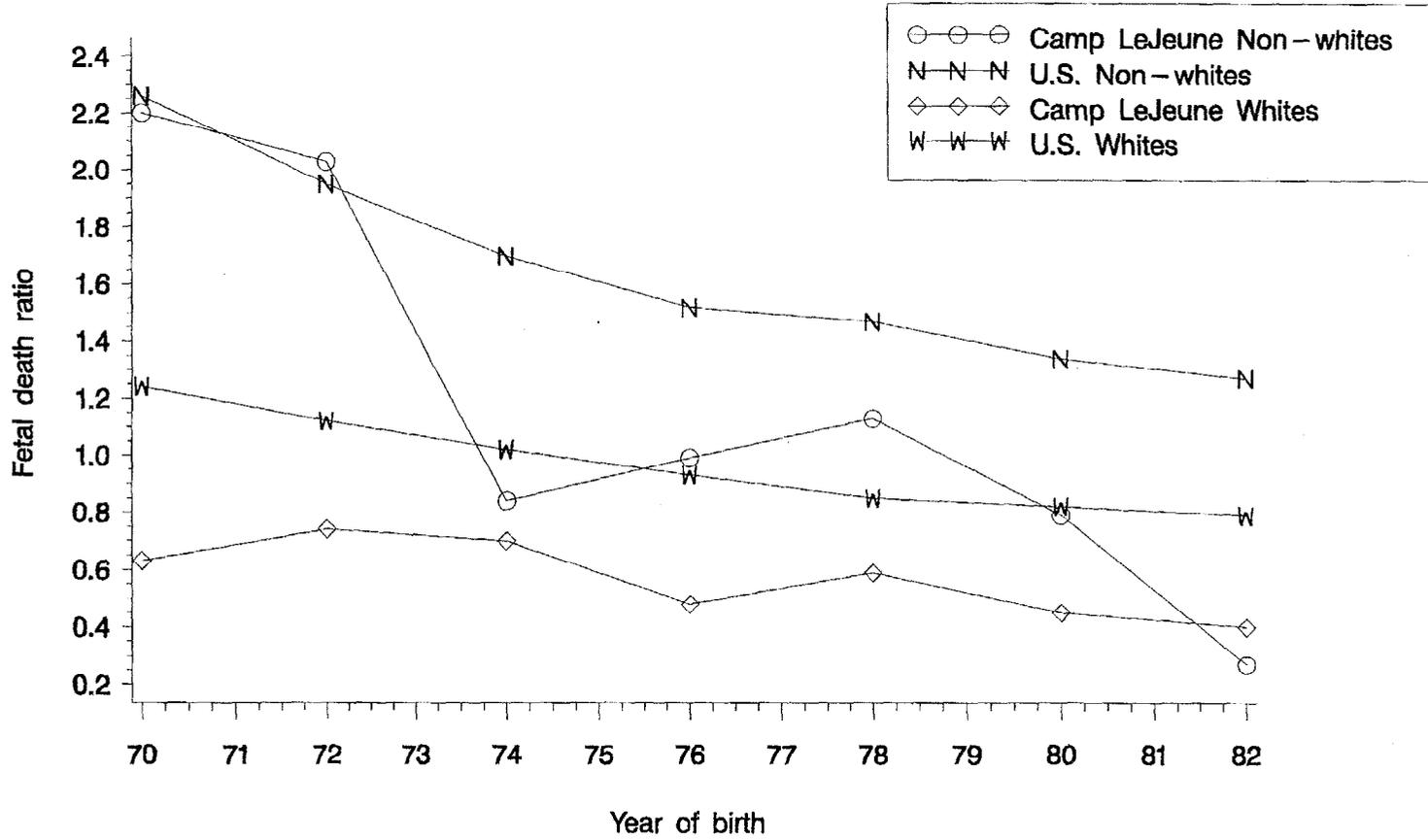


Figure 2.—Birth weight following short-term exposure to TCE by time elapsed between exposure and birth
(Preterm births are excluded)

79

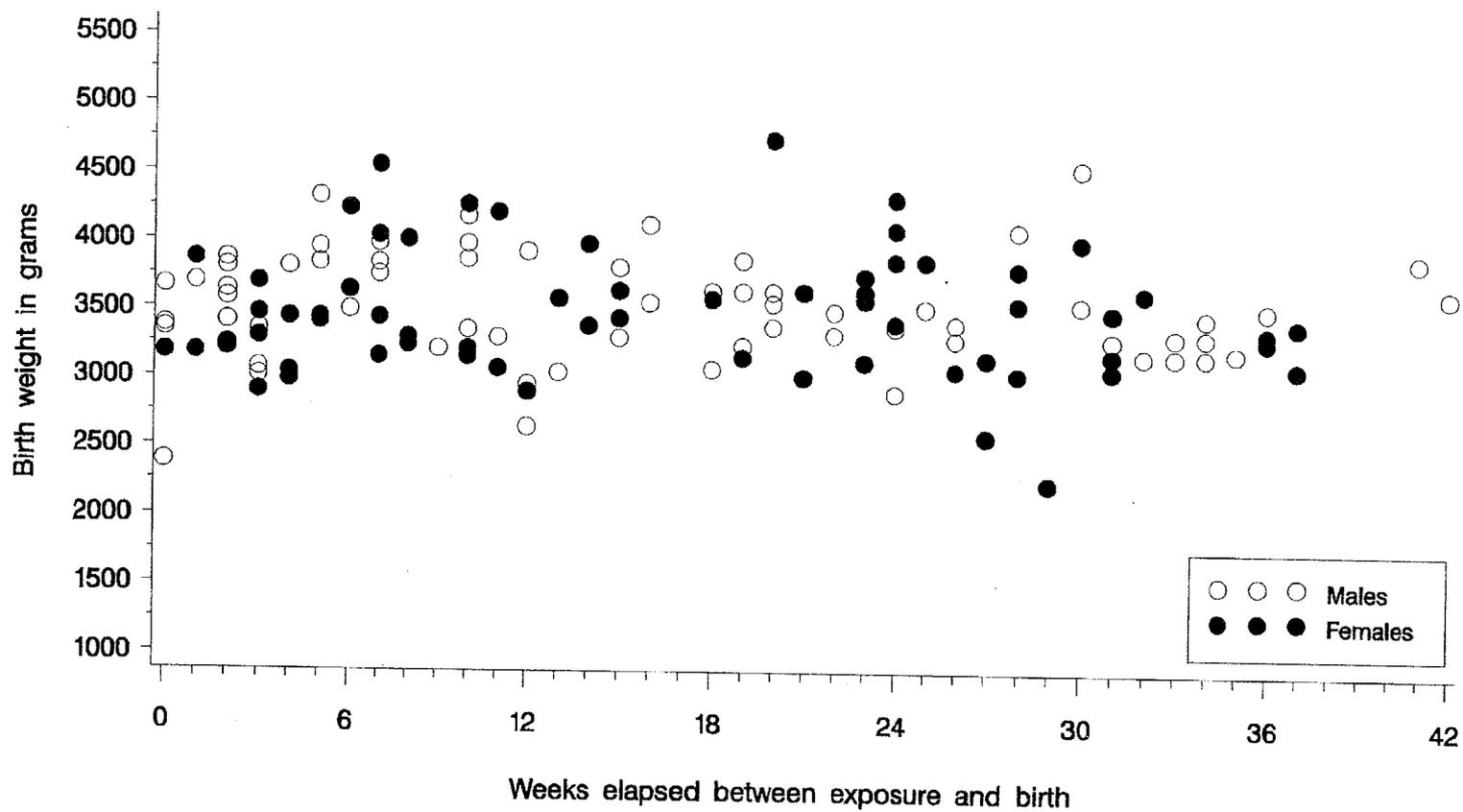
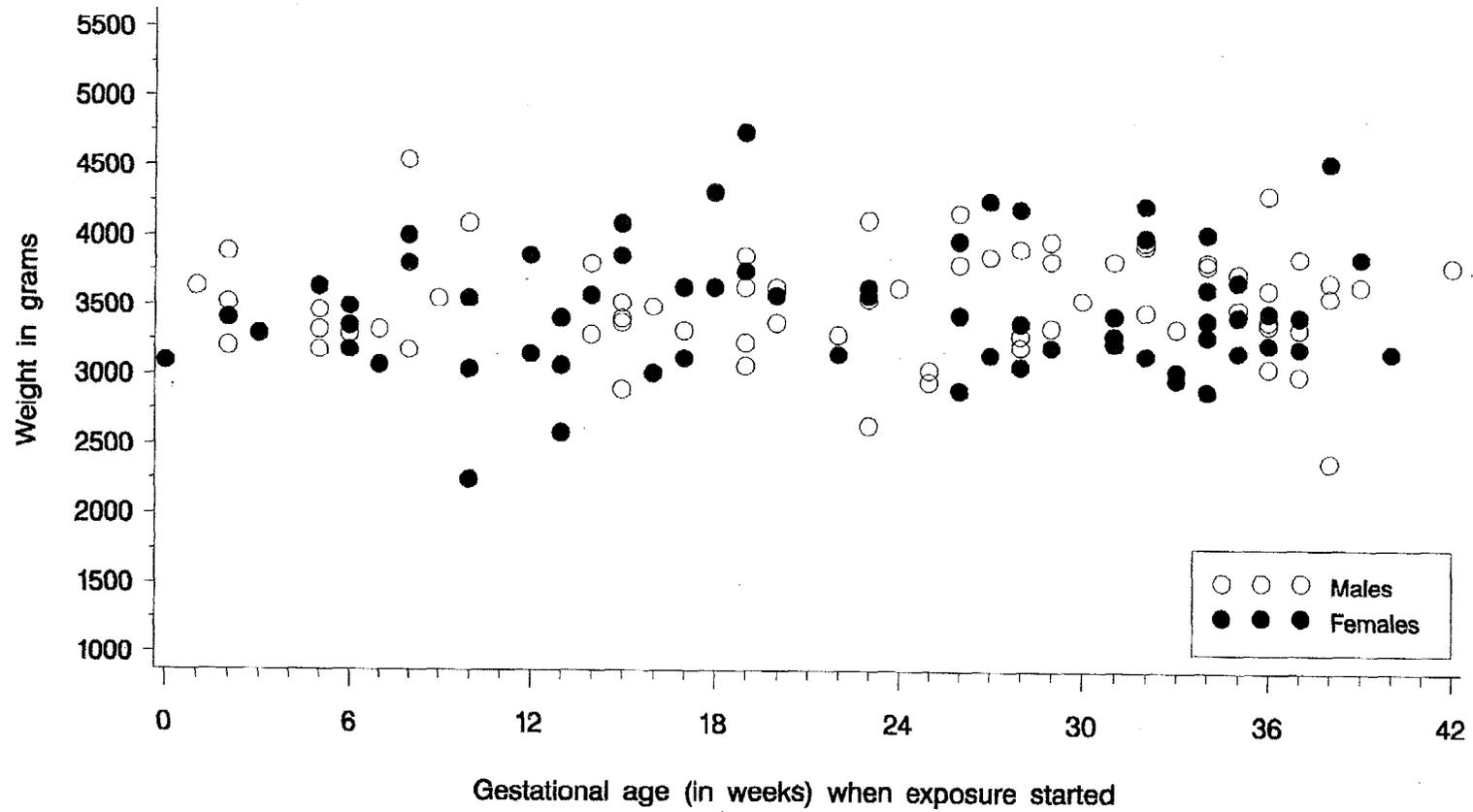


Figure 3. -- Birth weight following short-term exposure to TCE by gestational age when exposure started
(Preterm births are excluded)



APPENDICES

The contents of Appendices A through C are presented in their entirety as submitted by the author and have not been revised to conform with Agency for Toxic Substances and Disease Registry editing guidelines.

Appendix A—Validation of Mother’s Residential History.

VALIDATION OF MOTHER'S RESIDENTIAL HISTORY

This appendix describes the Agency for Toxic Substances and Disease Registry (ATSDR) evaluation of a valuable time- and cost-saving assumption made regarding a mother's residential history. Misclassification of exposure is an important concern in every epidemiologic study and is particularly troublesome in studies of the health effects of environmental exposures. One potential source of misclassification in this study was the high turnover rate of residents in base family housing units. Throughout this study, each mother was assumed to have lived in one—and only one—base housing unit during pregnancy. This assumption made it possible to distinguish between exposed and unexposed women and to measure duration of exposure for each pregnancy on the basis of information regarding mothers' residences at the time of delivery. The primary advantage of making this assumption was that each birth certificate was matched to one and only one housing record. It was estimated that more detailed matching of birth certificates to multiple housing records would have doubled the period of data collection and increased the study cost by about 25% to 50%.

Camp Lejeune personnel suggested that the assumption that women resided in one and only one housing unit during pregnancy was reasonable in most cases. Nonetheless, because many women in the study moved during pregnancy, and more than half of the housing units on base received contaminated water, it seemed possible that some women who were classified as unexposed had moved from an exposed housing area during their pregnancy. Similarly, women who were thought to have lived in exposed housing for only a short period of time before delivery might have actually had a longer exposure to volatile organic compounds (VOCs) if their previous housing accommodations were also supplied with VOC-contaminated drinking water. Therefore, a small validity study was conducted on a sample of base residents to evaluate the potential impact on study results of the assumption that each mother studied resided in one and only one base family housing unit during the course of her pregnancy.

For previous residences that were not located on the U.S. Marine Corps Base at Camp Lejeune location, it was assumed that no exposure had occurred because the municipal drinking water for the city of Jacksonville has not been found to be contaminated and because, in general, most drinking water does not contain VOCs. Although this assumption probably led to some misclassification of exposure, there were, unfortunately, no feasible means to evaluate it.

To simplify discussion of this subject, classification of exposure and measurement of duration of exposure based only on review of the housing record for residence at the time of delivery is herein referred to as "partial record review." Classification of exposure and measurement of duration of exposure based on review of all base family housing records for each woman during pregnancy is referred to as "full record review."

OBJECTIVES

This validity study had four objectives:

1. To determine if the housing record database was complete enough to conduct a validity study based on a review of its record.
2. To determine what proportion of mothers resided in more than one base family housing unit during pregnancy.
3. To determine how well VOC-exposure was classified dichotomously into “ever” and “never” exposure categories by partial record review when compared with full record review.
4. To determine how well duration of exposure to VOCs classified on the basis of a partial record review correlated with duration of exposure to VOCs that was based on a full record review.

The first objective was addressed by reviewing the proportion of all eligible birth certificates for which no housing records were available. Exclusions and inclusions were the same as for the main analyses with the following exceptions. Any birth that was considered eligible for the main analysis but did not have a complete birth certificate address was not included in the analysis of housing record completeness and accuracy. In addition, 9 of the 10 births were eliminated from the main analyses because they occurred after contamination had ceased and the dates of occupancy could not be determined because there were no housing records included in the analysis of housing record completeness and accuracy. The tenth birth in this category was excluded because there was no information regarding the mother’s last menstrual period.

The remaining three objectives were addressed by reviewing housing records for a sample of births used in the main analyses of the study. To minimize the need to review long, alphabetized lists, the sample was not selected entirely at random, but rather was selected from the beginning of the alphabet. Specifically, the database of eligible births was sorted by the last name printed on the housing record that corresponded to the mother’s residence at the time of delivery. The first 500 births to mothers who moved during pregnancy were selected. (The 500 names started with the letters “A” through “Bo”.) A search of the housing record database was conducted to identify other housing units whose occupants bore the same name and first initial as that listed on the housing record for each birth selected. Searches using spelling variations for each last name were also conducted. The housing records for exact and near-name matches were reviewed to obtain (1) the dates of occupancy for each housing unit and (2) the middle initial and rank of the active-duty member of the household. This information was used to determine which of these potential matches represented housing units in which the mothers lived during pregnancy.

All births to mothers who had not moved during pregnancy were included in the calculations if they preceded the 500th mobile mother in the alphabetically sorted database described previously. The nonmobile mothers were included in the calculations because they contributed both to the negative predictive value of the exposure classification scheme and to the correlation between duration of exposure with the two different methods. Births for which no housing record existed, either for the mother's address at the time she delivered or for some other residence during pregnancy, were eliminated from these calculations.

The degree to which partial record review classified exposure correctly was measured by estimating the negative predictive value and sensitivity for this method (1,2) using a hand-held calculator. By definition, the positive predictive value and specificity of this measure were both 100% because a woman known to have at least 1 week of exposure to VOCs at her current residence always had at least 1 week of exposure, regardless of whether she was exposed at a previous residence. Therefore, for women classified as exposed, the measure of interest was duration of exposure (in weeks). The degree to which duration of exposure measured by full and partial record review were correlated was assessed by computing the Pearson product-moment correlation using SAS statistical software package (3).

RESULTS

Completeness of Housing Records

Table A1 contains results from the analysis of record completeness. Approximately 97% (11,435 of 11,832) of the birth certificates agreed exactly with housing records. Only 1% of the birth certificates lacked housing records entirely. Records were slightly less complete for long-term TCE-exposed births, but the level of completeness was still high (90%).

Partial Record Review Compared with Full Record Review

Calculations were based on housing records for 913 mothers whose last names began with the letters "A" through "Bo". This included the 500 mothers who moved during their pregnancy who were used to select the sample and 413 mothers for whom duration of residence was as long or longer than their pregnancy. Thus, 55% of the women in the validity study sample moved during their pregnancy, approximately the same number as moved in the study as a whole. Of these 913 mothers, 32 (3.5%) moved from one base family housing unit to another during pregnancy. In addition, one woman had ambiguous information so that it was unclear whether her family had occupied more than one housing unit during her pregnancy. To provide the worst-case scenario, the woman with the ambiguous information was treated as if she had occupied the previous housing unit.

None of the previous base residences identified in the validity study were supplied with water from the trichloroethylene (TCE)-contaminated source for any period of time, although 2 mothers had long-term exposure and 11 mothers had short-term exposure to TCE at the

housing units in which they resided when they delivered. One of the 11 mothers with short-term TCE exposure was found to have had a previous residence in tetrachloroethylene (PCE)-exposed housing. More detailed calculations were not conducted for the TCE-exposed births because of the small numbers in these groups.

The degree of agreement in classifying PCE exposure between the full and partial record review is shown in Table A2. The 13 TCE-exposed births were eliminated from calculations involving PCE exposure because they were not included in the PCE analyses in the main study. For PCE-exposure, the negative predictive value was 99.3%, and the sensitivity was 99.4%.

The mean duration of exposure among the 473 women classified as exposed to PCE on the basis of the partial record review was 29.4 weeks (standard error [SE]: 0.59). The mean duration of exposure among the 476 women classified as exposed on the basis of the full record review method was 29.8 weeks (SE: 0.58). When the 900 PCE-exposed and unexposed infants were included in the model, the correlation coefficient for duration of exposure between the full and partial record reviews was .99. When only the 476 PCE-exposed births were included in the model, the correlation between full and partial record reviews was .96.

DISCUSSION

Completeness of Housing Records

The housing records appeared to be a relatively complete source of information on residence in base family housing units. Only 1% of birth certificates contained no housing record information. For birth certificates that conflicted with the housing records, typographical errors were equally likely in either set of records. In those instances in which only the unit numbers were in conflict, this did not affect the ability of the study to classify births. The housing and birth certificate records might have been even more accurate than the statistics suggested because many of the records for which there were conflicts might have been explained by reasons other than human error. For example, if a mother was staying with friends at the time she delivered, she might have listed her friend's home as her residence or she might have reported her last permanent residence. If she listed her friends' address, then her friends would have been listed as the occupants of the housing unit (row 5 of Table A1). If she listed her last permanent residence, then the birth certificate and housing record would have agreed, but the dates of occupancy for the housing record would not have included the date of birth (row 6 of Table A1). At any rate, given that the housing records were quite complete, most mothers who moved from one base housing unit to another during pregnancy should have been identifiable from the housing records.

Partial Record Review Compared with Full Record Review

The results of these analyses demonstrate that partial record review provided almost as much information as a full record review both in classifying infants as exposed or unexposed to

TCE and PCE and in measuring duration of exposure to PCE. Despite the large number of women who moved during pregnancy, less than 4% of women moved from one base housing unit to another. The sensitivity and negative predictive value for classification of PCE exposure were both greater than 99%, and the correlation between duration of exposure among PCE-exposed mothers based on full and partial records was .96.

None of the women who were classified as unexposed on the basis of partial record review were found to be TCE-exposed on full record review. However, the number of TCE-exposed women was too small to permit detailed analysis. Nonetheless, there was no reason to anticipate that the results would have been much different for women in these groups.

One ambiguity that was not addressed was the possibility that the mother and father had different residences. However, except in cases in which the mothers were themselves on active duty or were children of an active-duty person, the mothers in the study had to have been married when they moved into base family housing. There are, of course, many other sources of possible misclassification of exposure, not only from residences off base or at other bases, but also from occupational sources. However, the purpose of this validity study was not so much to address all potential sources of possible misclassification, but rather to evaluate the validity of an assumption that saved thousands of hours of time in data entry and data management time.

CONCLUSIONS

The housing records were, overall, quite complete, and the number of mothers who moved from one housing unit to another during pregnancy was low. Relative to a full record review, partial record review was a cost-effective and adequate method for measuring exposure to TCE and PCE and for measuring duration of exposure to PCE.

References

1. Hulley SB, Cummings SR. Designing clinical research: an epidemiologic approach. Baltimore: Williams and Wilkins, 1988:91-2.
2. Maclure M, Willett WC. Misinterpretation and misuse of the kappa statistic. Am J Epidemiol 1987;126:161-9.
3. The CORR Procedure. In: SAS user's guide: basics, version 5. Cary, North Carolina: SAS Institute, 1989:861-74.

Table A1.—Distribution of live births in each exposure group by level of agreement between the housing record and birth certificate.

Characteristic	# (%) Unexposed	# (%) PCE-exposed	# (%)	# (%)
Total live births with complete birth certificate information	5,606	6,049	31	146
Birth certificate and housing record agree	5,410 (96.5)	5,857 (96.8)	28 (90.3)	140 (95.9)
No housing record or gap in housing record	88 (1.6)	44 (0.7)	3 (9.7)	4 (3.4)
Birth certificate and housing record	44 (0.8)	46 (0.8)	0 (0.0)	1 (0.7)
Birth certificate and housing record conflict	56 (1.0)	98 (1.6)	0 (0.0)	1 (0.7)
Birth certificate and housing record agree	8 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)

PCE - Tetrachloroethylene

Table A2.—Agreement between classification of PCE exposure based on full and partial record reviews.

		Full Method		
		PCE exposed	Not exposed	Total
Partial Method	PCE exposed	473	0	473
	Not exposed	3	424	427
	Total	476	424	900

PCE – Tetrachloroethylene

Appendix B—Medical Records Pilot Study

Medical Records Pilot Study

The purpose of the medical records pilot study was to evaluate the feasibility and usefulness of reviewing a sample of prenatal and neonatal medical records of Camp Lejeune base family housing residents. Birth and fetal death certificates from base family housing residents had been reviewed before the pilot study. However, data from these vital records were thought to be of varying quality. Based on a large body of literature, it is known that gestational age is sometimes misreported or not reported. Furthermore, there is often greater misclassification among blacks than whites, and larger discrepancies in gestational age estimates of preterm and post term infants (1,2). In addition, medical records contained detailed information that was not available on birth and fetal death certificates. Because review of medical records for all participants would have been costly and labor intensive, the goal was to evaluate the feasibility of reviewing medical records in a pilot study. The primary objectives of the pilot study were:

1. To determine how completely medical records could be traced and located.
2. To determine whether the study participants whose medical records were located were representative of the entire study population or if location rates of records differed with pregnancy outcome, hospital, year, or race.
3. To assess the completeness of the information contained in the medical records, especially for data not available from vital records (e.g., mother's smoking history) to determine whether the completeness rate varied with pregnancy outcome and to determine whether completeness of the medical record varied with the completeness of birth certificates.
4. To assess the accuracy of the information obtained from vital records by comparing it with information reported in the medical records and to describe the degree to which reviewing medical records improved overall data quality and added new information.

Secondary objectives of the pilot study were to validate the reporting of birth defects on the birth certificates and to obtain additional insight regarding the clinical course of pregnancies that resulted in a child with birth defects.

Methods

An attempt was made to locate and abstract 35 records from each of 6 different groups randomly sampled from the birth and fetal death records for Camp Lejeune residents. These groups were fetal deaths, live-born infants for whom data were missing or illogical in the last menstrual period or birth weight fields, small for gestational age (SGA) live-born infants, preterm live-born infants, live-born infants to mothers whose medical records indicated complications of pregnancy or labor, and healthy live-born infants with no apparent complications.

Obstetric and gynecologic records for each mother and infant in the study sample were traced through the two hospitals in Onslow County, the Navy Regional Medical Center (NRMC) and the Onslow Memorial Hospital (OMH) and were abstracted on site. To assess reliability between abstractors, 10% of records were resampled. No attempt to locate records from hospitals outside of Onslow County was made because there were too few births or fetal deaths at any one hospital to make this feasible. Sampling, tracing, and abstraction of medical records were conducted in two phases because eligible births during 1975-1985 were computerized and, therefore, identified before births during 1968-1974.

The abstraction form used for this pilot study is included in Appendix C. Data were abstracted for the following variables: birth date; birth weight; mother's last menstrual period; mother's and father's ages; mother's address at first prenatal-care visit; reported birth defects; maternal medical conditions, especially pregnancy induced-hypertension and gestational diabetes; maternal prepregnancy weight; maternal smoking habits; maternal alcohol consumption habits; adequacy of prenatal care; anemia; and mother's past pregnancy history. For each of these variables, the completeness of the data was assessed. The time needed to abstract each record was measured during the second phase of abstraction.

Because a time lag was anticipated between sampling of records and their location and abstraction, the records were sampled before the main analyses were conducted. This introduced a few minor inconsistencies between the methods for the pilot study and the methods for the main analyses. For example, the records for the pilot study were sampled before the main database was completely cleaned of records that were ineligible based on maternal residence outside the housing areas of interest. Therefore, the population from which the pilot study sample was drawn included 13,805 births and 110 fetal deaths, which was approximately 10% larger than the population studied in the main analyses. A slightly more serious deviation from the main protocol that resulted from early selection of records for location and abstraction occurred in the selection of SGA infants. These infants had to be selected for sampling before this category had been formally defined for the main analyses using an external standard population. Instead, SGA infants were selected for the pilot study based on an internal standard, that is, using the gestational age-specific birth weight distribution within the Camp Lejeune data set itself. As a result, 11 preterm infants that were sampled as SGA, based on the weight distribution within the data set, were not SGA using an external population-based standard. This somewhat surprising result was indicative of the larger problem of misclassification of full-term infants as preterm, which will be discussed in greater detail later. These infants were subsequently eliminated from the analysis that evaluated agreement between the medical records and the birth certificates in classifying SGA. These minor deviations in methods from the main analyses allowed for the collection of pilot study data within Fiscal Year 1996.

Gestational age data obtained from medical records and birth certificates were compared for infants falling into the healthy live-born, preterm, small for gestational age, and maternal medical complications categories. Gestational age from the birth certificate was computed on the basis of the time between the mother's last menstrual period and birth as reported on the birth certificate. Gestational age from the medical record was computed two ways, based on (1) the

mother's last menstrual period as reported on the medical record and (2) the clinician's estimate of the infant's due date. In addition to evaluating agreement regarding gestational age, it was deemed desirable to assess the extent to which the disease status of infants would have been classified differently in the main analyses if medical records had been available for a larger proportion of study participants. Inaccuracies in birth certificate data are known to contribute to some misclassification of preterm and SGA infants. However, clinical estimates of gestational age are also a problem because clinicians use the size of infants to help judge their age. Using the example of Zhang et al. (3), the clinical estimate of gestational age was used instead of the last menstrual period if an infant's birth weight was heavier than the 90th percentile in weight within its sex-specific gestational age category. The 90th percentile was based on the Williams (4) standard, the same standard used to define SGA in the main analyses. Because clinicians' estimates of gestational age are based on birth weight, a clinician's judgment that an infant is not small for gestational age is rarely reliable. Therefore, an SGA infant was not reclassified as an infant of normal weight based on the clinician's observations unless there were notes in the medical record to indicate that the mother's reported last menstrual period was not reliable. When the last menstrual period on the medical record differed from the last menstrual period on the birth certificate, the gestational age most consistent with the infant's birth weight was used.

The occurrence of maternal complications as reported on the medical records was described by birth outcome category for healthy live-born, preterm infants, SGA infants, and infants whose birth certificates indicated that their mothers had medical complications. Complications of interest included (1) a clinical diagnosis of hypertension, toxemia, or preeclampsia, or one or more blood pressure readings higher than 140/100; (2) a clinical diagnosis of diabetes or one or more glucosuria readings of ≥ 1 ; (3) a clinical diagnosis of a sexually transmitted disease or a nonsexually transmitted disease of the genital or urinary tract, or a report of bacteriuria, vaginitis, or other irritation indicative of a lower urogenital tract infection; and (4) a clinical history of problem pregnancies, including previous stillbirths, miscarriages, SGA infants, and preterm deliveries. Complications of delivery, descriptions of the circumstances surrounding the outcome itself (e.g., premature rupture of the membranes and placenta previa), factors (e.g., mild asthma) for which the effects on pregnancy were not well established and factors likely to result in maternal morbidity with no effect on infant outcome (e.g., pyelonephritis or postpartum hemorrhaging) were categorized as "other." A one-time reading of $\geq 1+$ proteinuria that was unexplained by diabetes, hypertension, or infection was also considered unimportant. Glucosuria that was associated with yeast infections was not considered indicative of diabetes unless there was other evidence of diabetes, such as a clinical diagnosis of diabetes or an abnormal glucose-tolerance test.

Birth Defects

Another aspect of the feasibility study was the review of medical records for infants with birth defects. Specific objectives were to validate the information reported on the birth certificate so that birth certificate-based rates could be computed and to determine the usefulness of medical records in reporting information regarding birth defects. Medical records were sought for every

infant with a birth certificate that indicated a birth defect. It is generally known that birth certificates severely underascertain the existence of birth defects (5). Nonetheless, birth defects are of such tremendous concern that medical records were sought for all infants whose birth certificates indicated a birth defect to validate the defects reported on the birth certificates. Birth defects were not reported on birth certificates until 1978. Because all birth certificates with information on birth defects were sampled, there was no reason to formally include these certificates in the feasibility study. There are no more records that fall into this category to locate. Hence, separate analysis of the feasibility of locating records within this group would not have been helpful.

Birth defect data obtained from the medical record and the birth certificate were compared. The ICD-9 code listed on the birth certificate for the years 1980 through 1985 and the ICD-8 code listed on the birth certificate for the years 1978 and 1979 was used to classify birth defects as reportable or nonreportable based on the categorization scheme devised for the Metropolitan Atlanta Congenital Defects Program (6). Certain birth defects are considered to be nonreportable because they are very minor. Other characteristics sometimes noted on a birth certificate (e.g., extra fingers) are considered to be normal variants that are not birth defects. These characteristics are also considered to be nonreportable. Medical records were used to confirm the diagnosis listed on the birth certificate and to distinguish between reportable and nonreportable defects in the event that a particular ICD code was consistent with both reportable and nonreportable birth defects. Prevalence rates for reportable birth defects within each organ system were computed for the study population by exposure category. Exposure throughout the main analyses referred to exposure occurring at any time throughout pregnancy. However, for birth defects analyses, infants were considered to be exposed only if housing records indicated that their parents resided in VOC-exposed housing during the first trimester of pregnancy.

To assess the degree of underreporting of birth defects on birth certificates, the prevalence of birth defects in each organ system for all eligible births combined was compared to prevalence data from the North Carolina Birth Defects Monitoring Program (NCBDMP) (7) for the years 1984 through 1986. The NCBDMP uses hospital discharge summaries, vital records, Medicaid claims, Children's Special Health Services files, and neonatal intensive-care unit discharge data to estimate rates of birth defects diagnosed within the first year of life (8). A severe limitation of the registry as it applies to the Camp Lejeune study is that no information was collected from military hospitals.

Results

With assistance from NRMC and OMEM, the Agency for Toxic Substances and Disease Registry (ATSDR) attempted to trace records for a total of 193 fetal deaths and live-born infants without birth defects. Table B1 contains frequencies of births and fetal deaths within each of the six categories for which location was attempted and frequencies of records located within each category. In the categories of SGA births, mothers with maternal medical complications, and birth certificates with missing data, one record was randomly selected twice. Therefore, only 34 records were traced in each of these 3 categories. As discussed previously, an additional 11

of the SGA infants were excluded from analyses after they were sampled. Some records were sampled in more than one category. One live-born infant that was sampled as preterm was also sampled as SGA. Two live-born infants that were sampled as preterm was also sampled in the maternal medical complications category. In addition, two live-born infants that were sampled for the maternal medical complications category were also SGA. Although not sampled specifically for the SGA category, these two infants were included in the SGA analyses because so many of the births sampled in the SGA category had to be deleted.

Also included in Table B1 is the approximate proportion of live-born infants that fell into each of the live infant categories in the sample's source population. This information can be used to assess how much factors that affect only a single category might influence data for the overall source population. (For example, the location rate for fetal deaths affected less than 1% of the total source population.)

No medical records were located for any of the fetal deaths. For all live-born infants combined, 66% of mothers' medical records and 76% of infants' records were located. At least one medical record (either mother's or infant's) was located for 77% of all live-born infants. The proportion of healthy live-born infants with no complications for which at least one medical record (mother's or infant's) was located was compared with the proportion of records located for live-born infants in each of the adverse-outcome categories (i.e., preterm deliveries, SGA infants, and maternal medical complications). The adverse outcome and missing data categories all had location rates similar to the healthy live-born infant category (χ^2 , 2 df ranged from 0.01 to 0.76). Location rates for mothers' medical records were lower than location rates for infants' medical records in every category.

Table B2 contains location rates for all live-born infants by the hospital of delivery as reported on the birth certificate. Although the actual hospital of delivery was not listed on the birth certificate, the only hospital within the city of Jacksonville in Onslow County, North Carolina was Onslow Memorial Hospital. The only hospital in Onslow County but outside the Jacksonville city limits was the Navy Regional Medical Center. Location of both infants' and mothers' medical records was almost 80% at the NRMC. Location of infants' records at OMH was also quite high. However, mothers' records were not available for any study participant born at OMH.

Table B3 contains location rates for all live-born infants by the race of the mother. A total of 55% of black mothers' records were located, while 68% of white mothers' records were located, a difference that was statistically significant ($\chi^2 = 5.5$, 2 df, $p = .06$). This difference reflected the higher proportion of black mothers (23%) who delivered at OMH relative to white mothers (11%) who delivered at OMH. The proportion of mothers for whom at least one record was located did not differ between whites (76%) and blacks (77%). The location rate for records in the "other race" category was high (91% for both mothers' and infants' records). However, too few mothers of other races were traced to perform statistical analyses on this group.

The choice of hospital did not appear to have been related to an underlying risk for adverse pregnancy outcome. Neither OMH nor NRMC is a tertiary-care facility, and both hospitals would have referred the highest risk patients to other hospitals, such as Pitt County Hospital or a Navy hospital equipped for tertiary care of pregnant women and neonates. However, because a higher percentage of black than white Camp Lejeune residents delivered at OMH, the risk for adverse pregnancy outcome at OMH might have appeared to be greater.

Table B4 contains location rates for all live-born infants by year of birth. Different hospitals had different successes in locating birth records from different years. NRMC was able to locate fewer records for 1983 and 1985 than for other years. Therefore, location rates were particularly low for mothers' records in the years 1981 through 1985. The lower number of infant records located by NRMC for the years 1981 through 1985 was offset by the greater number of infant records located by OMH beginning in 1976. OMH maintained records only for 20 years after an infant was born. Location rates for infants' records were particularly high in the years 1976 through 1980 because the rates of location of OMH records and NRMC records were high during this time. Because none of the mothers' records were located from OMH, year of birth did not influence location rates of mothers' records at OMH.

Completeness of Information

Table B5 contains the frequency and percentage of live-born infants with medical record information for different variables of interest. Live-born infants for whom no record was located were included in these statistics to provide realistic figures for the overall increase in information that would be obtained by a review of medical records. Table B5 has been sorted by the proportion of records located for each variable of interest starting with the most commonly reported information and ending with the least commonly reported information. The information that was most commonly reported in the medical record, such as birth weight and mother's last menstrual period, was information also available from the birth certificate. Many of the clinical indicators (e.g., maternal blood pressure and hematocrit) that would be used to detect maternal medical complications during pregnancy were reported in more than 70% of located records. However, this information was still limited because it is conceivable that women might have had a medical condition at a time when they were not tested for it. Maternal cigarette smoking (yes or no during pregnancy), maternal alcohol consumption (yes or no during pregnancy), and maternal occupation were each reported for less than 40% of located records and for less than 30% of total records. Completeness of reporting varied little by sampling category (Table B6).

For hospital of delivery, completeness varied primarily for maternal prepregnancy weight, maternal smoking and alcohol consumption, and maternal occupation (Table B7). Data for all of these variables were reported less frequently at OMH than at NRMC, which probably reflects the fact that OMH records were available only for the infant. Of these, the biggest discrepancy was noted for maternal prepregnancy weight, which was reported in 87% of the records located at NRMC and in no records located at OMH. Although some of the mothers' prenatal care visits were included on the infants' medical records from OMH so that adequacy of prenatal care could be measured, the information on prenatal care from OMH was much less

accurate than that from the NRMC. Using data abstracted from the medical record alone, only 1 (7%) of 14 records abstracted from OMH indicated that a mother had adequate prenatal care (using Kotelchuck's criteria for adequacy (9)). Applying the same criteria to the birth certificate data, 7 (50%) mothers who delivered at OMH had adequate prenatal care.

Completeness also varied by year of birth (Table B8). Urine glucose and protein, maternal prepregnancy weight, maternal smoking, maternal alcohol consumption, and maternal occupation were all reported less frequently in earlier study years than in later years. For example, from 1976 through 1985 maternal smoking data were reported in 56% of located records (43 % of all records). Maternal smoking data were not reported in any medical records for births prior to 1976. Urine glucose and protein measurements were recorded in 68% of located medical records for the years 1976 through 1985, but were recorded in only 33% of located records for the years 1968 through 1975. Completeness of reporting differed only slightly by race (Table B9), except for maternal prepregnancy weight, which was reported less commonly for black mothers than for white mothers. This probably reflects the higher proportion of black mothers who delivered at OMH.

Gestational Age on the Birth Certificate and Medical Record

Table B10 contains information on agreement between the medical records and the birth certificates regarding the gestational age of live-born infants estimated to be 27 to 44 weeks based on the birth certificates. As expected, preterm infants were more likely to have older gestational ages listed in the medical records, while post term infants were more likely to have younger gestational ages listed in the medical records. The use of ultrasound to compute an infant's gestational age became prevalent around 1980; however, its use was not uniformly reported. Overall, 88% of births with both medical record and birth certificate data for last menstrual period agreed exactly on this field. Three-way exact agreement between gestational age calculated from the birth certificate's last menstrual period date, the medical record's last menstrual period date, and the clinician's estimated date of confinement was 59%, with another 13% of records having no more than a 2-week discrepancy between these three methods.

Table B11 shows the proportion of preterm and full-term births for which outcome status was reclassified on the basis of additional gestational age information from the clinical record. Based on the birth certificate alone, 9 (26%) of 35 preterm infants had weights above the 90th percentile for their gestational age; most of these infants were probably not actually preterm. Of the 35 preterm infants, 5 (14%) were reclassified as full term based on either the last menstrual period on the medical record (2 births) or the clinical estimate of gestational age (3 births). One of the heavy preterm births was not reclassified based on the clinical estimate of gestational age because the medical record also noted that the mother had class A diabetes, which might have explained the infant's large size. Three preterm births that could not be reclassified based on a clinical estimate of gestational age were still quite heavy and might not have been preterm. None of the full-term births were reclassified as preterm.

Table B12 contains information on the proportion of SGA and normal for gestational age births for which there was agreement between the birth certificate and medical record. As discussed in the Methods section, clinical estimates of gestational age tend toward the norm, and hence result in an underestimate of SGA infants. Therefore, only the two SGA infants for whom the last menstrual periods on the medical records were indicative of a normal weight infant were reclassified as normal for gestational age. The proportion of SGA infants falsely classified as SGA was estimated to be 11%. There were no normal for gestational age births reclassified based on review of the medical records. However, this latter statistic could have been misleading; given the rarity of the occurrence of SGA, the sample size of healthy live-born infants might have been too small to identify—based on the birth certificate data alone—live-born infants falsely classified as normal weight births.

Of 30 birth certificates with missing or illogical gestational ages, 18 (60%) had medical records with credible estimates of gestational age; 4 (13%) had gestational age estimates that were illogical or inconsistent with the infant weight data, and 8 (27%) had no information regarding gestational age for the medical record. Only four birth certificates were missing information on birth weight. No medical records were located for any of the birth certificates missing birth weight data.

Pregnancy History

One piece of data that was especially interesting was maternal pregnancy history. In the results section of the report that this appendix accompanies, a high risk for SGA was associated with the combination of exposure to tetrachloroethylene (PCE) and maternal history of fetal loss. Records were located for 23 mothers whose previous fetal losses were reported on their infants' birth certificates. Of these, 16 (70%) had medical records that identified prior losses as miscarriages, and 2 (9%) had had both a miscarriage and a stillbirth. One record (4%) had no information about pregnancy history, and 4 (23%) had information documenting a fetal loss before the sixth month but did not distinguish between miscarriages and induced abortions. Out of the remaining 99 medical records abstracted, only 4 (4%) mothers had had previous fetal losses (3 had miscarriages, 1 had a stillbirth).

Medical Complications

Table B13 contains a summary of complications reported on the medical record for different categories of births. The frequencies in the table do not add to 100% because many of the women with medical complications had more than one complication reported in their records. With the exception of bleeding or spotting during pregnancy, medical complications were not more common in records for SGA and preterm births than for full-term births of normal weight. Because of the sampling strategy employed to select the medical records, it would have been difficult to make inferences regarding data quality by comparing observed and expected rates of complications.

Having reviewed the complications reported, it is apparent that a variety of data on different laboratory tests and medical conditions were recorded in the medical records. However, more specific case definitions for hypertension and diabetes should be employed in future efforts to abstract medical record information.

Birth Defects

Medical records were sampled for 62 infants specifically because their birth certificates indicated that they had birth defects. Table B14 contains the proportion of birth defects reported on the birth certificate that were reportable based on medical record review. Birth certificates for 22 (35%) had ICD codes corresponding only to reportable defects; 39 (63%) had ICD codes for which it was not possible to determine whether the defects were reportable; and 1 (2%) had a vaginal skin tag, a nonreportable anomaly. Of the 22 ICD codes corresponding to reportable defects, half (11) of the defects were confirmed by medical records. Nine medical records were not located for infants with birth certificates indicating reportable defects. Because each of these ICD codes corresponded to important defects, they were included in the computed rates. Two medical records contained information suggesting that the birth certificates were coded based on probable, but unconfirmed, diagnoses. After consultation with the Metropolitan Atlanta Congenital Defects Program, these latter were excluded from the computed prevalence rates.

Of the 39 ICD codes corresponding to both reportable and nonreportable defects, 24 (63%) had medical records confirming that the characteristics were not reportable defects. Most were skin tags, extra fingers, and birthmarks. Two (5%) records had reportable birth defects consistent with the ICD codes reported. Two (5%) records had serious reportable birth defects that were inconsistent with the ICD codes reported on the birth certificates. Three (8%) records had vague information on the medical record that could neither confirm nor verify the defect. Eight (21%) of the records were not located. Given that most of the records in this category were for nonreportable defects, the eight births in this category with no medical records were eliminated from the computed birth defect rates.

Table B15 lists the frequency of 25 reportable defects by organ system for each PCE exposure category separately. Two of these defects were identified from fetal death certificates and were not part of the medical records sample. One infant with a reportable defect was eliminated because his parents did not reside within the study area before his birth. Infants with defects in more than one organ system were included in the table for each organ system affected. Most organ systems had only one or two defects in each exposure category. The prevalence of all birth defects combined in the PCE-exposed group was less than half of the rate in the unexposed group (OR: 0.4 [90% CI: 0.2, 1.1]). The total number of defects in each organ system was so small that no statistical tests were performed for the organ systems separately. No infants exposed to TCE were reported to have birth defects.

Table B16 compares the prevalence of reportable birth defects recorded on the birth certificates to the prevalence of these defects from NCBDMP. Depending on the organ system,

the rates of reportable birth defects recorded on birth certificates were from 2 to 30 times lower than the rates recorded in the NCBDMP.

Three infants whose birth certificates did not indicate any birth defects had medical records with reportable birth defects. All three defects occurred in different organ systems. One infant was born in 1968, before birth defects were recorded on birth certificates. Two were born during the period from 1978 through 1985, when birth defects should have been recorded on birth certificates.

Other Aspects of Feasibility

The length of time needed to complete the abstraction form was recorded for 84 records. The length of time required to complete the abstraction form ranged from 8 to 54 minutes, with a mean of 23 minutes.

Discussion

The overall rate of locating at least one medical record (mother's or infant's) was 77%, which was close to the target location rate of 80%. The location rate was even higher for infants born at the NRMHC. Records for infants born at OMH will become increasingly more difficult to identify with each year that elapses, although current location rates are good. An under representation of black mothers' records was observed, which resulted from the use of different hospitals for delivery.

Data obtained from the medical records were more useful in some cases than in others. Of particular interest was the high degree of complete information in the medical records characterizing the type of previous fetal loss (i.e., miscarriage or stillbirth) that mothers reported. Miscarriages reflect abnormalities associated primarily with the first trimester environment, while stillbirths reflect abnormalities associated primarily with the third trimester environment. Because an association was observed in the main analyses between PCE exposure and SGA infants born to mothers who had previous fetal losses, it would be valuable to characterize the type of fetal loss experienced by at least a sample of women who had previous fetal losses.

The improvements in data quality used to estimate gestational age and SGA were modest at best. Fourteen percent of births that were listed as preterm on birth certificates were determined not to be preterm after review of the medical records and birth weights. In the absence of medical record information, it was necessary to delete 26% of the preterm births from the main analyses. Nonetheless, preterm births were not the primary focus of the study. Only 8% of SGA infants were reclassified as normal infants based on review of the medical records. There were also disagreements in gestational age estimates between the medical records and the birth certificates for healthy live-born infants, but none of these disagreements resulted in the reclassification of these infants as preterm or SGA. As listed in Table B1, infants with missing or illogical data made up an estimated 3% of the total source population. Therefore,

obtaining medical records for infants in this category would improve data quality for approximately 2% of the total data, a minimal improvement for the cost.

Other variables that had reasonable completeness rates and might be useful included maternal height and father's military rank (which was reported closer to the time of birth than the information on rank provided in the housing record). Medical record data on maternal smoking, alcohol use, and occupation were available for a minimal proportion of infants and were, therefore, not useful.

Data on medical complications were of modest usefulness. It seems likely that the abstraction form could be improved to increase its value. Particular recommendations for improvement are the use of clear case definitions for hypertension, gestational diabetes, and preeclampsia, and the exclusion of single high blood pressure or high glucose readings that are not confirmed by follow-up measurements or notations in the medical records. Access to these data for a larger sample of women might have provided a clearer interpretation of the associations observed in the main analyses between PCE and TCE exposure and SGA.

Birth defects as recorded on birth certificates occurred less frequently in PCE-exposed infants than in nonexposed infants. However, the total number of birth defects that occurred was so small that the rates were statistically unstable. Toxic substances rarely affect every organ system; however, there were too few defects to analyze the data separately for each organ system. Birth certificates are known to be an incomplete source of birth defect data (5). For the years of interest at Camp Lejeune, rates of reported birth defects were between one-half and one-thirtieth of the rates observed from the NCBDMF. Given that the NCBDMF is a passive registry system which is itself likely to suffer from underreporting (7-8), this suggests severe underreporting at Camp Lejeune. The reality of under ascertainment was reinforced by the finding of two birth defects in medical records for the years 1978 through 1985 for infants whose birth certificates gave no indication of an anomaly. Superficially, it appears that infants exposed to PCE in the first trimester were less likely to have been born with birth defects than infants unexposed to PCE in the first trimester. However, given the extreme underascertainment of birth defects on the birth certificates, the possibility that contaminated drinking water at Camp Lejeune might have resulted in birth defects could not be reasonably evaluated.

Proper assessment of the potential impact of PCE exposure on birth defects rates at Camp Lejeune would require information about birth defects for every infant. Accomplishing this by reviewing as many of the 12,000 medical records as might be located would be extremely time consuming and would overburden the NRMF, the source of most of the medical record data in this study. A more efficient way to identify infants with birth defects has been proposed as part of a study to identify children diagnosed with childhood leukemia. This proposal is currently under review.

The medical records contained much more detailed information about birth defects than did the birth certificates. Medical records were used to distinguish between reportable and non-reportable defects in a number of cases, and contained information on birth defects not reported

on the birth certificates. In the event that a data source other than the birth certificates could be used to identify infants who are likely to have had birth defects, then reviewing medical records for these infants would be useful. However, the medical records were still limited because most contained data for less than the first week of the infant's life. Therefore, several suspected birth defects could not be confirmed, and birth defects that are not easily recognized at birth were not identified. No congenital heart defects were noted even though heart defects are known to be common. It is recommended that, in any future attempt made to review medical records for birth defects, provisions be made to obtain all records for the infant's first year of life.

Conclusions and Recommendations

1. Overall, a high proportion of infant and maternal records were located. Location rates were sufficient to allow for a valid medical record review.
2. Variables containing complete information in more than 65% of the sampled records included last menstrual period, expected date of confinement, maternal pregnancy history, maternal height, maternal blood pressure, and father's rank.
3. Data were insufficient for maternal smoking, alcohol use, and occupation. Each of these variables was available for less than 30% of the sampled records.
4. In any additional work involving medical record abstraction, the abstraction form should be revised to exclude single readings of high blood pressure, glucosuria, or proteinuria that were not confirmed by additional tests. Clear case definitions for hypertension, gestational diabetes, and preeclampsia should be employed. More information regarding the treatment and course of medical complications should be included on the abstraction forms.
5. A substantial proportion of heavy preterm births were reclassified as full-term after the medical records were reviewed. While obtaining medical records for all heavy preterm births would improve data quality for the preterm birth analysis, the importance of this analysis to the overall scope of the Camp Lejeune study should be considered before investing more time and resources into improving this analysis.
6. Medical records clearly distinguished between women with histories of miscarriage and women with histories of stillbirth. Therefore, obtaining medical records for a sample of the infants whose mothers had histories of fetal loss would be useful in distinguishing between these two groups of women, especially in light of the findings reported in the main analyses.
7. Birth defects as reported on the birth and fetal death certificates during the period from 1978 through 1985 were grossly underascertained based on a comparison between reported and expected rates.

8. If one is interested in studying birth defects, there is little point in reviewing neonatal records for the first few days of life, nor identifying birth defects from birth certificates. If a strictly records-based study of birth defects is desirable, it would be more appropriate to review all records in the cohort study for the first year of life. In the absence of the resources to undertake such an expensive endeavor and the availability of records for that entire time period, alternative approaches, such as identifying children with birth defects through maternal or self-report, would be preferable.

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Table B1. Frequency and percentage of records located in each of the categories sampled.

Category (Estimated % of source population)	Result of Tracing	Frequency (%)
Fetal deaths (1%)	Mother's record located	0 (0)
	Infant's record located	0 (0)
	Either record located	0 (0)
	No records located	35 (100)
	Total records traced	35
Healthy live-born infants with no missing data (64 %)	Mother's record located	23 (66)
	Infant's record located	25 (71)
	Either record located	26 (74)
	No records located	9 (26)
	Total records traced	35
Preterm deliveries (8 %)	Mother's record located	27 (77)
	Infant's record located	28 (80)
	Either record located	29 (83)
	No records located	6 (17)
	Total records traced	35
Small for gestational age births (10%)	Mother's record located	15 (65)
	Infant's record located	18 (78)
	Either record located	18 (78)
	No records located	5 (22)
	Total records traced	23
Maternal medical complications (20%)	Mother's record located	23 (68)
	Infant's record located	28 (82)
	Either record located	28 (82)
	No records located	6 (18)
	Total records traced	34
Missing data for LMP or birth weight (4%)	Mother's record located	18 (53)
	Infant's record located	24 (71)
	Either record located	24 (71)
	No records located	10 (29)
	Total records traced	34
All live-born infant categories combined (99%)	Mother's record located	104 (66)
	Infant's record located	120 (76)
	Either record located	122 (77)
	No records located	36 (23)
	Total records traced	158

Table B2. Frequency and percentage of maternal and neonatal records located by city and county of delivery (fetal deaths excluded).

County and City	Result of Tracing	Frequency (%)
Onslow County outside Jacksonville city limits (born at NRMC)	Mother's record located	104 (79)
	Infant's record located	106 (81)
	Either record located	108 (82)
	No records located	<u>23</u> (18)
	Total records traced	131
Onslow County inside Jacksonville city limits (born at OMEM)	Mother's record located	0 (0)
	Infant's record located	14 (74)
	Either record located	14 (74)
	No records located	<u>5</u> (26)
	Total records traced	19
Born outside Onslow County	Mother's record located	0 (0)
	Infant's record located	0 (0)
	Either record located	0 (0)
	No records located	<u>5</u> (100)
	Total records traced	5
Born at home	Mother's record located	0 (0)
	Infant's record located	0 (0)
	Either record located	0 (0)
	No records located	<u>3</u> (100)
	Total records traced	3

Table B3. Frequency and percentage of maternal and neonatal records located by race of mother (fetal deaths excluded).

Mother's Race	Result of Tracing	Frequency (%)
White	Mother's record located	71 (68)
	Infant's record located	79 (75)
	Either record located	80 (76)
	No records located	<u>25</u> (24)
	Total records traced	105
Black	Mother's record located	23 (55)
	Infant's record located	32 (76)
	Either record located	32 (76)
	No records located	<u>10</u> (24)
	Total records traced	42
Other	Mother's record located	10 (91)
	Infant's record located	10 (91)
	Either record located	10 (91)
	No records located	<u>1</u> (9)
	Total records traced	11

Table B4. Frequency and percentage of maternal and neonatal records located by year of birth (fetal deaths excluded).

Year of Birth	Result of Tracing	Frequency (%)
1968-1970	Mother's record located	14 (70)
	Infant's record located	14 (70)
	Either record located	14 (70)
	No records located	6 (30)
	Total records traced	20
1971-1975	Mother's record located	26 (68)
	Infant's record located	26 (68)
	Either record located	26 (68)
	No records located	12 (32)
	Total records traced	38
1976-1980	Mother's record located	32 (80)
	Infant's record located	31 (78)
	Either record located	33 (83)
	No records located	7 (18)
	Total records traced	40
1981-1985	Mother's record located	32 (53)
	Infant's record located	49 (82)
	Either record located	49 (82)
	No records located	11 (18)
	Total records traced	60

Table B5. Frequency and percentage of complete data in variables abstracted from the medical record.

Variable Name	Number Complete	Percent Complete Among Located Records	Percent Complete Among All Records
Birth weight	122	100	77
Birth date	122	100	77
Mother's age	122	100	77
Parity	121	99	77
Maternal pregnancy history	120	98	76
Maternal history of infectious diseases	118	96	75
Father's age	116	95	73
Pelvic inflammatory disease	116	95	73
Expected date of confinement	115	94	73
Mother's last menstrual period	114	93	72
Father's rank	113	94	72
Maternal height	111	91	70
Rh compatibility	108	89	68
Blood pressure*	107	88	68
Access to prenatal care	104	85	66
Hematocrit*	98	80	62
Urine glucose and protein*	85	70	54
Maternal prepregnant weight	84	69	53
Maternal smoking	43	35	27
Maternal alcohol Consumption	39	32	25
Mother's occupation	31	25	20

* Measured at least once during pregnancy

Table B6. Frequency and percentage of complete data in variables abstracted from the medical record by sampling category.

Variable Name	Number Records with Completed Fields for Full-term Normal Weight Births with No Medical Complications	Number Records with Completed Fields in Records for Preterm Births	Completed fields in records for small for gestational age births	Completed Fields in Records for Births with Maternal Medical Complications	Completed Fields in Records with Missing or Illogical Birth Certificate Data
Number records located/ number records traced	26/35	29/35	18/23	28/34	24/34
Birth weight	26 (100) [74]	29 (100) [83]	18 (100) [78]	28 (100) [82]	24 (100) [71]
Birth date	25 (96) [70]	29	18	28	24
Mother's age	26	29	18	28	24
Parity	26	29	18	28	23 (96) [68]
Maternal pregnancy history	24 (92) [68]	29	18	28	24
Maternal history of infectious diseases	26	29	15 (83) [65]	27 (96) [79]	23
Father's age	24	29	18	27	24
Pelvic inflammatory disease	25	29	16 (89) [70]	24 (86) [71]	22 (92) [65]
Expected date of confinement	25	28 (97) [80]	16	27	21 (88) [62]
Mother's last menstrual period	25	26 (90) [74]	16	23 (82) [68]	18 (75) [53]
Father's rank	25	26	17 (94) [74]	26 (93) [76]	22 (92) [65]

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(% of records found in this category with complete information)
 [% of all records in this category with complete information]

Table B6. Continued.

Variable Name	Number Records with Completed Fields for Full-term Normal Weight Births with No Medical Complications	Number Records with Completed Fields in Records for Preterm Births	Completed Fields in Records for Small for Gestational Age Births	Completed Fields in Records for Births with Maternal Medical Complications	Completed Fields in Records with Missing or Illogical Birth Certificate Data
Number records located/ Number records traced	26/35	29/35	18/23	28/34	24/34
Maternal height	26 (100) [74]	27 (77) [93]	15 (83) [65]	25 (89) [74]	21 (88) [62]
Rh compatibility	26	29 (100) [83]	15	27 (96) [79]	22 (92) [65]
Blood pressure*	25	24 (83) [68]	15	26 (93) [76]	20 (83) [59]
Access to prenatal care	24	23 (79) [66]	12 (67) [52]	26	18 (75) [53]
Hematocrit*	21 (81) [60]	24	12	25	18
Urine glucose and protein*	19 (73) [54]	19 (66) [54]	14 (78) [61]	25	15 (63) [44]
Maternal prepregnant weight	23 (89) [66]	25 (86) [71]	13 (72) [57]	21 (75) [62]	16 (66) [49]
Maternal smoking	4 (15) [11]	12 (41) [34]	5 (28) [22]	17 (61) [50]	10 (42) [29]
Maternal alcohol Consumption	3 (12) [9]	10 (34) [29]	6 (33) [26]	16 (57) [47]	8 (33) [24]
Mother's occupation	3 (12) [9]	8 (28) [22]	4 (22) [17]	13 (46) [38]	5 (21) [15]

(% of records found in category with complete information)

[% of all records in category with complete information]

* Measured at least once during pregnancy.

Table B7. Frequency and percentage of complete data in variables abstracted from the medical record by hospital.

Variable Name	Onslow Memorial Hospital	Navy Regional Medical Center
Number records located/number records traced	14/19	97/118
Birth weight	14 (100) [74]	97 (100) [82]
Birth date	14	97
Mother's age	14	97
Parity	13 (93) [68]	97
Maternal pregnancy history	13	96 (99) [81]
Maternal history of infectious diseases	13	94 (97) [80]
Father's age	12 (86) [63]	95 (98) [81]
Pelvic inflammatory disease	13	92 (95) [78]
Expected date of confinement	12	92
Mother's last menstrual period	10 (71) [53]	86 (89) [73]
Father's rank	11 (79) [58]	93 (96) [79]
Maternal height	12	89 (92) [75]
Rh compatibility	12	93
Blood pressure*	12	84 (87) [71]
Access to prenatal care	10	71 (73) [68]
Hematocrit*	12	74 (76) [63]
Urine glucose and protein*	11	70 (72) [59]
Maternal prepregnant weight	0	84 (87) [71]
Maternal smoking	1 (70) [5]	42 (43) [36]
Maternal alcohol consumption	1	38 (39) [32]
Mother's occupation	4 (29) [21]	29 (30) [25]

(% of records found in category with complete information)

[% of all records in category with complete information]

* Measured at least once during pregnancy.

Table B8. Frequency and percentage of complete data in variables abstracted from the medical record by year of birth.

Variable Name	1968-1970	1971-1975	1976-1980	1981-1985
Number records located/Number records traced	14/20	26/38	33/40	49/60
Birth weight	14 (100) [70]	26 (100) [68]	33 (100) [83]	49 (100) [80]
Birth date	14	26	33	49
Mother's age	14	26	33	49
Parity	14	26	33	48 (97) [80]
Maternal pregnancy history	14	26	32 (97) [80]	48
Maternal history of infectious diseases	14	25 (96) [66]	33	46 (94) [77]
Father's age	14	26	33	48
Pelvic inflammatory disease	14	25	33	44 (90) [73]
Expected date of confinement	13 (93) [65]	23 (88) [61]	33	46
Mother's last menstrual period	13	25	30 (91) [75]	39 (80) [65]
Father's rank	14	26	32	43 (88) [72]
Maternal height	12 (86) [60]	25	32	42 (86) [70]
Rh compatibility	14	25	32	45 (92) [75]
Blood pressure*	13	24 (92) [63]	30	40 (82) [67]
Access to prenatal care	11 (79) [55]	20	32	37 (76) [62]
Hematocrit*	12	18 (69) [47]	28 (85) [70]	39
Urine glucose and protein*	5 (36) [25]	8 (31) [21]	30	26 (53) [43]
Maternal prepregnant weight	12	25	28	29 (59) [48]
Maternal smoking	0	0	18 (55) [45]	25 (51) [42]
Maternal alcohol consumption	0	0	15 (45) [38]	24 (49) [40]
Mother's occupation	1 (7) [5]	0	10 (30) [25]	23 (47) [38]

(% of records found in category with complete information)
[% of all records in category with complete information]

* Measured at least once during pregnancy.

Table B9. Frequency and percentage of complete data in variables abstracted from the medical record by mother's race.

Variable Name	White	Black	Other
Number records located/Number records traced	80/105	32/42	10/11
Birth weight	80 (100) [76]	32 (100) [76]	10 (100) [91]
Birth date	80	32	10
Mother's age	80	32	10
Parity	79 (99) [75]	32	10
Maternal pregnancy history	79	31 (97) [74]	10
Maternal history of infectious diseases	77 (96) [73]	31	10
Father's age	78 (98) [74]	29 (91) [74]	9 (90) [82]
Pelvic inflammatory disease	75 (94) [71]	31	10
Expected date of confinement	76 (95) [72]	30 (94) [71]	9
Mother's last menstrual period	71 (89) [68]	28 (88) [67]	8 (80) [73]
Father's rank	76	29	10
Maternal height	72 (90) [69]	29	10
Rh compatibility	76	30	10
Blood pressure*	72	27 (84) [64]	8
Access to prenatal care	67 (84) [64]	23 (72) [55]	8
Hematocrit*	66 (83) [63]	25 (78) [60]	7 (70) [64]
Urine glucose and protein*	56 (70) [53]	22 (69) [52]	7
Maternal prepregnant weight	65 (90) [62]	21 (72) [50]	8
Maternal smoking	29 (36) [28]	11 (34) [26]	3 (30) [27]
Maternal alcohol consumption	26 (33) [25]	10 (31) [24]	3
Mother's occupation	20 (25) [19]	11 (34) [26]	3

(% of records found in category with complete information)

[% of all records in category with complete information]

* Measured at least once during pregnancy.

Table B10. Agreement between gestational age on birth certificate and gestational age as reported on medical record. The birth certificate might disagree with either the last menstrual period or the clinical estimate recorded in the medical record.

Gestational Age Using Birth Certificate LMP	Medical Record Estimate More than 2 Weeks less than Birth Certificate Age	Medical Record Estimate Within 2 Weeks of Birth Certificate Age	Medical Record Estimate More than 2 Weeks Greater than Birth Certificate Age	No Medical Record	Total
27-36	0	20	9	7	36
37-38	1	2	1	5	9
39-41	4	22	1	12	39
42-44	3	5	0	1	9
Total	8	49	11	25	93

Table B11. Proportion of preterm births reclassified as term and term births reclassified as preterm after reviewing medical record information

Gestational Age Based on Birth Certificate	Preterm after Review of Medical Record Information	Full-term after Review of Medical Record Information	No Medical Record Information on Gestational Age	Total
Preterm	23	5	7	35
Full-term	0	25	10	35
Total	23	30	17	70

Table B12. Frequency and percentage of small for gestational age births reclassified as normal weight and normal weight births reclassified as small for gestational age based on review of medical records.

Weight for Gestational Age Based on Birth Certificate	SGA According to Clinical Estimate and Last Menstrual Period on Medical Record	Normal Weight for Gestational Age According to Clinical Estimate or Last Menstrual Period on Medical Record	Outcome Status Changed Based on Medical Record Review	No medical record information on gestational age	Total
Small	10 (40)	8 (32)	2 (8)	7 (28)	25
Normal	0 (0)	25 (71)	0 (0)	10 (29)	35

Table B13. Frequency and percentage of maternal medical complications reported in the medical record by outcome status.

Medical Complication	Full-term Normal Weight Births (located records)	Preterm or Small for Gestational Age Births (% located records)	Total (% located records)
Anemia	4 (5.4)	4 (8.3)	8 (6.6)
Bleeding or spotting during pregnancy	2 (2.7)	6 (12.8)	8 (6.6)
Diabetes or 1+ sugar	2 (2.7)	2 (4.3)	5 (4.1)
Hypertension, toxemia, preeclampsia	6 (8.1)	3 (6.4)	9 (7.4)
History of adverse pregnancy outcome	6 (8.1)	3 (6.4)	9 (7.4)
Infection such as vaginitis, urinary tract infection, or streptococcus without severe complications	11 (14.9)	6 (12.8)	17 (13.9)
Infection with severe complication such as chorioamnitis, sepsis or pyelonephritis	1 (1.4)	2 (4.3)	3 (2.5)
No complications	47 (63.5)	27 (57.4)	73 (59.8)
No record found	25	11	36
Total records	99	59	158

B-30

Table B14. Frequency of birth certificates with birth defects recorded on them by whether they could be classified as reportable based on the medical record.

Birth Certificate Information	Medical Record Indicates Reportable Defect	Medical Record Indicates No Defect or Confirms a Non-reportable Defect	Medical Record Too Vague to Confirm Defect	Medical Record Not Located	Total
Birth defect reportable	11	0	2	9	22
Cannot determine from birth certificate whether defect is reportable	4	24	3	8	39
Defect on birth certificate is not reportable	0	1	0	0	1
Total	15	25	5	17	62

Table B15. Prevalence of reportable birth defects at Camp Lejeune from 1978 through 1985 in PCE-exposed and unexposed births.

Birth Defect	PCE Exposed Frequency (N = 1,723)	Unexposed Frequency (N = 4,044)
<u>Musculoskeletal System</u>	0	7
Limb reduction defects		2
Foot deformities		3
Abdominal wall defects		1
Other limb anomalies		1
<u>Oral Clefts</u>	0	3
Cleft palate		2
Cleft lip and palate		1
<u>Chromosomal Defects</u>	2	1
Down's syndrome	1	1
Turner's syndrome	1	0
<u>Central Nervous System (CNS)</u>	1	5
Anencephaly		2
Hydrocephalus		1
Microcephaly	1	
Spina bifida		1
Brain reduction defect		1
<u>Genitourinary</u>	0	2
Kidney dysplasia		1
Hypospadias		1
<u>Digestive</u>	1	1
Intestinal atresia	1	1
<u>Eye</u>	0	1
Congenital ptosis (with blindness and exotropia)		1
<u>Respiratory</u>	0	1
Choanal atresia		1
Total Frequency	4	21
Total Rate per 10,000	23	52

Table B16. Prevalence of reportable birth defects at Camp Lejeune from 1978 through 1985, compared with rates in the North Carolina Birth Defects Registry (NCBDR).

Birth defect (ICD-9 Code) (ICD Code)	Camp Lejeune Rate per 10,000 (Frequency)	NCBDR Rate per 10,000
Musculoskeletal defects (754.0-756.9)	12.2 (7)	101.3
Oral clefts (749.0-749.2)	5.2 (3)	11.2
Chromosomal defects (758.0-758.9)	5.2 (3)	11.6
Central nervous system (740.0-742.9)	10.6 (6)	22.6
Genitourinary (752.0-753.9)	3.5 (2)	81.8
Digestive (750.1-753.9)	3.5 (2)	24.1
Eye (743.0-743.9)	1.7 (1)	4.8
Respiratory (748.0-748.9)	1.7 (1)	14.8

Appendix C—Medical Records Abstraction Form

Accession #: _____
Cert ID #: _____

Medical Records Abstraction Form (Revised 6/28/96)

Instructions to abstractors: All of the information on this sheet is confidential and should be maintained according to the Privacy Act of 1974 (5 U.S.C. Section 552a(e)). These confidential records must be kept out of sight of unauthorized persons and stored in locked cabinets or locked rooms. You may not photocopy this form without authorization.

Hospital delivered in : _____ ID Number located? [Y] [N]

1. Which records were located?

- 1-Mother's record located
- 2-Infant's record located
- 3-Both records located
- 4-No records located

Certificate

Medical Record

If the name on the birth certificate is identical, place a check next to the field number. If the name is different, fill in the blank.

Mother's first name:	1.1 _____
Mother's last name:	1.2 _____
Child's first name:	1.3 _____
Child's last name:	1.4 _____
Father's first name:	1.5 _____
Father's last name:	1.6 _____

2. Mother's rank: _____
88 = None

3. Father's rank: _____
88 = None

CERT ID #: | _____ |

Medical Records Abstraction Form
General information

4. Mother's occupation: _____
99 = Not reported

5. Mother's age at delivery: ____

6. Father's age at delivery: ____

7. Mother's race:
1- White
2- Black
3- American Indian
4- Other
9- No information

8. Mother's parity: ____

Labor and Delivery

9. Date of birth: ____/____/____

10. Birthweight: ____ lbs ____ / ____ oz

11. Vital status of offspring:
1- live birth -----> Skip to 12.
2- fetal death -----> Go to 11.1

11.1 If fetal death, cause of death:

- a. _____
- b. _____
- c. _____
- d. _____
- e. _____

12. Sex: 1- male
2- female

13. Apgar: ____/____
1 min 5 min

CERT ID #: | _____ |

Medical Records Abstraction Form
Labor and delivery

14. Were there any complications of labor or delivery?

1- Yes

2- No -----> Skip to 15.

14.1 If yes, please describe:

- a. _____

- b. _____

- c. _____

- d. _____

- e. _____

15. Were any congenital anomalies noted?

1-Yes

2-No -----> Skip to 16.

15.1 If yes, please describe:

- a. _____

- b. _____

- c. _____

- d. _____

- e. _____

CERT ID #: | _____ |

Medical Records Abstraction Form
Prenatal care record

16. Maternal Height: __ feet __ inches

17. Maternal Weight at 1st visit: ___ lbs

18. Maternal Weight at last visit: ___ lbs

18a. Usual weight: ___ lbs

19. Last Menstrual Period Date: __/__/__

20. Expected Date of Confinement: __/__/__

21. 1st prenatal care visit date: __/__/__

22. Last prenatal care visit date: __/__/__

23. Total number visits: __

24. Gestational age at 1st prenatal care visit: __ weeks

CERT ID #: | _____ |

Medical Records Abstraction Form
Prenatal care record

25. Was blood pressure higher than 140/100 on any visit?

- 1-Yes -----> Go to 25.1a
- 2-No -----> Skip to 26
- 9-Blood pressure not recorded-----> Skip to 26

25.1a. Date blood pressure > 140/100 first recorded: ___ ___ / ___ ___ / ___ ___

25.1b. Blood pressure reading: ___ ___ / ___ ___

25.2a. Date blood pressure > 140/100 last recorded: ___ ___ / ___ ___ / ___ ___

25.2b. Blood pressure reading: ___ ___ / ___ ___

26. Was protein or sugar found in mother's urine?

- 1- Protein in urine -----> Answer 26.1a-26.1b
- 2- Sugar in urine -----> Answer 26.1c-26.1d
- 3- Protein and sugar in urine -----> Answer 26.1a-26.1d
- 4- Neither in urine -----> Answer 26.2
- 9- No urinalysis -----> Skip to 27

26.1a Date protein first noted in urine: ___ ___ / ___ ___ / ___ ___

26.1b Highest protein reading recorded: ___ ___

26.1c Date sugar first noted in urine: ___ ___ / ___ ___ / ___ ___

26.1d Highest sugar reading recorded: ___ ___

26.2 If not elevated, date protein/sugar last tested in urine: ___ ___ / ___ ___ / ___ ___

CERT ID #: | _____ |

**Medical Records Abstraction Form
Prenatal care record (continued)**

27. Were any of the hematocrit tests less than 30?

- 1-Yes
- 2-No
- 9-Hematocrit not measured

27.1 If yes, what was the first low hematocrit and when was it measured?

___ Hct ___ / ___ / ___

27.2 What was the last low hematocrit and when was it measured?

___ Hct ___ / ___ / ___

28. Was pelvic inflammatory disease reported?

- 1-Yes
- 2-No

29. Were any infectious disease reported?

- 1-Yes
- 2-No

30. Was mother's Rh incompatible?

- 1-Yes
- 2-No

31. Were there any other complications of pregnancy?

- 1- Yes ----- > GO TO 31.1
- 2- No ----- > GO TO 32.

31.1 If yes, please describe:

- a. _____
- b. _____
- c. _____
- d. _____
- e. _____

CERT ID #: | _ _ _ _ _ |

Medical Records Abstraction Form
Prenatal care record (continued)

32. Did the mother smoke cigarettes?

- 1-Yes
- 2-No
- 9-No information

32.1 If yes, how many cigarettes did she smoke a day? _ _
88 = mother didn't know
99 = no information

33 Did the mother drink alcohol?

- 1-Yes
- 2-No
- 9-No information

33.1 If yes, how many drinks did she have a week? _ _
88 = mother didn't know
99 = no information

33.2 If yes, did her quantity of drinking change in the last year?

- 1-yes
- 2-no
- 8-mother didn't know
- 9-no information

34. Did the mother have any past pregnancies?

- 1-Yes
- 2-No
- 9-No information

34.1 If yes, how many past pregnancies did she have? _ _

34.2 If yes, how many past pregnancies did she carry for 6 months or more? _ _

CERT ID #: _____

**Medical Records Abstraction Form
Prenatal care record (continued)**

35. What was the outcome of the most recent past pregnancy?

- 1-Ended in livebirth
- 2-Ended in late fetal death
- 3-Ended in miscarriage
- 9-No information

35.1 Pregnancy Ending Date: ___/___/___

35.2 Weeks gestation: ___

35.3 Birthweight: ___ lbs ___ oz

35.4 Were there congenital anomalies or complications of this pregnancy, labor or delivery?

- 1-Complications of pregnancy
- 2-Complications of labor or delivery
- 3-No complications
- 4-Congenital anomalies
- 5-A combination of one of these problems
- 9-No information

35.5 Please describe any complications:

- a. _____

- b. _____

- c. _____

- d. _____

- e. _____

CERT ID #: | _____ |

**Medical Records Abstraction Form
Prenatal care record (continued)**

Past pregnancy 2:

36.1 What was the outcome of the 2nd most recent past pregnancy?

- 1-Ended in livebirth
- 2-Ended in late fetal death
- 3-Ended in miscarriage
- 9-No information

36.2 Pregnancy Ending Date: ___ ___ / ___ ___ / ___ ___

36.3 Weeks gestation: ___ ___

36.4 Birthweight: ___ ___ lbs ___ ___ oz

36.5 Were there congenital anomalies or complications of this pregnancy, labor or delivery?

- 1-Complications of pregnancy
- 2-Complications of labor or delivery
- 3-No complications
- 4-Congenital anomalies
- 5-A combination of one of these problems
- 9-No information

36.6 Please describe any complications:

- a. _____

- b. _____

- c. _____

- d. _____

- e. _____

CERT ID #: | _____ |

**Medical Records Abstraction Form
Prenatal care record (continued)**

Past pregnancy 3:

37.1 What was the outcome of the 3rd most recent past pregnancy?

- 1-Ended in livebirth
- 2-Ended in late fetal death
- 3-Ended in miscarriage
- 9-No information

37.2 Pregnancy Ending Date: ___ ___ / ___ ___ / ___ ___

37.3 Weeks gestation: ___ ___

37.4 Birthweight: ___ ___ lbs ___ ___ oz

37.5 Were there congenital anomalies or complications of this pregnancy, labor or delivery?

- 1-Complications of pregnancy
- 2-Complications of labor or delivery
- 3-No complications
- 4-Congenital anomalies
- 5-A combination of one of these problems
- 9-No information

37.6 Please describe any complications:

- a. _____

- b. _____

- c. _____

- d. _____

- e. _____

CERT ID #: | _____ |

Medical Records Abstraction Form
Prenatal care record (continued)

Past pregnancy 4:

38.1 What was the outcome of the 4th most recent past pregnancy?

- 1-Ended in livebirth
- 2-Ended in late fetal death
- 3-Ended in miscarriage
- 9-No information

38.2 Pregnancy Ending Date: ___ / ___ / ___

38.3 Weeks gestation: ___

38.4 Birthweight: ___ lbs ___ oz

38.5 Were there congenital anomalies or complications of this pregnancy, labor or delivery?

- 1-Complications of pregnancy
- 2-Complications of labor or delivery
- 3-No complications
- 4-Congenital anomalies
- 5-A combination of one of these problems
- 9-No information

38.6 Please describe any complications:

- a. _____

- b. _____

- c. _____

- d. _____

- e. _____

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