Population-Based Surveillance and Etiological Research of Adverse Reproductive Outcomes and Toxic Wastes

PHASE IV-B

Public Drinking Water Contamination and Birthweight, and Selected Birth Defects

NEW JERSEY DEPARTMENT OF HEALTH
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POPULATION-BASED SURVEILLANCE AND ETIOLOGICAL RESEARCH OF ADVERSE REPRODUCTIVE OUTCOMES AND TOXIC WASTES

REPORT ON PHASE IV-B: PUBLIC DRINKING WATER CONTAMINATION AND BIRTHWEIGHT, AND SELECTED BIRTH DEFECTS

A CASE-CONTROL STUDY

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POPULATION-BASED SURVEILLANCE AND ETIOLOGICAL RESEARCH OF ADVERSE REPRODUCTIVE OUTCOMES

REPORT ON PHASE IVB: PUBLIC DRINKING WATER CONTAMINATION AND BIRTHWEIGHT, AND SELECTED BIRTH DEFECTS A CASE-CONTROL STUDY

Frank J. Bove, Mark C. Fulcomer, Judith B. Klotz, Jorge Esmart, Ellen M. Dufficy, Rebecca T. Zagraniski, and Jonathan E. Savrin

EXECUTIVE SUMMARY

This report comprises the fifth and last product of the multi-year cooperative agreement between the New Jersey Department of Health and the Centers for Disease Control entitled, Population-based Surveillance and Etiologic Research on Adverse Reproductive Outcomes and Toxic Wastes. Under Phase IV of the overall project, two individual-based studies were conducted utilizing the environmental databases which were identified in Phase II as the most appropriate for this purpose: i.e., the database for the drinking water sampling of public systems established in 1984 under the New Jersey "A-280" statute and the databases on monitoring of inorganics and trihalomethanes for public water systems. Vital records and the New Jersey Birth Defects Registry were utilized to ascertain individual subjects.

The studies focused on four counties in northern New Jersey. These counties were not selected based on their rates of adverse reproductive outcomes, but rather, were chosen because they were among the five counties in the state with the highest number of public drinking water samples detecting one or more "A-280" contaminants during the first year of the A-280 program. In addition, a high percentage of the population in these four counties were served by relatively well-defined public water systems, including systems utilizing groundwater alone, surface water alone, or a mixture of the two, thus offering a variety of contamination situations (i.e. no detected contaminants, trihalomthanes only, one or more "A-280" contaminants only, or both types of contaminants detected.)

Since no data were available on private well contamination, towns in these four counties which were considered to have greater than 20% of their population on private wells were excluded from these studies. In addition, since birth certificate information was incomplete for those born in out-of-state hospitals, towns with 10% or more of their births born out-of-state (such as in New York City), were also excluded. Out of a total of 146 towns in these four counties, 75 were selected for these two studies. This report describes a case-control study of selected categories of birth defects and low birthweight. The outcomes selected were cardiac defects, neural tube defects, oral clefts, "very" low birthweight (< 1500 grams) and "intermediate" low birthweight (1500 - 2499 grams). The study period was January 1, 1985 - December 31, 1988, the four years commencing when the Birth Defects Registry was initiated and the New Jersey drinking water monitoring statute took effect. The study population was all singleton births and fetal deaths during the study period occurring in mothers of 18 years of age or older residing in one of the 75 study towns at time of birth or fetal death.

All occurrences of the selected birth defect groups among singleton livebirths and fetal deaths during the four year timeframe were included in the birth defect case series. Controls and low birthweight cases were randomly selected without replacement from all singleton livebirths occurring among the study population during the four year timeframe, with equal size samples taken from each six month interval of the study period. Chromosomal defects that could be identified through the Birth Defects Registry or fetal death certificates were excluded from all case and control series. Sampled low birthweight cases with registered major or minor birth defects were excluded from the low birthweight case series. Controls were neither low birthweight nor registered as having a major or minor birth defect.

The specific exposures of primary interest were water contamination by total trihalomethanes (TTHM) and volatile organic compounds (VOCs) regulated under the New Jersey "A-280" law, including trichloroethylene (TCE), tetrachloroethylene or "perchloroethylene" (PCE), total dichloroethylenes (DCE), 1,1,1-trichloroethane (TCA), carbon tetrachloride (CTC), 1,2-dichloroethane or "ethylene dichloride" (EDC), and benzene. In addition, nitrates and the type of water source used by the water company (groundwater, surface water, or a mixture of the two) were evaluated.

Mothers of cases and controls were interviewed by telephone during the period July 1989 to May 1990. The interviewers were not aware of the estimated levels of contaminants in the drinking water supplied to the homes of the subjects' mothers, and the exposure assignments were made without knowledge of the reproductive outcome status of the subjects. Information was obtained pertaining to the period from three months prior to conception through the end of the index pregnancy concerning mothers' residences, primary source(s) of drinking water, tap water consumption, showering habits, and exposures to potential risk factors such as occupation exposures, smoking, alcohol consumption, exposures in and around the home, prescription drugs, medical history, and previous adverse reproductive outcomes. A total of 563 mothers were interviewed.

For <u>neural tube defects</u>, statistically significant associations were found for TTHM at concentrations greater than 80 ppb with an odds ratio (OR) of 4.3 and for greater than 15 ppb with an OR of 3.8. Associations were also found with mixed water source (OR = 18). A less precise association ($p < 0.05$, one-tail, but the 95% confidence interval included the null OR of 1.0) was found with PCE (>5 ppb, OR = 4.1). After adjustment for the confounding effects of TTHM exposure, statistically significant associations were found with PCE (>5 ppb, OR = 4.0) and nitrates (>2 ppm, OR = 5.3).

For <u>oral clefts</u>, no associations were statistically significant. A less precise association was found with CTC (detected levels, OR = 5.4). A less precise association with decreased prevalence of oral clefts was found for TCA (>1 ppb, OR = 0.37), but this association was not found for TCA at concentrations greater than 2 ppb. A statistically significant association was found between the subgroup of cleft palate only with surface water source (OR = 4.9). A less precise association was found with cleft palate and DCE (> 2 ppb, OR = 5.3).

For major cardiac defects, no associations were statistically significant. Less precise associations were found with surface water source (OR = 2.2), mixed water source (OR = 2.9) and TTHM (> 15 ppb, OR = 2.0).

For ventricular septal defects (with no other cardiac defect) a statistically significant association was found with CTC (detected, OR = 9.2). Less precise associations were found with TVOC (> 5 ppb, OR = 3.0), and TCA (>2 ppb, OR = 3.9).

For very low birthweight, statistically significant associations were found with TVOC (> 5 ppb, OR = 2.9) and TCE (>1 ppb, OR = 2.5). A less precise association was found with PCE (>10 ppb) for which there were four cases and no controls.

For intermediate low birthweight, no associations were statistically significant. A less precise association was found with surface water source (OR = 1.6). A less precise association was also found with decreased prevalence of intermediate low birthweight and >1 ppb-5 ppb TVOC (OR = 0.52), but this finding was contradicted by the next range of >5 ppb - 10 ppb, for which the prevalence was elevated, although not statistically significant (OR = 2.2).

When water use habits were taken into account in the analyses of the various outcomes and drinking water contaminants (specifically, consumption of bottled vs tap water and duration of showering) no clear patterns emerged. The equivocal results obtained were probably due to the small numbers of cases and controls in each stratum of the variables for water consumption and duration of showering. In addition, given the considerable length of time between the pregnancies and the interviews, it is likely that the mothers of the subjects did not accurately recall their drinking water and showering habits during pregnancy.

Although the design of the study made it possible to interview mothers about their residences and exposures to a wide range of risk factors during their index pregnancies, there were a number of limitations. Most importantly, a majority (53.3%) of the mothers of the sampled cases and controls could not be located and interviewed, causing a potential source of selection bias. Secondly, the ability to account for the wide range of risk factors queried may have been limited by inaccurate recall of the mothers, due to the lag between the pregnancy and the interview. Finally, the sample size for the study was small, resulting in low statistical power and a lack of precision (i.e. extremely wide confidence intervals) in the estimation of the odds ratios, particularly since there were few cases and controls at the higher exposure levels of the contaminants.

Selection bias can result from the failure to interview all mothers of case and control subjects if the failure is related to both the reproductive outcome status and the exposure status (e.g. if a higher proportion of exposed controls were lost than unexposed controls). In order to assess the extent of this bias, analyses were conducted to evaluate how the results might have been different if the mothers of all cases and controls had been interviewed. The drinking water contaminant exposures of those who were not interviewed were estimated using the results from the concurrent individual-based "cross-sectional" study on this population (Phase IVA). Those estimates used the assumption that the non-interviewed mothers' residence at the time of birth was the same throughout the pregnancy. The non-interviewed subjects were then combined with the interviewed subjects and odds ratios were calculated. This evaluation of selection bias indicated that for virtually all of the results involving low birthweight and neural tube defects, the bias led generally to overestimates of the associations with the contaminants. In addition, for most of the outcomes studied, the selection bias led to an overestimate of the associations with TTHM, surface water source, and mixed water source. On the other hand, for birth defect outcomes other than neural tube defects, selection bias resulted generally in underestimations of the associations with the A-280 contaminants and with nitrates. Given the important effects of selection bias and the relatively small changes in the associations when the potential risk factors elicited by the interviews were accounted for, it appears that the case-control designed provided few advantages in this study over the cross-sectional design used in the concurrent study.

The observed associations should be interpreted cautiously: 1) nondifferential exposure misclassification could lead to underestimation of effects, 2) differential biases, such as selection bias and inaccurately or unmeasured confounding, could lead to underestimation or overestimation of effects of exposure, and 3) associations could be chance occurrences. In themselves, the positive associations found in this study do not provide sufficient evidence to make the claim that these contaminants cause adverse reproductive outcomes at the levels commonly found in public drinking water systems, and the scarcity of other toxicological and epidemiologic research on the reproductive effects of these drinking water contaminants prevents us from making such claims. Further, the findings of this study do not imply that pregnant women or women considering pregnancy should drink only bottled water; exposures to the contaminants in the study while bathing or showering can be at least as high as exposures through drinking water, and it cannot be assumed that bottled water has lower concentrations of the contaminants studied than does tap water. Nor does this study indicate that citizens should install household filtering systems, particularly since such systems tend to be expensive and require regular maintenance.

Nevertheless, from a public health perspective, these associations should be taken seriously and investigated further. The findings of this study and the cross-sectional study also support continued and enhanced vigilance on the part of USEPA and the states to (1) enforce and/or improve the regulations of the federal Safe Drinking Water and the Clean Water Acts and the analogous state laws and to (2) promote the development of new technologies and practices designed to reduce or eliminate the concentrations of these contaminants in drinking water.

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REPORT ON PHASE IVB
CASE-CONTROL STUDY OF PUBLIC DRINKING WATER SYSTEMS AND SELECTED BIRTH DEFECTS AND LOW BIRTHWEIGHT

Frank J. Bove, Mark C. Fulcomer, Judith B. Klotz, Jorge Esmart, Ellen M. Dufficy, Rebecca T. Zagraniski, and Jonathan E. Savrin

1.0 INTRODUCTION

There is public concern in New Jersey (NJ) that exposure to drinking water contamination may result in an increased risk of adverse reproductive outcomes. This case-control study is the third study under a cooperative agreement of the Centers for Disease Control and the New Jersey Department of Health (NJDOH) on reproductive outcomes and environmental contamination.

New Jersey is in a unique position to evaluate the impact of public water system contamination on reproductive outcomes. During 1984, NJ established a population-based birth defects registry. At the inception of this study, data were available from January 1, 1985 through December 31, 1988, on major and minor defects for the entire state. In addition, NJ was unique in requiring all public water purveyors to sample their distribution systems twice annually and to submit these samples to New Jersey Department of Environmental Protection (NJDEP) certified laboratories for analysis of 14 volatile organic chemicals (VOCs), polychlorinated biphenyls (PCBs), and chlordane. This program, known as the "A-280 Program", began in late 1984. At the inception of this study, "A-280 Program" data which met NJDEP's quality assurance/quality control (QA/QC) requirements were available from the years 1984 through 1988.

For this case-control study, the NJDOH utilized its population-based birth defects registry and its vital records (birth certificate and fetal death tapes), as well as data obtained from the NJDEP on the levels of VOCs, total trihalomethanes (TTHM) and nitrates in the state's public water systems. These databases were used to examine the association of residential exposure to VOCs, TTHM and nitrates in drinking water supplied by public systems with selected major birth defects and low birthweight. Phone interviews of the mothers of the cases and controls were performed to obtain information on various risk factors.

1.1 Previous Studies

Some of the VOCs which have been detected in several drinking water supplies in NJ have been found to be associated with birth defects or low birthweight in animal studies. These VOCs include benzene, 1,1,1-trichloroethane (TCA), trichloroethylene (TCE) and perchloroethylene (PCE). To date, there is no evidence from animal studies that trihalomethanes (e.g., chloroform) or nitrates have adverse effects on reproduction.

Major limitations of the existing literature on adverse reproductive outcomes and population exposures to VOCs include conflicting findings, small sample sizes, poor statistical power, the grouping of diseases with various etiologies, and questionable exposure assumptions. The major studies were reviewed in greater detail in the report on the cross-sectional study (Bove et al., 1992), and are briefly described below. A summary of these studies are also presented in Table 1.

Associations between low birthweight and possible population exposures to VOCs (through routes other than drinking water) have been found at toxic waste sites such as Love Canal (Vianna and Polan, 1984) and the Lipari Landfill in NJ (NJDOH, 1989). Studies in Finland have implicated maternal exposure to organic solvents at the workplace and/or at home with elevations of birth defects of the central nervous system (Holmberg et al., 1982), oral clefts (Holmberg and Nurminen, 1980), and the cardiovascular system (Tikkanen and Heinonen, 1988). In a study of maternal work exposures to PCE and other solvents in dry cleaning shops, PCE was not found to be associated with low birthweight or birth defects, but the "handling of other solvents" (spot removers, acetone) was associated with birth defects (Kyyronen, et al. 1989).

Studies of adverse reproductive outcomes among those exposed to drinking water supplies contaminated with VOCs have produced conflicting results. These include:

1) In the Woburn Study (Lagakos et al., 1986a), statistically significant associations were found between exposure to drinking water contaminated with TCE, PCE, and dichloroethylenes with increased risk of perinatal mortality, eye and ear anomalies and central nervous system, chromosomal and oral cleft anomalies. However, the Woburn study was seriously limited by small numbers of cases and by the analytic approach of combining diseases with diverse mechanisms and etiologies into broad categories.

2) A study of private well contamination in the Battle Creek, Michigan area (Freni and Bloomer, 1988) found no associations between exposure to VOCs and adverse reproductive effects. However, due to a very small number of cases included in the analysis (stillbirths [N=2], low birthweight [N=11], and prematurity [N=7]), this study has too many limitations for its results to contribute significantly to the weight of evidence regarding VOCs in drinking water and adverse reproductive outcomes.

3) In Santa Clara County, a census tract containing a TCA-contaminated public well had a statistically significant increased rate of birth defects compared to an unexposed census tract (Wrensch et al., 1990; Swan et al., 1989; California Department of Health Services (CADOHS), 1985). However, the spatio-temporal pattern of cardiac defects in the service area did not fit the modeled distribution of water from the contaminated well or the timing of the potential exposure from the well. The investigators concluded: "The evidence does not support the contamination from Well 13 as the cause of this cluster."

4) A study of drinking water in the Tucson Valley area of Arizona (Goldberg et al., 1990) reported that mothers residing in areas supplied by water contaminated with TCE, 1,1-dichloroethylene, and chromium had a greater prevalence of cardiac defect children than mothers residing in areas supplied

by uncontaminated water). There were several design problems with the study, including the selection of the control population, characterization of exposures, and consideration of potential confounding.

5) In an Iowa study of trihalomethanes in public drinking water systems and intrauterine growth retardation (IUGR), prematurity, and low birthweight (Kramer et al., 1992), no association was found for prematurity or low birthweight, but increased risk of IUGR was found at chloroform levels equal to or above 10 ppb.

1.2 Study Hypotheses

The following two main hypotheses were evaluated:

1. average exposure during the first trimester to total volatile organics (TVOC) and/or total trihalomethanes (TTHM) in drinking water is associated with an increased risk of neural tube defects, cardiac defects or oral clefts.

2. average exposure during the entire pregnancy to TVOC and/or TTHM in drinking water is associated with an increased risk of low birthweight.

Additional hypotheses focused on the association of the same outcomes with nitrates and the following "A-280" VOCs:

trichloroethylene (TCE)	1,1,1-trichloroethane (TCA)
tetrachloroethylene (PCE)	total dichloroethylenes (DCE)
carbon tetrachloride (CTC)	1,2-dichloroethane (EDC)
benzene	

In addition, surface water systems and systems using supplies from both surface and groundwater sources were compared to groundwater systems. Other "A-280" VOCs could not be evaluated because they were detected too infrequently (or not at all) in the study area. Methylene chloride was not evaluated since it is found frequently on method blanks (see Bove et al., 1992).

A total of 66 null hypotheses were formally evaluated in this study: eleven exposures (TVOC, TCE, PCE, DCE, TCA, CTC, EDC, benzene, nitrates, TTHM, type of water source) and six outcomes (NTD, oral clefts, major cardiacs defects, VSDs, very low birthweight and intermediate low birthweight). It should be noted that many of these comparisons were not independent since some of the exposures were related (e.g., the variable TVOC was a sum of all the evaluated VOCs). Nevertheless, each of the 66 formal comparisons were evaluated separately, as if it were the only comparison made in the study (Rothman, 1990). (See the discussion on the issue of multiple comparisons below, Section 4.5).

Each exposure variable-outcome relationship was evaluated once formally to determine how compatible the result was with the null hypothesis. This formal evaluation was usually of the adjusted result unless the unadjusted result was similar using a "15% rule": i.e., the adjusted and unadjusted results differed by no more than 15% (Mickey and Greenland, 1989). In addition, this formal evaluation used <u>one</u> of the characterizations of each exposure; i.e., the one that produced the highest adverse reproductive effect estimate with precision measured by the confidence interval. This position was based on the following: 1) our belief that non-differential exposure misclassification was a major source of bias in the study due to the difficulty of interpreting the available water data and the numerous assumptions needed in order to estimate contaminant levels; and 2) a general public health concern that associations worth pursuing should not be missed. (The effect of selection bias on this evaluation process is discussed in Section 4.3).

In addition to the formal comparisons, other results were presented for informative and exploratory purposes. These included additional characterizations of the exposures, subgroupings of specific birth defects (i.e., cleft palate, cleft lip with or without cleft palate, single and multiple neural tube defects) and both unadjusted and adjusted results.

2.0 METHODS

2.1 Study Design

Birth defect cases were initially ascertained through the birth defects registry (NJDOH, 1986). Subsequently, additional cases of anencephaly were identified through the fetal death and infant death tapes. Birth certificate tapes were used to identify and sample low birthweight cases and a control series.

The specific outcomes selected for study were: very low birthweight (defined as under 1500 grams), "intermediate" low birthweight (defined as between 1500 and 2499 grams), major cardiac defects, ventricular septal defects (VSDs) with no other major cardiac defects, oral clefts, and neural tube defects (NTDs). Additional analyses were performed on subsets of neural tube defects (single & multiple) and oral clefts (cleft palate without cleft lip & cleft lip with or without cleft palate). These outcomes were chosen based on the results of previous animal and human studies. In addition, these outcomes could be considered as "sentinel" events since: 1) they are easily diagnosed (or, in the case of low birthweight, easily determined from the birth certificate) with a fairly high incidence, 2) they have been statistically linked to certain environmental factors and 3) the timing of the disturbance in morphogenesis of the selected birth defects has been elucidated by prior studies.

Data from NJDEP's A-280 Program were used to estimate levels of VOCs in drinking water. NJDEP's quarterly database on the levels of TTHM in public water systems in NJ serving a population of at least 1,000 was used to estimate levels of TTHM. NJDEP also provided information on the levels of nitrates in the public systems during the study period.

2.2 Study Area

The study area consisted of four contiguous counties in northern NJ. As of 1985, these counties were among the five counties with the highest number of detectable samples of total volatile organics (TVOC) in public water systems, according to the NJDEP's A-280 Program. Over 80% of the populations of these four counties were served by public water systems in 1988. All four counties had public water systems which utilized groundwater, surface water or a mixture of groundwater and surface water. Some systems were free of contamination while others were contaminated with VOCs and/or TTHM. A complete description of the study area is provided in the cross-sectional study (Bove et al., 1992). A brief description is provided below.

The water companies in the four counties offered a variety of exposure situations. Those utilizing groundwater as their source of supply tended to have VOC contaminants (due to industrial spills and discharges or to leaching from landfills) or to be uncontaminated. Those utilizing surface water as their source of supply tended to have higher levels of TTHM due to the reactions between the chlorine treated water and organic matter in the water. Water from companies utilizing both sources of water often contained detectable "A-280" contaminants and TTHM. Most of the towns in these four counties were served almost entirely by public water rather than private wells for which no data were available, and the distribution systems of the water companies serving the four counties were less complex than those in other areas of the state.

The following criteria were used to select towns in the four counties for inclusion in the study:

1) The town was within Bergen, Essex, Morris or Passaic counties;

2) Virtually all of the town's population was served by public water, based on information supplied by NJDEP's Bureau of Safe Drinking Water (BSDW);

3) Less than 10% of the town's birth certificates had missing information on birthweight. (Missing data on birthweight were typically due to births which occurred in New York City or Philadelphia).

because Newark had twice as many births per year as the next largest city in the study area and Newark's water supply came from surface water. Therefore, Newark's inclusion would have given the study a primarily urban focus and shifted the entire focus of the study away from the "A-280" contaminants in groundwater. The study area consisted of the remaining 75 towns. The selected towns provided a balance of urban and suburban communities as well as a variety of types of water supply (groundwater, surface water, mixture).

The selection of particular towns for inclusion in the study area was not based on information about adverse reproductive outcome rates or on drinking water contamination levels. The four county area itself was not selected based on prior knowledge of an adverse reproductive outcome problem.

2.3 Study Population

The study population consisted of all singleton livebirths and stillbirths identified by NJDOH vital records tapes (birth certificates and fetal death certificates) born during the period January 1, 1985 to December 31, 1988, to NJ residents who at the time of the births were 18 years of age or older and lived in the 75 towns that met the above criteria. The size of the study population over the 4-year period was 81,654: 81,055 singleton livebirths and 599 singleton fetal deaths. The ranges of the towns' births per year population density, population density, and median household income are presented in the report on the cross-sectional study (Bove et al. 1992).

2.3.1 Selection of the Case Series

The primary source for the ascertainment of birth defects in the study population was the NJ Birth Defects Registry. In addition, infant death and fetal death certificates were searched for additional cases of anencephaly (and other defects included in this study) which were not registered. All cases of the selected birth defects were included in the study. The list of diagnoses of the birth defect cases is presented in Table 2.

The neural tube defect case series included all anencephaly, spina bifida (except spina bifida occulta) and encephalocele in the study population (ICD-9

The neural tube defect case series included all anencephaly, spina bifida (except spina bifida occulta) and encephalocele in the study population (ICD-9 codes: 740.0 - 740.2, 741.0 - 741.9, 742.0). The oral cleft case series include all cleft palate alone and cleft lip with or without cleft palate in the study population (ICD-9: 749.0, 749.1-749.2). The major cardiac defect case series included all conotruncal defects (transposition of the great arteries, double outlet right ventricle, tetralogy of Fallot, truncus arteriosus, aortico-pulmonary window) and flow lesion defects (hypoplastic left heart, aortic stenosis, pulmonary valve stenosis, coarctation of aorta) in the study population (ICD-9: 745.0, 745.01, 745.1, 745.2, 745.3 746.01, 746.02, 746.1, 746.3, 746.7, 747.1). An additional cardiac defect series included all ventricular septal defects (ICD-9: 745.4) in the study population who did not have an additional severe cardiac defect as defined above.

Cases of "intermediate" low (1500g - 2499g) and very low (<1500g) birthweight were identified using the birth certificate tapes for 1985-1988. Since birthweight was not recorded for births occurring in New York City, potential low birthweight cases born in NYC were lost. Block random samples of very low and "intermediate" low birthweight cases were obtained by sampling without replacement equal numbers (N = 35) from each six month period of the study. After drawing each very low or "intermediate" low birthweight live-birth, birth certificate data for the potential case was compared to the data from the Birth Defects Registry, including the date of birth, municipality of residence at birth, the name of the child and the name of the mother. If the potential case was <u>not</u> registered as having a major or minor birth defect, the birth was included in the very low or intermediate low birthweight case series.

Any potential case which was identified as having a chromosomal defect was excluded from the study. Additionally, subjects were ineligible if they were not singleton births, if no birth certificate was on file (e.g., due to name changes since birth and errors on the birth certificate tape such as name misspellings and wrong year of birth) or if the mother's residence at time of birth was outside the study area (miscoding of town on computer tape).

accurate data on gestational age as well as birthweight. At the time this study was designed, it was believed that the information on gestational age on the birth certificate tape was of poor quality due to a lack of sufficient quality assurance and control of data entry. It was also believed that many records would be missing data on last menstrual period. In addition, it was suspected that the quality of the information on the hard copy birth certificate itself was hospital-specific. For these reasons, the categories "very low birthweight" and "intermediate low birthweight" were used to approximate prematurity and SGA respectively. Virtually all the "very low birthweight" cases were expected to be premature and many of the "intermediate" low birthweight cases were expected to be SGA. (Subsequently, while performing extensive analyses of the data on the computer tape in the Cross-sectional Study, as part of this Cooperative Agreement, it was learned that the data on gestational age was not as poor as first thought and the number of livebirths with missing data on the last menstrual period was only about 6%).

2.3.2 Selection of Controls

A block random sample (without replacement) of livebirths who were not low birthweight was obtained from the birth certificate tapes by taking equal numbers (N = 35) from each six month period of the study. Since birthweight was not recorded for births occurring in NYC (about 3% of total births in the 75 towns), these births were excluded from the control series. After drawing each potential livebirth control from the birth certificate tapes, the individual's birth certificate data were compared to data in the Birth Defects Registry. If the potential control was <u>not</u> registered as having a major or minor birth defect, the birth was included in the control series.

2.3.3 Subject Contact Procedures

The mother of each selected birth was contacted first by letter indicating that she had been selected as a possible study participant. The letter explained the general purpose of the study, the basis for her selection to participate in the study, what her participation would involve, and that participation was voluntary. The letter informed the woman that she could refuse participation in the study, and that she could do so by returning a self-addressed enclosed postcard, letting us know when the interviewer contacted her by phone, or calling the study office. Letters were sent to mothers of all defect cases. As stated above, sample sizes of 35 from each six month period of the study were taken of very low birthweight, "intermediate" low birthweight and control livebirths. Letters were mailed in July 1989 and were sent to the mothers of all subjects selected.

For low birthweight cases and controls, the following procedures were used to locate the mother if the first letter was returned as undeliverable:

> If the mother could not be contacted using the address on the birth certificate, the local post office was contacted for a forwarding address. Next, a request was made to NJ Division of Motor Vehicles for current information on her address. If necessary, the obstetrician and pediatrician listed on the birth certificate were contacted. If these efforts failed, then the birth tapes were examined for possible more recent births by the same mother in order to obtain a more recent address. If all the above methods failed to locate the case or control, certified letters were sent.

For birth defect cases, the following procedures were used to locate the mother if the first letter was returned as undeliverable:

> If the mother could not be contacted using the address provided by the registry, the NJDOH Special Child Health Service (SCHS) county case managers were contacted for current information on the mother's address and telephone number. (These case managers have early and on-going direct contact with registered families.) Next, specialized birth defect clinics in the study area were contacted for current information on the address of the family. If these efforts failed, the above used the procedures described above for controls and low birthweight cases.

Tables 3A and 3B indicate the outcomes of interest, the number of subjects ascertained (birth defects) or sampled (low birthweight and controls) and the number of completed interviews for each outcome. Also included in the table are the numbers of subjects lost to the study due to the mother's refusal to participate or difficulties locating subject's mothers.

2.3.4 Additional Eligibility Requirements and Exclusions

After review of birth certificates and birth defect registrations, sampled low birthweight cases and controls were considered ineligible for the study if the mothers did not reside in one of the 75 towns at time of birth or if the case or control was non-singleton, had a birth defect or the birth certificate (or fetal death certificate) could not be located. Low birthweight cases who also had one of the defects of interest were included in the defect series only. Two major cardiac defect cases also had oral cleft defects and were included in both the oral cleft series and the major cardiac series.

Birthweight discrepancies between the computer tape and the birth certificate were resolved only for those low birthweight cases and controls whose mothers were successfully contacted and agreed to be interviewed. Hospital labor and delivery logs were used to resolve these discrepancies. Six initial very low birthweight cases were later found to be intermediate low birthweights and were included in the intermediate low birthweight case series, and two were found to have a weight above 2500 grams and were included in the control series. Similarly, two intermediate low birthweight cases were switched to the very low birthweight case series and two were switched to the control series.

No water quality data were available for public systems outside the state of NJ or for private wells. Therefore, based on information from the interviews with the mothers of the cases and controls, additional exclusions were necessary for those mothers who, during part or all of their pregnancy, resided outside the state of NJ or whose residence was served by a private well. Exclusions from the analyses of the birth defects series were made if, during the first trimester, a case or control resided outside the state of NJ or if the residence was served by a private well. For the analyses of the low birthweight series, exclusions were made if the case or control resided outside the state of NJ or utilized private well water for more than three months of the pregnancy. These exclusions are presented in Tables 3A and 3B.

2.3.5 Interviewing Procedures

All interviews were conducted by telephone by trained interviewers who were cognizant of the mother's case or control status but did not know the exposure status. Interviews took an average of one hour, and were carried out during the period July 1989 to May 1990. Questions about drinking water use were embedded in the middle of the questionnaire. (Other general areas of the questionnaire are described in section 2.4 below). Appendix A comprises the interview questionnaire.

2.4 Exposure Assessment

Data on public drinking water contamination were obtained from the NJ Department of Environmental Protection (NJDEP) Bureau of Safe Drinking Water (BSDW) (NJDEP, 1990; NJDEP, 1987; NJDEP, 1986). Samples representing the distribution system for each water company serving the 75 towns in the study for the period 1985-88 were used to characterize total VOC (TVOC) and individual VOC levels in each town's system on a monthly basis. The number of distribution samples varied considerably by water company. Problems that arose in assessing exposure were partially due to water companies utilizing several wells or wellfields, purchasing large amounts of water from another supplier, and deciding where in the distribution system it would sample. (Different locations might be sampled on each occasion.)

If an A-280 contaminant was not detected in a particular sample, the contaminant was assigned a value of zero for that sample. Usually, a simple average (or weighted average) of the distribution samples was appropriate to estimate levels in a company's distribution system. If a water company with a complex system did not provide information on the amount utilized from each source, then additional assumptions were necessary in the estimation process. To estimate monthly levels for some of the highly complex systems, it was sometimes necessary to pool samples taken over several adjacent months and calculate a weighted average of these samples. (The algorithm that was developed for extrapolating between sampling dates is described in the report on the cross-sectional study (Bove et al. 1992)).

developed for extrapolating between sampling dates is described in the report on the cross-sectional study (Bove et al. 1992)).

BSDW's database on total trihalomethane (TTHM) levels in the distribution system of each water company serving at least 1,000 people was obtained on a quarterly basis for the period 1984-1988. It was assumed that the water companies, as required by NJDEP, performed the sampling at the furthest reaches of their distribution systems in order to obtain the highest readings of TTHM. There were no TTHM data available for water companies that served less than 1,000 people. These companies utilize groundwater as their source of water supply, which typically have TTHM levels at or near the detection limit of 1 ppb and only rarely exceed 5 ppb. After consultation with BSDW, it was assumed that TTHM levels for these companies were at or near 1 ppb.

For each water company, the results of a sampling date were assumed to characterize the season in which the samples were taken. The mean of the quarterly samples (or the number of samples taken during the year) was calculated and assigned to the season covered by the sampling date. As with the estimation of "A280" contaminants, it was necessary to weight the TTHM levels in each source by the proportion the source contributed to the total supply. If the seasonal estimate was less than 5 ppb, it was recoded to zero.

BSDW also supplied data on nitrate levels for the water companies in the study area. Although the Maximum Contamination Levels (MCLs) for nitrates (10 ppm) was never exceeded in the study area, the actual levels detected were given in the database. (Other inorganic contaminants were not evaluated since most of the data merely indicated that levels were below the federal MCLs in drinking water, without supplying the actual levels detected.) When available, levels detected in each annual sample was used to characterize the nitrate exposure for the year in which the sample occurred. Unfortunately, for more than 75% of the companies in the study, only two or three samples were often recorded over the entire period 1984 through 1988. For those systems that did not sample on an annual basis, the average of all the samples taken during the period 1984 through 1988 was used to characterize nitrate exposure over the entire study period. If a water company changed its source of water supply at some point during the study period, the sample level that appeared to reflect

During the estimation process, nineteen water companies serving twenty-two towns in the study area were found to have systems complex enough to warrant further evaluation. A system was considered complex if part of a town was served by a surface water supply and another part of town by ground-water wells, or if a system utilized numerous wells of which some but not all were contaminated. These companies were contacted by phone and mail. Seventeen of the nineteen water companies responded. The companies were given the street blocks for those subjects with completed interviews whose mothers resided at any time during their pregnancies in the towns served by these companies but not the case or control status of the subject. For each block, a company was asked to provide information on the water distribution system serving the block (e.g., which well primarily served the block) during the time period when the mother of the subject resided there and was pregnant with the subject. This information was used to estimate contaminant levels for these subjects.

The entire estimation process was performed by one investigator who was blind to the case or control status of the study subjects. In addition, the monthly contaminant levels for each town were estimated without knowledge of each town's prevalence of the selected outcomes.

Information on mother's residence(s) during pregnancy, drinking water source (public system, private well, bottled water, filtered water), drinking water consumption and showering habits were obtained from cases and controls by the telephone interview. To estimate average exposure over the entire pregnancy, any month in which no drinking water data were available (i.e., if private well water was used or the mother of the study subject resided outside NJ) was not included in the calculation. In the analyses of birth defects, only the first trimester exposures to drinking water contaminants were considered. In the analyses of birthweight, SGA and prematurity, the mean drinking water exposures over the entire pregnancy were considered.

2.5 Information on Other Potential Risk Factors

The phone interviews obtained information on the following potential risk factors before and during the index pregnancy: medical history, pregnancy history, occupational history, lifestyle activities, home and environment exposures, stressful life events, smoking and alcohol use and socioeconomic factors (see questionnaire in Appendix A).

2.6 Methods of Data Analysis

All analyses were performed on a microcomputer using EGRET (Statistics and Epidemiology Research Corporation, 1991) and SPSS/PC+ (Norusis et al., 1989). Unconditional logistic regression methods were used. All variables were categorized. Non-adjusted and adjusted odds ratios (ORs) as well as 95% confidence intervals and two-tailed p-values were computed for the water contaminant variables. In the unadjusted analyses, the odds ratios and two-tailed p-values were obtained by logistic regression, and the 95% confidence intervals were obtained using the exact methods available in EGRET. In the unadjusted analyses, tests for trends were also performed using the exact method. In the adjusted analyses, the odds ratios, two-tailed p-values and 95% confidence intervals were obtained by logistic regression. Given the small number of cases and controls in the study that were exposed to the higher levels of each contaminant, no attempt was made to assess effect modification. An association was considered statistically significant if its two-tailed p-value was less than 0.05. An association was deemed "noteworthy" or "less precise" if its one-tailed p-value was less than 0.05 and its 95% confidence interval included 1.0.

Besides variables for drinking water contamination exposures, factors considered for inclusion in the analyses were maternal age, race, education, occupational exposure, pregnancy history, medical history, home exposures, smoking, alcohol and caffeine consumption, stressful life events and income. Descriptions of these variables are given in Appendix B.

2.6.1 Three-Stage Model Development Process

A three-stage process was used to develop the model for each outcome. In the first stage, a variable was considered as a candidate for inclusion in the final model for an outcome if previous studies indicated that the variable was a known or suspected risk factor or if the association between the factor and the outcome (i.e., the odds ratio, OR) was equal to or greater than 1.50 (or equal to or less than 0.6). Significance tests were not used in the selection process since the sample sizes were not large enough to detect moderate risk factors with sufficient power.

In the second stage, correlational analyses were used in order to reduce the number of candidate variables identified in the first stage. Correlation matrices were reviewed to identify "highly correlated" variables (i.e., $r \geq 0.40$). For candidate variables that were highly correlated to each other (e.g., mother's educational level and father's educational level), only the variable with the greater odds ratio was selected for consideration in the next stage. For candidate variables less highly correlated but still considerably correlated to each other (e.g., income and education; $r \geq 0.20$), an attempt was made to assess the potential magnitude of confounding effect for each variable. This assessment was made by examining the correlations between these variables and the drinking water exposure variables as well as the associations between these variables and the outcome. If no clearly superior candidate emerged from this process, then both of the correlated variables were included for consideration in the next stage.

In the final stage, logistic regression was used to regress the outcome variable on the surviving candidate variables. Using a backward elimination process (based on the odds ratio, not the p-value), those variables were removed whose odds ratios fell in the range between 0.60 and 1.50.

2.6.2 Three Models per Outcome

For each outcome, three models were used. The first model would attempt to include all the surviving variables after the final stage of selection. However, if more than 15 variables remained in the "risk factor model" (i.e., not counting the drinking water exposure variable), the model was further trimmed by raising the cut-off odds ratio to 2.0 (and lowering it to 0.50 for "protective" risk factors). It was felt that due to the small numbers of cases and controls, no risk factor model should exceed 15 variables.

A second model was created that included some of the variables in the first model, but excluded those considered a priori not to be actual risk factors but complications brought on by the adverse reproductive outcome itself (e.g., bleeding during pregnancy, the use of ultrasound during pregnancy). Other factors that were considered highly unlikely risk factors were also eliminated. This model also contained variables remaining after the final stage but excluded from the first model if it was believed a priori that these variables were highly likely to be actual risk factors. This second model is the one presented in the adjusted analysis tables.

Finally, a third model was created consisting of no more than eight variables. This model included only the most likely risk factors for the outcome from among the variables remaining after the final stage.

One further attempt at model building started with the variables remaining after the final stage was completed and evaluated the confounding effect of each of these variables alone on the associations between the drinking water exposure variables and the specific outcome. However, for each outcome, only one or a few of the variables appeared, individually, to be a confounder. It should be noted that even though a risk factor did not individually confound an association, this did not rule out its capability of confounding the association when included in a model with other risk factors. Since this approach did not produce satisfactory models, it was abandoned.

Although the results of only the second model are presented in the tables, the results of the other two models are reported if they conflict with the table results. The variables included in the second model for each outcome are listed on the adjusted tables.

2.6.3 Use of the Fifteen Percent Rule

In order to decide whether to evaluate the null hypotheses using the adjusted or unadjusted results, the previously mentioned "15% rule" was used. This rule stipulated that unadjusted results could be used if the adjusted results did not differ by more than 15% (Mickey and Greenland, 1989).

One problem with the "15% rule" was that the unadjusted and adjusted results were not strictly comparable since those study subjects with missing values for any of the potential confounders included in the models were excluded from the adjusted analyses. Often, the unadjusted odds ratios obtained prior to excluding those with missing values were profoundly different from the unadjusted odds ratios obtained after the exclusions were made. In order to take into account the impact of these exclusions, the unadjusted odds ratios obtained after making these exclusions (called the "crude odds ratio" in the tables presenting the adjusted results for the categorical outcomes) were compared to the adjusted odds ratios to determine if the "15% rule" was met.

2.6.4 Statistically Significant and Less Precise Associations

The results presented in the tables and summarized in the text below uses the following designations for the observed associations: "statistically significant" associations for which the 95% confidence interval of the odds ratio excluded 1.0 and the two-tail p-value was below 0.05. "Less precise" associations have one-tail p values below 0.05 (two-tail below 0.10) but 95% confidence intervals which include 1.0.

3.0 RESULTS

3.1 Neural Tube Defects (NTDs)

The unadjusted results for NTDs are presented in Table 4. **Statistically significant associations were found for TTHM (above 80 ppb, OR = 4.25), surface water source (OR = 7.33) and mixed water sources (OR = 18.46). An exact test for trend for the TTHM results was also statistically significant.** A less precise association was found for PCE (above 5 ppb, OR = 4.07). The adjusted results are presented in Table 5. For TTHM and surface water, the adjusted results shown did not differ by more than 15% from the "crude" results. However, for TTHM, the odds ratios were reduced by more than 15% in the other two models. The lowest odds ratio for the level above 80 ppb was 2.90, obtained from model three, whereas the odds ratio from model 1 was 3.28. For both odds ratios, the p-values were greater than 0.10. When TTHM was recategorized (> 15 ppb vs ≤ 15 ppb), the odds ratios for the three models ranged from 3.22 to 3.65 ("crude" OR = 3.70) and all were statistically significant. Since none of these adjusted odds ratios varied by more than 15% from the "crude" odds ratio, the unadjusted result was used for TTHM > 15ppb: OR = 3.75, p < .015, 95% exact confidence interval (CI) = 1.32, 13.0.

The adjusted odds ratio for mixed water source was much higher in all three models than the unadjusted and the "crude" odds ratios. This was probably due to the small number of groundwater cases. The adjusted results for PCE did not vary from the unadjusted results. No other statistically significant or less precise associations were found.

In the cross-sectional study (Bove et al., 1992), it was noted that TTHM was inversely related to nitrates and the A-280 contaminants. Therefore, since TTHM was associated with NTDs, it might also confound the associations between NTDs and these other contaminants. This was the case for nitrates and PCE in the cross-sectional study and was also found in the present study. **The odds ratio for nitrates after adjusting for TTHM was statistically significant (OR = 3.91, p < .045, exact 95% CI = 1.05, 16.2).** Including TTHM in the three models increased the odds ratio for nitrates substantially (OR = 5.28, p < .025, 95% CI = 1.3, 21.4, for model 2). (Note: the odds ratios for nitrates obtained from the other two models with TTHM included were higher). Similarly, for PCE above 5 ppb, a statistically significant odds ratio was obtained after adjusting for TTHM (OR = 7.01, p < .05, exact 95% CI = 1.02, 53.5). After including TTHM in the models, the adjusted odds ratios for PCE ranged from 6.37 to 8.71 and were all statistically significant. Although inclusion of TTHM also increased the odds ratios of the other A-280 contaminants, there were no further statistically significant or less precise associations observed.

Unadjusted results for single defect NTDs and multiple defect NTDs are presented in Tables 6 and 7. The effects of TTHM, surface water source, mixed water sources and PCE were primarily among the single defect NTDs. The effect of nitrates was among the multiple defect NTDs.

In summary, statistically significant associations were found between neural tube defects and TTHM, surface water source, and mixed water sources. A less precise association was found for PCE. After adjustment for the confounding effects of TTHM, statistically significant associations were found for PCE and nitrates.

3.2 Oral Clefts

The unadjusted results for oral clefts are shown in Table 8. There were no statistically significant associations, but a less precise association was found for carbon tetrachloride (for detectable amounts, OR = 4.0, p < .08, exact 95% CI = 0.64, 28.1). No other contaminants appeared to be associated with oral clefts. The adjusted results are presented in Table 9. After adjustment, the association between carbon tetrachloride (CTC) and oral clefts remained less precise (OR = 5.39, p < .085, exact 95% CI = 0.81, 36.0). There was also a less precise negative association found for TCA at concentrations greater than 1 ppb, but when TCA was categorized as > 2 vs ≤ 2 ppb, that association was not observed.

When subgroupings of oral clefts were analyzed (see Tables 10 and 11), a less precise association was found between cleft palate and DCE (OR = 5.29, p < .08, exact 95% CI = 0.41, 48.9). **A statistically significant association was found for cleft palate and surface water source (OR = 4.88, p < .04, exact 95% CI = 1.06, 45.3).** A less precise association was found between lower levels of TTHM and cleft palate but not for higher levels. The effect of CTC was also primarily seen for cleft palate cases.

3.3 Major Cardiac Defects

The unadjusted results for major cardiac defects are presented in Table 12. **A statistically significant odds ratio was obtained for surface water source (OR = 2.22, p < .045, exact 95% CI = 0.99, 5.3). A statistically significant association was also found for low levels of TTHM (> 15 ppb - 50 ppb) but not for higher levels.** When TTHM was recategorized (> 15 ppb vs ≤ 15 ppb), the association was less precise (OR = 2.03, p < .055, exact 95% CI = 0.96, 4.5). No other associations were found. The adjusted results are shown in Table 13. For surface water source and for the recategorized variable for TTHM, the adjusted results for all three models did not differ by more than 15% from the "crude" odds ratios, so the unadjusted results were used.

The results for mixed sources were conflicting between the three models. For the second and third models, the odds ratio increased by more than 15% over the "crude' odds ratio and the association was less precise (e.g., for the second model, OR = 2.86, p < .10, 95% CI = 0.82, 9.9). However, for the first model, the odds ratio did not exceed 15% of the "crude" odds ratio and so the unadjusted result would be used. No other associations were found.

3.4 Ventricular Septal Defects (VSD)

The unadjusted results for VSD are presented in Table 14. No statistically significant associations were found, but less precise associations were found for TVOC (> 5 ppb) and TCA (> 2 ppb). For TVOC, there was also a trend (1-sided, positive p < .065, for the variable: > 1 ppb - 5 ppb, > 5 ppb). No other associations were found.

The adjusted results for VSD are shown in Table 15. TVOC and TCA remained less precisely associated. The effect of the adjustment was to increase their odds ratios by more than 15% over their "crude" odds ratios. After adjustment, a statistically significant association was found for CTC (for detected amounts, OR = 9.19, $p < .035$, 95% CI = 1.18, 71.8). This result was more than twice as high as the "crude" odds ratio of 3.41. No other associations were found.

3.5 Very Low Birthweight

The unadjusted results for very low birthweight are presented in Table 16. No statistically significant or less precise associations were found except for PCE at concentrations greater than 10 ppb, for which there were no controls and four cases (exact, 2-tailed $p < .055$).

The adjusted findings are shown in Table 17. After adjustment, the odds ratio for TVOC (> 5 ppb) increased by more than 15% over the "crude" odds ratio in all three models and was statistically significant in models one and two, while less precise in model three. For model two, the odds ratio was 2.87 ($p < .03$, 95% CI = 1.14, 7.2). When TCE was adjusted, the odds ratios at each level increase by more than 15% over the "crude" odds ratios and a less precise association was found at the low TCE level (> 1 ppb - 5 ppb) but not the higher levels. When TCE was recategorized (> 1 ppb vs ≤ 1 ppb), the adjusted odds ratio was statistically significant (OR = 2.53, $p < .025$, 95% CI = 1.13, 5.7; "crude" OR = 1.54). No other associations were found.

3.6 Intermediate Low Birthweight

The unadjusted results for intermediate low birthweight are shown in Table 18. No statistically significant associations were found. A less precise, negative association with TVOC exposures between 1 ppb and 5 ppb (OR = 0.52, $p < .06$) was contradicted at the next range of >5 ppb - 10 ppb, for which the prevalence was elevated, but not statistically significant (OR = 2.21).. A less precise positive association was found for surface water source (OR = 1.62, $p < .095$, exact 95% CI = 0.89, 3.0).

The adjusted results (Table 19) for TVOC and surface water did not differ from the "crude" results by more than 15% so the unadjusted results were used. No other associations were found.

3.7 Evaluation of Potential Risk Factors

Information on potential risk factors obtained from the interviews was used to construct variables for inclusion in the analyses. Appendix B contains descriptions of these variables and Appendix C presents the unadjusted odds ratios for these variables and each of the outcomes.

For all the birth defect series, the odds ratios for cigarette smoking were below 1.5. Odds ratios above 1.5 were obtained for the following: caffeine consumption (NTDs), alcohol consumption (oral clefts), education level of the mother (all birth defect series), education level of the father (all birth defect series), receiving government assistance (NTDs and oral clefts), prenatal care (oral clefts), parity (NTDs and major cardiac defects), maternal age (all defect series), mother's occupation around the time of conception (oral clefts and major cardiac defects), and mothers who worked with chemicals around the time of conception (oral clefts). Odds ratios greater than 1.5 for all birth defect series were obtained for diabetes and for high blood pressure around the time of conception. Variables indicating maternal exposures to electric blankets, toxic waste dumps and industrial odors had odds ratios greater than 1.5 for major cardiac defects.

For both intermediate low and very low birthweight, odds ratios greater than 1.5 were obtained for the following: caffeine consumption, alcohol consumption, education level of the father, parity, weight of the mother prior to conception, high blood pressure during pregnancy and high fevers during pregnancy. For intermediate low birthweight alone, odds ratios greater than 1.5 were obtained for cigarette smoking, exposure to passive smoke, prenatal care, height of the mother, diabetes, mothers who worked with chemicals during their pregnancy, and mothers exposed to electric blankets during pregnancy. For very low birthweight alone, odds ratios greater than 1.5 were obtained for education level of the mother, receiving governmental assistance, previous stillbirth or miscarriage, maternal age, and use of oral contraceptives.

3.8 Analysis of Water Usage Information from Interviews

3.8.1 Bottled, Tap, and Filtered Tap Water Usage

During the telephone interviews, data on habits of water usage were obtained from mothers of cases and controls pertaining to each trimester of their pregnancy and the three months prior to conception. These variables included the source and type of water (tap, bottled, filtered tap), the number of cold glasses of water consumed per day, and the typical number of minutes spent showering or bathing.

Table 20 presents the bivariate associations of these variables, independent of levels of water contamination, with the reproductive outcomes. Of the interviewed mothers, 26% (N=149) consumed bottled water only, and 7% (N=39) used filtered tap water. However, there was no specific information on the type of filters which were used by each mother, and some devices designated as "filters" may have been water softeners only. Compared to those who drank tap water, drinkers of bottled water only consistently had non-significant odds ratios of less than 1.0 for all outcomes. Filtered tap water use was suggestive for major cardiac defects and positively related to VSD and low birthweight. Filtered tap water use was also negatively related to NTDs and oral clefts. The associations between the drinking water contaminants and the outcomes were then examined stratifying by type of water consumed to determine if any of the positive associations identified above were affected by bottled water usage (Tables 21-26).

For neural tube defects (Table 21), the effects of TTHMs, nitrates, and PCE are most apparent in the tap and the tap plus filtered water users. For water source, the results for the tap water users resembled the unstratified finding. (No bottled water users were in the reference (groundwater) group, precluding calculation of an odds ratio). Among tap plus filtered water consumers, however, a previously non-significant positive finding for TVOC was increased to less precise status ($p < 0.095$), 1-tail trend test). In general, positive associations appeared to be stronger in the tap water consumers, but elevated ORs were also found in the bottled water users (e.g. for PCE and DCE).

For oral clefts (Table 22) the association with carbon tetrachloride was similar and non-significant for each type of water consumed. While for TTHM, there was no clear pattern regarding effect of type of water consumed, for the A-280 contaminants and surface water source, the odds ratios were generally higher for the tap water consumers.

For major cardiac defects (Table 23), the associations with TTHM and surface water did not show clear patterns with regard to type of water, but the odds ratios for both surface and mixed water sources among bottled water users were higher than for tap water consumers. Additionally, all cases exposed to EDC and benzene were born to mothers who drank bottled water. Bottled water usage did not decrease apparent risks of cardiac defects.

For VSDs (Table 24) the effects indicated above were seen exclusively in the tap water strata for TVOC and TCA, but there was no clear pattern for CTC, and bottled water had much higher odds ratios for surface and mixed water sources.

For very low birthweight, (Table 25) the effects of TVOC and TCE noted above were entirely in the tap water group, but again bottled water users exhibited higher associations for TTHM and water source. There was no evidence that the suggestive association of intermediate low birthweight (Table 26) was higher for surface water source among tap water consumers than bottled water users.

In summary, the associations of birth defects and low birthweight with chlorination byproducts and surface water source tended to be equivocal or to be somewhat greater among bottled water consumers and there was an overall tendency for the associations with A-280 compounds (typical of groundwater contamination) to be more marked among tap water users. Furthermore, no clear pattern emerged regarding number of glasses of cold tap water which were consumed daily. Recall bias and small numbers limited these analyses.

3.8.2 Duration of Showering

Because of small numbers, the variable for showering duration was dichotomized at 12 minutes or less as the reference group. For NTDs, the association with TTHM (which are volatile) was primarily seen among subjects whose mothers took longer showers. A similar pattern was seen for nitrates (which are not volatile). No other patterns emerged for other contaminants or for water source variables.

For oral clefts, there were too few cases exposed to CTC for evaluation of this variable. For major cardiac defects the only observed pattern was a slightly stronger association with TTHM among those with longer showers. For VSDs, odds ratios for TVOC and TCA were higher among those with shorter showers, and the number of cases were too few to evaluate for CTC. Lastly, for very low birthweight, the effects of TVOC, and particularly TCE, were positively related to showering time while for intermediate low birthweight the association with surface water was unaffected.

In summary, although more exposures to mothers who tended to take longer showers would be expected for VOCs, including THMs, most results analyzing this variable were equivocal.

4.0 DISCUSSION

This chapter presents an evaluation of some of the major strengths and limitations of the study design and data sources, a summary of the primary findings of the study, analyses of potential selection biases, and general recommendations drawn from an interpretation of all these issues.

4.1 Summary of Major Strengths and Limitations of the Study

<u>Strengths:</u> This case-control investigation was population-based, utilizing established, systematic, and generally reliable pregnancy outcome databases. The outcome and the principal exposure measures were ascertained independently from each other. The interviewing for the purpose of establishing residence history, details on water exposure, and details on potential risk factors were conducted by a small number of trained and skilled team of interviewers. The concurrent cross-sectional investigation which paralleled this study enabled various potential biases to be examined.

<u>Limitations:</u> The exposure database, i.e. water sampling data submitted by purveyors to the N.J. Department of Environmental Protection, had numerous inherent problems of consistency and reliability which decreased the confidence that true exposure of subjects' mothers could be accurately estimated. The difficulty of quantifying the degree of exposure to water contaminants is compounded by uncertainties regarding the quality of other sources of water (e.g. bottled water and workplace) consumed by the subjects' mothers and regarding relative exposures via ingestion, dermal, and inhalation routes. Further, a sizable proportion of subjects' mothers could not be interviewed, introducing the possibility of selection bias (see discussions below). The small number of subjects, potential recall bias for confounders, and data limitations on possible confounders also limited the study.

4.2 Summary of Positive Findings

For <u>Neural Tube Defects</u>, statistically significant associations were found for TTHM, surface water source, and mixed water sources. A less precise association was found for PCE. After adjustment for the confounding effects of TTHM, statistically significant associations were found for PCE and nitrates. The effects of TTHM, surface water source, mixed water sources and PCE were primarily among the single defect NTDs. The effect of nitrates was among the multiple defect NTDs.

For oral clefts, a suggestive association was found for CTC. When subgroupings were evaluated, a statistically significant association was found between surface water source and cleft palate. A less precise association was also found between cleft palate and DCE. The effect of CTC was seen primarily for cleft palate. A negative association was observed with TCA.

For major cardiac defects, a statistically significant association was found for surface water source and a less precise association was found for TTHM. A less precise association was also found for mixed water source in two of the three models used for adjustment. For ventricular septal defects, less precise associations were found for TVOC, TCA, and a statistically significant association was found with CTC.

For very low birthweight, statistically significant associations were found for TVOC and TCE and a less precise association with PCE. For intermediate low birthweight, a less precise association was found for surface water source. A less precise negative association was found for the low level of TVOC (> 1-5 ppb) but at the next exposure level the odds ratio was elevated (OR=2.21), although not statistically significant.

Evaluations of type of water consumed (i.e., bottled water, tap unfiltered and filtered tap), the number of glasses of cold and hot water consumed daily, and time spent in the shower or bath were inconclusive. Although bottled water users in general tended to have lower odds ratios for many of the contaminants and outcomes evaluated, there were conflicting results which make interpretation difficult. Results for glasses of water consumed and time in the bath or shower were also conflicting and equivocal.

4.3 Potential Selection Bias

The above results may reflect real processes or they may be due to chance or bias. In particular, the inability to locate many of the birth defect cases, the sampled low birthweight cases, and the sampled controls may be a source of bias ("selection bias") if the failure to locate is related to both disease status and exposure status (e.g., if a higher proportion of exposed controls are lost to the study than unexposed controls). Similarly, if refusal to participate is related to both exposure status and disease status, selection bias would be introduced into the study. However, if loss of study subjects is not related to both exposure status and disease status, no bias is introduced but the sample size is reduced; the reduction in sample size decreases the statistical power of the study.

4.3.1 Proportion of Potential Subjects Interviewed

The overall proportion of potential subjects for which interviews were accomplished was 52% as described in Tables 3A and 3B. About 66% of those eligible for the birth defect series were interviewed. The corresponding proportions for the control series and the low birthweight series were 55% and 42% respectively. By far the greatest obstacle to participation in the study was an inability to locate the cases and controls. This was especially true for the low birthweight series. Over 40% of the total low birthweight cases sampled could not be located. The range for the birth defect series was about 13% for NTDs to about 30% for oral clefts. About 28% of the controls could not be located.

The participation rate, once contact was established with the mother of the case or control, was 78% (see Tables 3A and 3B). Among the birth defect series, participation rates once contact was established were greater than 80%. Among the control series and the low birthweight series, the corresponding rates were about 75%.

4.3.2 Demographic Comparison of Subjects Whose Mothers Were and Were Not Interviewed

Of those sampled, 553 mothers could not be interviewed. An attempt was made to obtain demographic information on these subjects from their birth certificates or fetal death certificates. The birth certificate or fetal death certificate was not available for 11 of the subjects lost to the study whose names were obtained from the birth defects registry. Failure to locate the birth certificate could be due to name changes after birth or errors in the birth certificate computer tape (e.g., the misspelling of the child's name or the wrong year of birth). An additional 11 of those lost to the study had birth certificate numbers that did not match the list of birth certificates for the study area during the period 1985 through 1988. These subjects, also obtained from the birth defects registry, were born to mothers who did not reside in the study area at time of birth and were therefore excluded from the study. Finally, one subject was a twin and six subjects had chromosomal defects and were excluded from the study.

Information on sociodemographic factors from the birth certificate or fetal death certificates was available for 523 of the 553 subjects eligible for the study but whose mothers were not interviewed. A summary of this information is provided in Table 27. Comparisons between the interviewed and non-interviewed mothers are presented in Table 28. Striking differences between interviewed and non-interviewed mothers are apparent for race, adequacy of prenatal visits, and mother's education (percent of mothers with a high school degree). The non-interviewed group had a higher percentage of mothers under 22 years of age, although it also had a lower percentage of primiparous mothers. The interviewed group had a higher percentage of mothers with a previous miscarriage and/or a previous stillbirth.

Comparisons between interviewed and non-interviewed mothers by case/control group are presented in Tables 29-31. Among controls, the disparities between those interviewed and not interviewed on maternal race, education and inadequate prenatal care are apparent. Similar disparities were also evident between interviewed and non-interviewed birth defect cases and low birthweight cases. For example, less than 30% of eligible control mothers who did not complete high school were interviewed while over half of the control mothers who had finished high school degree and almost three quarters of the control mothers who had a college degree were interviewed; similarly, only about one quarter of the eligible low birthweight case mothers who were not high school graduates were interviewed while about 38% of high school graduates mothers and more than two thirds of college graduate mothers were interviewed.

In summary, those lost to the study differed sharply from those interviewed on various demographic factors such as maternal race, education and adequacy of prenatal care visits.

4.3.3 Simulation of Results With the Inclusion of Non-Interviewed Mothers

As stated previously, if participation rates for cases or controls are associated with exposure (e.g. if unexposed cases tend not to participate) then estimates of the odds ratios will be biased. In order to assess the potential impact of the lost study subjects on the results, analyses were performed to evaluate how the results of the study might have been different if all those eligible subjects lost to the study were included in the analyses. Estimates of drinking water exposures during pregnancy for those lost to the study were made using the residence of the mother at time of birth. (The interviewed cases and controls retained their exposure estimates based on mother's residence during the pregnancy.) Interviewed and non-interviewed cases and controls were combined and unadjusted odds ratios were obtained for each drinking water contaminant.

The results for NTDs are presented in Table 32. The addition of the non-interviewed NTD cases and controls tended to reduce the odds ratios for the contaminants. For PCE, CTC, EDC, nitrates, TTHM, surface water, and mixed water sources, the odds ratios were reduced, in some instances dramatically: the odds ratios for surface water and mixed water sources were reduced from 7.33 to 2.27 and from 18.46 to 5.25 respectively. For the > 80 ppb level of TTHM, the odds ratio was reduced from 4.25 to 1.47.

The results for oral clefts are presented in Table 33. The odds ratios for TVOC, TCE, PCE, TCA, CTC, and nitrates increased appreciably when non-interviewed subjects were included in the analysis. On the other hand, the effects of TTHM and surface water source were reduced. The impact of including the non-interviewed cleft cases and controls on the associations found in the previous analysis was minimal for CTC, and for TCA, the negative association disappeared.

The results for major cardiac defects are shown in Table 34. Except for DCE, the odds ratios for the A-280 contaminants, nitrates, and mixed water source increased when non-interviewed subjects were included in the analysis. However, the odds ratios for the exposures previously found to be associated with cardiac defects, i.e. TTHM and surface water source, decreased slightly.

For VSDs, the positive association with TVOC was only slightly affected and the positive association with TCA increased. For CTC and EDC, the odds ratios were sharply reduced. The remaining contaminants were minimally affected or their odds ratios were increased.

The results for very low birthweight and intermediate low birthweight are presented in Tables 35-36. For virtually all contaminants, the effect of including non-interviewed subjects was to reduce the odds ratios. This was true for the exposures that were positively associated with very low (TVOC and TCE) and intermediate low (surface water source) birthweight. For PCE and very low birthweight, the number of cases exposed to > 10 ppb increased from four cases to five cases while there remained no controls exposed to this level.

In Summary, the bias introduced by the loss of cases and controls was away from the null value for some of the positive associations with NTDs and for virtually all of the contaminants in relation to the low birthweight outcomes. In general, the bias was away from the null value for TTHM and surface water source regardless of outcome. Especially biased were the odds ratios for surface water and mixed water source and TTHM at the > 80 ppb level in relation to NTDs. These odds ratios were sharply reduced when the non-interviewed NTD cases and controls were included. On the other hand, for the A-280 contaminants and nitrates, the bias was generally either towards the null or was minimal.

4.3.4 Exposure Comparisons Between Interviewed and Non-Interviewed Mothers

Comparisons were made between the interviewed and non-interviewed cases as well as the interviewed and non-interviewed controls in order to determine the primary source of the selection bias. For NTDs, the differences in drinking water contaminant exposures between interviewed and non-interviewed cases were the primary source of bias. For example, the interviewed cases were more highly exposed to surface water (OR = 5.54) and mixed water source (OR = 11.00). On the other hand, there was a minimal difference between interviewed and non-interviewed controls on mixed water source exposure (OR = 0.90). Interviewed controls were less likely to be exposed to surface water (OR = 0.56), thereby contributing to the bias introduced by the difference between the interviewed and non-interviewed NTD cases.

Interviewed NTD cases were also more highly exposed to TTHM than non-interviewed cases (OR = 4.67 for the combined level of > 60 ppb; at the > 80 ppb level there were seven interviewed cases and zero non-interviewed cases). Contributing to the bias of the TTHM association with NTD was the lower TTHM exposure of interviewed controls compared to non-interviewed controls (OR = 0.37 at the > 80 ppb level and 0.70 at the combined > 60 ppb level).

For PCE, interviewed controls were slightly less exposed (OR = .84 for the > 5 ppb level) than non-interviewed controls whereas interviewed NTD cases were more highly exposed (OR = 2.53 for the > 5 ppb level) than non-interviewed NTD cases. For nitrates, interviewed NTD cases were also more highly exposed (OR = 5.79), but the fact that the interviewed controls were more exposed (OR = 1.38) than the non-interviewed controls provided a slight countervailing bias.

For the other A-280 contaminants, there were minimal differences between interviewed and non-interviewed NTD cases except for TVOC (OR = 2.22 for the > 10 ppb level) and TCA (OR = .58 for the > 2 ppb level). The fact that the interviewed controls were also more highly exposed to TVOC (OR = 1.42 at the > 10 ppb level) helped to counteract some of the bias introduced by difference between the interviewed and non-interviewed NTD cases. However, the difference between interviewed and non-interviewed controls on TCA exposure (OR = 9.69 at the > 2 ppb level) contributed even more bias than the difference between the NTD cases, producing the illusion that TCA was negatively associated with NTDs.

In general, the negative associations found for TCA can be attributed to the bias introduced by the difference in exposures between the interviewed and non-interviewed controls. (Although, the negative association seen between TCA and oral clefts can also be partly attributed to the difference between interviewed and non-interviewed cleft cases: OR = 0.48 for the > 2 ppb level.) The bias away from the null for the associations of all outcomes with TTHM and surface water source can be attributed at least partly to the difference between interviewed and non-interviewed controls. However, as we have seen, the main source of bias away from the null for the associations between the drinking water exposures and NTDs is the exposure difference between interviewed and non-interviewed NTD cases.

4.4 Potential Recall Bias

The potential for recall bias in a case-control study is present since the cases may be more likely to recall and report exposures in their search for the causes of their illnesses. Healthy controls, on the other hand, have no comparable stimulus to jog their memories and so may not have comparable recall of exposures. Recall bias tends to cause a differential misclassification of exposure and to bias the exposure odds ratio estimate either towards or away from the null value (i.e., the exposure odds ratio is overestimated or underestimated). Recall bias could be a particular problem in studies of birth defects when healthy babies are used for controls.

4.4.1 Previous Evaluation of Recall Bias in Pregnancy Outcome Studies

In a classic study of the potential of recall bias in a study of adverse reproductive outcomes, Klemetti and Saxen (1967) found that the outcome of the pregnancy and the condition of the child born did not play a major role in explaining the great discrepancy between prospective and retrospective 'memory'. In another study, women who had adverse reproductive outcomes and women who had healthy babies were interviewed early in pregnancy and after delivery. The researchers found no evidence of recall bias. Changes between the two interviews in the reporting of exposure was not associated with pregnancy outcome, maternal concern about the baby or maternal sociodemographic characteristics (Mackenzie et al., 1989). The authors concluded that mothers of healthy babies could be used as controls in adverse reproductive outcome studies.

Three other studies, examining prescription drug use during pregnancy, found no differences in recall between cases and controls. Furthermore, in at least two studies of oral contraceptives, cases reported <u>more accurately</u> than controls about dose and duration of use (Harlow et al., 1989), and controls <u>over-reported</u> their use of estrogens (i.e., they reported use that was not confirmed by their medical records), which would bias the exposure odds ratio estimate <u>towards</u> the null value if there were a positive association between estrogen use and adverse pregnancy outcomes (i.e., the exposure odds ratio would be underestimated). If there truly was no association between estrogen use and adverse pregnancy outcomes, the exposure odds ratio would be biased away from the null value (of OR = 1.0) in a negative direction (i.e., estrogen use would appear to be "protective").

In a recent study, researchers found that recall bias was "exposure-specific" (Werler et al., 1989). Cases more accurately recalled their use of birth control after conception, but cases and controls had similar recall for medication use during pregnancy, spotting or bleeding during pregnancy, elective abortion history, and nausea and vomiting during pregnancy. In addition, mothers of severely malformed infants had no better recall than mothers of nonseverely malformed infants or mothers of healthy infants (controls) for these exposures.

Given the above findings and the fact that our assessment of exposure to drinking water contaminants is based primarily on an objective source (i.e., sample data from the water purveyors), it was expected that recall bias would <u>not</u> directly affect the associations found between the drinking water contaminants and the outcomes. However, the small numbers and the possibility of inaccurate recall of drinking water and showering habits may have obscured the effects of those variables. It is not apparent whether any differential recall of drinking water use or showering duration existed between cases and controls.

The possibility remained that recall bias could affect the associations indirectly by introducing inaccuracies (misclassification) in the assessment of exposures to potential confounding factors (i.e., risk factors for the outcomes that also are associated with the drinking water contaminants). If confounding factors are incorrectly measured, the bias they introduce cannot be adequately accounted for.

4.4.2 Potential Effect of Recall Bias on Confounding.

The advantage of case-control sampling and extensive interviewing of sampled subjects over a study design that relies solely on the use of vital records and disease registry data is the availability of information on many potential confounding factors (and potential "effect modifiers" such as bottled water usage) and on the residence of the mother during the entire pregnancy. In the present study, however, adjusting for risk factors did not appreciably change the results for most contaminants and outcomes. It appeared that the vast majority of the risk factors had little association with the drinking water exposures.

In only a few instances did the adjusted analyses produce results that conflicted with the unadjusted results. For oral clefts, the adjusted analysis produced a suggestive negative association with TCA that was not found in the unadjusted results. For VSD, the adjusted analysis produced a suggestive positive association with CTC that was not present in the unadjusted results. For very low birthweight, statistically significant positive associations were found for both TVOC and TCE in the adjusted analyses but not in the unadjusted analyses. Finally, for major cardiac defects, the adjusted analysis indicated a less precise positive association with exposure to mixed water sources (although one of the three models used did not show such a result) but not the unadjusted results. In general, after adjustment, the odds ratios for the A-280 contaminants increased as often as they decreased. For the birth defect outcomes, the odds ratios for TTHM were usually unaffected by adjustment. For the low birthweight outcomes, the odds ratios for TTHM were reduced after adjustment. Finally, the odds ratios for nitrates were usually minimally affected by adjustment.

4.5 Multiple Comparisons

The issue of multiple comparisons is often raised in studies such as this one in which there are several exposures of interest and several outcomes examined. The contention is that when many comparisons are made, some statistically significant associations will be found even when the null hypothesis of no association is true (i.e., "false positives" will occur). Armitage addressed this issue by making a distinction between a focused approach to the data where "scrutiny is restricted to those comparisons on which the data was designed to throw light" vs. "data dredging". He claimed that multiple comparisons were not a problem with the former approach (Armitage, 1971). Rothman recommends that no adjustments (e.g., Bonferroni adjustment) be made when many comparisons are performed. Instead he recommends that each finding "be reported as if it alone were the sole focus of a study" and that all comparisons be reported if possible or, if not possible, then the number of comparisons performed should be stated (Rothman, 1986). In this study, only a priori hypotheses are evaluated and all comparisons are reported.

In recent articles, Rothman, Greenland, and Robins have argued against the use of multiple-comparisons procedures when the goals are to summarize comparisons of the data with null (or other) hypotheses, to interpret patterns in the data in the light of background information, and to identify promising leads for further research (Rothman, 1991; Greenland and Robins, 1991). Greenland and Robins have argued persuasively that one multiple-comparison adjustment, empirical-Bayes adjustments, may be useful if the objective is a decision-analytic one; e.g., to provide a basis for resource allocation. Clearly this was not the objective of the present study. Given the nascent stage of research on the reproductive effects of drinking water contaminants, the use of multiple-comparisons adjustments in this study would be counterproductive and would obstruct the public health goal of the study by making it unduly difficult to identify promising leads for further research.

4.6 Potential Bias Due to Migration

Using the information from the interviews on the mothers' residence throughout pregnancy, comparisons could be made between the estimates of first trimester exposures based on this information and estimates of first trimester exposure based only on birth certificate data about maternal residence at time of birth. In the present study, almost 12% (N=67) of the interviewed mothers (N=565) resided at a different address during the first month of pregnancy than at the time of birth. About 8.5% (N=48) resided at an address for the entire first trimester that was different than the residence at birth. No doubt, this is an underestimate of the amount of migration occurring in the birth population during pregnancy since those who tended to move more frequently would also be the more difficult to locate for the study.

The impact of migration for the present study was on the participation rate. For the previous study (Bove et al., 1992), the impact of migration would be to bias the exposure estimates of the study subjects, since the estimates were based on maternal residence at time of birth. The bias due to migration during the pregnancy would be especially acute for the birth defect outcomes since the relevant exposure period is early in the first trimester. Since the present study obtained information on maternal residences throughout pregnancy, it was now possible to assess the likely impact of migration bias on the findings of the previous study. This assessment was performed by comparing the exposure estimates for the birth defect cases in the present study, which were based on actual residence during the first trimester, with the exposure estimates the cases would have received if maternal residence at time of birth were used as the basis for the estimates.

For TVOC, 87% of the birth defect cases who were assigned the combined level "> 5 ppb" based on first trimester residence from the interview had the same exposure estimate based on residence at time of birth from the birth certificate. For the "> 10 ppb" level the agreement was 93.3%. For the baseline value, the agreement was 90%. Overall, 85% of the birth defect cases would have been correctly classified for TVOC exposure using residence at time of birth on the birth certificate. Most of the misclassified cases came in the "1-5 ppb" level (only 78% correctly identified) and the "5-10 ppb" level (only 38% correctly identified). If residence at birth was used to estimate first trimester exposure, the resulting misclassification would have led to an overestimate of TVOC exposure for the birth defect cases (OR = 1.49 for the combined "> 5 ppb" level and OR = 1.43 for the "> 10 ppb" level).

For TTHM, 78% of the birth defect cases assigned to the level "> 80 ppb" based on first trimester residence from the interview had the same exposure estimate based on residence at time of birth from the birth certificate. For the baseline level, the agreement was 89%. Overall, 23% would be misclassified if residence at time of birth was used instead of the interview data. Most of the misclassification occurred in the "20-40 ppb" level (59% correctly identified) and the "60-80 ppb" level (65% correctly identified). For the "> 80 ppb" level, the use of the birth certificate address led to a <u>slight overestimation</u> of exposure (OR=1.13). Combining the two highest exposure levels (i.e., "> 60 ppb"), the use of the birth certificate address led to a <u>slight underestimate</u> of exposure (OR=0.89).

Overall, about 7% of birth defect cases were misclassified as to drinking water source exposure. Agreement between exposure based on interview and exposure based on the birth certificate was high for groundwater source (98%) and surface water source (94%) and moderate for mixed water source (81%). For surface water source and mixed water source, exposures were <u>underestimated slightly</u> (OR = 0.88 and OR = 0.91, respectively).

For TCE, all of the birth defect cases assigned to the "> 10 ppb" level and the combined "> 5 ppb" level based on the interview would have also been correctly assigned using the birth residence. For the baseline group, agreement was 94%. Overall, 7% of the cases would be misclassified if birth residence was used. Exposures to the "> 10 ppb" level and the combined "> 5 ppb" would be overestimated (OR = 1.68 and 1.37 respectively).

For PCE, all of the birth defect cases assigned to the "> 10 ppb" level based on the interview would have also been correctly assigned using the birth residence. Agreement for the combined "> 5 ppb" level was 75%. For the baseline group, agreement was 91%. Overall, 11% of the cases would be misclassified if birth residence was used. Exposures to the "> 10 ppb" level and the combined "> 5 ppb" would be overestimated (OR = 1.09 and 1.49 respectively).

For DCE, only 2% would be misclassified and exposures would be over-estimated (OR = 1.35). On the other hand, for TCA, exposures would not be overestimated (OR = 1.0) even though 3.4% of the cases would be misclassified. For nitrates, 3.4% of the cases would be misclassified and exposures would be overestimated (OR = 1.20). Finally, for CTC, no misclassification would have occurred.

In summary, the misclassification of first trimester exposure introduced by an estimation process relying on maternal residence at time of birth from birth certificates would have a minimal impact on TTHM, nitrate and drinking water source exposures. On the other hand, exposures to the A-280 contaminants would tend to be overestimated, although for some contaminants the estimates would not be affected (i.e., CTC and TCA). The methods used in this study eliminated this source of exposure misclassification. However, the magnitude of this bias was much smaller than the selection bias introduced by the methods used in this study.

5.0 CONCLUSION

The primary objective of this study was to use available sample data on drinking water contaminants in public water systems and detailed information from mothers of cases with certain birth defects and low birthweight and control mothers to investigate potential relationships between exposures to drinking water contamination and adverse reproductive outcomes.

5.1 Recommendations for Follow-up Investigations, Considering Findings and Selection Bias

Prior to consideration of the impact of selection bias due to the failure to interview all sampled subjects, neural tube defects were the outcome most strongly associated with exposure to drinking water contaminants. After a review of the possible impact of selection bias, the associations between NTDs and TTHM, PCE, and nitrates appear questionable. Although the selection bias drastically inflated the odds ratios for surface water and mixed water sources, the association between these exposures and NTDs cannot be as easily argued away. Even after the non-interviewed subjects were included in the analysis, the odds ratios for these exposures remained high. Combining these results for NTDs with the results found in the cross-sectional study (Bove et al., 1992), it is suggested that future research on NTDs and drinking water emphasize the following associations: TVOC, TCE, PCE, DCE, CTC, TTHM, nitrates, surface water source and mixed water source.

The association found between oral clefts and CTC was not affected by selection bias. The negative association with TCA was found to be primarily due to selection bias. The association between surface water exposure and cleft palate is questionable since the selection bias inflated the odds ratio for this variable. However, the association between DCE and cleft palate was not affected by the selection bias. Combining these results for oral clefts with the results found in the cross-sectional study (Bove et al., 1992), it is suggested that future research on oral clefts focus on the following associations: TVOC, TCE, PCE, DCE, and CTC.

Selection bias did not greatly inflate the odds ratios for major cardiac defects, but the inclusion of the non-interviewed would probably eliminate the suggestive association with TTHM. On the other hand, inclusion of the non-interviewed subjects increased the odds ratio for mixed water source thereby strengthening the suggestive association found for this variable. Combining these results with the results from the cross-sectional study (Bove et al., 1992), it is suggested that future research on major cardiac defects focus on the following associations: EDC, TTHM, surface water source, and mixed water source.

After inclusion of non-interviewed ventricular septal defect cases and controls, the odds ratio for CTC was sharply reduced, weakening the association found in the adjusted analysis but probably not eliminating it altogether. The associations with TVOC and TCA were minimally affected. Combining these results with the results from the cross-sectional study (Bove et al., 1992), it is suggested that future research on ventricular septal defects focus on associations with TVOC, TCA, and CTC.

After inclusion of non-interviewed very low birthweight cases and controls, the odds ratios for TVOC and TCE were reduced compared to the findings in the unadjusted analysis. However, in the adjusted analysis, the odds ratios were sharply increased over the unadjusted results. Therefore, it is not clear that the associations would disappear if all sampled subjects had been interviewed. Combining these results with the results from the cross-sectional study (Bove et al., 1992), it is suggested that future research focus on the associations with TVOC, TCE, PCE, and surface water source.

When non-interviewed intermediate low birthweight cases and controls were included, the odds ratio for surface water source was reduced, so that the association was questionable. Given that this was the only association with this outcome found in this study, our suggestions for future research are based on the cross-sectional study (Bove et al., 1992): TTHM, surface water source, mixed water source, and CTC.

Table 37 presents a summary of findings that merit follow-up. Other than isolated studies of major contamination episodes (e.g., Woburn, Santa Clara, Tucson), research on the effects of drinking water contaminants on reproduction was nonexistent. In particular, no studies had investigated the reproductive effects of these contaminants at the relatively low levels commonly found in public drinking water systems. Therefore, an additional goal of this study is to encourage other agencies, particularly states, to investigate the reproductive effects of drinking water contamination using sample data on public systems that have (or will) become available. The USEPA regulations of the Safe Drinking Water Act Amendments of 1986 require public water systems to sample for the specific contaminants evaluated in the present study as well as additional contaminants. In addition, data on TTHM and nitrates have been available for a number of years. It is true that the use of these databases to estimate potential exposures requires much interpretative work on the part of researchers.

5.2 Comparison of the Case-Control and Cross-Sectional Studies

At least for drinking water studies and reproductive outcomes, the study design used in the concurrent cross-sectional study (Bove et al., 1992) that relied solely on information from vital records, the birth defects registry, and the drinking water databases appears to be superior to the study design used in the present study. The advantages listed above for the case-control sampling method and extensive interview of those sampled appeared for the most part to be inconsequential when compared to the selection bias introduced by the failure to interview all those sampled. Despite the more detailed information available on individual cases and controls for this case-control study, in comparison to the extent of data on each subject which was available in the parallel cross-sectional study, the uncertainties introduced by the smaller number of controls and cases and the potential selection biases discussed at length above suggest that this case-control study may <u>not</u> have had a greatly increased ability to control for confounding or account accurately for the degree of exposure to water contaminants in order to detect true associations between exposures and reproductive outcomes than the cross-sectional study. In order to pursue the findings here, a new set of data and rapid ascertainment are needed which might include drinking water sampling at individual residences closer in time to the pregnancies.

5.3 Public Health Implications

In themselves, the associations found in this study do not provide sufficient evidence to make the claim that these contaminants cause adverse reproductive outcomes at the levels commonly found in public drinking water systems; the paucity of other toxicological and epidemiologic research on the reproductive effects of these drinking water contaminants prevents us from making such claims. Nevertheless, from a public health perspective, these associations should be taken seriously and investigated further, utilizing the methodological considerations discussed above. Furthermore, even considering the various limitations of the study, the findings support vigilance on the part of USEPA and the states to both enforce the regulations of the federal Safe Drinking Water and the Clean Water Acts and analogous state laws and also to promote the development of new technologies and practices that will reduce or eliminate these contaminants in drinking water.

It may be noted that the exposures in this study which are typical of groundwater (TVOCs and their components) now have lower concentrations in most public water systems than they did when the study was initiated. Further, the current national and state standards for these compounds have become stricter. Conversely, the levels and regulations for surface water contaminants such as TTHMs, which are principally chlorination byproducts, have not appreciably changed. This study, as its concurrent cross-sectional investigation, were made possible in part by the existence of environmental and health outcome databases. Other such investigations are dependent upon the continuation and improvement of these systems.

TABLES

TABLE 1

SUMMARY OF STUDIES OF DRINKING WATER CONTAMINATION AND ADVERSE REPRODUCTIVE OUTCOMES

STUDY POPULATION	EXPOSURE	POSITIVE FINDINGS
Woburn, MA (Lagakos, 1986a)	TCE (max = 267 ppb) PCE (max = 21 ppb) Dichloroethylenes (max = 28 ppb) in public water supply	Perinatal mortality, mostly stillbirths (OR = 10, at highest exposure level) The eye/ear defect grouping (OR = 14.9, highest exposure level) The CNS/oral cleft/ chromosomal grouping (OR = 2.3, at highest exposure level)
Battle Creek, MI (Freni, 1988)	TCE, PCE and 1,1-Dichloroethylene in private wells	No positive findings
Santa Clara County, CA (Wrensch, 1990; Swan, 1989)	TCA (max = 1.7 ppm) in a public well serving a census tract.	Cardiac defects? (the spatio-temporal pattern of cardiac defects did not fit the modeled distribution of water from the contaminated well).
Tucson Valley AZ (Goldberg, 1990)	TCE (max = 239 ppb) Dichloroethylene (max = 24 ppb) Chromium in a public wellfield serving the southwestern portion of the city of Tucson	Cardiac defects (exposure prevalence among cases was 3 1/2 times exposure prevalence among controls)
Iowa (Kramer, 1992)	THMs in public drinking water	Small for gestational age (OR = 1.8 with $\geq$ 10 ppb chloroform)

TABLE 1 (continued)

STUDY POPULATION	EXPOSURE	POSITIVE FINDINGS
Massachusetts (Zierler, 1988)	Inorganic levels in public water systems	Arsenic and coarctation of aorta (OR = 3.4)
Massachusetts (Aschengrau, 1989)	Inorganic levels, water hardness, source of water supply (surface or groundwater) - public water systems	Spontaneous abortion and potassium (OR = 2.6); silica (OR = 1.9); water hardness (OR = 2.9); surface water source (OR = 2.2)
South Australia (Dorsch, 1984)	Nitrate levels in drinking water, source of water supply (groundwater contaminated with nitrates or surface water)	Birth defects Neural tube defects (OR = 3.5) Oral clefts (OR = 4.0)
New Brunswick, Canada (Arbuckle, 1988)	Nitrate levels in public water systems and private wells (most of the population exposed to levels below 12 ppm; virtually all public supplies had levels below the US MCL of 10 ppm)	CNS defects for "high" (26 ppm) nitrate levels in private wells (OR = 2.3) (No association found for the lower levels of nitrates found in public water systems)

TABLE 2

DIAGNOSES OF THE BIRTH DEFECT SERIES
INCLUDED IN THE NEW JERSEY STUDY;
NJDOH, 1992

DIAGNOSIS		1985-1988 NUMBER OF CASES
Cleft Lip with or without Cleft Palate		30
	Single:	23
	Multiple:	7*
Cleft Palate (without cleft lip)		19
	Single:	8
	Multiple:	11*
Anencephaly		12
Spina Bifida		20
Encephalocele		5
Single Defect NTDs		23
Multiple Defect NTDs		14
Tetralogy of Fallot		11
Transposition of the Great Vessels		8
Common Truncus		2
Hypoplastic Left Heart		17
Coarctation of the Aorta		9*
Anomalies of the Pulmonary Valve		5
Anomalies of the Pulmonary Artery		2
Common Ventricle		1
Atresia or Stenosis of the Aorta		1
Tricuspid Atresia or Stenosis		1
Endocardial Cushion Defect		1

* One cleft lip case also had coarctation of the aorta, hypoplastic left heart and transposition of the great vessels. One cleft palate case also had coarctation of the aorta. These cases were included in the major cardiac case group as well as in the oral cleft group.

TABLE 3A

SUMMARY OF STATUS OF CASE-CONTROL STUDY SUBJECTS
1985-1988 Birth Defect Series; NJDOH, 1992

STATUS	NEURAL TUBE DEFECTS	ORAL CLEFT DEFECTS	MAJOR CARDIAC DEFECTS	VENTRICULAR SEPTAL DEFECTS	SUB-TOTAL and PERCENT
Total eligible:	56	83	84	77	298 (100%)
Unable to contact:	7 (13%)	25 (30%)	13 (15%)	20 (26%)	65 (22%)
Refused to participate:	6 (11%)	9 (11%)	10 (12%)	11 (14%)	36 (12%)
Interviews completed:	43 (77%)	49 (59%)	61 (73%)	46 (60%)	197* (66%)
Resided outside NJ during first trimester:	1**	0	3	1	5 (3%)
Residence supplied by private wells during first trimester:	6	0	0	2	8 (4%)
Total In Study:	37	49	58	43	185 (94%)

* Two of the oral cleft defects also had major cardiac defects. They were included in both defect groupings.

** The NTD residing outside NJ was supplied by a private well.

TABLE 3B

SUMMARY OF STATUS OF CASE-CONTROL STUDY SUBJECTS
1985-1988 Low Birthweight Series and Control Series: NJDOH, 1992

STATUS	INTERMEDIATE LOW BIRTHWEIGHT (1500g - 2499g)	VERY LOW BIRTHWEIGHT (< 1500g)	CONTROLS	SUB-TOTAL and PERCENT
Number sampled:	280	280	280	840
Not eligible:**	22	32	9	63
Shift from the other birthweight group or controls:*	+ 8	+ 2	+ 4	+14
Total eligible	266	250	275	791 (100%)
Unable to contact:	114 (43%)	114 (46%)	76 (28%)	304 (32%)
Refused to participate:	36 (14%)	36 (14%)	49 (18%)	121 (15%)
Interviews completed:	116 (45%)	100 (40%)	150 (55%)	366 (46%)
Resided outside NJ for more than three months of pregnancy:	1	1	1	3 (0.4%)
Residence supplied by private well for more than three months of pregnancy:	2	2	9	13 (2%)
Total In Study:	113 (42%)	97 (39%)	140 (51%)	350 (44%)
# control residing outside NJ during first trimester:			3	
# controls with residence supplied by private well during first trimester:			9	
# controls in birth defect series analyses:			138	

* See text (section 2.3)

** Birth certificates could not be located, non-singleton births, birth defects, mother did not live in the study area at time of birth.

TABLE 4

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Neural Tube Defects (NTDs)

CASES = 37 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	23	99	1.00	---	---
> 1 ppb - 5 ppb	9	26	1.49	0.54 - 3.9	NS
> 5 ppb - 10 ppb	2	5	1.72	0.15 - 11.3	NS
> 10 ppb	3	8	1.61	0.26 - 7.4	NS
> 5 ppb	5	13	1.66	0.42 - 5.6	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	33	122	1.00	---	---
> 1 ppb - 5 ppb	2	6	1.23	0.12 - 7.3	NS
> 5 ppb - 10 ppb	0	6	---	---	
> 10 ppb	2	4	1.85	0.16 - 13.5	NS
> 5 ppb	2	10	0.74	0.08 - 3.7	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	30	122	1.00	---	---
> 1 ppb - 5 ppb	3	12	1.02	0.17 - 4.1	NS
> 5 ppb - 10 ppb	3	3	4.07	0.51 - 31.5	< .10
> 10 ppb	1	1	4.07	0.05 - 322.0	NS
> 5 ppb	4	4	4.07	0.71 - 22.9	< .06
Test for trend: 1-sided, positive p < .075					
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	35	135	1.00	---	---
> 2 ppb	2	3	2.57	0.21 - 23.2	NS
n.d. - 1 ppb (ref)	33	130	1.00	---	---
> 1 ppb	4	8	1.97	0.41 - 7.9	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	36	132	1.00	---	---
> 2 ppb	1	6	0.61	0.01 - 5.3	NS
n.d. - 1 ppb (ref)	31	117	1.00	---	---
> 1 ppb	6	21	1.08	0.33 - 3.1	NS

TABLE 4 (continued)
OUTCOME: NTDs

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	36	137	1.00	---	---
> 1 ppb	1	1	3.81	0.05 - 301.0	NS
not detected (ref)	36	135	1.00	---	---
detected	1	3	1.25	0.13 - 12.4	NS
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	36	137	1.00	---	---
> 1 ppb	1	1	3.81	0.05 - 301.0	NS
not detected (ref)	36	137	1.00	---	---
detected	1	1	3.81	0.05 - 301.0	NS
BENZENE:					
not detected (ref)	37	136	1.00	---	---
detected	0	2	---		
NITRATES:					
n.d. - 2 ppm (ref)	29	119	1.00	---	---
> 2 ppm	8	19	1.73	0.59 - 4.6	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	6	51	1.00	---	---
> 20 ppb - 40 ppb	6	14	3.64	0.82 - 15.8	< .05
> 40 ppb - 60 ppb	11	36	2.60	0.79 - 9.3	< .085
> 60 ppb - 80 ppb	7	23	2.59	0.65 - 10.4	NS
> 80 ppb	7	14	4.25	1.02 - 17.7	< .025
Exact test for trend p < .035 (2-sided) 1-sided, positive p < .025)					
n.d.- 15 ppb (ref)	5	51	1.00	---	---
> 15 ppb - 50 ppb	15	31	4.94	1.49 - 18.8	< .01
> 50 ppb - 75 ppb	9	35	2.62	0.71 - 10.8	NS
> 75 ppb	8	21	3.89	0.97 - 16.7	< .035
Exact test for trend < .09 (2-sided), 1-sided, positive p < .05					
SOURCE OF WATER SUPPLY:					
ground water (ref)	2	47	1.00	---	---
surface water	24	77	7.33	1.67 - 66.2	< .01
mixture of sources	11	14	18.46	3.29 - 182.0	< .001

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 5

Adjusted Odds Ratios New Jersey Dept. of Health 1985-1988
OUTCOME: Neural Tube Defects (NTDs)

CASES = 36 CONTROLS = 131

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL A-280 VOLATILES:				
> 1 ppb - 5 ppb	1.20	0.40 - 3.6	NS	1.23
> 5 ppb - 10 ppb	3.63	0.52 - 25.1	NS	1.60
> 10 ppb	1.24	0.25 - 6.3	NS	1.50
> 5 ppb	1.84	0.50 - 6.8	NS	1.54
TRICHLOROETHYLENE:				
> 1 ppb - 5 ppb	1.59	0.23 - 11.1	NS	1.20
> 5 ppb - 10 ppb	---			
> 10 ppb	---			
> 5 ppb	0.54	0.09 - 3.3	NS	0.72
TETRACHLOROETHYLENE:				
> 1 ppb - 5 ppb	2.28	0.48 - 10.8	NS	0.99
> 5 ppb - 10 ppb	5.93	0.86 - 41.1	< .075	3.97
> 10 ppb	1.64	0.07 - 40.9	NS	3.97
> 5 ppb	4.37	0.78 - 24.7	< .095	3.97
The DICHLOROETHYLENES:				
> 2 ppb	3.05	0.38 - 24.4	NS	2.51
> 1 ppb	2.73	0.63 - 11.9	NS	1.92
1,1,1-TRICHLOROETHANE:				
> 2 ppb	0.33	0.03 - 4.3	NS	0.60
> 1 ppb	0.50	0.14 - 1.8	NS	0.84
CARBON TETRACHLORIDE:				
> 1 ppb	12.22	0.45 - 330.	NS	3.71
detected	2.11	0.17 - 25.7	NS	1.22
1,2-DICHLOROETHANE:				
> 1 ppb	2.46	0.12 - 49.1	NS	3.71
detected	2.46	0.12 - 49.1	NS	3.71

TABLE 5 (continued)

OUTCOME: NTDs

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
NITRATES:				
> 2 ppm	2.43	0.82 - 7.2	NS	1.79
TOTAL TRIHALOMETHANES:				
> 20 ppb - 40 ppb	4.41	1.04 - 18.7	< .045	4.08
> 40 ppb - 60 ppb	2.16	0.58 - 8.0	NS	2.47
> 60 ppb - 80 ppb	2.04	0.54 - 7.7	NS	2.49
> 80 ppb	3.87	0.90 - 16.7	< .075	4.08
> 15 - 50 ppb	6.39	1.71 - 23.9	< .01	5.08
> 50 - 75 ppb	2.26	0.59 - 8.7	NS	2.59
> 75 ppb	3.47	0.84 - 14.4	< .09	3.73
WATER SOURCE:				
surface water	7.64	1.36 - 43.0	< .025	7.35
mixture of sources	50.28	7.04 - 359.0	< .001	19.46

* The unadjusted odds ratio after removal of cases and controls with missing data on any of the factors included in the model.

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 6

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Single Neural Tube Defects (NTDs)

CASES = 23 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	14	99	1.00	---	---
> 1 ppb - 5 ppb	5	26	1.36	0.35 - 4.5	NS
> 5 ppb - 10 ppb	2	5	2.83	0.24 - 19.2	NS
> 10 ppb	2	8	1.77	0.17 - 10.2	NS
> 5 ppb	4	13	2.18	0.45 - 8.4	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	20	122	1.00	---	---
> 1 ppb - 5 ppb	2	6	2.03	0.19 - 12.4	NS
> 5 ppb - 10 ppb	0	6	---		
> 10 ppb	1	4	1.52	0.03 - 16.4	NS
> 5 ppb	1	10	0.61	0.01 - 4.7	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	18	122	1.00	---	---
> 1 ppb - 5 ppb	2	12	1.13	0.11 - 5.7	NS
> 5 ppb - 10 ppb	2	3	4.52	0.35 - 41.7	NS
> 10 ppb	1	1	6.78	0.08 - 536.0	NS
Test for trend p < .055, 1-sided and 2-sided					
> 5 ppb	3	4	5.08	0.68 - 32.3	< .045
Test for trend p < .095, 2-sided; p < .065, 1-sided positive					
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	21	135	1.00	---	---
> 2 ppb	2	3	4.29	0.33 - 39.2	NS
n.d. - 1 ppb (ref)	20	130	1.00	---	---
> 1 ppb	3	8	2.44	0.38 - 11.2	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	23	132	1.00	---	---
> 2 ppb	0	6	---		
n.d. - 1 ppb (ref)	21	117	1.00	---	---
> 1 ppb	2	21	0.53	0.06 - 2.5	NS

TABLE 6 (continued)
OUTCOME: Single NTDs

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	22	137	1.00	---	---
> 1 ppb	1	1	6.23	0.08 - 492	NS
not detected (ref)	22	135	1.00	---	---
detected	1	3	2.05	0.04 - 26.7	NS
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	23	137	1.00	---	---
> 1 ppb	0	1			
not detected (ref)	23	137	1.00	---	---
detected	0	1			
BENZENE:					
not detected (ref)	23	136	1.00	---	---
detected	0	2			
NITRATES:					
n.d. - 2 ppm (ref)	19	119	1.00	---	---
> 2 ppm	4	19	1.32	0.29 - 4.6	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	3	51	1.00	---	---
> 20 ppb - 40 ppb	3	14	3.64	0.43 - 29.6	NS
> 40 ppb - 60 ppb	7	36	3.31	0.69 - 20.9	< .10
> 60 ppb - 80 ppb	4	23	2.96	0.45 - 21.5	NS
> 80 ppb	6	14	7.29	1.31 - 49.1	< .015
Test for trend p < .02, 2-sided; p < .01 1-sided positive					
n.d.- 15 ppb (ref)	2	51	1.00	---	---
> 15 ppb - 50 ppb	9	31	7.40	1.37 - 73.3	< .015
> 50 ppb - 75 ppb	6	35	4.37	0.72 - 46.0	< .085
> 75 ppb	6	21	7.29	1.15 - 77.3	< .025
Test for trend p < .05, 2-sided; p <.03, 1-sided positive					
SOURCE OF WATER SUPPLY:					
ground water (ref)	1	47	1.00	---	
surface water	14	77	8.55	1.21 - 369.0	< .045
mixture of sources	8	14	26.86	3.0 - 1,216	4 < .005

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 7

Unadjusted (Bivariate) Odds Ratios, New Jersey Dept. of Health 1985-1988
OUTCOME: Multiple Neural Tube Defects (NTDs)

CASES = 14 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	9	99	1.00	---	---
> 1 ppb - 5 ppb	4	26	1.69	0.35 - 6.7	NS
> 5 ppb - 10 ppb	0	5	---		
> 10 ppb	1	8	1.38	0.03 - 12.5	NS
> 5 ppb	1	13	0.85	0.02 - 7.1	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	13	122	1.00	---	---
> 1 ppb - 5 ppb	0	6	---		
> 5 ppb - 10 ppb	0	6	---		
> 10 ppb	1	4	2.35	0.04 - 26.0	NS
> 5 ppb	1	10	0.94	0.02 - 7.6	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	12	122	1.00	---	---
> 1 ppb - 5 ppb	1	12	0.85	0.02 - 6.8	NS
> 5 ppb - 10 ppb	1	3	3.39	0.06 - 45.6	NS
> 10 ppb	0	1	---		
> 5 ppb	1	4	2.54	0.05 - 28.3	NS
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	14	135	1.00	---	---
> 2 ppb	0	3	---		
n.d. - 1 ppb (ref)	13	130	1.00	---	---
> 1 ppb	1	8	1.25	0.03 - 10.7	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	13	132	1.00	---	---
> 2 ppb	1	6	1.69	0.03 - 15.7	NS
n.d. - 1 ppb (ref)	10	117	1.00	---	---
> 1 ppb	4	21	2.23	0.46 - 8.6	NS

TABLE 7 (continued)
OUTCOME: Multiple NTDs

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	14	137	1.00	---	---
> 1 ppb	0	1	---		
not detected (ref)	14	135	1.00	---	---
detected	0	3	---		
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	13	137	1.00	---	---
> 1 ppb	1	1	10.54	0.12 - 833.0	NS
not detected (ref)	13	137	1.00	---	---
detected	1	1	10.54	0.12 - 833.0	NS
BENZENE:					
not detected (ref)	14	136	1.00	---	---
detected	0	2	---		
NITRATES:					
n.d. - 2 ppm (ref)	10	119	1.00	---	---
> 2 ppm	4	19	2.51	0.52 - 9.8	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	3	51	1.00	---	---
> 20 ppb - 40 ppb	3	14	3.64	0.43 - 29.6	NS
> 40 ppb - 60 ppb	4	36	1.89	0.30 - 13.6	NS
> 60 ppb - 80 ppb	3	23	2.22	0.27 - 17.7	NS
> 80 ppb	1	14	1.21	0.02 - 16.5	NS
n.d.- 15 ppb (ref)	3	51	1.00	---	---
> 15 ppb - 50 ppb	6	31	3.29	0.64 - 21.5	NS
> 50 ppb - 75 ppb	3	35	1.46	0.18 - 11.5	NS
> 75 ppb	2	21	1.62	0.13 - 15.1	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	1	47	1.00	---	---
surface water	10	77	6.10	0.81 - 270	< .09
mixture of sources	3	14	10.07	0.71 - 540	< .055

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 8

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Oral Clefts

CASES = 49 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	34	99	1.00	---	---
> 1 ppb - 5 ppb	9	26	1.01	0.38 - 2.5	NS
> 5 ppb - 10 ppb	2	5	1.16	0.11 - 7.5	NS
> 10 ppb	4	8	1.46	0.30 - 5.8	NS
> 5 ppb	6	13	1.34	0.39 - 4.2	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	43	122	1.00	---	---
> 1 ppb - 5 ppb	2	6	0.95	0.09 - 5.6	NS
> 5 ppb - 10 ppb	3	6	1.42	0.22 - 7.0	NS
> 10 ppb	1	4	0.71	0.01 - 7.4	NS
> 5 ppb	4	10	1.13	0.25 - 4.2	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	42	122	1.00	---	---
> 1 ppb - 5 ppb	6	12	1.45	0.42 - 4.5	NS
> 5 ppb - 10 ppb	0	3	---		
> 10 ppb	1	1	2.88	0.04 - 230	NS
> 5 ppb	1	4	0.73	0.01 - 7.6	NS
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	46	135	1.00	---	---
> 2 ppb	3	3	2.93	0.38 - 22.5	NS
n.d. - 1 ppb (ref)	46	130	1.00	---	---
> 1 ppb	3	8	1.06	0.17 - 4.7	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	46	132	1.00	---	---
> 2 ppb	3	6	1.43	0.22 - 7.0	NS
n.d. - 1 ppb (ref)	43	117	1.00	---	---
> 1 ppb	6	21	0.78	0.24 - 2.2	NS

TABLE 8 (continued)
OUTCOME: Oral Clefts

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	48	137	1.00	---	---
> 1 ppb	1	1	2.85	0.04 - 226	NS
not detected (ref)	45	135	1.00	---	---
detected	4	3	4.0	0.64 - 28.1	< .08
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	49	137	1.00	---	---
> 1 ppb	0	1	---		
not detected (ref)	49	137	1.00	---	---
detected	0	1	---		
BENZENE:					
not detected (ref)	49	136	1.00	---	---
detected	0	2	---		
NITRATES:					
n.d. - 2 ppm (ref)	45	119	1.00	---	---
> 2 ppm	4	19	0.56	0.13 - 1.8	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	16	51	1.00	---	---
> 20 ppb - 40 ppb	7	14	1.59	0.46 - 5.1	NS
> 40 ppb - 60 ppb	9	36	0.80	0.28 - 2.2	NS
> 60 ppb - 80 ppb	10	23	1.39	0.48 - 3.8	NS
> 80 ppb	7	14	1.59	0.46 - 5.1	NS
n.d.- 15 ppb (ref)	16	51	1.00	---	---
> 15 ppb - 50 ppb	12	31	1.23	0.47 - 3.2	NS
> 50 ppb - 75 ppb	11	35	1.00	0.37 - 2.6	NS
> 75 ppb	10	21	1.52	0.52 - 4.3	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	14	47	1.00	---	
surface water	33	77	1.44	0.67 - 3.2	NS
mixture of sources	2	14	0.48	0.05 - 2.5	NS

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 9

Adjusted Odds Ratios New Jersey Dept. of Health 1985-1988
OUTCOME: Oral Clefts

CASES = 49 CONTROLS = 138

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL A-280 VOLATILES:				
> 1 ppb - 5 ppb	0.73	0.27 - 2.0	NS	1.01
> 5 ppb - 10 ppb	1.11	0.18 - 6.9	NS	1.16
> 10 ppb	0.66	0.15 - 2.9	NS	1.46
> 5 ppb	0.80	0.24 - 2.7	NS	1.34
TRICHLOROETHYLENE:				
> 1 ppb - 5 ppb	0.89	0.15 - 5.1	NS	0.95
> 5 ppb - 10 ppb	0.60	0.11 - 3.4	NS	1.42
> 10 ppb	0.58	0.06 - 6.0	NS	0.71
> 5 ppb	0.59	0.14 - 2.4	NS	1.13
TETRACHLOROETHYLENE:				
> 1 ppb - 5 ppb	0.97	0.25 - 3.7	NS	1.45
> 5 ppb	0.42	0.04 - 4.3	NS	0.73
The DICHLOROETHYLENES:				
> 2 ppb	1.48	0.20 - 10.8	NS	2.93
> 1 ppb	0.48	0.10 - 2.5	NS	1.06
1,1,1-TRICHLOROETHANE:				
> 2 ppb	0.55	0.10 - 3.0	NS	1.43
> 1 ppb	0.37	0.11 - 1.2	< .10	0.78
CARBON TETRACHLORIDE:				
> 1 ppb	2.75	0.14 - 55.5	NS	2.85
detected	5.39	0.81 - 36.0	< .085	4.0
NITRATES:				
> 2 ppm	0.57	0.17 - 1.9	NS	0.56

TABLE 9 (continued)

OUTCOME: Oral Clefts

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL TRIHALOMETHANES:				
> 20 ppb - 40 ppb	1.77	0.54 - 5.8	NS	1.59
> 40 ppb - 60 ppb	0.94	0.34 - 2.6	NS	0.80
> 60 ppb - 80 ppb	1.35	0.48 - 3.8	NS	1.39
> 80 ppb	1.77	0.52 - 6.0	NS	1.59
> 15 - 50 ppb	1.54	0.59 - 4.0	NS	1.23
> 50 - 75 ppb	0.94	0.33 - 2.7	NS	1.00
> 75 ppb	1.59	0.55 - 4.6	NS	1.52
WATER SOURCE:				
surface water	1.62	0.71 - 3.7	NS	1.44
mixture of sources	0.85	0.16 - 4.6	NS	0.48

* The unadjusted odds ratio after removal of cases and controls with missing data on any of the factors included in the model.

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 10

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988

OUTCOME: Cleft Lip With or Without Cleft Palate

CASES = 30 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	22	99	1.00	---	---
> 1 ppb - 5 ppb	4	26	0.69	0.16 - 2.3	NS
> 5 ppb - 10 ppb	2	5	1.80	0.16 - 11.8	NS
> 10 ppb	2	8	1.13	0.11 - 6.2	NS
> 5 ppb	4	13	1.38	0.30 - 5.1	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	27	122	1.00	---	---
> 1 ppb - 5 ppb	1	6	0.75	0.02 - 6.6	NS
> 5 ppb - 10 ppb	2	6	1.51	---	
> 10 ppb	0	4	---	0.14 - 9.0	NS
> 5 ppb	2	10	0.90	0.09 - 4.6	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	25	122	1.00	---	---
> 1 ppb - 5 ppb	4	12	1.63	0.35 - 5.9	NS
> 5 ppb - 10 ppb	0	3	---		
> 10 ppb	1	1	4.88	0.06 - 386	NS
> 5 ppb	1	4	1.22	0.02 - 13.0	NS
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	29	135	1.00	---	---
> 2 ppb	1	3	1.55	0.03 - 20.1	NS
n.d. - 1 ppb (ref)	29	130	1.00	---	---
> 1 ppb	1	8	0.56	0.01 - 4.5	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	28	132	1.00	---	---
> 2 ppb	2	6	1.57	0.15 - 9.4	NS
n.d. - 1 ppb (ref)	26	117	1.00	---	---
> 1 ppb	4	21	0.86	0.20 - 2.9	NS

TABLE 10 (continued)

OUTCOME: Cleft Lip With or Without Cleft Palate

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	30	137	1.00	---	---
> 1 ppb	0	1	---		
not detected (ref)	28	135	1.00	---	---
detected	2	3	3.21	0.26 - 29.2	NS
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	30	137	1.00	---	---
> 1 ppb	0	1	---		
not detected (ref)	30	137	1.00	---	---
detected	0	1	---		
BENZENE:					
not detected (ref)	30	136	1.00	---	---
detected	0	2	---		
NITRATES:					
n.d. - 2 ppm (ref)	28	119	1.00	---	---
> 2 ppm	2	19	0.45	0.05 - 2.0	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	12	51	1.00	---	---
> 20 ppb - 40 ppb	3	14	0.91	0.15 - 4.1	NS
> 40 ppb - 60 ppb	5	36	0.59	0.15 - 2.0	NS
> 60 ppb - 80 ppb	5	23	0.92	0.23 - 3.3	NS
> 80 ppb	5	14	1.52	0.36 - 5.7	NS
n.d.- 15 ppb (ref)	12	51	1.00	---	---
> 15 ppb - 50 ppb	5	31	0.69	0.17 - 2.4	NS
> 50 ppb - 75 ppb	6	35	0.73	0.20 - 2.4	NS
> 75 ppb	7	21	1.42	0.41 - 4.6	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	12	47	1.00	---	---
surface water	17	77	0.86	0.35 - 2.2	NS
mixture of sources	1	14	0.28	0.01 - 2.3	NS

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 11

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Cleft Palate (no cleft lip)

CASES = 19 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	12	99	1.00	---	---
> 1 ppb - 5 ppb	5	26	1.59	0.4 - 5.4	NS
> 5 ppb - 10 ppb	0	5	---		
> 10 ppb	2	8	2.06	0.19 - 12.1	NS
> 5 ppb	2	13	1.27	0.12 - 6.8	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	16	122	1.00	---	---
> 1 ppb - 5 ppb	1	6	1.27	0.03 - 11.6	NS
> 5 ppb - 10 ppb	1	6	1.27	0.03 - 11.6	NS
> 10 ppb	1	4	1.91	0.04 - 20.8	NS
> 5 ppb	2	10	1.52	0.15 - 8.1	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	17	122	1.00	---	---
> 1 ppb - 5 ppb	2	12	1.2	0.12 - 6.1	NS
> 5 ppb - 10 ppb	0	3	---		
> 10 ppb	0	1	---		
> 5 ppb	0	4	---		
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	17	135	1.00	---	---
> 2 ppb	2	3	5.29	0.41 - 48.9	< .08
n.d. - 1 ppb (ref)	17	130	1.00	---	---
> 1 ppb	2	8	1.91	0.18 - 10.7	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	18	132	1.00	---	---
> 2 ppb	1	6	1.22	0.03 - 11.0	NS
n.d. - 1 ppb (ref)	17	117	1.00	---	---
> 1 ppb	2	21	0.66	0.07 - 3.1	NS

TABLE 11 (continued)
OUTCOME: Cleft Palate (no cleft lip)

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	18	137	1.00	---	---
> 1 ppb	1	1	7.61	0.09 - 602.0	NS
not detected (ref)	17	135	1.00	---	---
detected	2	3	5.29	0.41 - 48.9	< .08
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	19	137	1.00	---	---
> 1 ppb	0	1	---		
not detected (ref)	19	137	1.00	---	---
detected	0	1	---		
BENZENE:					
not detected (ref)	19	136	1.00	---	---
detected	0	2	---		
NITRATES:					
n.d. - 2 ppm (ref)	17	119	1.00	---	---
> 2 ppm	2	19	0.74	0.08 - 3.5	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	4	51	1.00	---	---
> 20 ppb - 40 ppb	4	14	3.64	0.59 - 21.8	< .095
> 40 ppb - 60 ppb	4	36	1.42	0.25 - 8.1	NS
> 60 ppb - 80 ppb	5	23	2.77	0.53 - 15.1	NS
> 80 ppb	2	14	1.82	0.15 - 14.2	NS
n.d.- 15 ppb (ref)	4	51	1.00	---	---
> 15 ppb - 50 ppb	7	31	2.88	0.66 - 14.4	NS
> 50 ppb - 75 ppb	5	35	1.82	0.36 - 9.8	NS
> 75 ppb	3	21	1.82	0.24 - 11.7	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	2	47	1.00	---	
surface water	16	77	4.88	1.06 - 45.3	< .04
mixture of sources	1	14	1.68	0.03 - 34.2	NS

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 12

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Major Cardiac Defects

CASES = 58 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	44	99	1.00	---	---
> 1 ppb - 5 ppb	10	26	0.87	0.34 - 2.0	NS
> 5 ppb - 10 ppb	0	5	---		
> 10 ppb	4	8	1.12	0.24 - 4.5	NS
> 5 ppb	4	13	0.69	0.16 - 2.4	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	53	122	1.00	---	---
> 1 ppb - 5 ppb	3	6	1.15	0.22 - 5.5	NS
> 5 ppb - 10 ppb	1	6	0.38	0.02 - 3.4	NS
> 10 ppb	1	4	0.58	0.02 - 5.7	NS
> 5 ppb	2	10	0.46	0.05 - 2.3	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	53	122	1.00	---	---
> 1 ppb - 5 ppb	3	12	0.58	0.10 - 2.3	NS
> 5 ppb - 10 ppb	2	3	1.53	0.12 - 13.8	NS
> 10 ppb	0	1	---		
> 5 ppb	2	4	1.15	0.10 - 8.3	NS
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	57	135	1.00	---	---
> 2 ppb	1	3	0.79	0.01 - 10.1	NS
n.d. - 1 ppb (ref)	55	130	1.00	---	---
> 1 ppb	3	8	0.89	0.15 - 3.9	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	58	132	1.00	---	---
> 2 ppb	0	6	---	---	
n.d. - 1 ppb (ref)	53	117	1.00	---	---
> 1 ppb	5	21	0.53	0.15 - 1.5	NS

TABLE 12 (continued)

OUTCOME: Major Cardiac Defects

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	58	137	1.00	---	---
> 1 ppb	0	1	---	---	
not detected (ref)	58	135	1.00	---	---
detected	0	3	---	---	
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	57	137	1.00	---	---
> 1 ppb	1	1	2.4	0.03 - 190.0	NS
not detected (ref)	57	137	1.00	---	---
detected	1	1	2.4	0.03 - 190.0	NS
BENZENE:					
not detected (ref)	56	136	1.00	---	---
detected	2	2	2.43	0.17 - 34.1	NS
NITRATES:					
n.d. - 2 ppm (ref)	52	119	1.00	---	---
> 2 ppm	6	19	0.72	0.22 - 2.0	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	16	51	1.00	---	---
> 20 ppb - 40 ppb	9	14	2.05	0.65 - 6.2	NS
> 40 ppb - 60 ppb	16	36	1.42	0.58 - 3.5	NS
> 60 ppb - 80 ppb	11	23	1.52	0.55 - 4.1	NS
> 80 ppb	6	14	1.37	0.37 - 4.6	NS
n.d.- 15 ppb (ref)	13	51	1.00	---	---
> 15 ppb - 50 ppb	24	31	3.04	1.26 - 7.5	< .01
> 50 ppb - 75 ppb	12	35	1.35	0.50 - 3.6	NS
> 75 ppb	9	21	1.68	0.54 - 5.0	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	11	47	1.00	---	---
surface water	40	77	2.22	0.99 - 5.3	< .045
mixture of sources	7	14	2.14	0.58 - 7.4	NS

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 13

Adjusted Odds Ratios New Jersey Dept. of Health 1985-1988
OUTCOME: Major Cardiac Defects

CASES = 58 CONTROLS = 137

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL A-280 VOLATILES:				
> 1 ppb - 5 ppb	0.80	0.32 - 2.0	NS	0.90
> 5 ppb	0.54	0.14 - 2.1	NS	0.69
TRICHLOROETHYLENE:				
> 1 ppb - 5 ppb	1.13	0.23 - 5.7	NS	1.14
> 5 ppb - 10 ppb	0.31	0.03 - 2.9	NS	0.38
> 10 ppb	0.43	0.04 - 4.7	NS	0.57
> 5 ppb	0.36	0.07 - 1.9	NS	0.46
TETRACHLOROETHYLENE:				
> 1 ppb - 5 ppb	0.59	0.11 - 3.1	NS	0.57
> 5 ppb	0.75	0.11 - 5.1	NS	1.14
The DICHLOROETHYLENES:				
> 2 ppb	0.47	0.03 - 6.6	NS	0.78
> 1 ppb	0.60	0.12 - 3.0	NS	0.88
1,1,1-TRICHLOROETHANE:				
> 1 ppb	0.44	0.14 - 1.4	NS	0.55
1,2-DICHLOROETHANE:				
> 1 ppb	2.62	0.15 - 44.6	NS	2.39
detected	2.62	0.15 - 44.6	NS	2.39
BENZENE:				
detected	1.21	0.13 - 11.4	NS	2.41
NITRATES:				
> 2 ppm	0.59	0.19 - 1.8	NS	0.72

TABLE 13 (continued)

OUTCOME: Major Cardiac Defects

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL TRIHALOMETHANES:				
> 20 ppb - 40 ppb	1.63	0.52 - 5.1	NS	2.01
> 40 ppb - 60 ppb	1.48	0.58 - 3.7	NS	1.39
> 60 ppb - 80 ppb	1.79	0.67 - 4.8	NS	1.49
> 80 ppb	1.27	0.37 - 4.3	NS	1.34
> 15 - 50 ppb	2.80	1.13 - 7.0	< .03	2.98
> 50 - 75 ppb	1.63	0.61 - 4.4	NS	1.32
> 75 ppb	1.64	0.55 - 4.9	NS	1.65
> 15 ppb	2.06	0.94 - 4.5	< .075	1.99
WATER SOURCE:				
surface water	2.22	0.95 - 5.2	< .07	2.17
mixture of sources	2.86	0.82 - 9.9	< .10	2.09

* The unadjusted odds ratio after removal of cases and controls with missing data on any of the factors included in the model.

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 14

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Ventricular Septal Defects (VSD)

CASES = 43 CONTROLS = 138

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	26	99	1.00	---	---
> 1 ppb - 5 ppb	9	26	1.32	0.48 - 3.4	NS
> 5 ppb - 10 ppb	4	5	3.05	0.56 - 15.1	NS
> 10 ppb	4	8	1.90	0.39 - 7.8	NS
> 5 ppb	8	13	2.34	0.75 - 6.8	< .09
Test for trend, < .065, 1-sided					
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	35	122	1.00	---	---
> 1 ppb - 5 ppb	3	6	1.74	0.27 - 8.6	NS
> 5 ppb - 10 ppb	4	6	2.32	0.45 - 10.4	NS
> 10 ppb	1	4	0.87	0.02 - 9.2	NS
> 5 ppb	5	10	1.74	0.44 - 6.0	NS
> 1 ppb	8	16	1.74	0.59 4.7	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	37	122	1.00	---	---
> 1 ppb - 5 ppb	5	12	1.37	0.35 - 4.5	NS
> 5 ppb - 10 ppb	1	3	1.10	0.02 - 14.1	NS
> 10 ppb	0	1	---	---	
> 5 ppb	1	4	0.83	0.02 - 8.7	NS
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	43	135	1.00	---	---
> 2 ppb	0	3	---		
n.d. - 1 ppb (ref)	41	130	1.00	---	---
> 1 ppb	2	8	0.79	0.08 - 4.2	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	38	132	1.00	---	---
> 2 ppb	5	6	2.90	0.66 - 12.0	< .095
Exact test for trend, p < .09, 1-sided					
n.d. - 1 ppb (ref)	33	117	1.00	---	---
> 1 ppb	10	21	1.69	0.64 - 4.2	NS

TABLE 14 (continued)
OUTCOME: VSD

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	42	137	1.00	---	---
> 1 ppb	1	1	3.26	0.04 - 258	NS
not detected (ref)	40	135	1.00	---	---
detected	3	3	3.38	0.43 - 26.0	NS
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	41	137	1.00	---	---
> 1 ppb	2	1	6.68	0.34 - 397	
not detected (ref)	41	137	1.00	---	---
detected	2	1	6.68	0.34 - 397	
BENZENE:					
not detected (ref)	43	136	1.00	---	---
detected	0	2	---		
NITRATES:					
n.d. - 2 ppm (ref)	37	119	1.00	---	---
> 2 ppm	6	19	1.02	0.31 - 2.9	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	18	51	1.00	---	---
> 20 ppb - 40 ppb	4	14	0.81	0.17 - 3.1	NS
> 40 ppb - 60 ppb	11	36	0.87	0.33 - 2.2	NS
> 60 ppb - 80 ppb	7	23	0.86	0.27 - 2.6	NS
> 80 ppb	3	14	0.61	0.10 - 2.6	NS
n.d.- 15 ppb (ref)	18	51	1.00	---	---
> 15 ppb - 50 ppb	12	31	1.10	0.42 - 2.8	NS
> 50 ppb - 75 ppb	9	35	0.73	0.26 - 2.0	NS
> 75 ppb	4	21	0.54	0.12 - 1.9	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	16	47	1.00	---	
surface water	20	77	0.76	0.34 - 1.8	NS
mixture of sources	7	14	1.47	0.42 - 4.8	NS

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 15

Adjusted Odds Ratios New Jersey Dept. of Health 1985-1988
OUTCOME: Ventricular Septal Defects (VSD)

CASES = 42 CONTROLS = 136

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL A-280 VOLATILES:				
> 1 ppb - 5 ppb	1.59	0.50 - 5.0	NS	1.34
> 5 ppb - 10	5.25	1.01 - 27.2	< .05	3.10
> 10 ppb	1.95	0.44 - 8.7	NS	1.94
> 5 ppb	3.00	0.94 - 9.6	< .065	2.39
TRICHLOROETHYLENE:				
> 1 ppb - 5 ppb	2.24	0.42 - 11.8	NS	1.76
> 5 ppb - 10 ppb	1.89	0.40 - 9.0	NS	2.35
> 10 ppb	0.68	0.05 - 9.1	NS	0.88
> 5 ppb	1.41	0.38 - 5.3	NS	1.76
> 1 ppb	1.69	0.58 - 4.9	NS	1.76
TETRACHLOROETHYLENE:				
> 1 ppb - 5 ppb	1.70	0.47 - 6.2	NS	1.39
> 5 ppb	0.44	0.03 - 6.8	NS	0.83
The DICHLOROETHYLENES:				
> 1 ppb	0.97	0.16 - 5.9	NS	0.80
1,1,1-TRICHLOROETHANE:				
> 2 ppb	3.91	0.91 - 16.8	< .07	2.93
> 1 ppb	2.31	0.83 - 6.5	NS	1.17
CARBON TETRACHLORIDE:				
> 1 ppb	4.19	0.07 - 264	NS	3.29
detected	9.19	1.18 - 71.8	< .035	3.41
1,2-DICHLOROETHANE:				
> 1 ppb	7.49	0.38 - 146	NS	6.75
detected	7.49	0.38 - 146	NS	6.75
NITRATES:				
> 2 ppm	0.83	0.25 - 2.7	NS	1.03

TABLE 15 (continued)

OUTCOME: VSD

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL TRIHALOMETHANES:				
> 20 ppb - 40 ppb	0.87	0.22 - 3.5	NS	0.92
> 40 ppb - 60 ppb	0.90	0.30 - 2.7	NS	0.94
> 60 ppb - 80 ppb	0.84	0.25 - 2.9	NS	0.91
> 80 ppb	0.36	0.07 - 1.8	NS	0.64
> 15 - 50 ppb	1.19	0.42 - 3.4	NS	1.20
> 50 - 75 ppb	0.68	0.22 - 2.1	NS	0.79
> 75 ppb	0.39	0.09 - 1.6	NS	0.57
WATER SOURCE:				
surface water	0.66	0.26 - 1.7	NS	0.84
mixture of sources	2.01	0.57 - 7.1	NS	1.57

* The unadjusted odds ratio after removal of cases and controls with missing data on any of the factors included in the model.

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 16

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Very Low Birthweight (VLBW)

CASES = 97 CONTROLS = 140

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	64	96	1.00	---	---
> 1 ppb - 5 ppb	18	32	0.84	0.41-1.7	NS
> 5 ppb - 10 ppb	5	4	1.88	0.39-9.8	NS
> 10 ppb	10	8	1.88	0.63-5.8	NS
> 5 ppb	15	12	1.88	0.76-4.7	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	80	123	1.00	---	---
> 1 ppb - 5 ppb	10	9	1.71	0.59-5.0	NS
> 5 ppb - 10 ppb	6	6	1.54	0.40-6.0	NS
> 10 ppb	1	2	0.77	0.01-15	NS
> 5 ppb	7	8	1.35	0.40-4.4	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	78	120	1.00	---	---
> 1 ppb - 5 ppb	14	15	1.44	0.60-3.4	NS
> 5 ppb - 10 ppb	1	5	0.31	0.01-2.8	NS
> 10 ppb	4	0	infinite	(0.98-infinite)	p < .055*
> 5 ppb	5	5	1.54	0.34-6.9	NS
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	95	136	1.00	---	---
> 2 ppb	2	4	0.72	0.06-6.9	NS
n.d. - 1 ppb (ref)	89	132	1.00	---	---
> 1 ppb	8	8	1.48	0.47-4.7	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	93	130	1.00	---	---
> 2 ppb	4	10	0.56	0.12-2.0	NS
n.d. - 1 ppb (ref)	88	117	1.00	---	---
> 1 ppb	9	23	0.52	0.20-1.2	NS

* Exact, 2-sided p value

TABLE 16 (continued)
OUTCOME: VLBW

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	95	139	1.00	---	---
> 1 ppb	2	1	2.93	0.15-174	NS
not detected (ref)	95	136	1.00	---	---
detected	2	4	0.72	0.06-5.1	NS
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	97	139	1.00	---	---
> 1 ppb	0	1	---		
not detected (ref)	96	138	1.00	---	---
detected	1	2	0.72	0.01-14	NS
BENZENE:					
not detected (ref)	97	138	1.00	---	---
detected	0	2	---		
NITRATES:					
n.d. - 2 ppm (ref)	89	121	1.00	---	---
> 2 ppm	8	19	0.57	0.21-1.5	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	39	51	1.00	---	---
> 20 ppb - 40 ppb	10	12	1.09	0.38-3.1	NS
> 40 ppb - 60 ppb	25	35	0.93	0.46-1.9	NS
> 60 ppb - 80 ppb	16	36	0.58	0.26-1.3	NS
> 80 ppb	7	6	1.53	0.40-6.0	NS
n.d.- 15 ppb (ref)	38	51	1.00	---	---
> 15 ppb - 50 ppb	22	33	0.89	0.43-1.9	NS
> 50 ppb - 75 ppb	25	41	0.82	0.40-1.7	NS
> 75 ppb	12	15	1.07	0.41-2.8	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	32	49	1.00	---	---
surface water	50	74	1.03	0.56-1.9	NS
mixture of sources	15	17	1.35	0.54-3.3	NS

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 17

Adjusted Odds Ratios New Jersey Dept. of Health 1985-1988
OUTCOME: Very Low Birthweight (VLBW)

CASES = 97 CONTROLS = 140

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL A-280 VOLATILES:				
> 1 ppb - 5 ppb	0.80	0.37 - 1.8	NS	0.84
> 5 ppb - 10	3.65	0.86 - 15.4	< .08	1.88
> 10 ppb	2.53	0.85 - 7.5	< .095	1.88
> 5 ppb	2.87	1.14 - 7.2	< .03	1.88
TRICHLOROETHYLENE:				
> 1 ppb - 5 ppb	2.80	0.99 - 7.9	< .055	1.71
> 5 ppb - 10 ppb	2.46	0.71 - 8.5	NS	1.54
> 10 ppb	1.46	0.12 - 18.4	NS	0.77
> 5 ppb	2.23	0.72 - 6.9	NS	1.35
> 1 ppb	2.53	1.13 - 5.7	< .025	1.54
TETRACHLOROETHYLENE:				
> 1 ppb - 5 ppb	1.55	0.66 - 3.7	NS	1.44
> 5 ppb	1.87	0.45 - 7.7	NS	1.54
> 1 ppb	1.63	0.75 - 3.5	NS	1.46
The DICHLOROETHYLENES:				
> 2 ppb	1.32	0.22 - 7.9	NS	0.72
> 1 ppb	2.41	0.78 - 7.4	NS	1.48
1,1,1-TRICHLOROETHANE:				
> 2 ppb	0.82	0.24 - 2.8	NS	0.56
> 1 ppb	0.57	0.22 - 1.5	NS	0.52
CARBON TETRACHLORIDE:				
> 1 ppb	3.57	0.27 - 48.0	NS	2.93
detected	0.86	0.14 - 5.3	NS	0.72
1,2-DICHLOROETHANE:				
> 1 ppb				
detected	0.87	0.07 - 10.8	NS	0.72
NITRATES:				
> 2 ppm	0.66	0.25 - 1.7	NS	0.57

TABLE 17 (continued)

OUTCOME: VLBW

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL TRIHALOMETHANES:				
> 20 ppb - 40 ppb	1.36	0.46 - 4.0	NS	1.09
> 40 ppb - 60 ppb	0.83	0.40 - 1.7	NS	0.93
> 60 ppb - 80 ppb	0.54	0.24 - 1.2	NS	0.58
> 80 ppb	0.95	0.25 - 3.6	NS	1.53
> 15 - 50 ppb	0.90	0.42 - 2.0	NS	
> 50 - 75 ppb	0.73	0.35 - 1.5	NS	
> 75 ppb	0.99	0.37 - 2.6	NS	
WATER SOURCE:				
surface water	0.93	0.49 - 1.8	NS	1.03
mixture of sources	1.45	0.58 - 3.6	NS	1.35

---

* The unadjusted odds ratio after removal of cases and controls with missing data on any of the factors included in the model.

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 18

Unadjusted (Bivariate) Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Intermediate Low Birthweight

CASES = 114 CONTROLS = 140

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
A-280 TOTAL VOLATILE ORGANICS:					
n.d. - 1 ppb (ref)	87	96	1.00	---	---
> 1 ppb - 5 ppb	15	32	0.52	0.24 - 1.06	< .06
> 5 ppb - 10 ppb	8	4	2.21	0.56 - 10.3	NS
> 10 ppb	4	8	0.55	0.12 - 2.2	NS
> 5 ppb	12	12	1.10	0.43 - 2.8	NS
TRICHLOROETHYLENE:					
n.d. - 1 ppb (ref)	105	123	1.00	---	---
> 1 ppb - 5 ppb	3	9	0.39	0.07 - 1.6	NS
> 5 ppb - 10 ppb	4	6	0.78	0.16 - 3.4	NS
> 10 ppb	2	2	1.17	0.08 - 16.4	NS
> 5 ppb	6	8	0.88	0.24 - 3.0	NS
TETRACHLOROETHYLENE:					
n.d. - 1 ppb (ref)	102	120	1.00	---	---
> 1 ppb - 5 ppb	8	15	0.63	0.22 - 1.7	NS
> 5 ppb - 10 ppb	4	5	0.94	0.18 - 4.5	NS
> 10 ppb	0	0	---	---	
> 5 ppb	4	5	0.94	0.18 - 4.5	NS
DICHLOROETHYLENES:					
n.d. - 2 ppb (ref)	113	136	1.00	---	---
> 2 ppb	1	4	0.30	0.01 - 3.1	NS
n.d. - 1 ppb (ref)	111	132	1.00	---	---
> 1 ppb	3	8	0.45	0.07 - 1.9	NS
1,1,1-TRICHLOROETHANE:					
n.d. - 2 ppb (ref)	108	130	1.00	---	---
> 2 ppb	6	10	0.72	0.21 - 2.3	NS
n.d. - 1 ppb (ref)	99	117	1.00	---	---
> 1 ppb	15	23	0.77	0.35 - 1.6	NS

TABLE 18 (continued)
OUTCOME: Intermediate Low Birthweight

CONTAMINANT LEVELS	# CASES	# CONTROLS	ODDS RATIO	EXACT 95% CONFIDENCE INTERVAL	2-TAIL P-VALUE
CARBON TETRACHLORIDE:					
n.d. - 1 ppb (ref)	114	139	1.00	---	---
> 1 ppb	0	1			
not detected (ref)	114	136	1.00	---	---
detected	0	4			
1,2-DICHLOROETHANE:					
n.d. - 1 ppb (ref)	112	139	1.00	---	---
> 1 ppb	2	1	2.48	0.13 - 147	NS
not detected (ref)	112	138	1.00	---	---
detected	2	2	1.23	0.09 - 17.2	NS
BENZENE:					
not detected (ref)	114	138	1.00	---	---
detected	0	2			
NITRATES:					
n.d. - 2 ppm (ref)	104	121	1.00	---	---
> 2 ppm	10	19	0.61	0.24 - 1.5	NS
TOTAL TRIHALOMETHANES:					
n.d.- 20 ppb (ref)	37	51	1.00	---	---
> 20 ppb - 40 ppb	12	12	1.38	0.50 - 3.8	NS
> 40 ppb - 60 ppb	36	35	1.42	0.72 - 2.8	NS
> 60 ppb - 80 ppb	19	36	0.73	0.34 - 1.5	NS
> 80 ppb	10	6	2.30	0.68 - 8.4	NS
n.d.- 15 ppb (ref)	35	51	1.00	---	---
> 15 ppb - 50 ppb	36	33	1.59	0.80 - 3.2	NS
> 50 ppb - 75 ppb	28	41	1.00	0.50 - 2.0	NS
> 75 ppb	15	15	1.46	0.58 - 3.7	NS
SOURCE OF WATER SUPPLY:					
ground water (ref)	29	49	1.00	---	
surface water	71	74	1.62	0.89 - 3.0	< .095
mixture of sources	14	17	1.39	0.55 - 3.5	NS

n.d. - not detected
ref. - reference
NS - Not Significant

TABLE 19

Adjusted Odds Ratios New Jersey Dept. of Health 1985-1988
OUTCOME: Intermediate Low Birthweight

CASES = 113 CONTROLS = 140

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL A-280 VOLATILES:				
> 1 ppb - 5 ppb	0.47	0.22 - 1.01	< .055	0.52
> 5 ppb - 10	2.12	0.53 - 8.5	NS	2.23
> 10 ppb	0.51	0.13 - 2.0	NS	0.56
> 5 ppb	1.01	0.39 - 2.6	NS	1.12
TRICHLOROETHYLENE:				
> 1 ppb - 5 ppb	0.63	0.15 - 2.7	NS	0.39
> 5 ppb - 10 ppb	0.74	0.18 - 3.0	NS	0.79
> 10 ppb	1.43	0.14 - 15.0	NS	1.18
> 5 ppb	0.88	0.26 - 2.9	NS	0.89
TETRACHLOROETHYLENE:				
> 1 ppb - 5 ppb	0.77	0.29 - 2.1	NS	0.63
> 5 ppb	0.75	0.16 - 3.5	NS	0.95
The DICHLOROETHYLENES:				
> 2 ppb	0.49	0.05 - 5.4	NS	0.30
> 1 ppb	0.44	0.10 - 2.0	NS	0.45
1,1,1-TRICHLOROETHANE:				
> 2 ppb	0.69	0.22 - 2.1	NS	0.73
> 1 ppb	0.68	0.3 - 1.5	NS	0.78
1,2-DICHLOROETHANE:				
> 1 ppb	1.98	0.12 - 31.5	NS	2.50
detected	0.83	0.09 - 7.6	NS	1.24
NITRATES:				
> 2 ppm	0.77	0.31 - 1.9	NS	0.62

TABLE 19 (continued)

OUTCOME: Intermediate Low Birthweight

AVERAGE CONTAMINANT LEVELS DURING PREGNANCY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	2-TAIL P-VALUE	"CRUDE" ODDS RATIO*
TOTAL TRIHALOMETHANES:				
> 20 ppb - 40 ppb	1.56	0.54 - 4.5	NS	1.38
> 40 ppb - 60 ppb	1.32	0.66 - 2.6	NS	1.42
> 60 ppb - 80 ppb	0.56	0.25 - 1.2	NS	0.73
> 80 ppb	1.79	0.52 - 6.1	NS	2.07
> 15 - 50 ppb	1.55	0.76 - 3.1	NS	1.59
> 50 - 75 ppb	0.82	0.40 - 1.7	NS	1.00
> 75 ppb	1.22	0.47 - 3.1	NS	1.36
WATER SOURCE:				
surface water	1.40	0.75 - 2.6	NS	1.60
mixture of sources	1.46	0.56 - 3.8	NS	1.39

* The unadjusted odds ratio after removal of cases and controls with missing data on any of the factors included in the model.

NS - Not Significant

TABLE 20

WATER CONSUMPTION HABITS
New Jersey Dept. of Health 1985-1988)
ODDS RATIONS AND EXACT 95% CONFIDENCE INTERVALS

WATER USAGE	NEURAL TUBE DEFECT	ORAL CLEFT DEFECT	MAJOR CARDIAC DEFECT	VENTRI-CULAR SEPTAL DEFECT	VERY LOW BIRTH-WEIGHT	INTER-MEDIATE LOW BIRTH-WEIGHT
Tap Water **	1.00	1.00	1.00	1.00	1.00	1.00
Bottled Water Only	0.48 0.17-1.3	0.74 0.33-1.6	0.86 0.39-1.8	0.67 0.27-1.6	0.60 0.37-6.6	0.86 0.74-9.8
Tap Water Filter	0.51 0.01-4.5	0.42 0.01-3.7	3.32 0.93-12.5 ($p < .10$)	1.54 0.37-6.6	2.52 0.74-9.8	1.46 0.22-7.4
Minutes In Shower: (< 7 min)**	1.00	1.00	1.00	1.00	1.00	1.00
7 - 12 Minutes	0.75 0.27-2.2	0.60 0.23-1.6	0.72 0.29-1.8	0.46 0.17-1.2	0.66 0.31-1.4	0.72 0.34-1.5
13 - 17 Minutes	0.88 0.24-3.1	0.94 0.30-2.9	1.29 0.47-3.6	0.70 0.21-2.2	1.14 0.47-2.7	1.13 0.48-2.7
≥ 18 Minutes	0.66 0.15-2.6	0.98 0.31-3.0	0.73 0.22-2.3	0.73 0.22-2.3	1.12 0.45-2.8	1.37 0.58-3.3
Glasses/Day Drank of Cold Tap Water:						
0 **	1.00	1.00	1.00	1.00	1.00	1.00
1 - 5	2.79 1.04-8.4 ($p < .05$)	0.95 0.41-2.2	1.89 0.91-4.0 ($p < .10$)	1.78 0.74-4.5	2.23 1.15-4.4 ($p < .05$)	1.64 0.91-3.0
≥ 6	1.93 0.55-7.0	1.40 0.55-3.5	0.50 0.13-1.6	1.54 0.52-4.5	1.60 0.71-3.6	0.61 0.26-1.4

* Also includes those who drank both tap and bottled water.
** Reference Group

TABLE 21

Unadjusted Odds Ratios, New Jersey Dept. of Health 1985-1988
OUTCOME: <u>Neural Tube Defects (NTDs)</u>

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
TVOC:						
> 1 - 5 ppb	0.65	0.01 - 7.0	1.79	0.57 - 5.4	1.82	0.58 - 5.4
> 5 - 10 ppb	1.89	0.03 -30	1.79	0.03 -36.3	1.93	0.03 -39.0
> 10 - ppb	0		1.44	0.13 - 9.7	2.31	0.33 -13.2
> 5 ppb	0.97	0.02 -11.4	1.54	0.23 - 7.6	2.20	0.43 - 9.8
TCE:						
> 1 - 5 ppb	2.98	0.04 -66.2	0		0.79	0.02 - 8.4
> 5 - 10 ppb	0		0		0	
> 10 - ppb	0		1.94	0.15 -17.9	2.08	0.17 -19.2
> 5 ppb	0		1.17	0.11 - 7.7	1.26	0.11 - 8.2
PCE:						
> 1 - 5 ppb	0		1.66	0.25 - 8.5	1.78	0.27 - 9.1
> 5 - 10 ppb	2.90	0.04 -64.5	6.52	0.33 -398.0	7.00	0.35 -428.0
> 10 - ppb	inf		0		3.53	0.04 -285.0
> 5 ppb	2.90	0.04 -64.5	3.29	0.23 -47.6	5.27	0.57 -66.5
DCE:						
> 2 ppb	6.71	0.08 -575.0	1.53	0.03 -30.4	1.58	0.03 -31.4
> 1 ppb	2.23	0.04 -33.8	1.23	0.11 - 8.0	1.97	0.29 -10.9
TCA:						
> 2 ppb	0		0.75	0.01 - 8.0	0.78	0.02 - 8.3
> 1 ppb	0		1.37	0.39 - 4.4	1.31	0.38 - 4.1
CTC:						
> 1 ppb	inf		3.07	0.04 -247.0	3.17	0.04 -254.0
detected	0		1.53	0.03 -30.4	1.58	0.03 -31.4
NITRATES:						
> 2 ppm	0.88	0.02 - 9.3	2.00	0.59 - 6.3	2.07	0.62 - 6.5

TABLE 21 (continued)

OUTCOME: NTDs

CONTAMINANT LEVELS	BOTTLED WATER		TAP WATER*		TAP + FILTERED*	
	OR	95% CI	OR	95% CI	OR	95% CI
SOURCE:						
SURFACE H_2O	inf**		6.10	1.32 -57.8	5.92	1.28 -55.9
MIXED H_2O	inf**		19.47	3.14 -223	17.61	3.0 -193
TTHM:						
> 20 - 40 ppb	6.85	0.45 -419.0	1.91	0.15 -15.1	2.64	0.34 -17.2
> 40 - 60 ppb	1.63	0.02 -139.0	2.68	0.73 -11.3	2.63	0.72 -11.0
> 60 - 80 ppb	1.63	0.02 -139.0	2.86	0.61 -14.0	3.02	0.65 -14.8
> 80 ppb	2.83	0.03 -251.0	4.91	0.98 -26.5	4.64	0.95 -24.3
TTHM:						
> 15 - 50 ppb	4.77	0.40 -262.0	4.87	1.19 -24.5	5.08	1.29 -24.9
> 50 - 75 ppb	1.48	0.02 -125.0	2.79	0.66 -14.2	2.84	0.67 -14.3
> 75 ppb	2.07	0.02 -179.0	4.44	0.95 -24.4	4.37	0.94 -23.8

* includes those who also drank bottled water.
** no cases in reference group
CI Confidence Interval
inf Infinity

TABLE 22

Unadjusted Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Oral Clefts

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
TVOC:						
> 1 - 5 ppb	0.65	0.06 - 4.0	1.02	0.29 - 3.2	1.20	0.37 - 3.5
> 5 - 10 ppb	0		2.67	0.18 -38.8	2.88	0.20 -41.7
> 10 - ppb	0.97	0.02 -13.8	1.62	0.23 - 9.1	1.74	0.25 - 9.7
> 5 ppb	0.49	0.01 - 4.9	1.92	0.44 - 7.8	2.07	0.47 - 8.4
TCE:						
> 1 - 5 ppb	0		1.31	0.11 - 9.7	1.37	0.12 -10.1
> 5 - 10 ppb	0		3.89	0.42 -48.8	4.06	0.44 -50.7
> 10 - ppb	3.0	0.04 -248	0		0	
> 5 ppb	0.62	0.01 - 6.4	1.57	0.23 - 8.7	1.64	0.24 - 9.0
PCE:						
> 1 - 5 ppb	1.09		1.29	0.20 - 6.5	1.84	0.36 - 8.4
> 5 ppb	0		1.29	0.02 -25.6	1.38	0.02 -27.4
DCE:						
> 2 ppb	3.48	0.04 -288	2.58	0.18 -37.0	2.68	0.19 -38.4
> 1 ppb	1.14	0.02 -15.7	1.01	0.09 - 6.5	1.05	0.10 - 6.8
TCA:						
> 2 ppb	0		1.96	0.27 -12.3	2.03	0.28 -12.7
> 1 ppb	0.53	0.01- 5.1	0.88	0.23 - 2.9	0.85	0.22 - 2.7
CTC:						
> 1 ppb			0		0	
detected	3.48	0.04 -288	3.98	0.43 -49.7	4.13	0.45 -51.5
NITRATES:						
> 2 ppm	0.96	0.09 - 6.1	0.39	0.04 - 1.9	0.40	0.04 - 2.0
SOURCE:						
SURFACE H_2O	1.0	0.22 - 5.4	1.90	0.74 - 5.2	1.66	0.67 - 4.4
MIXED H_2O	0.66	0.01 - 9.3	0.53	0.01 - 5.1	0.38	0.01 - 3.4

TABLE 22 (continued)

OUTCOME: Oral Clefts

CONTAMINANT LEVELS	BOTTLED WATER		TAP WATER*		TAP + FILTERED*	
	OR	95% CI	OR	95% CI	OR	95% CI
TTHM:						
> 20 - 40 ppb	0.64	0.01 - 8.5	2.60	0.59 -11.4	2.22	0.52 - 9.1
> 40 - 60 ppb	0.84	0.06 - 7.3	0.87	0.25 - 2.9	0.78	0.23 - 2.5
> 60 - 80 ppb	1.24	0.15 - 9.3	1.53	0.41 - 5.5	1.49	0.41 - 5.2
> 80 ppb	2.10	0.24 -18.8	1.53	0.28 - 7.2	1.33	0.25 - 5.9
TTHM:						
> 15 - 50 ppb	0.63	0.05 - 5.3	1.80	0.56 - 5.8	1.57	0.51 - 4.8
> 50 - 75 ppb	1.12	0.13 - 8.3	1.03	0.31 - 3.3	0.96	0.29 - 3.0
> 75 ppb	2.09	0.29 -15.1	1.42	0.35 - 5.3	1.28	0.33 - 4.6

* includes those who also drank bottled water.
CI Confidence Interval

TABLE 23

Unadjusted Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Major Cardiac Defects

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
TVOC:						
> 1 - 5 ppb	0.27	0.01 - 2.4	1.52	0.52 - 4.2	1.16	0.41 - 3.1
> 5 ppb	0.81	0.07 - 5.4	0.78	0.07 - 4.5	0.63	0.06 - 3.6
TCE:						
> 1 - 5 ppb	1.41	0.02 -29.3	1.23	0.11 - 9.1	1.06	0.09 - 7.8
> 5 - 10 ppb	0		1.23	0.02 -24.5	1.06	0.02 -21.0
> 10 - ppb	2.78	0.03 -229	0		0	
> 5 ppb	0.57	0.01 - 5.9	0.50	0.01 - 4.7	0.43	0.01 - 4.0
PCE:						
> 1 - 5 ppb	1.0	0.09 - 6.7	0.41	0.01 - 3.6	0.35	0.01 - 3.1
> 5 - 10 ppb	1.49	0.02 -31.0	2.40	0.03 -193	2.08	0.03 -167.0
> 10 - ppb**						
> 5 ppb	1.49	0.02 -31.0	1.21	0.02 -24.0	1.05	0.02 -20.7
DCE:						
> 2 ppb	0		1.26	0.02 -25.0	1.09	0.02 -21.6
> 1 ppb	0.98	0.02 -13.4	1.01	0.09 - 6.5	0.87	0.08 - 5.6
TCA:						
> 2 ppb						
> 1 ppb	0.46	0.01 - 4.3	0.68	0.15 - 2.4	0.54	0.12 - 1.9
EDC:						
detected	3.0	0.04 -247.0	0		0	
NITRATES:						
> 2 ppm	1.31	0.19 - 7.0	0.60	0.10 - 2.4	0.51	0.09 - 2.1
SOURCE:						
SURFACE H_2O	2.46	0.43 -26.4	1.75	0.67 - 4.9	2.21	0.88 - 6.0
MIXED H_2O	3.65	0.32 -56.5	1.56	0.22 - 8.8	1.66	0.30 - 7.9

TABLE 23 (continued)

OUTCOME: Major Cardiac Defects

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
TTHM:						
> 20 - 40 ppb	0		2.78	0.68 - 11.6	3.30	0.91 - 12.5
> 40 - 60 ppb	1.64	0.24 - 11.3	0.91	0.28 - 2.9	1.33	0.47 - 3.8
> 60 - 80 ppb	1.64	0.24 - 11.3	1.21	0.31 - 4.4	1.49	0.41 - 5.2
> 80 ppb	2.18	0.24 - 18.9	0.71	0.06 - 4.3	1.0	0.15 - 5.0
TTHM:						
> 15 - 50 ppb	2.04	0.32 - 15.9	3.15	1.08 - 9.6	3.54	1.27 - 10.4
> 50 - 75 ppb	1.48	0.16 - 13.4	0.71	0.17 - 2.7	1.29	0.40 - 4.1
> 75 ppb	2.75	0.36 - 24.3	1.05	0.20 - 4.5	1.28	0.29 - 5.1

* includes those who also drank bottled water.
** no cases and no controls
CI Confidence Interval

TABLE 24

Unadjusted Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Ventricular Septal Defects (VSD)

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
TVOC:						
> 1 - 5 ppb	0.47	0.01 - 4.5	1.90	0.60 - 5.7	1.72	0.56 - 5.0
> 5 - 10 ppb	1.37	0.02 - 20.4	3.75	0.25 - 55.2	5.40	0.58 - 69.0
> 10 - ppb	1.37	0.02 - 20.4	2.27	0.32 - 13.1	2.19	0.31 - 12.5
> 5 ppb	1.37	0.11 - 10.2	2.70	0.60 - 11.4	3.12	0.77 - 12.3
TCE:						
> 1 - 5 ppb	0		1.57	0.13 - 11.7	2.34	0.32 - 14.8
> 5 - 10 ppb	1.15	0.02 - 14.0	4.66	0.50 - 58.7	4.64	0.50 - 58.3
> 10 - ppb	4.42	0.05 -373.0	0		0	
> 5 ppb	1.83	0.15 - 14.0	1.88	0.27 - 10.5	1.88	0.27 - 10.4
PCE:						
> 1 - 5 ppb	1.49	0.12 - 10.6	0.99	0.09 - 6.0	1.48	0.22 - 7.5
> 5 - 10 ppb						
> 10 - ppb						
> 5 ppb	0		1.48	0.02 - 29.4	1.48	0.02 - 29.4
DCE:						
> 2 ppb						
> 1 ppb	0		1.18	0.11 - 7.7	1.15	0.10 - 7.5
TCA:						
> 2 ppb	0		4.14	0.82 - 22.5	3.96	0.79 - 21.4
> 1 ppb	0		2.25	0.75 - 6.5	2.27	0.80 - 6.3
CTC:						
> 1 ppb			0		0	
detected	4.58	0.05 -383	1.48	0.02 - 29.4	2.94	0.20 - 42.1
EDC:						
detected	4.58	0.05 -383				

TABLE 24 (continued)

OUTCOME: VSD

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
NITRATES:						
> 2 ppm	0.59	0.01 - 5.7	1.26	0.32 - 4.4	1.22	0.31 - 4.1
SOURCE:						
SURFACE H_2O	2.94	0.30 -148	0.55	0.21 - 1.5	0.62	0.24 - 1.6
MIXED H_2O	7.01	0.45 -440	0.94	0.14 - 4.9	1.01	0.20 - 4.4
TTHM:						
> 20 - 40 ppb	1.63	0.11 - 18.5	0.33	0.01 - 3.0	0.60	0.06 - 3.6
> 40 - 60 ppb	1.69	0.18 - 15.1	0.55	0.15 - 1.8	0.71	0.71 - 2.1
> 60 - 80 ppb	1.11	0.08 - 11.7	0.81	0.19 - 3.0	0.86	0.86 - 3.1
> 80 ppb	0		0.85	0.13 - 4.2	0.80	0.80 - 3.8
TTHM:						
> 15 - 50 ppb	2.04	0.32 - 15.9	0.67	0.16 - 2.4	0.89	0.89 - 2.8
> 50 - 75 ppb	1.00	0.07 - 10.5	0.57	0.16 - 1.8	0.68	0.68 - 2.1
> 75 ppb	0		0.70	0.14 - 2.8	0.69	0.69 - 2.7

* includes those who also drank bottled water.
CI Confidence Interval

TABLE 25

Unadjusted Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Very Low Birthweight

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
TVOC:						
> 1 - 5 ppb	0.59	0.09 - 2.8	0.86	0.36 - 2.0	0.92	0.40 - 2.1
> 5 - 10 ppb	0.44	0.01 - 5.0	inf	0.91 - inf	inf	0.89 - inf
> 10 - ppb	0.44	0.01 - 5.0	3.24	0.84 - 15.3	3.16	0.82 - 14.9
> 5 ppb	0.44	0.04 - 2.6	4.67	1.33 - 21.0	4.55	1.37 - 20.4
TCE:						
> 1 - 5 ppb	0.64	0.01 - 8.6	2.21	0.66 - 8.0	2.11	0.63 - 7.6
> 5 - 10 ppb	0		2.94	0.60 - 19.0	2.81	0.57 - 18.1
> 10 - ppb	0		1.48	0.02 -118.0	1.41	0.02 -112.5
> 5 ppb	0		2.58	0.62 - 12.6	2.46	0.60 - 12.0
PCE:						
> 1 - 5 ppb	0.28		2.17	0.76 - 6.6	2.29	0.82 - 6.8
> 5 - 10 ppb	0.65		0		0	
> 10 - ppb						
> 5 ppb	1.29	0.10 - 12.4	2.17	0.24 - 26.8	2.11	0.23 - 0.26
DCE:						
> 2 ppb	0		0.85	0.07 - 7.7	0.83	0.07 - 7.4
> 1 ppb	0.52	0.01 - 5.7	2.38	0.57 - 11.6	2.30	0.56 - 11.1
TCA:						
> 2 ppb	0		0.85	0.17 - 3.8	0.82	0.16 - 3.6
> 1 ppb	0		0.70	0.24 - 1.9	0.72	0.26 - 1.9
CTC:						
> 1 ppb			2.60	0.13 -156.0	2.53	0.13 -151.0
detected	0		0.85	0.07 - 7.7	0.83	0.07 - 7.4
NITRATES:						
> 2 ppm	0.91	0.14 - 4.6	0.50	0.13 - 1.6	0.49	0.13 - 1.6

TABLE 25 (continued)

OUTCOME: Very Low Birthweight

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
SOURCE:						
SURFACE H_2O	1.78	0.43 - 9.0	0.90	0.44 - 1.9	0.94	0.46 - 1.9
MIXED H_2O	3.56	0.53 - 26.8	1.0	0.32 - 3.1	1.01	0.34 - 3.0
TTHM:						
> 20 - 40 ppb	2.07	0.23 - 16.8	0.93	0.25 - 3.3	0.90	0.25 - 3.2
> 40 - 60 ppb	1.51	0.34 - 7.0	0.85	0.34 - 2.1	0.84	0.36 - 2.0
> 60 - 80 ppb	0.95	0.12 - 5.8	0.51	0.20 - 1.3	0.50	0.20 - 1.2
> 80 ppb	2.71	0.16 - 45.5	1.06	0.18 - 6.2	1.28	0.25 - 7.1
TTHM:						
> 15 - 50 ppb	2.71	0.62 - 13.3	0.66	0.26 - 1.7	0.61	0.24 - 1.5
> 50 - 75 ppb	1.04	0.17 - 6.0	0.81	0.35 - 1.9	0.77	0.34 - 1.7
> 75 ppb	2.46	0.27 - 21.0	0.68	0.20 - 2.2	0.84	0.27 - 2.6

* includes those who also drank bottled water.
CI Confidence Interval
inf Infinity

TABLE 26

Unadjusted Odds Ratios. New Jersey Dept. of Health 1985-1988
OUTCOME: Intermediate Low Birthweight

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
TVOC:						
> 1 - 5 ppb	1.04	0.28 - 3.7	0.42	0.15 - 1.1	0.36	0.13 - 0.91
> 5 - 10 ppb	0.67	0.06 - 5.2	inf	1.27 - inf	inf	1.16 - inf
> 10 - ppb	1.00	0.13 - 6.6	0.29	0.01 - 3.0	0.26	0.01 - 2.7
> 5 ppb	0.84	0.19 - 3.4	1.99	0.48 - 9.8	1.80	0.43 - 8.8
TCE:						
> 1 - 5 ppb	0.94	0.07 - 8.8	0.20	0 - 1.7	0.18	0 - 1.6
> 5 - 10 ppb	0.94	0.07 - 8.8	0.79	0.06 - 7.1	0.73	0.06 - 6.5
> 10 - ppb	2.77	0.14 -170.0	0		0	0.06 - 6.5
> 5 ppb	1.4	0.24 - 8.2	0.59	0.05 - 4.3	0.55	0.05 - 3.9
PCE:						
> 1 - 5 ppb	0.54	0.08 - 2.6	0.78	0.19 - 2.9	0.72	0.18 - 2.6
> 5 - 10 ppb						
> 10 - ppb						
> 5 ppb	0.84	0.07 - 7.8	1.25	0.09 - 17.7	1.15	0.08 - 16.2
DCE:						
> 2 ppb	1.37	0.02 -110.0	0		0	
> 1 ppb	0.66	0.06 - 5.0	0.31	0.01 - 3.2	0.29	0.01 - 3.0
TCA:						
> 2 ppb	0.32	0.01 - 3.5	1.06	0.24 - 4.4	0.98	0.23 - 4.0
> 1 ppb	1.24	0.34 - 4.5	0.69	0.24 - 1.9	0.59	0.20 - 1.6
EDC:						
> 1 ppb	2.80	0.14 -171.0		**		**
detected	1.38	0.10 - 20.0		**		**
NITRATES:						
> 2 ppm	0.55	0.08 - 2.7	0.60	0.18 - 1.9	0.66	0.21 - 1.9

TABLE 26 (continued)

OUTCOME: Intermediate Low Birthweight

CONTAMINANT LEVELS	BOTTLED WATER OR	BOTTLED WATER 95% CI	TAP WATER* OR	TAP WATER* 95% CI	TAP + FILTERED* OR	TAP + FILTERED* 95% CI
SOURCE:						
SURFACE H_2O	1.62	0.50 - 5.7	1.40	0.67 - 2.9	1.63	0.80 - 3.4
MIXED H_2O	2.90	0.56 - 16.5	0.82	0.22 - 2.9	0.90	0.26 - 3.0
TTHM:						
> 20 - 40 ppb	1.40	0.17 - 10.5	1.27	0.36 - 4.5	1.36	0.41 - 4.7
> 40 - 60 ppb	1.72	0.49 - 6.3	1.20	0.49 - 2.9	1.32	0.58 - 3.1
> 60 - 80 ppb	1.46	0.34 - 6.3	0.56	0.21 - 1.5	0.54	0.21 - 1.4
> 80 ppb	1.85	0.12 - 29.6	2.20	0.49 - 11.4	2.40	0.57 - 12.1
TTHM:						
> 15 - 50 ppb	2.46	0.68 - 9.5	1.13	0.46 - 2.8	1.31	0.57 - 3.1
> 50 - 75 ppb	1.46	0.38 - 5.8	0.90	0.37 - 2.2	0.86	0.37 - 2.0
> 75 ppb	1.57	0.19 - 11.9	1.32	0.44 - 4.0	1.37	0.47 - 4.0

* includes those who also drank bottled water
** no cases and no controls
CI Confidence Interval
inf Infinity

TABLE 27

SOCIODEMOGRAPHICS OF SUBJECTS LOST TO THE STUDY

VARIABLE	NUMBER	PERCENT
RACE OF THE MOTHER:		
WHITE	282	53.8%
BLACK	223	42.6%
"OTHER"	15	2.9%
MISSING DATA	4	0.8%
MISSING DATA ON PRENATAL CARE	45	8.6%
MOTHER DID NOT FINISH HIGH SCHOOL	124	23.7%
MISSING DATA ON EDUCATION	10	1.9%
AGE OF THE MOTHER:		
18 - 21	27	5.2%
22 - 34	444	84.7%
35 -	53	10.1%
PRIMIPAROUS	235	44.8%
MISSING DATA ON PARITY	1	0.2%
PREVIOUS MISCARRIAGE/STILLBIRTH	113	21.6%
SEX OF CHILD:		
MALE	253	48.3%
FEMALE	271	51.7%

(New Jersey Dept. of Health 1985-1988)

TABLE 28

COMPARISONS BETWEEN INTERVIEWED SUBJECTS
AND SUBJECTS LOST TO THE STUDY

VARIABLE	INTERVIEWED		LOST TO STUDY	
% white	80.1%	(442)	54.2%	(282)
% black	17.8%	(98)	42.9%	(223)
% other	2.2%	(12)	2.9%	(15)
% inadequate prenatal care visits	26.2%	(141)	47.4%	(227)
% mothers with high school degree	90.7%	(496)	75.9%	(390)
% mothers age 18-21 years	2.2%	(12)	5.2%	(27)
% mothers age 35 and over	13.1%	(73)	10.1%	(53)
% primiparous	49.7%	(272)	44.9%	(235)
% previous miscarriage and/or stillbirth	25.3%	(140)	21.6%	(113)

NOTE: For each comparison, those with missing data are excluded.

(New Jersey Dept. of Health 1985-1988)

TABLE 29

COMPARISONS WITHIN GROUPS BETWEEN INTERVIEWED SUBJECTS
AND SUBJECTS LOST TO THE STUDY
CONTROLS

VARIABLE	INTERVIEWED		LOST TO STUDY	
% white	84.0%	(126)	63.5%	(80)
% black	13.3%	(20)	34.9%	(44)
% other	2.7%	(4)	1.6%	(2)
% inadequate prenatal care visits	18.2%	(27)	40.2%	(49)
% mothers with high school degree	92.7%	(140)	78.0%	(99)
% mothers age 18-21 years	1.3%	(2)	1.6%	(2)
% mothers age 35 and over	17.9%	(27)	11.8%	(15)
% primiparous	46.0%	(69)	46.5%	(59)
% previous miscarriage and/or stillbirth	27.8%	(42)	15.0%	(19)

NOTE: For each comparison, those with missing data are excluded.

(New Jersey Dept. of Health 1985-1988)

TABLE 30

COMPARISONS WITHIN GROUPS BETWEEN INTERVIEWED SUBJECTS AND SUBJECTS LOST TO THE STUDY
BIRTH DEFECT CASES

VARIABLE	INTERVIEWED		LOST TO STUDY	
% white	86.8%	(165)	72.1%	(62)
% black	11.6%	(22)	23.3%	(20)
% other	1.6%	(3)	4.7%	(4)
% inadequate prenatal care visits	29.1%	(53)	40.7%	(35)
% mothers with high school degree	90.9%	(170)	70.2%	(59)
% mothers age 18-21 years	1.6%	(3)	10.1%	(9)
% mothers age 35 and over	8.4%	(16)	7.9%	(7)
% primiparous	47.6%	(88)	43.8%	(39)
% previous miscarriage and/or stillbirth	16.9%	(32)	15.7%	(14)

NOTE: For each comparison, those with missing data are excluded.

(New Jersey Dept. of Health 1985-1988)

TABLE 31

COMPARISONS WITHIN GROUPS BETWEEN INTERVIEWED SUBJECTS AND SUBJECTS LOST TO THE STUDY
LOW BIRTHWEIGHT CASES

VARIABLE	INTERVIEWED		LOST TO STUDY	
% white	71.2%	(151)	45.5%	(140)
% black	26.4%	(56)	51.6%	(159)
% other	2.4%	(5)	2.9%	(9)
% inadequate prenatal care visits	29.3%	(61)	52.8%	(143)
% mothers with high school degree	89.0%	(186)	76.6%	(232)
% mothers age 18-21 years	3.3%	(7)	5.2%	(16)
% mothers age 35 and over	14.0%	(30)	10.1%	(31)
% primiparous	45.8%	(97)	55.4%	(170)
% previous miscarriage and/or stillbirth	30.8%	(66)	26.0%	(80)

NOTE: For each comparison, those with missing data are excluded.

(New Jersey Dept. of Health 1985-1988)

TABLE 32

BIVARIATE ANALYSIS OF NEURAL TUBE DEFECTS:
(New Jersey Dept. of Health 1985-1988)
INTERVIEWED ALONE vs ALL ELIGIBLE SAMPLED SUBJECTS

CONTAMINANT LEVELS	ODDS RATIO INTERVIEWED	ODDS RATIO INTERVIEWED AND NON-INTERVIEWED
A-280 TOTAL VOLATILE ORGANICS:		
> 1 ppb - 5 ppb	1.49	1.02
> 5 ppb - 10 ppb	1.72	1.89
> 10 ppb	1.61	1.45
> 5 ppb	1.66	1.64
TRICHLOROETHYLENE:		
> 1 ppb - 5 ppb	1.23	2.01
> 5 ppb	0.74	0.94
TETRACHLOROETHYLENE:		
> 1 ppb - 5 ppb	1.00	0.71
> 5 ppb - 10 ppb	4.07	2.27
> 10 ppb	4.07	4.53
> 5 ppb	4.07	2.52
DICHLOROETHYLENES:		
> 2 ppb	2.57	2.76
1,1,1-TRICHLOROETHANE:		
> 2 ppb	0.61	1.50
CARBON TETRACHLORIDE:		
> 1 ppb	3.81	2.25
1,2-DICHLOROETHANE:		
detected	3.81	1.12
NITRATES:		
> 2 ppm	1.73	1.30
TOTAL TRIHALOMETHANES:		
> 20 - 40 ppb	3.64	1.96
> 40 - 60 ppb	2.60	1.53
> 60 - 80 ppb	2.59	1.61
> 80 ppb	4.25	1.47
SOURCE OF WATER SUPPLY:		
Surface Water	7.33	2.27
Mixture of Sources	18.46	5.25

TABLE 33

BIVARIATE ANALYSIS OF ORAL CLEFT DEFECTS:
(New Jersey Dept. of Health 1985-1988)
INTERVIEWED ALONE vs ALL ELIGIBLE SAMPLED SUBJECTS

CONTAMINANT LEVELS	ODDS RATIO INTERVIEWED	ODDS RATIO INTERVIEWED AND NON-INTERVIEWED
A-280 TOTAL VOLATILE ORGANICS:		
> 1 ppb - 5 ppb	1.01	0.89
> 5 ppb - 10 ppb	1.16	1.13
> 10 ppb	1.46	2.62
> 5 ppb	1.34	1.97
TRICHLOROETHYLENE:		
> 1 ppb - 5 ppb	0.95	1.08
> 5 ppb - 10 ppb	1.42	3.77
> 10 ppb	0.71	0.84
> 5 ppb	1.13	2.01
TETRACHLOROETHYLENE:		
> 1 ppb - 5 ppb	1.45	0.90
> 5 ppb	0.73	1.59
DICHLOROETHYLENES:		
> 2 ppb	2.93	2.95
1,1,1-TRICHLOROETHANE:		
> 2 ppb	1.43	3.78
CARBON TETRACHLORIDE:		
> 2 ppb	2.85	3.63
detected	4.0	3.74
NITRATES:		
> 2 ppm	0.56	1.13
TOTAL TRIHALOMETHANES:		
> 20 - 40 ppb	1.59	1.08
> 40 - 60 ppb	0.80	0.58
> 60 - 80 ppb	1.39	0.95
> 80 ppb	1.59	0.94
SOURCE OF WATER SUPPLY:		
Surface Water	1.44	0.94
Mixture of Sources	0.48	0.50

TABLE 34

BIVARIATE ANALYSIS OF MAJOR CARDIAC DEFECTS:
(New Jersey Dept. of Health 1985-1988)
INTERVIEWED ALONE vs ALL ELIGIBLE SAMPLED SUBJECTS

CONTAMINANT LEVELS	ODDS RATIO INTERVIEWED	ODDS RATIO INTERVIEWED AND NON-INTERVIEWED
A-280 TOTAL VOLATILE ORGANICS:		
> 1 ppb - 5 ppb	0.87	0.83
> 5 ppb	0.69	0.99
TRICHLOROETHYLENE:		
> 1 ppb - 5 ppb	1.15	1.21
> 5 ppb - 10 ppb	0.38	0.57
> 10 ppb	0.58	1.13
> 5 ppb	0.46	0.90
TETRACHLOROETHYLENE:		
> 1 ppb - 5 ppb	0.58	0.30
> 5 ppb	1.15	1.76
DICHLOROETHYLENES:		
> 2 ppb	0.79	0.67
1,1,1-TRICHLOROETHANE:		
> 1 ppb	0.53	0.89
1,2-DICHLOROETHANE:		
detected	2.4	2.59
BENZENE:		
detected	2.43	2.79
NITRATES:		
> 2 ppm	0.72	1.06
TOTAL TRIHALOMETHANES:		
> 20 - 40 ppb	2.05	2.17
> 40 - 60 ppb	1.42	1.59
> 60 - 80 ppb	1.52	1.40
> 80 ppb	1.37	1.08
SOURCE OF WATER SUPPLY:		
Surface Water	2.22	2.08
Mixture of Sources	2.14	2.31

TABLE 35

BIVARIATE ANALYSIS OF VERY LOW BIRTHWEIGHT:
New Jersey Dept. of Health 1985-1988)
INTERVIEWED ALONE vs ALL ELIGIBLE SAMPLED SUBJECTS

CONTAMINANT LEVELS	ODDS RATIO INTERVIEWED	ODDS RATIO INTERVIEWED AND NON-INTERVIEWED
A-280 TOTAL VOLATILE ORGANICS:		
> 1 ppb - 5 ppb	0.84	0.81
> 5 ppb - 10 ppb	1.88	1.14
> 10 ppb	1.88	1.28
> 5 ppb	1.88	1.22
TRICHLOROETHYLENE:		
> 1 ppb - 5 ppb	1.71	1.43
> 5 ppb - 10 ppb	1.54	1.25
> 10 ppb	0.77	0.55
> 5 ppb	1.35	0.92
TETRACHLOROETHYLENE:		
> 1 ppb - 5 ppb	1.44	1.07
> 5 ppb	1.54	0.86
DICHLOROETHYLENES:		
> 2 ppb	0.72	0.89
1,1,1-TRICHLOROETHANE:		
> 2 ppb	0.56	0.77
CARBON TETRACHLORIDE:		
> 2 ppb	2.93	2.15
1,2-DICHLOROETHANE:		
detected	0.72	0.42
NITRATES:		
> 2 ppm	0.50	0.40
TOTAL TRIHALOMETHANES:		
> 20 - 40 ppb	1.09	0.91
> 40 - 60 ppb	0.97	1.03
> 60 - 80 ppb	0.58	0.62
> 80 ppb	1.53	1.02
SOURCE OF WATER SUPPLY:		
Surface Water	1.03	1.03
Mixture of Sources	1.35	1.32

TABLE 36

BIVARIATE ANALYSIS OF INTERMEDIATE LOW BIRTHWEIGHT:
New Jersey Dept. of Health 1985-1988)
INTERVIEWED ALONE vs ALL ELIGIBLE SAMPLED SUBJECTS

CONTAMINANT LEVELS	ODDS RATIO INTERVIEWED	ODDS RATIO INTERVIEWED AND NON-INTERVIEWED
A-280 TOTAL VOLATILE ORGANICS:		
> 1 ppb - 5 ppb	0.52	0.66
> 5 ppb - 10 ppb	2.21	1.46
> 10 ppb	0.55	0.56
> 5 ppb	1.10	0.95
TRICHLOROETHYLENE:		
> 1 ppb - 5 ppb	0.39	0.60
> 5 ppb - 10 ppb	0.78	0.68
> 10 ppb	1.17	0.63
> 5 ppb	0.88	0.66
TETRACHLOROETHYLENE:		
> 1 ppb - 5 ppb	0.63	0.76
> 5 ppb	0.94	0.66
DICHLOROETHYLENES:		
> 2 ppb	0.30	0.33
1,1,1-TRICHLOROETHANE:		
> 2 ppb	0.72	1.09
1,2-DICHLOROETHANE:		
> 1 ppb	2.48	1.33
detected	1.23	0.99
NITRATES:		
> 2 ppm	0.61	0.59
TOTAL TRIHALOMETHANES:		
> 20 - 40 ppb	1.38	1.09
> 40 - 60 ppb	1.42	1.15
> 60 - 80 ppb	0.73	0.59
> 80 ppb	2.30	1.50
SOURCE OF WATER SUPPLY:		
Surface Water	1.62	1.23
Mixture of Sources	1.39	1.14

TABLE 37

SUMMARY OF FINDINGS MERITING FOLLOW-UP *

OUTCOME	CONTAMINANTS	COMMENTS
Neural Tube Defects	TTHM	D
	Surface Water	D
	Mixed Water	D
	PCE	T
	Nitrates	T
Oral Clefts	CTC	S,I
	Surface Water	D
	DCE	S
Major Cardiac Defects	TTHM	S,D
	Surface water	D
	Mixed water	S,I
Ventricular Septal Defects	TVOC	S
	TCA	S,I
	CTC	D
Very Low Birthweight	TVOC	D
	TCE	D
	PCE	S
Intermediate Low Birthweight	Surface water	S,D

* - Associations Are Positive and Statistically Significant, Unless Otherwise Indicated
S - Suggestive Association ($0.05 < p < 0.1$)
D - Odds Ratio Decreased When Non-Interviewed Subjects Were Included
I - Odds Ratio Increased When Non-Interviewed Subjects Were Included
T - After Adjustment for the Confounding Effects of TTHM

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