

Health Consultation

HEALTH STATISTICS REVIEW FOLLOW-UP
Cancer and Birth Outcome Analysis

ENDICOTT AREA INVESTIGATION
ENDICOTT AREA, TOWN OF UNION,
BROOME COUNTY, NEW YORK

MAY 15, 2008

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333

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Prepared by:

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Center for Environmental Health
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under a cooperative agreement with

The U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry
Public Health Service
Atlanta, Georgia

Forward:

This health consultation is a follow-up to the health statistics review of reproductive outcomes and cancer in the Endicott area (ATSDR, 2006). The analytical methods used in this review are similar to those of the original review and therefore are bound by the same types of limitations of the previous review.

A health statistics review uses existing health data from data sources like birth certificates and health registries to determine whether health outcomes in a particular community are occurring at a higher, lower, or about the same level compared to statewide or national levels after taking into account factors such as gender and age of individuals within the community.

A health statistics review does not tell us why elevations or deficits in certain health outcomes exist and can not prove a cause and effect relationship between exposure to chemicals and health outcomes. A health statistics review can take risk factors such as age, race and sex that are commonly found on health records into account. Because it relies on previously existing data, a health statistics review may not be able to take into account certain individual risk factors such as medical history, smoking, genetics, and occupational exposures which may explain the elevations or deficits in health outcomes. This is one reason that we reviewed medical records, birth certificates, and residential address information. Information gained through a health statistics review can generate hypotheses and may indicate whether a more rigorous study should be considered.

This health statistics review follow-up is one part of an ongoing approach to addressing health outcome concerns related to environmental contamination in Endicott, NY.

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Executive Summary

This follow-up investigation was conducted to address concerns and to provide more information related to elevated cancers and adverse birth outcomes identified in the initial health statistics review entitled “Health Statistics Review: Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York” (ATSDR; 2006). The initial health statistics review was carried out to address concerns about health issues among residents in the Endicott area who may have been exposed to volatile organic compounds (VOCs) through a pathway known as soil vapor intrusion. The initial health statistics review reported a significantly elevated incidence of kidney and testicular cancer among residents in the Endicott area. In addition, elevated rates of heart defects and low birth weight births were observed. The number of term low birth weight births, a subset of low birth weight births, and the number of small for gestational age (SGA) births were also significantly higher than expected.

The purpose of this follow-up investigation was to gather more information and conduct a qualitative examination of medical and other records of individuals identified with adverse birth outcomes and cancers found to be significantly elevated. Quantitative analyses were also carried out for two additional birth outcomes, conotruncal heart defects (specific defects of the heart’s outflow region), and spontaneous fetal deaths (stillbirths), and for cancer incidence accounting for race.

The follow-up was released as a draft for public comment in March 2006, with the public comment period extending through August 2007. Specific responses to written public comments are provided in the Appendix, page 45. Input from Endicott area stakeholders and discussions among stakeholders, NYS DOH and ATSDR staff about follow-up health outcome investigation issues also occurred during the public comment period at meetings of the Western Broome Environmental Stakeholders Coalition. Changes made in this final version of the document include minor updates to the Recommendations section of the document, the addition of a new Section 9, Action Plan, an Addendum on “Study Design and Statistical Power Considerations,” and the Appendix, “Response to Comments.”

Spontaneous Fetal Deaths: The rate of spontaneous fetal deaths in the study area was compared to standardized rates in New York State, exclusive of New York City using an ecologic study design. Because of data quality issues, the review was limited to late term spontaneous fetal deaths, i.e. stillbirths, occurring during the years 1978-1993.

Results: Results of the spontaneous fetal death analysis did not support an association between living in the exposure area and an increased risk of fetal deaths, although the analysis was limited by issues with data quality and completeness.

Conotruncal Heart Defects: The prevalence of a certain class of heart defects known as conotruncal heart defects among births in the area was compared to the prevalence of these birth defects in New York State, exclusive of New York City, for the years 1983-2000, using multivariate regression analysis. These specific defects of the heart’s

outflow tract were examined because they may be associated with the types of exposures found in the Endicott area.

Results: Results of the conotruncal heart defect analysis did show a significantly elevated risk among women living in the study area; however, interpretation of these results must be made with caution due to the extremely small number of infants born with these birth defects.

Birth Certificate Review and Reanalysis: Birth certificates of children with heart defects, Down syndrome, term low birth weight and small for gestational age births in the Endicott study area were examined for information on maternal smoking status, occupation, health conditions and family history which may have contributed to the observed elevations. Analyses that adjusted for smoking history were performed for low birth weight, small for gestational age, and term low birth weight infants for the years 1998 through 2002. Smoking has been linked to heart defects and is the major risk factor for fetal growth restriction, which is related to low birth weight births.

Results: The review of smoking data for all births in the Endicott area showed that a higher proportion of Endicott women smoked during pregnancy compared to women in New York State, excluding New York City, and the United States. Analyses that accounted for mothers' smoking showed results that differed from the prior review's findings. Taking account of smoking information from individual birth certificates resulted in the risk of having a low birth weight or small for gestational age (SGA) child in the study area declining so that it was no longer significantly elevated (although it was still somewhat elevated). The risk of having a term low birth weight infant also declined when maternal smoking was taken into account, but it did remain significantly elevated.

While this analysis included only the last five years of the 25 year study period, these are the years when the risk of SGA was greatest in the first review. Therefore, this review suggests that the elevated smoking rate among women in this area is at least partly responsible for the elevated rates of low birth weight and small for gestational age births. Information on mothers' medical histories and pregnancy conditions indicated that pregnancy complications may also have contributed to some of the low birth weight births. While no unusual patterns of maternal occupational history were identified from birth certificates, many women reported working in the manufacturing and electronics fields which may have exposed them to chemicals in the workplace. However, given the long industrial history of the village it is not unusual that a large proportion of women worked in these industries.

Cancer Incidence adjusting for Race: Because a higher percentage of the population in the study area was white compared to the comparison population, we examined the incidence of cancer among whites in the study area compared to the incidence in the white population of New York State, excluding New York City. Cancer incidence among whites was evaluated for the years 1980-2001.

Results: Limiting the analysis of cancer to only white individuals had little effect on overall cancer rates or standardized incidence ratios compared to those of the entire study

area population analyzed previously. The only difference was that lung cancer which had been borderline non-significantly elevated was now borderline significantly elevated.

Cancer Case Record Review: We reviewed medical and other records of individuals with kidney and testicular cancers to try to determine smoking, occupational and residential histories. A number of preexisting data sources were used including: hospital medical records; cancer registry records; death certificates; newspaper obituaries; Motor Vehicle records; and city and telephone directories.

Results: The case record review did not reveal any unusual patterns in terms of age, gender, year of diagnosis, cell type, or mortality rate among individuals with kidney or testicular cancer. There was some evidence of an increased prevalence of smoking among those with kidney cancer and some indication that several individuals diagnosed with testicular and kidney cancer may have been recent arrivals to the study area.

Conclusions/Recommendations

The purpose of the additional analyses reported in the draft for public comment follow-up report was to provide information on certain cancers and reproductive outcomes which were elevated in the initial health statistics review. Although these additional analyses could not determine whether there was a causal relationship between VOC exposures in the study area and the increased risk of several health outcomes that were observed, they did provide more information to help guide additional follow-up. The March 2007 public comment report provided a list of follow-up options for consideration and stated, “Although an analytical (case-control) epidemiologic study of cancer or birth defects within this community is not recommended at this time, we describe several follow up options for discussion with the Endicott community. A case-control study would be the preferable method for progressing with this type of investigation, but the potentially exposed population in the Endicott area is too small for conducting a study that would be likely to be able to draw strong conclusions about potential health risks.

Alternative follow-up options were discussed at meetings with Endicott stakeholders and were the subject of responses to comments on the draft report. From these discussions and written responses, NYS DOH has noted community interest in two possible options for future activities: a health statistics review based on historic outdoor air emissions modeling, and a multi-site epidemiologic study examining cancer outcomes in communities across the state with VOC exposures similar to Endicott. NYS DOH has considered these comments and examined whether these options would be able to accomplish one of two goals: either to advance the scientific knowledge about the relationship between VOC exposure and health outcomes or to be part of a response plan to address community concerns.

An additional health statistics review using historic outdoor air emission modeling results to identify and study a larger population of residents potentially exposed to TCE is not likely to meet either of these goals at this time. Because of the limitations of the health statistics review for drawing conclusions about cause and effect, conducting an additional health statistics review is not likely to increase our understanding of whether exposures in the Endicott area are linked to health outcomes. Limitations with the available historic

outdoor air data also would make it difficult to accurately define the appropriate boundaries for the exposure area. ATSDR historic outdoor air emissions modeling activity was unable to model TCE due to a lack of available records.

A multi-site epidemiologic study of health outcomes in communities across the state with VOC exposures similar to Endicott offers some promise of meeting the goal of advancing the scientific knowledge about the relationship between VOC exposures and health outcomes. The community has indicated its preference that such a study focus on cancer outcomes. Given the complex issues involved in conducting such a study (e.g., tracking down cases or their next of kin after many years, participants' difficulty in accurately remembering possible risk factors from many years ago, and the long time period between exposure to a carcinogen and the onset of cancer), we do not consider a multi-site case-control study of cancer as the best option at this time. An occupational cancer study is a better option than a community-based study because it can better incorporate information about past workplace exposures and could use corporate records to assist in finding individual employees many years after exposure.

Heart defects have been associated with TCE exposure in other studies. Given the shorter latency period, and thus the shorter time period in which other risk factors could come into play, a multi-site study of heart defects has some merit as a possible option. Currently, NYS DEC and NYS DOH are investigating many communities around New York State which could have VOC exposure patterns similar to Endicott, and thus could be included in such a multi-site epidemiologic study. However, in most of these communities exposure information sufficient to identify a study population is not yet available. NYS DOH will continue to evaluate these areas as additional exposure information becomes available, with the goal of identifying other communities for possible inclusion in a multi-site epidemiologic study of heart defects.

NYS DOH will continue to keep the Endicott community and stakeholders informed about additional information regarding other communities with exposures similar to those that occurred in the Endicott area. NYS DOH staff will be available as needed to keep interested Endicott area residents up-to-date on the feasibility of conducting a multi-site study that includes the Endicott area.

1.0 Background and Introduction

The New York State Department of Health (NYS DOH) conducted a health statistics review entitled “Health Statistics Review: Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York” due to concerns about health issues associated with environmental contamination in the Endicott, NY area (ATSDR, 2006). Residents in the Endicott area may have been exposed to volatile organic compounds (VOCs) through a pathway known as soil vapor intrusion. Groundwater in the Endicott area is contaminated with VOCs as a result of leaks and spills associated with local industry and commercial businesses. In some areas of Endicott, VOC contamination from the groundwater has contaminated the adjacent soil vapor which has migrated through the soil into some structures through cracks in building foundations (soil vapor intrusion). Trichloroethene (TCE), tetrachloroethene (PCE) and several other VOCs were found in the soil vapor and in the indoor air of some structures. The initial review examined existing public health data to determine whether the residents of this area had rates of cancer and adverse reproductive outcomes that differed from the residents in the rest of New York State, excluding New York City. The study area is shown in Figure 1.

The initial health statistics review reported a significantly elevated incidence of kidney and testicular cancer and somewhat elevated rates of lung and esophageal cancer (ATSDR, 2006). In addition, elevated rates of heart defects and low birth weight births were observed. The number of term low birth weight births, a subset of low birth weight births, and the number of small for gestational age (SGA) births were also significantly higher than expected.

The following steps were taken to follow-up on these results as recommended in the health statistics review.

- **Spontaneous Fetal Deaths:** The rate of spontaneous fetal deaths in the study area was compared to New York State rates, exclusive of New York City.
- **Conotruncal Heart Defects:** The prevalence of a type of heart defects known as conotruncal heart defects was evaluated to see if these birth defects, which may be the most likely birth defects related to this type of chemical exposure, were elevated.
- **Birth Certificate Review:** Birth certificates of infants with heart defects, Down syndrome, term low birth weight and SGA were reviewed to see if any unusual factors may have contributed to these conditions.
- **Cancer Incidence adjusting for Race:** Because a higher percentage of the population in the study area was white compared to the comparison population, we examined the incidence of cancer among whites to account for these differences.
- **Case Record Review - Cancer:** We conducted a review of individual medical records of persons with kidney and testicular cancers to see if any unusual factors may have contributed to these conditions in the study area.

2.0 Spontaneous Fetal Deaths

2.1 Background

Several studies in the literature have reported an increased risk of spontaneous fetal death (also called spontaneous abortions or miscarriages) among women exposed to VOCs. A retrospective case-control study among women occupationally exposed to TCE and other solvents found a threefold risk of spontaneous fetal deaths compared to women with little or no exposure to the solvent (Windham et al., 1991). In addition, the same study found a nearly five-fold risk of spontaneous fetal death among women occupationally exposed to PCE. Several case-control studies of women exposed to PCE in the dry cleaning industry have also reported an increased risk of spontaneous fetal death (ATSDR, 1997).

2.2 Methods

An ecological study design was used to determine if rates of spontaneous fetal deaths in the Endicott area were different from those in the rest of the New York State, excluding New York City. Analyses were based on data grouped for each study area. Study areas used were the same as in the initial health statistics review. Spontaneous fetal death rates were adjusted only for the age of the woman and the year that the spontaneous fetal death occurred. No further analysis was done to evaluate the effects of race, education, prenatal care or parity on spontaneous fetal death rates since individual level information on these characteristics was not available for women in the comparison group.

NYS DOH reviewed spontaneous fetal death (see New York State Public Health Law (§4160) for definition) data for a 25-year period from 1978 through 2002 to determine whether the study area had an increased number or unusual pattern of spontaneous fetal deaths. While this definition includes both induced abortions and spontaneous fetal deaths only the latter were evaluated in the study.

NYS DOH attempted to identify all spontaneous fetal deaths to women living in ZIP Code 13760 by reviewing residential address information stored on spontaneous fetal death records. New York State Public Health Law requires all spontaneous fetal deaths be registered regardless of gestational age, however many spontaneous fetal deaths occurring before the 20th week of gestation are not reported (NYSDOH, 2002). Because of this and because only late term (≥ 20 weeks) spontaneous fetal death rates in Upstate New York were available in the annual New York State Vital Statistics Reports to use for comparison purposes prior to 1991, only spontaneous fetal deaths occurring in the 20th week of pregnancy or later were evaluated.

To determine the number of spontaneous fetal deaths occurring to women living in the study area, records were geocoded using the methods discussed in the initial report. Because of a change in NYS Public Health Law (§4161), beginning in 1993, women were no longer required to provide their name or address when their physicians registered a spontaneous fetal death. As a result, approximately 90% of the records from 1993 on did not have address information beyond the ZIP Code. Because of this, it was not possible to determine whether or not the women lived within the study area. Therefore,

the analysis of spontaneous fetal deaths was limited to late term spontaneous fetal deaths occurring between 1978 and 1993.

Age specific rates for spontaneous fetal deaths occurring among women living in New York State, exclusive of New York City, are published annually by the NYS DOH Bureau of Biometrics. This served as the basis for our comparison group. Rates for spontaneous fetal deaths were calculated for the following 9 age groups: 10-14, 15-17, 18-19, 20-24, 25-29, 30-34, 35-39, 40-44 and 45 and older. The expected number of spontaneous fetal deaths was calculated by applying the rate for each age group to the total number of fetal deaths plus births in the study area for that age group. Data were summed across age groups and across the 16 years of the study period to determine the expected number of spontaneous fetal deaths. These were then compared to the observed number of spontaneous fetal deaths in the each study area. In addition, observed and expected numbers of these spontaneous fetal deaths were also compared for time periods (1978-1982, 1983-1987, 1988-1993) to identify any temporal patterns in the data.

Spontaneous fetal death rates were calculated by dividing the number of spontaneous fetal deaths in an area by the number of spontaneous fetal deaths plus the number of live births. Standardized incidence ratios¹ (SIR) were also calculated for spontaneous fetal deaths in the area along with 95% Confidence Intervals (95% CI). The Poisson probability distribution, which is used to describe the occurrence of rare events, was used to calculate 95% confidence intervals. Two-tailed tests were used to identify significant excesses and deficits. The 95% CI is the range in which there is a 95% probability of including the true SIR.

2.3 Results

Because late term spontaneous fetal deaths are rare, there were few spontaneous fetal deaths expected in the study area between 1978 and 1993. A total of 5 spontaneous fetal deaths ≥ 20 weeks were observed among women in both study areas combined between 1978 and 1993 while about 7.5 were expected during the same time period (SIR 0.66; 95% CI 0.22-1.55). Two late term spontaneous fetal deaths were reported in the Western Study Area while three late term spontaneous fetal deaths were reported in the larger Eastern Study Area. In both areas the number observed was similar to what would have been expected in the study area over the 16 year period. When the results were broken down by the three time periods, no significant excesses or deficits of spontaneous fetal deaths were noted in any of the three time periods.

¹ An SIR is the number of observed cases of a health outcome divided by the expected number of cases. If an SIR is greater than one, then there is an excess of spontaneous fetal deaths in the study population compared to the general population. If an SIR is less than one, then there is a lower than expected number of spontaneous fetal deaths in the study population. The magnitude of the excess or deficit can also be determined from the SIR. For instance, if twice as many cases are observed as expected, the SIR would be 2.0, while a 50% excess in cases observed, compared to the number expected, would result in an SIR of 1.5. On the other hand, if only half the expected number of cases were observed, this would result in an SIR of 0.5.

2.4 Discussion

Spontaneous fetal deaths were evaluated because previous studies, both human and animal, suggested an increased risk of spontaneous fetal deaths due to exposure to TCE (ATSDR, 1997; Windham et al., 1991). We did not detect evidence of an increased risk of spontaneous fetal deaths in the Endicott population. Therefore, the results of this analysis do not offer any evidence of an association between the TCE and increased risk of spontaneous fetal deaths. However, the results must be interpreted with caution.

A number of factors may have limited the ability of this study to detect meaningful increases or deficits of spontaneous fetal deaths. Late term spontaneous fetal deaths are relatively rare events, occurring in just 0.8% of live births plus fetal deaths. This combined with the relatively small population size in the study area resulted in very few spontaneous fetal deaths expected even after combining 16 years of data. Additional limitations of this type of study have been discussed in detail in the previous health statistics review (ATSDR, 2006). Briefly, these included limited information about: the levels of VOCs in individual homes; the duration of the exposure; the amount of time residents spent in the home each day; and the multiple exposures and exposure pathways that likely existed among long term residents of the Endicott area. In addition, personal information such as medical history; dietary and lifestyle choices such as smoking and drinking; and occupational exposures to chemicals were not examined.

As mentioned previously there were also limitations with the spontaneous fetal death data itself that limited our ability to investigate this outcome. Much of the identifying information was missing on spontaneous fetal deaths occurring after 1993; thus, these records lacked the detail needed for this evaluation. In addition, lack of early spontaneous fetal death (< 20 weeks of gestation) tables prior to 1991 prevented us from evaluating this outcome. Finally, unlike the reproductive outcomes previously investigated, we were limited in our comparison group to using published tables of spontaneous fetal deaths. No individual level data were available on spontaneous fetal deaths statewide, and thus, we were unable to control for race, ethnicity, socioeconomic status or adequacy of prenatal care as was done for other reproductive outcomes investigated.

3.0 Conotruncal Heart Defects

3.1 Background

In the original health statistics review, the birth prevalence of heart defects was significantly higher than expected (ATSDR 2006). The objective of the current analysis was to evaluate the association between living in the study area and the risk of conotruncal malformations, a specific type of heart defect which may be associated with exposure to TCE.

Conotruncal heart defects are anomalies of the outflow tract of the heart. This includes anomalies related to the arterial flow of blood from the right and left ventricles through the pulmonary artery and aorta. Both animal and human studies of TCE exposures have suggested an association with conotruncal defects and with certain other defects such as neural tube defects and cleft palate (review by Bove et al., 2002). However, the associations observed in community based epidemiologic studies were based on small numbers of births to women exposed to VOCs in contaminated drinking water (Bove et al., 1995; Goldberg et al., 1990). A review of the scientific literature regarding the associations between exposure to TCE and heart defects as well as other risk factors for heart defects was included in the initial report (ATSDR, 2006).

3.2 Methods

NYS DOH reviewed conotruncal malformation data to determine whether the study area had a higher than expected number of infants born with this type of heart defect during the eighteen-year period from 1983 through 2000. As in the previous health statistics review, an ecological study design was used to determine if rates of conotruncal malformations in the Endicott area were different from those in the rest of the New York State, excluding New York City. The study areas used were the same as in the initial health statistics review.

The NYS DOH Congenital Malformation Registry (CMR) served as the source of birth defect data. The group of conotruncal heart defects analyzed was a subgroup of the heart defects reviewed in the previous study (See Table 1 for a list of conotruncal malformations examined).

Adjusted analyses were conducted using multivariable Poisson regression using births from New York State, excluding New York City as the comparison group. Individual-level information on each birth in both the study and comparison areas was used to evaluate the estimated risk for conotruncal heart defects for residents in the study area compared to the rest of the state, while adjusting for the estimated effects of maternal age (<19, 19-34, 35+ years), education (<high school, high school +), race (white, other), infant sex (male, female), total previous live births (0, 1, 2+), adequate prenatal care (modified Kessner index: adequate, intermediate, inadequate), and year of birth.

3.3 Results

Four conotruncal malformations were observed in the combined study areas between 1983 and 2000 which represents less than 25% of the 20 heart malformations identified in

the initial study (ATSDR, 2006). Three defects were reported in the larger Eastern study area and one defect was reported in the Western Study Area. The prevalence of conotruncal malformations in the study area was significantly elevated compared to the rest of the state with an adjusted Rate Ratio (aRR) of 4.83 (95% CI 1.81 – 12.89). The results remained significantly elevated (aRR 3.74; 95% CI 1.21 – 11.62) when infants with Down syndrome were excluded from the analysis. The Rate Ratio can be interpreted in a similar way as the SIR.

3.4 Discussion

Limiting the analysis to the more etiologically homogeneous group of conotruncal defects resulted in stronger associations (aRR 4.83; 95% CI 1.81 – 12.89) with residence at birth within the Endicott study area than did results for total heart defects in the initial analysis (aRR 1.94; 95% CI 1.21 – 3.12) (ATSDR, 2006). No other related defects (e.g. neural tube defects, cleft palate) were seen in the study area in the initial analysis (ATSDR, 2006). However, the expected number of infants born with each of these types of birth defects was very small.

There are a number of limitations in this follow-up analysis. Although a significant association was detected, the excess risk in conotruncal defects observed in the current study was based on a small number of infants with these birth defects in the study area and thus the results must be interpreted with caution. In a small population, adding or subtracting a single birth with a rare outcome such as a conotruncal heart defect can change the results dramatically. For example in the study area about one birth with a conotruncal birth defect would have been expected over the study period. Because the expected number is so small just one or two additional births with this type of birth defect results in a significantly elevated rate.

On the other hand if we look at a common birth occurrence, say the chance of being born a girl we can see that one or two additional girls born in the area would not change the results much. For example, we expect about one out of every two births, or just under 50%, to be a girl. If we looked at 1,400 births, we would expect about 700 to be girls. If 701 or 702 of the births are girls, those extra births of girls do not change the overall percentage of girls much. With large numbers, a few extra cases do not make a large difference, but with small numbers they can make a big difference.

In addition to problems with small numbers, there was also limited information on individual exposures to VOCs as discussed previously. While the analyses were adjusted for variables available in the electronic birth certificate files, a number of other risk factors for heart defects could not be controlled such as folic acid use, retinoic acid exposures, diabetes, smoking, and occupational exposures. The limitations are discussed in much greater detail in the original health statistics review (ATSDR, 2006).

4.0 Birth Certificate Review and Reanalysis: Heart defects, Down syndrome, SGA, and Term Low Birth Weight

4.1 Introduction

In addition to heart defects, the number of infants with Down syndrome was also found to be greater than expected in the original health statistics review (ATSDR, 2006). Term low birth weight and small for gestational age births, both measures of inadequate fetal growth, were significantly higher than expected as well with the greatest elevations observed in the Eastern Study area between 1998 and 2002. Birth certificates were reviewed to evaluate additional risk factors that were not available in the electronic birth certificate files to determine if any unusual factors may have contributed to the observed elevations of adverse reproductive outcomes in the study area. Additional factors that were assessed included maternal smoking, maternal health conditions (chronic and infectious), and occupation.

Heart Defects - Heart defects are the most common birth defects in New York State (NYSDOH, 2005b). However, very little is known about the causes of most birth defects, including heart defects. Infants born with Down syndrome are more likely to have heart defects (Torfs and Christianson, 1998). Other risk factors for heart defects include a family history of heart defects; maternal pre-existing diabetes; certain viruses such as rubella; maternal use of certain drugs and medicines such as Accutane (isotretinoin); alcohol use during pregnancy; and multiple births. Associations between exposure to TCE and heart defects have been observed in both animal studies and human epidemiological studies (ATSDR; 1997).

Down Syndrome - Increasing maternal age is the only well established risk factor for Down syndrome. In some studies, paternal age has been associated with Down syndrome (Fisch et al., 2003). Few other risk factors have been identified for Down syndrome. Prenatal exposure to ionizing radiation (Verger, 1997); exposure to certain pesticides (Czeizel et al., 1993) and low socioeconomic status of the mother and father (Torfs and Christianson, 2003; Christianson et al., 2004) may increase the risk for Down syndrome. New genetic techniques have recently been used to categorize Down syndrome by parental origin and timing of the chromosome error (Yang et al., 1999). The researchers found that younger mothers (<35 years) who smoke and have meiotic II error are at an increased risk of having children with Down syndrome. This study by Yang et al. suggests that environmental factors may play a role in the development of Down syndrome of maternal origin. However, no other evidence to date suggests that exposure to VOCs may increase the risk of Down syndrome.

Term Low Birth Weight and Small for Gestational Age Births - Cigarette smoking is the single largest risk factor for fetal growth restriction (Kramer, 1987). Studies have also found a persistent association between low birth weight and measures of socioeconomic status and poverty, including occupation, income and education (Hughes and Simpson, 1995). Poor nutritional status of the mother at conception and inadequate nutritional intake during pregnancy can result in term low birth weight births (Kramer, 1987). Studies of women exposed to TCE in contaminated drinking water have found some

evidence of an increased risk of low or very low birth weight and small for gestational age although the evidence is very limited (Bove et al., 2002; ATSDR, 1997; Sonnenfeld et al., 1998).

4.2 Methods

NYS DOH requested birth certificates for each of the 21 infants with heart defects or Down syndrome reported to the NYS CMR between 1983 and 2000 from the microfiched birth certificate files. Additionally, birth certificates for the 153 infants born between 1978 and 2002 who were classified as small for gestational age or term low birth weight were requested. Two birth certificates were from births to Endicott residents who delivered out of state and thus could not be acquired. The available records were reviewed and information on maternal smoking, health conditions, and occupation that was not originally available in the electronic birth certificate files was transcribed.

4.3 Results

Heart Defects

Maternal Smoking: Smoking information was available on the birth certificate for the years 1989 through 2002. Of the 11 (55%) pregnancies with heart malformations that also had smoking data, 3 (27%) mothers reported smoking during pregnancy.

Maternal Occupations: Maternal occupations were listed for 19 (95%) of the 21 infants with heart defects. The occupations reported were 6 homemakers; 5 health care field; 5 cashiers or clerks; and the remainder reported other fields of work including the electronics industry.

Maternal Conditions and Family History: None of the children with heart defects had congenital infections mentioned on the birth certificate, and the birth certificates made no mention of other maternal diseases, conditions, or medication use. One birth certificate indicated a radiation exposure during pregnancy. Two of the infants with major heart defects were siblings and another infant was a twin. Two infants with heart defects had a diagnosis of Down syndrome.

Down syndrome

No information on maternal smoking status was available for the mothers of infants with Down syndrome. Parental age did not appear unusual. All parents of infants with Down syndrome worked outside the home with several working in the electronics industry. No other exposures or maternal conditions were listed on the birth certificates of these infants.

Term Low Birth Weight and Small for Gestational Age Births

Maternal Smoking: Of the 88 (58%) women with small for gestational age births for whom smoking data were available, 55 (63%) reported smoking during pregnancy. Fifteen (68%) of 22 women with term low birth weight births reported smoking during pregnancy.

Maternal Occupations: Maternal occupational information was reported for 136 (90%) small for gestational age or term low birth weight infants. Eighty-nine of these women (65%) reported working outside the home during pregnancy. The occupations reported included manufacturing (20%); retail sales (19%); the medical field (18%); food service (18%); and education/childcare (7%), while the remainder worked in other fields.

Maternal Conditions and Family History: A number of birth certificates indicated placental problems (11%) including: early bleeding; placental abruption; and preeclampsia. Chronic health conditions of the mother such as hypertension, heart disease, kidney disease, and asthma were indicated on about 10% of the birth certificates. Additionally, low prepregnancy weight (4%) and history of previous preterm or low birth weight birth (2%) were recorded on some birth certificates.

4.4 Discussion

The purpose of the follow-up review of birth certificates for infants with heart defects, Down syndrome, and inadequate fetal growth was to gather information on maternal smoking, health, and occupation during the affected pregnancy. Smoking, adverse maternal health, and adverse occupational exposures during pregnancy, if more common in the study area than we would expect, may explain the elevations in adverse reproductive outcomes detected. If the study population was significantly different than the comparison population with respect to these factors, then a valid comparison of underlying disease rates was not possible because the calculated relative risk estimates would be confounded by these factors.

Smoking during Pregnancy: Since 1989, when smoking data became available on the birth certificate, smoking during pregnancy has decreased nationally from 20% in 1989 to 11% in 2002 (US Births, 2002). Data from the NYS electronic birth certificates, which have nearly 100% completeness for smoking data from 1998 through 2002, show that 13.8% of women reported some smoking during pregnancy. Although prenatal smoking is most likely underreported on the birth certificate, the national trends in maternal smoking based on birth certificate data have been supported by data from national surveys. Accuracy of reporting is affected by the lack of specific time reference for smoking status (specific trimester or entire pregnancy), variations in the source of tobacco use information, and the stigma associated with smoking during pregnancy. Data from the Pregnancy Risk Assessment Monitoring System (PRAMS) in New York State, a survey of pregnancy related health and behaviors showed that among women in New York State, excluding New York City, the prevalence of smoking during the last three months of pregnancy ranged from 14% to 19% in the 1993 to 1999 period (NYS DOH, 2003). Women who were young, less educated, not married, or on Medicaid were the most likely to smoke during pregnancy according to the survey.

Our review of smoking data available on the birth certificate for mothers in the Endicott study area showed that over 60% of mothers with term low birth weight and small for gestational age infants smoked at some point during pregnancy. In addition, data from the NYS electronic birth certificates from 1998 through 2002 show that 38.5% of women in the Endicott study area reported some smoking during pregnancy. The prevalence of

smoking during pregnancy among mothers in the Endicott study area, and particularly among mothers of low birth weight and small for gestational age infants is much higher than reported by mothers in state or national level data. Smoking is the major risk factor for fetal growth restriction.

When the results of the birth outcome analyses were adjusted for maternal smoking, the risks of having a low birth weight (aOR 1.48, Confidence Interval: 0.91-2.42) or small for gestational age (aOR 1.39, Confidence Interval: 0.95-2.04) child in the study area between 1998 and 2002 were no longer significantly elevated (although they were still somewhat elevated). The risk of having a term low birth weight infant (aOR 2.26, Confidence Interval: 1.22-4.20) declined when maternal smoking was taken into account; however, it remained significantly elevated. While this represents only the last 5 years of the 25 year study period, it is during these years that the greatest risk of SGA and low birth weight was observed in the original study. Therefore, this review suggests that elevated smoking prevalence among women in this area is at least partly responsible for the elevated rates of low birth weight and small for gestational age births. This does not mean, however, that exposure to TCE did not also play a role.

Smoking is not known to be a strong risk factor for heart defects, and the numbers of mothers of infants with heart defects who reported smoking during pregnancy are too small for drawing conclusions about whether smoking may have played a role.

Maternal Occupations: Occupational information was reviewed for indications of workplace exposures to chemicals, radiation, or infectious agents. Of the women who worked outside the home nearly 20% worked in the health care field. There is the potential for women in the health care field to be exposed to chemicals, diagnostic radiation, or infectious agents. Additionally, many women reported working in the manufacturing and electronics fields. Women working in manufacturing and electronics may be exposed to chemicals in the workplace. However, it would not be unusual for a large proportion of women to report working in these occupations in an area like Endicott which has long been a center of manufacturing. While there is some indication that many women in the study area may have worked in occupations where exposure to chemicals may have occurred, without further information on job type and prevalence of these occupations in the reference population it is not possible to quantify the effect that occupational exposures may have had on birth outcomes.

Maternal Conditions and Family History: Down syndrome and a family history of heart defects are strong risk factors for heart defects (Torfs and Christianson, 1998; Hoffman, 1990). In this review, two of the infants with heart defects were in infants with Down syndrome. However, when infants with Down syndrome were removed from the analysis in the health statistics review, the prevalence of heart defects remained significantly elevated. Additionally, two of the infants with major heart defects were siblings which may suggest that family history played a role. On the other hand, siblings also may share common environmental exposures.

Although older maternal age is a strong risk factor for Down syndrome, none of the three children born with Down syndrome in the study area was born to a mother older than 30 years. Elevations remained even after maternal age, race, and education were controlled in the Health Statistics Review.

Increases in the prenatal diagnosis and the subsequent elective termination of chromosomally abnormal pregnancies have affected the live birth prevalence of Down syndrome in New York State (Olsen et al., 1996). Prenatal diagnosis of Down syndrome has increased substantially since the early 1970s when amniocentesis in the second trimester was introduced primarily to women 35 and older (Olsen and Cross, 1997). Increases in the availability and development of new techniques used in prenatal screening, including the routine use of prenatal ultrasonography, use of chorionic villus sampling, and development of new biochemical screening for maternal biomarkers have increased rates of prenatal diagnosis of Down syndrome. Data from the New York State Chromosome Registry showed that the prenatal cytogenetic diagnosis of Down syndrome increased between 5 and 6-fold in New York State from 1979 through 1993. The proportion of women under 35 using prenatal diagnosis has steadily increased in association with an increase in prenatal tests performed because of abnormal maternal biochemical screening over the past two decades.

One potential explanation for the excess of infants with Down syndrome is inadequate access to early pregnancy screening and diagnostic tests for women under 35. Lower socioeconomic status (SES) and geographic distribution of laboratories may have prevented early screening and elective termination of Down syndrome affected pregnancies in the early years. As testing procedures improved and became less invasive and availability of laboratories and experts became more widespread over time, the differential screening by SES and geography would have been reduced. It is important to note that the excess was based on only three infants with Down syndrome while approximately one would have been expected in the study area over this period.

In mothers of infants with small for gestational age or term low birth weight, a number of conditions that may point to placental problems were recorded on the birth certificate including: early bleeding; placental abruption; and preeclampsia. Birth certificates also indicated chronic health conditions, low prepregnancy weight, and a history of previous preterm or low birth weight birth for mothers of infants with inadequate fetal growth. As in the case of heart defects, genetics or common environmental exposures may play a role in the pathophysiology of inadequate fetal growth.

There were a number of limitations in this case review. First, with the exception of the adjusted analysis of mothers' smoking status for births between 1998 and 2002, the review of birth certificate data was only a qualitative review of available data. Only the birth certificates of infants with these birth outcomes in the study area were reviewed so no comparison could be made with the New York State live birth population in the same time frame. Second, adverse pregnancy exposures (e.g. smoking, maternal disease) are more likely to be recorded on the birth certificate when an infant has a poor birth outcome. Third, data for smoking were not available for the entire study period but only

for the final 14 years of the study. However, the largest relative risk for SGA and low birth weight births occurred during the last 5 years of the study. Despite these limitations of the case review, the findings highlight the importance of smoking, potential occupational exposures, maternal and pregnancy conditions, and family history when reviewing adverse reproductive outcomes.

5.0 Cancer Incidence Adjusting for Race

5.1 Background

In the initial health statistics review (ATSDR 2006), significant excesses of testicular and kidney cancer were observed. In addition, non-significant excesses were observed for lung and esophageal cancers. Several reviewers of the initial health statistics review noted that there was a smaller proportion of minorities in the study area than among the group we used as our comparison group (New York State, excluding New York City). In the Endicott study area, the proportion of the population that was white ranged from 97% in 1980 to 89% in 2000, while in the comparison group the proportion of the population that was white was 92% in 1980 and 85% in 2000. Since the population of the study area was predominantly white throughout the study period, and because the incidence of several cancers found to be elevated differs by race, we have compared the incidence of cancer among whites in the study area to that of whites statewide, excluding NYC.

5.2 Methods

NYS DOH reviewed cancer incidence data for all sites of cancer both individually and combined among whites in the study area for the years 1980-2001. As in the previous study, the New York State Cancer Registry served as the source of information on individuals diagnosed with cancer used in this investigation. Methods used to evaluate the incidence of cancer among whites in the study area were identical to the initial health statistics review except as noted below.

Reports of diagnoses of cancers among whites were selected from the original study population. The number of expected cancer diagnoses was calculated using cancer incidence rates for whites only in New York State exclusive of New York City. All calculations were based on malignant cancers recorded in the New York State Cancer Registry database as of February 2006. Cancer rates for four periods of observation (1980-1984, 1985-1989, 1990-1994, and 1995-2001), and 18 five year age intervals (0-4 through 80-84 years and 85 years and older) were obtained to adjust for age and year of diagnosis.

Population estimates for the Census blocks comprising the study area were tabulated from the US Census of Population and Housing and used in the calculation of expected numbers of cancer cases for the study area. Since the study spans the period 1980-2001, population estimates from the 1980, 1990 and 2000 Censuses were used. The 1980 Census presented data differently than the 1990 and 2000 Censuses at the census block level. Data in several blocks in the 1980 Census were suppressed at the block level to maintain confidentiality. Additionally, the 1980 Census did not break down gender and race into 5 year age intervals, as we used for the cancer rate analyses.

In the 1980 Census, data for certain Census blocks with limited population were suppressed. For these blocks only the total number of persons in the block is reported, not the detailed information on age by gender by race of these individuals. To develop a distribution of age groups by gender for each of these blocks, the distribution by age group and gender of the larger block group to which the suppressed block belonged was

applied to the number of people in that block. For the 1980 calculations, 51 people from the Eastern study area and 84 people from the Western study area had their age group and gender imputed based on their block group distribution. This amounted to less than 4% of the population in our study area. None of the census blocks for which we imputed age groups, contained group quarters, such as nursing homes, which could have skewed the distribution of the population within a block.

The 1980 Census provided more limited information on race by age group. Detailed race data are presented for only 4 age groups at the block level: 0-4, 5-17, 18-64, and 65+. To determine an estimated white population in each of the 18 age groups, the total number of people within each block for each of the 18 age groups was multiplied by the percentage of whites within the broader age category into which the age group fell. Where the breaks for the available age ranges did not align with the original age ranges used in the analysis, data were weighted by the proportion of the age range covered. Because approximately 97% of the population in the study area identified themselves as being white in the 1980 Census, these estimations are unlikely to affect the analysis of the outcomes under investigation.

Age-adjusted standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated for each type of cancer among white males, white females, and both combined. As in the initial study, the Poisson probability distribution, which is used to describe the occurrence of rare events, was used to calculate 95% confidence intervals. Two-tailed tests were used to identify significant excesses and deficits in cancer.

5.3 Results

A total of 339 cancers were observed among the white population of the study areas between 1980 and 2001 while approximately 345 cases would have been expected in the study areas during this time based on statewide cancer rates among whites (excluding New York City). This represents over 97% of the cancers identified in the initial study. There were only 8 diagnoses of cancer in people of other races in the study area over the 22 year period. A table of observed and expected numbers of cancers for individual cancer sites among whites is not given in this report to protect confidentiality.

Overall incidence of cancers among whites in the two study areas was similar to that reported in the initial health statistics review for the entire population. In the Eastern study area, the standardized incidence ratio of kidney cancer among white males was significantly elevated (SIR 2.42; 95% CI 1.0 – 4.76). No other statistically significant elevations or deficits of cancer were observed among white males, white females or among males and females combined in the Eastern study area. In the Western study area, the standardized incidence ratio of testicular cancer among white males was significantly elevated (SIR 7.02; 95% CI 1.45 – 20.53). No other statistically significant elevations or deficits of cancer were observed among white males, white females or among males and females combined in the Western study area.

When the data from both study areas were combined there was an elevation in testicular cancer among white males (SIR 2.83; 95% CI 1.04 – 6.17). In addition, there was a

statistically significant elevation in lung cancer among white males (SIR 1.39; 95% CI 1.00 – 1.90). Lung cancer among males had shown a similar elevation in the initial health statistics review, however, the elevation was not statistically significant (ATSDR, 2006). There was no statistically significant elevation of any type of cancer among white females. When data from both sexes were combined, there was an excess risk of kidney cancer (SIR 1.94; 95% CI 1.09 – 3.20) and lung cancer (SIR 1.30; 95% CI 1.01 – 1.65). Again, there had been a similar elevation of lung cancer among both sexes combined in the initial health statistics review; however, this elevation was not statistically significant.

5.4 Discussion

Limiting the analysis to just white individuals in the study area had little effect on overall cancer rates or SIRs. All cancers that were statistically significantly elevated in the previous analysis of the entire population remained elevated when the analysis was restricted to just whites. The incidence of both testicular and kidney cancer remained significantly elevated and the SIRs for the incidence among whites for both types of cancer were very similar to those for the entire population reported in the initial report (ATSDR, 2006). Kidney cancer incidence is slightly higher among blacks than whites in the United States (McLaughlin et al., 2006); while testicular cancer rates are over 6 times higher among white men than black men in the US (Sarma et al, 2006). Although the study area had a slightly higher proportion of whites than the comparison area, these differences do not appear large enough to have influenced the results.

With the exception of lung cancer, there were no other significant excesses or deficits of any types of cancer in the restricted analysis. Lung cancer among white males and among males and females combined was significantly elevated whereas in the previous health statistics review it had been elevated but the elevation did not reach statistical significance, although it was very close. The SIRs observed among the white population of the study area were almost identical to the SIRs that had been observed among the entire study population. Incidence rates of lung cancer in New York State, excluding New York City, are slightly higher among black males than among white males but higher in white females than black females.

The risk factors for these types of cancers as well as any possible associations with TCE exposure are discussed in great detail in the original report (ATSDR, 2006). While the removal of race as a potential confounder has been achieved in the current review, a number of other risk factors could not be controlled. Chief among these is the role of smoking in the development of cancer. Smoking is the major risk factor for lung cancer and kidney cancer, both of which were significantly elevated. In addition, the review of birth records indicates that smoking may be more prevalent within this population than in the general population. The lack of control for smoking is a major limitation of this review. Other limitations included limited information on exposure; lack of personal information such as medical history, dietary and lifestyle choices; lack of information on occupational exposures; as well as a relatively small study population which can make studying rare diseases difficult. Limitations are discussed in greater detail in the original health statistics review (ATSDR, 2006).

6.0 Case Record Review: Cancer

6.1 Introduction

Because kidney and testicular cancers were significantly elevated in the previous health statistics review (ATSDR, 2006), the records of individuals with these cancers were reviewed in depth. While kidney cancer is among the cancers most often associated with TCE exposure among humans, few human studies have reported an association between the risk of testicular cancer and exposure to TCE. However, in animal studies TCE has been shown to cause benign testicular tumors in rats (ATSDR, 1997). Therefore, follow-up using available information to evaluate known and suspected risk factors for both elevated cancer types was warranted.

The goal of this case record review was to evaluate individual risk factors and potential exposures to determine if any unusual factors may have contributed to the observed elevations in the study area. Cigarette smoking has been established as a causal agent for both kidney and renal pelvis cancers (NCI, 2002; McLaughlin et al., 2006). Studies have identified some occupations with an elevated risk of cancers of the kidney and renal pelvis, including coke oven workers in steel plants, dry-cleaning workers and workers exposed to asbestos, cadmium or certain industrial solvents, including TCE (McLaughlin et al., 2006). Occupational exposures to polycyclic aromatic hydrocarbons, solvents and dyes, metals, metal dust and cutting oils have been associated with an increased risk of testicular cancer (Sarma et al, 2006). Cancer of the testis has been observed to be more common among men working in certain industries, including the military, aviation, petroleum and natural gas, printing and leather finishing industries (Sarma et al, 2006). Therefore, smoking and occupational histories are important information for this record review.

The causes of many cancers, including kidney and testicular, are complex. Some factors that increase the risk of kidney cancer include misuse of certain medications (phenacetin, diet pills); having certain health conditions (obesity, hypertension); and having certain genetic conditions or inherited syndromes such as von Hippel-Lindau disease (NCI, 2002). Some factors that increase the risk of testicular cancer include having had an undescended testicle at birth or abnormal development of the testicles, family history of testicular cancer, and having Klinefelter's syndrome (Sarma et al, 2006). Therefore, NYS DOH also tried to obtain a medical/health history for each individual diagnosed with kidney or testicular cancer.

Different types of cancers have latency periods of varying lengths. Latency refers to the length of time between exposure to a cancer-causing or cancer-promoting (carcinogenic) agent and the diagnosis of cancer. Latency in humans is estimated to be from five to forty years for most solid cancers in adults. Therefore, it would be unlikely that an individual's cancer diagnosis is related to potential exposures in Endicott if the individual is a recent arrival to the Endicott area as opposed to a lifelong resident. Due to latency and the fact that the Cancer Registry reports only the individual's address at the time of diagnosis, NYS DOH attempted to use additional sources of information to determine

residential histories to the greatest extent possible for each of these individuals diagnosed with cancer.

6.2 Methods

NYS DOH attempted to obtain information from multiple sources about each individual in the study area diagnosed with kidney and testicular cancer including: hospital medical records; cancer registry records; death certificates; newspaper obituaries or death notices (when deceased); NYS Department of Motor Vehicle (DMV) records; and city and telephone directories. City directories allow the lookup of individuals either by name or address. Information was not available for all individuals from all sources. For example, hospital medical records were not available for every cancer diagnosis, particularly when individuals were diagnosed many years ago or at a facility outside of New York State. Therefore, multiple, perhaps overlapping sources of information were used, seeking adequate information to evaluate risk factors and potential exposures for each individual.

NYS DOH requested and reviewed available hospital medical records. These records were reviewed both to confirm the cancer diagnosis and to gather information on health history and personal risk factors as well as occupational and residential histories, whenever possible. Additional data fields were requested from the cancer registry and reviewed for each cancer diagnosis. The additional data fields provided information about the cell type, including morphology and histology, and the grade of the tumors. Staff transcribed death certificate information from Vital Records files for any deceased individuals and obtained additional occupational and residential information from newspaper obituaries or death notices whenever possible. DMV records, historical telephone directories and city directories (Hill-Donnelly and Calkin-Kelly) were used to try to trace each individual's residential history and confirm dates of residence in Endicott.

6.3 Results

Kidney and Renal Pelvis

There were 15 individuals with kidney or renal pelvis cancer diagnosed in Endicott between 1980 and 2001. Nine were male, six were female and all were white. The average age at diagnosis was 69 years, with most individuals ranging in age from early 50's to mid-80's. Most of the individuals diagnosed with kidney cancer are deceased. In terms of anatomical site distribution, the vast majority were cancer of the kidney as opposed to renal pelvis. About half of the tumors were classified simply as "renal cell carcinoma" with no specific cell subtype reported. The small number of cell subtypes reported included clear and transitional cell carcinoma. Histologic grade² was not available for most of the kidney and renal pelvis cancers. Where information on grade was available, the majority were classified as "moderately differentiated".

² Histologic grade refers to the degree to which cancer cells resemble normal cells and can be taken as a measure of the aggressiveness of the tumor. "Well differentiated" cells resemble normal cells the most and are least aggressive, while "poorly differentiated" cells resemble normal cells the least and are most aggressive.

No smoking information was available for six of the individuals diagnosed with kidney/renal pelvis cancer. For the remaining nine individuals, pooled information from cancer registry records and hospital medical records suggests that approximately half were current or former smokers while the other half did not report smoking cigarettes. Of the 13 individuals diagnosed with kidney/renal pelvis cancer for which occupational history was known, about half had occupations or employers that suggest chemical exposures at work were possible or even likely.

No medical history was available for one-third of the kidney and renal pelvis cancers. Of the remaining ten, several individuals had medical conditions in their health histories which are potential risk factors for kidney cancer such as hypertension, previous cancer diagnoses, radiation therapy and history of hysterectomy.

Pooled information from city and phone directories as well as other sources suggests that about half of the individuals diagnosed with kidney cancer were long-term (greater than 20 years) Endicott residents. Of the remaining group, about half of the individuals could possibly be classified as “recent arrivals” to the Endicott area since their residence in the community can only be documented for less than five years. A small number appeared to be Endicott residents for just one or two years prior to diagnosis.

Testicular

Six individuals were diagnosed with testicular cancer among residents of the Endicott study area during 1980-2001. No medical records were available from the time of diagnosis for any of these individuals, so only a limited evaluation of some factors is possible. The average age of diagnosis was 39 (ranging from mid 20's to mid 50's). Both types of testicular cancer (seminoma and non-seminoma) were present in this group, with most of the cases being the more common seminoma type. No information on the stage of the cancer at diagnosis was available for any of the cases.

All cases were diagnosed during during a 12 year period from 1984-1996. Based on information collected from city and phone directories as well as other sources, the average length of time an individual diagnosed with testicular cancer lived in the study area was about 10 years (ranging from less than one year to almost 40 years). The median duration of residence was considerably less, however, at 4.5 years.

Information about the smoking habits of individuals diagnosed with testicular cancer was only available for about half of the individuals with some reporting being current smokers. Where it was available, none of the occupational histories suggested workplace chemical exposures. Of the six individuals diagnosed with testicular cancer, at least one had a known non-environmental risk factor for the disease.

6.4 Discussion

This case record review was a qualitative evaluation of available information. Quantitative measurements were not made. Therefore, no definitive statements can be made about the relationships between potential exposures and cancer occurrence in Endicott. Instead, NYS DOH hoped to gain insight into personal risk factors and

potential exposures for each individual diagnosed with cancer to determine if any unusual factors may have contributed to the observed elevations in the study area. The most severe limitation of this cancer case record review was a lack of available information, particularly for individuals diagnosed with testicular cancer where no medical records of the cancer diagnosis were available and death certificate or death notice information was also not available because none were deceased at the time of this investigation.

While the previous health statistics review identified a significant elevation in the number of kidney/renal pelvis cancers in Endicott, this case record review did not reveal any unusual patterns in terms of age, gender, year of diagnosis, anatomical site, cell type, or mortality rate. Kidney/renal pelvis cancer occurs more often among men than among women and is most frequently diagnosed in older people (current median age for kidney cancer diagnosis in the United States is 60 years). In Endicott, 60 percent of individuals diagnosed with kidney cancer were male and the median age at diagnosis was 69 years. Individuals were diagnosed throughout the 21 year period with no obvious clustering in time. The anatomical site and cell type distributions were as expected.

The case record review produced limited information about personal exposures (residential and occupational histories) and potential risk factors (cigarette smoking and health histories) for some but not all of the individuals diagnosed with kidney cancer. The information that we were able to gather through the record review suggests that cigarette smoking is an important risk factor and may have contributed to the elevated rates of cancer observed. Detailed residential and occupational histories for each kidney/renal pelvis would also be useful since information obtained through the case record review suggests that some individuals may not have been long-time Endicott residents and/or may have worked in jobs where they were exposed to chemicals or substances that have been associated with kidney cancer. Lastly, medical records were not available for some individuals or were not available for the hospital visit when the cancer diagnosis or surgery occurred, but rather for some other health condition or illness. Therefore, a detailed health history including risk factors pertinent to kidney cancer was often lacking and could not contribute to an evaluation of any unusual factors that may have played a role in the observed elevations in the study area.

Overall, while testicular cancer was significantly elevated, the pattern of the disease is about what we would expect. The individuals were diagnosed in the same age groups as we would expect, based on patterns of diagnosis in the US, where over 90% of testicular cancer is diagnosed among men aged 20-64. This is true both for testicular cancer as a whole and for the specific forms of testicular cancer diagnosed in this community. The type of testicular cancer is also consistent with the national distribution of testicular cancer.

An evaluation of the timing of these diagnoses is helpful in evaluating what we would expect to see if this elevation in testicular cancer is directly attributable to residing in Endicott. The diagnoses were also fairly evenly spread out during the time period covered by the health statistics review. This lack of temporal clustering suggests that the elevation may not have been due to a single event at one point in time. This is consistent

with the fact that residents of Endicott were likely exposed to site-related chemicals over an extended time period. However, the available information suggests that several individuals diagnosed with testicular cancer were recent arrivals in the area. Given the long latency between exposure to carcinogens and diagnosis of cancer, this information suggests that site-related chemicals were not likely related to at least some of these diagnoses.

7.0 Conclusions

This health statistics review was conducted to address concerns and to provide more information related to elevated cancers and adverse reproductive outcomes identified in the initial health statistics review (ATSDR, 2006). Additional quantitative analyses were carried out for birth outcomes and cancers among whites and a qualitative examination of medical and other records was conducted of individuals identified with certain adverse reproductive outcomes and cancers. Although these additional analyses cannot determine whether there is a causal relationship between VOC exposures in the study area and the increased risk of several health outcomes that were observed, they do provide more information to guide additional follow-up. We have identified a number of follow-up options which are outlined in the Recommendations section below.

Two additional reproductive outcomes, spontaneous fetal deaths and conotruncal heart defects, were examined because of evidence in the literature suggesting a possible association with TCE. Both of these outcomes are rare events and thus the analyses of both were limited by small numbers. Results of the spontaneous fetal death analyses did not support an association between living in the exposure area and an increased risk of fetal deaths although the analysis was further limited by issues with data quality and completeness. Because of these data issues no further review of existing fetal death records is recommended at this time. Results of the conotruncal heart defect analysis, however, did show a significantly elevated risk among women living in the study area. Interpretation of these results must be made with caution due to the extremely small number of infants with this type of birth defect in the study area.

Review of additional information did not change the interpretation from the previous review, that heart defects were elevated in the Endicott study area. Information about the heart defect and conotruncal heart defect elevations should be shared with the research community so that other researchers can consider these findings as they conduct birth outcome studies and/or surveillance.

The qualitative analysis of birth records provided some additional information on the role of potential risk factors for term low birth weight and SGA. The most compelling data showed that a high proportion of the mothers in the study area smoked during pregnancy. The prevalence of smoking among mothers of term low birth weight and SGA births was several times higher than that of statewide surveys of pregnant women. This suggests that elevated smoking prevalence among women in this area is at least partly responsible for the elevated rates of low birth weight and small for gestational age births; however, this does not mean that exposure to TCE did not also play a role. To learn more about the possible roles of smoking and VOC exposures any future studies would have to include individual level information about both types of exposures.

Limiting the analysis of cancer to just white individuals had little effect on overall cancer rates or SIRs. Results were similar among whites as those of the entire study area population analyzed previously. Nonetheless, it would be worthwhile to take race into account in any future analyses where possible.

The qualitative analysis of medical records of individuals diagnosed with testicular and kidney cancer provided some additional information on individual risk factors to identify any unusual patterns. However, the limited amount of information obtained from existing records suggests that direct contact with these individuals or next of kin (or control subjects) may be necessary to obtain the kind of information needed to fully evaluate residential, occupational and smoking history. One source of data not utilized, company records from IBM and other local employers, may provide useful information on occupational exposures.

As with the reproductive outcomes, there was some evidence of an increased prevalence of smoking among individuals diagnosed which may have played a role in the development of kidney cancer in some individuals. This does not mean that exposure to TCE did not also play a role. In addition, there was also some evidence that several of the individuals diagnosed with cancer may have been recent arrivals to the area suggesting that their cancers may not be related to site-related chemicals. However, we also have no information on individuals who may have lived in Endicott for many years but moved prior to being diagnosed with cancer and thus would not have been included in the study. Therefore, the follow-up review does not alter the original findings of elevated rates of kidney and testicular cancer in the Endicott study area.

8.0 Recommendations

Information from a variety of sources, summarized in this review, was considered as we assessed the feasibility of conducting various types of follow-up epidemiologic studies as the next action in the step-wise approach to addressing health concerns related to environmental contamination in Endicott. The results of the analyses of cancer (taking account of race), spontaneous fetal deaths, birth outcomes (taking into account smoking), and the case record reviews of kidney and testicular cancers, heart defects, Down Syndrome, and term low birth weight were examined along with the results from the earlier health statistics review. Also taken into consideration was information on historical exposures and the results of statistical power calculations (i.e., statistical analyses estimating the sample size required for a study to have the ability to detect an association between exposure and outcome if one exists).

At this time, an analytical (case-control) epidemiologic follow-up study of cancer or birth outcomes within this community is not feasible for several reasons. The health statistics reviews already conducted for the Endicott study area used statewide comparison data to evaluate whether outcomes in the study area were elevated. However, an in-depth epidemiologic study would gather individual information from people with and without cancer, or from mothers with and without adverse birth outcomes to make comparisons using much more detailed information than what is available in statewide databases. Statistical power calculations show that the size of the population in the Endicott study area is too small for conducting such an in-depth study, given that the health outcomes of concern (i.e., birth defects, cancer) are relatively rare. The health statistics reviews had sufficient statistical power because the analyses include data from statewide populations (excluding New York City). A more detailed examination of the statistical power calculations used to make this determination has been included as an addendum to this report.

The size of a study population is a major factor in determining what questions an epidemiologic study can answer. Another important factor is the proportion of the study population that has experienced the exposure of concern. While we could expand our study to include a much larger area in order to include larger numbers of health outcomes, this leads to a smaller proportion of people with the exposure of concern, and this also adds to the problem of low statistical power. Given the rarity of the health outcomes in question, the relatively small size of the Endicott area population, and the relative rarity of similar exposures within larger populations, the power calculations indicate that a study of health outcomes in the Endicott area would be too small to succeed. If a more thorough epidemiologic study does not demonstrate a significant relationship between an exposure and a disease under these conditions, the results may be interpreted as saying the exposure was not related to the disease, when, in fact, because of the low statistical power the study may never have had the ability to show a relationship between a disease and exposure in the first place.

While an analytic epidemiologic study of health outcomes in the Endicott study area is not feasible at this time, several possible options for follow-up are described below. Any

follow-up activities should be capable of accomplishing one of two goals: either to advance the scientific knowledge about the relationship between VOC exposure and health outcomes or to be part of a response plan to address community concerns. While not mutually exclusive, the distinction between these goals must be considered when developing a follow-up approach. NYS DOH worked with community members to discuss next steps and provide additional information during the comment period to inform the community about possible follow-up activities and encourage submission of comments about these options. The possible options are summarized in Table 2 and described more fully below.

Occupational Study

The exposures to TCE and other chemicals experienced by workers at the IBM site are likely to be significantly higher than those experienced by residents of the surrounding area. Furthermore, better information on exposure levels and duration of exposure may be available through occupational records to help quantify the occupational exposures. These factors may make a study of site workers a practical solution to examining associations between TCE exposure and health outcomes such as cancer. The National Institute for Occupational Safety and Health (NIOSH) has determined that an occupational health study of current and former IBM Endicott workers is feasible.

At the same time, we must also keep in mind that the exposures experienced by workers are likely to differ from those experienced by the residential population through environmental pathways. However, since IBM was a major employer in the area and many residents may have experienced exposures through a number of pathways, both environmental and occupational, an occupational study may provide valuable information to the community as a whole.

Health Statistics Review based on historic outdoor air emissions

ATSDR recently conducted a modeling exercise to evaluate the historic outdoor air emissions for several VOCs in the Endicott area (ATSDR, 2006b). Due to insufficient information, it was not possible to model TCE in this study; however the results for historical outdoor air emissions of methylene chloride and tetrachloroethene (PCE) both indicate that a larger geographic area was impacted via this pathway. ATSDR has estimated that the population possibly exposed to these chemicals in ambient air is several times larger than that of the current study area. A health statistics review of persons living in Endicott and the surrounding communities exposed to VOCs through historic outdoor air emissions should provide additional information on the potential impact of these exposures on the health of the community. A larger study population would provide researchers with greater power to detect significant elevations in health outcomes if they exist. If results are similar in the larger study area, it may indicate that additional exposure pathways may be contributing to disease in the community.

The health statistics review would, however, be an ecological study, similar in design to the one conducted previously and thus subject to similar limitations. Limited information on exposure, lack of personal information such as medical history; dietary and lifestyle choices; and lack of information on occupational exposures would limit the interpretation

of results. While we may use some of the lessons learned from the current analysis to better account for some of these factors, this type of study can not be used to draw causal inferences.

Update Health Statistics Review with additional 5 years of data

The results of the current health statistics review reflect cancer diagnoses during 1980-2001, birth defects during 1983-2001, and other adverse reproductive outcomes during 1978-2002. The health statistics review could be updated when an additional 5 years of data become available. This would include cancer diagnoses during 2002-2006, birth defects during 2001-2005, and other adverse reproductive outcomes during 2003-2007. By continuing to examine these health outcomes over a longer period of time, additional information may be obtained. Specifically, it may be possible to determine if the cancer elevations are persisting over time, and if the trends in reproductive outcomes are continuing. If those reproductive outcome trends continue into the future, they may not be related to the soil vapor intrusion pathway, as that problem was mitigated in 2003. These data will likely be available for analysis by 2008. As noted previously however, this update of the health statistics review would be an ecological study similar in design to the original one and thus subject to many of the limitations previously mentioned.

Case series review using interview information

The case record review completed on the kidney and testicular cancers and heart defects was subject to many limitations on the amount and type of information available in official documentation. These limitations constrained the conclusions that could be drawn about these specific individuals. A case series review conducted for infants with heart defect and individuals diagnosed with kidney and testicular cancer identified in Endicott, using interviews of parents, next of kin or the individuals themselves, should be able to elicit better information on exposures, risk factors, residential and occupational histories, and potential confounders. The additional information collected during such a study may allow more definite conclusions regarding the impact of potential risk factors on adverse health outcomes. However, this review would not have a comparison population to compare to the individuals under examination as an analytical epidemiologic study would. Therefore, we would not be able to draw causal inferences.

In addition, this activity could also serve as a pilot study for conducting the multi-site epidemiologic study described below. The level of success obtained in locating, contacting, and interviewing individuals who may have been diagnosed 25 years ago will give us an indication of how feasible this type of study would be on a larger population and of the resources that would be needed to conduct such a study.

Include Endicott residents in NYSDOH VOC Exposure Registry

NYS DOH currently maintains an exposure registry for individuals who live in areas where exposures to VOCs from drinking water or soil vapor intrusion have been documented. The Registry project begins with a list of potentially exposed households' addresses, and adds information over time on health effects for individuals residing at these addresses. Health outcome information comes from existing sources such as birth certificates and cancer records. The Registry currently includes areas impacted by a

variety of VOCs. The majority of households in the Registry to date were included due to exposures to TCE, PCE or methyl-*tert*-butyl ether (MTBE). At this time, the total number of households in the Registry due to either TCE and/or PCE exposures is approximately 214, much smaller than the total number of households in the Endicott study area.

The Registry's primary goal is to facilitate combining data from different geographic areas where similar exposures have been identified, so that health effects within larger populations can be assessed. Over time, depending on the number and size of additional communities that are identified as soil vapor intrusion sites, the Registry data could be used to combine areas for a health statistics review in a larger population. Because soil vapor intrusion as a pathway for exposure is currently being investigated at many sites in New York State, VOC Registry plans are being developed with the expectation that some other relatively large areas may be identified for inclusion in the Registry. However, it is not possible at this time to predict the size or number of these communities. In addition, as the Registry population grows over time, information about health effects among individuals living in VOC Exposure Registry areas could potentially be used to develop an analytic (case-control) study from within the VOC Registry population. This option is discussed next.

It is important to point out, however, that information derived from the VOC registry would not provide additional information specific to the health status of Endicott residents but rather would allow researchers to assess the health status of residents with similar exposures across the state.

Future multi-site epidemiologic study

An effort is being made to identify other communities across the state with VOC exposures similar to those in Endicott. When several communities with exposures similar to those in Endicott are identified it may be possible to develop a multi-site study of these populations. By aggregating these communities, the sample size and subsequent power limitations currently prohibiting an analytic epidemiologic study in Endicott may be overcome. Such a multi-site study would not provide information specific to the health status of Endicott residents. We are confident, however, that the communities selected for the study would be similar enough that the study conclusions could be applied to each of the communities included in the multi-site study.

9.0 Action Plan

Based on interactions with the community and comments on this report, community interest focused on two possible options for future activities: a health statistics review based on historic outdoor air emissions modeling and a multi-site epidemiologic study examining cancer outcomes in communities across the state with VOC exposures similar to Endicott. NYS DOH has considered these comments and examined whether these options would be able to accomplish one of two goals: either to advance the scientific knowledge about the relationship between VOC exposure and health outcomes or to be part of a response plan to address community concerns.

An additional health statistics review using historic outdoor air emission modeling results to identify and study a larger population of residents potentially exposed to TCE is not likely to meet either of these goals at this time. Because of the limitations of the health statistics review for drawing conclusions about cause and effect, conducting an additional health statistics review is not likely to increase our understanding of whether exposures in the Endicott area are linked to health outcomes. Limitations with the available historic outdoor air data also would make it difficult to accurately define the appropriate boundaries for the exposure area. ATSDR historic outdoor air emissions modeling activity was unable to model TCE due to a lack of available records.

A multi-site epidemiologic study of health outcomes in communities across the state with VOC exposures similar to Endicott offers some promise of meeting the goal of advancing the scientific knowledge about the relationship between VOC exposures and health outcomes. The community has indicated its preference that such a study focus on cancer outcomes. Given the complex issues involved in conducting such a study (e.g., tracking down cases or their next of kin after many years, participants' difficulty in accurately remembering possible risk factors from many years ago, and the long time period between exposure to a carcinogen and the onset of cancer), we do not consider a multi-site case-control study of cancer as the best option at this time. An occupational cancer study is a better option than a community-based study because it can better incorporate information about past workplace exposures and could use corporate records to assist in finding individual employees many years after exposure.

Heart defects have been associated with TCE exposure in other studies. Given the shorter latency period, and thus the shorter time period in which other risk factors could come into play, a multi-site study of heart defects has some merit as a possible option. Currently, NYS DEC and NYS DOH are investigating many communities around New York State which could have VOC exposure patterns similar to Endicott, and thus could be included in such a multi-site epidemiologic study. However, in most of these communities exposure information sufficient to identify a study population is not yet available. NYS DOH will continue to evaluate these areas as additional exposure information becomes available, with the goal of identifying other communities for possible inclusion in a multi-site epidemiologic study of heart defects. NYS DOH will continue to keep the Endicott community and stakeholders informed about additional information regarding other communities with exposures similar to those that occurred in

the Endicott area. NYS DOH staff will be available as needed to keep interested Endicott area residents up-to-date on the feasibility of conducting a multi-site study that includes the Endicott area.

10.0 References

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Table 1. Conotruncal heart defects examined in the Endicott area.

Conotruncal Heart Defects Examined*	ICD-9-CM code
Common truncus (or truncus arteriosus)	745.0
Double outlet right ventricle and D-transposition of the great arteries	745.1
Tetralogy of Fallot	745.2

* Due to the nonspecificity of ICD-9-CM codes for interrupted aortic arch (type B) and malalignment ventricular septal defects, codes 747.11 and 745.4 were not used. The impact of this exclusion should be minimal since these defects are very rare.

Table 2. Options for Endicott Follow-up Study Plan

Options	Strengths	Limitations
1. Analytical epidemiological study of cancer or birth defects within this community alone is <i>not</i> feasible at this time.	An analytical epidemiologic study is better able to show a causal relationship between an exposure and a health outcome. Additional risk factors for the disease can be better accounted for.	Small population, rare exposure and low power among this population limit the ability to detect meaningful differences.
2. An occupational study may be a more practical solution to analyze the associations between TCE and cancer within the Endicott area.	An occupational study would allow researchers to focus on individuals with higher and perhaps more quantifiable exposures.	Exposures experienced by workers in an occupational cohort are likely to differ from those experienced by the residential population through environmental pathways.
3. Conduct a health statistics review among persons in the Endicott and surrounding communities who were exposed to VOCs through historical outdoor air emissions.	ATSDR has estimated that populations several times that of the current study area may have been exposed to VOCs through this additional pathway. The greater sample size would give the study greater power to detect significant elevations in health outcomes if they exist. This would also allow NYS DOH to determine if the elevations in certain health outcomes observed are elevated throughout the region.	This would be an ecological study and thus subject to the limitations of this type of study. Limited information on exposure, lack of personal information such as medical history; dietary and lifestyle choices; and lack of information on occupational exposures would limit the interpretation of results. In addition, this type of study can not be used to draw causal inferences.

4. Update the current Endicott Health Statistics Review with an additional 5 years of data when they become available. It is estimated that the next 5 years of data will be available by 2008 for each of the outcomes.

Outcome	Data Years
Cancer	diagnosed 2002-2006
Birth Defects	births 2001-2005
Birth Outcomes	births 2003-2007

Cancer – Would determine if elevations observed previously continue to persist.

Birth outcomes – Would determine if trends observed previously continue. If elevated rates of birth defects, small for gestational age and term low birth weight continue then these outcomes may not be related to this particular exposure/pathway since the problem was mitigated in 2003.

Again, this would be an ecological study and thus subject to the limitations of this type of study described above.

5. Case Series Review: Interview study for the kidney (n=15) and testicular (n=6) cancer cases and heart defects (n=20) identified in Endicott.

This can also serve as a pilot study or feasibility study for conducting a future multi-site analytical epidemiological study described in option 7.

We will be able to elicit better information on exposures, risk factors, residential and occupational histories and potential confounders for the Endicott cases.

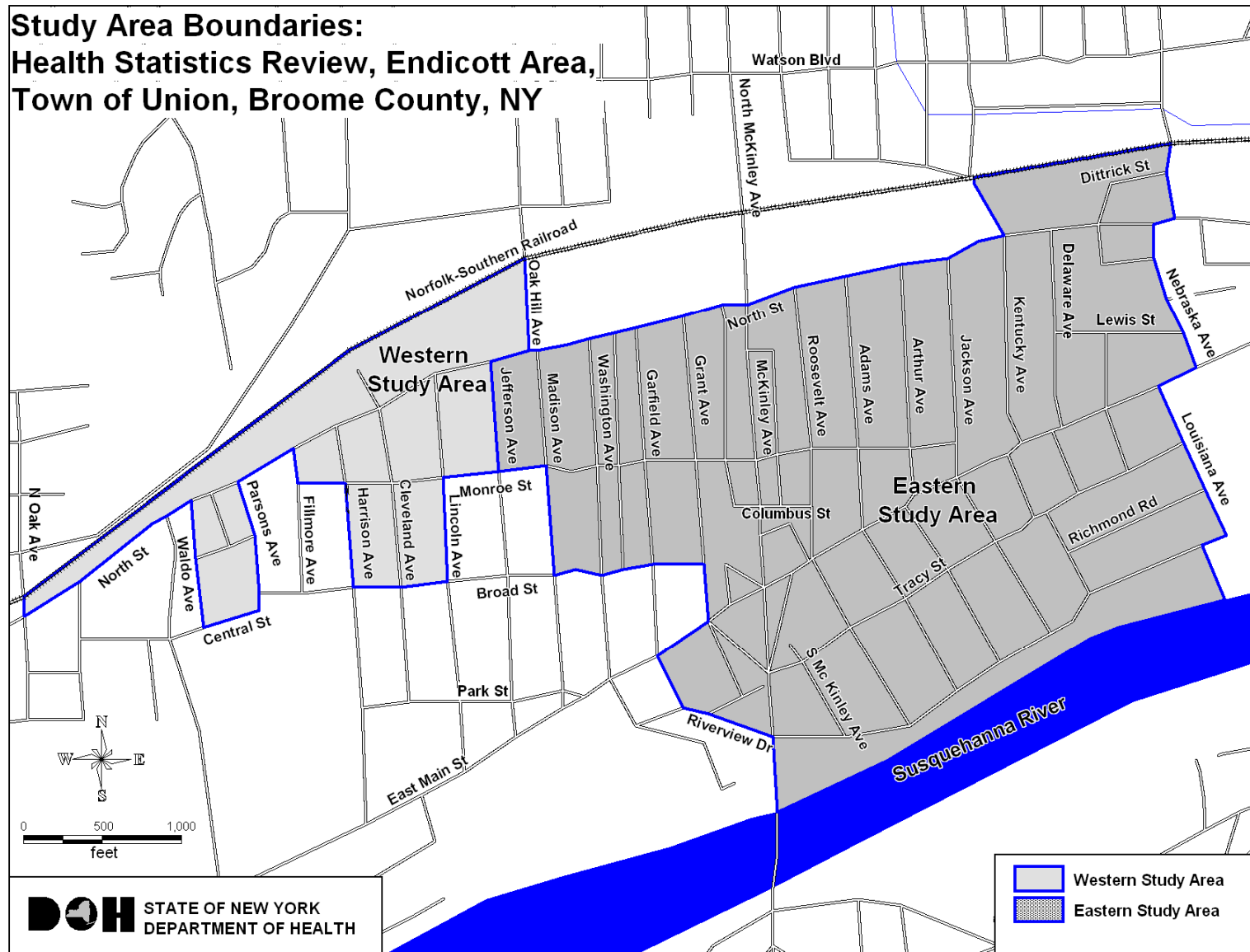
Attempting to locate, contact and interview individuals who may have been diagnosed up to 25 years ago will give us an indicator of the amount of time and resources needed to undertake the task on a larger basis, if in fact it is feasible at all.

In addition, the tool that is developed and used to gather information from the cases, parents and next of kin for this review will be at least as inclusive and will serve as the basis for the tool we would use in the multi-site analytical study discussed in option 7.

This review would not have a comparison population to compare to the population under examination as an analytical epidemiologic study would. Therefore, we would not be able to draw causal inferences

<p>6. Include Endicott residents in the NYSDOH VOC Exposure Registry (VOCER).</p>	<p>The VOC Exposure Registry is beginning to include vapor intrusion sites statewide. We will be able to identify and enroll other communities with similar TCE exposures, and potentially develop a multi-site study population with exposures similar to those in Endicott.</p>	<p>This option would not provide information specific to the health status of Endicott residents.</p>
<p>7. Future multi-site analytical epidemiological study.</p>	<p>Other NYS communities with exposures similar to Endicott will be identified through the VOCER. A multi-site analytical study (including Endicott) would overcome sample size limitations.</p> <p>The similarities between the communities selected for the study should allow the study conclusions to be accurately applied to each of the communities included in the multi-site study.</p>	<p>This study would not provide information specific to the health status of Endicott residents.</p>

Figure 1. Map of the two Endicott study areas.





New York State Department of Health
Center for Environmental Health

Information Sheet

May 11, 2007

**Study Design and Statistical Power Considerations for
Endicott Area Health Statistics Review
Analytic Follow-up Study Options:
Birth Weight Outcomes, Congenital Heart
Defects, Kidney Cancer and Testicular Cancer**

**May 2007 Addendum to Public Comment Draft Health
Consultation of March 2007,
Endicott Area Investigation Health Statistics Review Follow-up
Cancer and Birth Outcome Analysis,
Endicott Area, Town of Union,
Broome County, New York**

Prepared by:
The New York State Department of Health
Center for Environmental Health
Troy, New York

under a cooperative agreement with

The U.S. Department of Health & Human Services
Agency for Toxic Substances and Disease Registry
Public Health Service
Atlanta, Georgia

For more information about this information sheet, please contact James Bowers, New York State Department of Health, Center for Environmental Health, 1-800-458-1158, ext 27950 or via email at beoe@health.state.ny.us

Study Design and Statistical Power Considerations for Endicott Area Health Statistics Review Analytic Follow-up Study Options: Birth Weight Outcomes, Congenital Heart Defects, Kidney Cancer and Testicular Cancer

What is statistical power?

Before starting a study, researchers check to make sure there is a good likelihood their study plan will lead to definitive results. An important consideration is whether the study's statistical analyses are likely to show an association between the potential exposure and the health outcome, if such an association exists. This concept is called statistical power.

Statistical power calculations are most often used as a tool for deciding on the appropriate size for a study, and 80% power is the standard.¹ Researchers use the power calculations to plan a study that will be large enough to have an 80% probability of showing a statistically significant result, if there is indeed an association between the exposure and disease.

In order to estimate study power, researchers first make decisions about study design, study time frame and statistical tests. They have to estimate the numbers of expected health outcomes and the level of increased risk possibly associated with the exposure. They also have to make assumptions about what proportion of the people eligible for the study will be located, contacted, and willing to participate.

What type of study design was considered?

A population-based case-control interview study is an efficient design for follow-up of elevations in birth weight outcomes, birth defects, kidney and testicular cancer. Each person with the adverse health outcome (case) who resided in Broome County at the time of diagnosis would be eligible for the study. For each case, three people from Broome County without the outcome (controls) would be selected randomly.

For the purposes of calculating study power, the potentially exposed group is assumed to be the size of the population of the Endicott study area from the Health Statistics Review (HSR), which comprises approximately 1.5% of the County's population. About 2.2% of the County's births occurred in the Endicott study area during the years covered by the HSR. The study would compare the proportion of people with the disease (cases) who live in the potential exposure area to the proportion of people without the disease (controls) who live in the potential exposure area. Information gathered from interviews on occupational exposures, smoking history and other risk factors would be used in the analyses.

For birth weight outcomes, the study would cover the most recent ten-year period prior to the installation of mitigation systems for birth weight outcomes. We chose ten years because finding and recruiting people with health outcomes occurring further back in time would be increasingly difficult. Study participants' recall of information about risk

factors and details of a pregnancy declines over time. In addition, the elevations in birth weight outcomes were most prominent in the most recent five years of the HSR. However, for the birth defects and cancer outcomes, the study would include the most recent 20-year period prior to mitigation, despite the difficulties of interviewing and enrolling people from that long ago. The 20-year time frame is needed so that the heart defects and cancers in the original HSR are also eligible for the follow-up study.

How are power calculations used in evaluating study feasibility?

For a study of environmental exposures that occurred in a specific community, we do not have the option of simply increasing the study's size to gain statistical power of 80% or more. This is because the size of the population that is exposed to an environmental contaminant is already fixed. In our evaluation of the feasibility of conducting follow-up studies for various health outcomes for the Endicott area, we used the power calculations to make judgments about whether in-depth studies in the Endicott area alone would have sufficient statistical power.

Because power estimates differ depending on study design decisions and assumptions, particularly about how successful the study will be at locating and recruiting eligible study subjects, we drew conclusions using the assumptions we thought were most appropriate and realistic. We attempted to be moderate in our estimates and assumptions, neither overly optimistic nor pessimistic.

What assumptions were made about participation rates?

The rate of participation is the proportion of the eligible study subjects that we are actually able to find, to reach by telephone or in person, and who agree to participate by completing an interview about risk factors for either birth outcomes or cancer. Researchers seek to have as high a participation rate as possible, but it has become increasingly difficult to achieve high participation rates in studies.

We show power estimates using a 50% participation rate, which is the absolute minimum we would want to achieve, versus a 70% participation rate which is desirable but difficult to achieve. Our interpretation of the power estimates was based on the assumption that a 50% -60% participation rate is most realistic.

Why does study power matter?

Study power is important for community studies because we do not want to raise expectations that a study will provide definitive answers about possible associations between risk factors and adverse health outcomes if it can be predicted in advance that a particular study is very unlikely to be able to do so. While study power is an important consideration for determining study feasibility, low power does not in and of itself prevent the research from being done. Other considerations are also important, including for example, the severity and impact of the health outcomes, the information available for

assessing the exposures to individuals, the exposure types and levels, as well as what is already known about possible risks of the specific exposures.

What are the statistical power results?

The attached table shows power estimates supporting the determination that a study using the Endicott study area population alone for the exposed group would lack statistical power.

- 1. Birth Weight Outcomes:** For **small for gestational age** births, the most frequently occurring birth weight outcome, we estimated the ability of a study to detect increased risk by assuming that the increased risk is 39%, from the rate ratio of 1.39 in the health statistics review, after controlling for mothers' smoking. These assumptions resulted in a low estimate of power, 43%, for a ten-year study, assuming a 50% participation rate. For a 10-year study with a 70% participation rate, power was 53%. **Term low birth weight** is the smallest subset of birth weight outcomes, but it is the outcome that remained statistically significantly elevated after adjusting for smoking in the most recent 5 years of the HSR. We used the rate ratio from the analysis that adjusted for smoking, 2.26, to estimate power. For a 10-year study with 50% participation, the power is 59%; for 70% participation, the power is 70%.
- 2. Congenital Malformations: Congenital heart defects** occur less frequently than term low birth weight births. The subset of **major heart defects** occur even less frequently, but are preferable for study partly because their severity results in diagnoses that are not influenced by screening practices. For a 20-year study of major heart defects, power of 48% is achieved with a 50% participation rate, and 57% power is achieved with a 70% participation rate. For **conotruncal heart defects**, a subset of major heart defects, a 50% participation rate produces 44% power and a 70% participation rate results in 52% power.
- 3. Kidney Cancer:** For kidney cancer, 50% participation yields study power of 45%; 70% participation yields 54% power.
- 4. Testicular Cancer:** For testicular cancer, which is much rarer than kidney cancer, the power estimates show that a 50% participation rate would provide 41% power, and a 70% participation rate would provide 48% power.

How did we interpret the numbers in the table?

Our prior recommendation in the HSR about feasibility was based on the desirability of having at least an 80% probability of seeing an association between the exposure and health outcome, if there were such an association. Assuming a 50% participation rate, none of the power estimates is above 60%, and with a 70% participation rate, the highest power level is 70%, for term low birth weight. Because of these low power estimates, we stated our opinion in the HSR that a study of the Endicott area alone was not feasible.

We instead presented a list of follow-up options including the option of a multi-site study (of areas with similar potential exposures) in order to increase the study population size and statistical power.

References

1. Whitley, E and Ball, J. "Statistics review 4: Sample size calculations," Critical Care, August 2002, Vol. 6, No. 4.

Endicott Area Health Statistics Review Analytic Follow-up Study Options: Statistical Power Calculations

Proposed Study ¹	Broome Co. rate per 1,000 births ² (Study #1, 2) or per 100,000 population ³ (Study #3, 4)	Odds Ratio from Health Statistics Review ⁴	Study time frame (years) ⁵	Estimated cases available in Broome Co. ⁶	Power ⁷		Births ⁸ (#1,2) or Person-Years ⁹ (#3,4) needed for 80% power ¹⁰	
					50% Participation	70% Participation	50% Participation	70% Participation
1. Birth Weight Outcomes								
Small for Gestational Age	9.67	1.39	10	2017	43%	53%	63,917	45,655
Low Birth Weight	5.05	1.48	10	1053	37%	46%	83,523	59,659
Term Low Birth Weight	1.95	2.26	10	407	59%	70%	40,184	28,703
2. Congenital Malformations								
Major Heart Defects	0.36	2.52	20	191	48%	57%	155,109	110,792
Conotruncal Heart Defects	0.11	3.74	20	60	44%	52%	200,484	143,203
3. Kidney Cancer	13.3	1.90	20	610	45%	54%	14,189,372	10,135,265
4. Testicular Cancer	7.7	2.83	20	140	41%	48%	7,714,286	5,510,204

Footnotes:

1. Each of the four studies listed would be a population-based case-control study, with a 3 to 1 control to case ratio.
2. The birth weight outcome rates are the observed numbers per 1,000 singleton births in Broome County for 1993-2002. The congenital malformation rates are the observed numbers per 1,000 live births in Broome County for 1983-2000.
3. The kidney cancer rate is the average number of cases per year per 100,000 male and female population in Broome County, 2000-2004. The testicular cancer rate is the average number of cases per year per 100,000 male population.
4. The odds ratios from the Health Statistics Review (HSR) for birth weight outcomes are adjusted for smoking as well as other risk factors. The odds ratios for congenital malformations, kidney and testicular cancer are not adjusted for smoking because the HSR did not include such adjustment.
5. See the document text for an explanation of why a 10-year study is proposed for birth weight outcomes and 20-year studies are proposed for the other outcomes.
6. The number of cases available for a Broome County study are estimated using the observed numbers of cases in Broome County.
7. Power estimates are calculated based on conducting one-tailed statistical tests, $\alpha = 0.05$. The power calculations use uncorrected chi-square estimates. The power estimates also depend on the ratio of births and population in the Endicott study area versus the rest of Broome County.
8. To see the relative size of the number of births for a study of Broome County alone, compare the births needed in this column for birth weight outcomes to the number of singleton births in Broome County for a 10-year period = 20,861. For congenital heart defects, the number of live births in Broome County for a 20-year period is 53,701.
9. To see the relative size of the person years (population x years) in the study option for kidney cancer in Broome County alone, compare the person-years needed in this column for kidney cancer to the population of Broome County multiplied by 20 (person-years) = 4,063,600. Similarly, for testicular cancer, using only the male population, person-years in Broome County = 1,961,640.
10. These estimates assume the same ratio of exposed versus unexposed population as in the Endicott/Broome County area for the additional population needed to expand the study. They also assume that the added populations will have equivalent health outcome rates (birth and cancer outcomes) as Broome County residents for the years shown in footnotes 2 and 3.

*Dupont WD and Plummer WD: PS power and sample size program available for free on the Internet. *Controlled Clin Trials*, 1997; 18:24. www.mc.vanderbilt.edu/prevmed/ps/index.htm, version 1.2.31, 2004.

APPENDIX A

Summary of Public Comments and Responses
Health Statistics Review Follow-up
Cancer and Birth Outcome Analysis, Endicott Area
Town of Union, Broome County, New York
Public Health Consultation

This summary was prepared to address comments and questions on the public comment draft of the Public Health Consultation, Health Statistics Review Follow-up for the Endicott Area, which was released March 26, 2007. The public was invited to review the draft during the public comment period which ran for six months from March 27 to August 27, 2007. We solicited comments on the draft consultation to understand remaining community concerns and questions. In return, we provide this summary of comments and written responses. We received comments from 29 entities, including current and former residents, local employees, and representatives of citizen groups. Some comments may be consolidated or grouped together to incorporate similar concerns. If you have any questions about this responsiveness summary, please contact James Bowers, NYS DOH, toll-free at 1-800-458-1158, ext 27950.

Comments About Future Activities

Comment 1. NYS DOH should conduct a multi-site epidemiologic study/expanded health statistics review to further evaluate the health of individuals potentially exposed to TCE and other chemicals.

NYS DOH received many comments advocating both a multi-site epidemiologic study of cancer, and an additional health statistics review using historic outdoor air emissions to define study areas. We have noted the community's input and have taken it into consideration while making decisions about what future activities will be conducted. For additional information about future activities, please see the "Action Plan" section of the Health Statistics Review Follow-up on page 27.

Comment 2. NYS DOH should provide additional information explaining the statistical power calculations used to determine that an analytical epidemiologic study of cancer or birth outcomes is not feasible within the Endicott community.

A more detailed examination of the statistical power calculations to make the determination about study feasibility is included as an addendum to this report.

Comments About Outreach Activities

Comment 3. NYS DOH should present the information from the Health Statistics Review Follow-up in a way that is easily understood by individuals without familiarity with public health or toxicology.

NYS DOH agrees that outreach activities in the Endicott area are important, and that information should be presented in a manner that can be easily understood by the average citizen. If there are specific comments on how this could be better accomplished, please contact James Bowers, NYS DOH, toll-free at 1-800-458-1158, ext 27950. For this report, outreach efforts have included activities such as:

- Production of information sheets designed to convey the main points of the health statistics review follow-up in a shorter and more simplified manner.
- Holding public availability sessions where NYS DOH representatives are available to answer questions and have one-on-one discussions with residents about the report.
- Routinely meeting with the local citizens group to discuss information with interested residents who then serve as knowledgeable resources for other community members.
- Disseminating contact information including toll-free phone numbers and email addresses of NYS DOH representatives who can answer questions and address concerns.

We will continue to work with the community on outreach activities and welcome continued input, advice, and partnership in our efforts.

Comments Outside the Scope of this Report

Comment 4. People all around me have been diagnosed with cancer. I am worried about the health of my family.

The original Health Statistics Review for the Endicott area, and the current Follow-up report have shown that the total number of all types of cancer within the study area are similar to what is expected in a community this size. These studies did identify elevations in testicular, kidney, and lung cancer (after adjusting for race) that are unlikely to be due to chance alone. However, this type of study cannot establish a cause and effect relationship between an exposure and a health outcome.

Unfortunately, cancer is a very common disease. One in two men and one in three women will be diagnosed with cancer at some time during their life. While cancer develops in people of all ages, it occurs most often in the middle-aged and the elderly. The number of cancer cases has risen over the past 40 years, but much of this increase is a reflection of the increase in the population, particularly in older age groups. The nature of cancer is often misunderstood. Cancer is not a single disease, but is rather a group of

diseases. There are more than 100 different types of cancer, each with different risk factors. Cancers of the prostate, lung and colon are the most common types diagnosed among adult males. Breast, lung and colon cancer are the most common among adult females.

If you have concerns about the health of your family, we recommend that you speak with your physician about ways to reduce your risk for cancer.

Comment 5. The testing of air, drinking water, and soil should be expanded to obtain a better understanding of what is happening in the Endicott area.

The NYSDEC, in consultation with the NYSDOH, is currently conducting an environmental investigation throughout the Endicott area as part of the Endicott Area Wide Study. The objective of this study is to define the extent of soil vapor and groundwater contamination outside of the IBM study area, as well as to identify any additional sources of environmental contamination. To provide comments or to obtain additional information, please contact Sally Dewes of the NYSDEC at 1-888-212-9586.

Comment 6. I was a long term resident of Endicott, and was diagnosed with a cancer identified as elevated in Endicott after moving away. I would like to be included in this study.

Unfortunately, including your cancer diagnosis in this particular review isn't possible, as it examines only those individuals whose cancer cases were diagnosed while they resided in the Endicott study area within the specified time period. To include persons who previously resided in the area for this type of study, we would need to contact and track all persons ever living in the entire study area back to 1980 to determine the appropriate number of expected cases and accurately determine the number of observed cases of cancer. To recreate this historic cohort of persons would be extremely challenging, given the mobility of the population and the percentage of renters.

Comment 7. NYS DOH and other governmental agencies have not done enough to protect the health of Endicott residents.

The NYSDOH, along with the Agency for Toxic Substances and Disease Registry (ATSDR) and the Broome County Health Department, drafted a public health response plan (PHRP) designed to document historic, on-going, and planned public health actions being undertaken to address specific human exposure(s) to environmental contaminants. One component of this document is an overview of actions that have been completed or are being proposed to address public health concerns. This document, along with documents relating to the on-going projects in Endicott, may be reviewed, at the George F. Johnson Memorial Library, Village of Endicott, 1001 Park Street, Endicott, NY 13760. Comments about this document can be made by calling Mr. Justin Deming at 1-800-458-1158 (extension 2-7880), by faxing at (518) 402-7859, or by emailing to BEEI@health.state.ny.us.

Comments on the NIOSH Feasibility Study

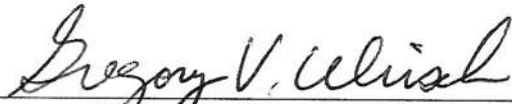
Comment 8. I would like to comment on the NIOSH study.

NYS DOH received a number of comments related to the NIOSH examination of the feasibility of conducting a study of cancer in current and former IBM-Endicott employees. NYS DOH forwarded these comments on to NIOSH so they could be considered by NIOSH during the comment period.

This report was updated to include NIOSH's determination about the feasibility of conducting a study of cancer in current and former IBM-Endicott employees.

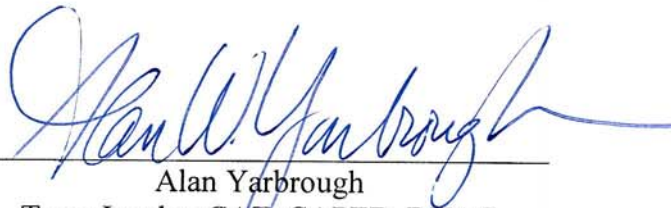
CERTIFICATION

The health consultation for the Village of Endicott Investigation, Endicott, New York, was prepared by the New York State Department of Health under a cooperative agreement with the Agency for Toxic Substances and Disease Registry. It is in accordance with approved methodology and procedures existing at the time the health consultation were initiated.



Gregory V. Ulirsch, MS, PhD
Technical Project Officer, CAT, CAPEB, DHAC
Agency for Toxic Substances and Disease Registry

The Division of Health Assessment and Consultation (DHAC), ATSDR, has reviewed this health consultation and concurs with its findings.



Alan Yarbrough
Team Leader, CAT, CAPEB, DHAC
Agency for Toxic Substances and Disease Registry