A CASE-CONTROL STUDY OF THE ASSOCIATION BETWEEN BIRTH DEFECTS ELEVATED IN NUECES COUNTY AND SITES OF CONCERN TO CITIZENS FOR ENVIRONMENTAL JUSTICE

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EXECUTIVE SUMMARY

Background In May 2001, a data request from Citizens for Environmental Justice (CFEJ), led to a series of reports by the Texas Department of Health looking at birth defects in the area around Corpus Christi Texas. The last of those reports recommended that a case-control study be conducted when there were more years of data available from the Texas Birth Defects Registry (TBDR). In July 2006, an analysis of TBDR data found that birth defects in the Corpus Christi area were 84% higher than in the rest of the Registry, and identified 15 birth defects to be examined in the case-control study. This report presents the results of the case-control study.

Objective The objective of this case-control study was to measure the association between the 15 selected birth defects and proximity of mother's residence to (mothers living near) the sites of concern as listed by CFEJ.

Methods The study examined births from 1996 through 2003 in Nueces, San Patricio, and Kleberg Counties (Corpus Christi is in Nueces County). Cases had to have one of the 15 birth defects. All live births without birth defects were used as the control group. The sites of concern (selected by CFEJ) included 46 landfills, 23 refineries or chemical manufacturing plants, 3 military airfields, Oso Creek, and 3 other sites: the old city incinerator, a toxic injection well, and a battery recycling plant. The boundaries of each site and the maternal residences at delivery of cases and controls were geocoded by the Texas Department of State Health Services Geographic Information Systems (GIS) group. The GIS group then calculated distance of each maternal residence to the nearest boundary of the nearest landfill, refinery / chemical manufacturing plant, airfield, Oso Creek, and other site. Those distances were categorized, and odds ratios calculated to measure the association between each of those types of sites and each of the 15 birth defects. Odds ratios were both crude and adjusted for potential alternative explanatory variables. Three criteria were examined that together increase the likelihood that associations are causal: high odds ratios (1.50 or greater), statistical significance, and proximity-response (higher odds ratios in mothers living closer to sites).

Conclusions In this study, there were no compelling associations observed between any of the 15 selected birth defects and proximity of mother's residence to Oso Creek. Gastroschisis exhibited high odds ratios and proximity-response with landfills, but this association was not statistically significant. Similarly, mother's residence near refineries and chemical manufacturing plants showed high odds ratios and proximity-response with anomalies of the diaphragm and gastroschisis, but those associations were not statistically significant.

There were some high and sometimes statistically significant associations between proximity to military airfields and heart valve defects, but those did not show proximity-response.

Maternal residence near the old city incinerator was highly and significantly associated with atresia/stenosis of the large intestine or anus in offspring but there was no apparent proximity-response. Odds ratios for obstructive genitourinary defects were high and showed proximity-response, but were not statistically significant.

The battery recycling site showed some high odds ratios with 5 of the birth defects. A proximity-response pattern seemed to be present for ventricular septal defect and obstructive genitourinary defect. However, none of the associations for the 5 defects were statistically significant.

Because the above associations did not meet all three criteria of high odds ratios, statistical significance, and proximity-response, there is little evidence that maternal residential proximity to those sites actually caused the birth defects examined in this report.

Further studies of the above birth defects especially near military airfields, the old city incinerator, or the battery recycling plant might produce more compelling results if conducted by investigators with the expertise and the time to gather additional data (for example, on operations information, wind speed and direction), conduct detailed exposure assessment, and perform complex analyses, such as the Centers for Disease Control and Prevention (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR), or a university researcher.

DETAILED REPORT

BACKGROUND

In May 2001, a data request was received from Citizens for Environmental Justice (CFEJ) regarding the occurrence of birth defects in an area comprising almost all of Nueces County, Texas. This led to a series of four reports that culminated in a case-control study of six birth defects with prevalences that were significantly higher than expected:

- Tetralogy of Fallot (a heart defect)
- Ventricular septal defect (a heart defect)
- Atrial septal defect (a heart defect)
- Patent ductus arteriosus (a heart defect)
- Obstructive genitourinary defect
- Possible/probable fetal alcohol syndrome (FAS) and other alcohol-related birth defects.

That initial case-control study compared cases with one or more of those birth defects, to children born without any birth defects. It was restricted to Nueces, San Patricio, and Kleberg counties. The study used the available data in the Texas Birth Defects Registry at that time, births in 1996 and 1997. The results suggested associations between mothers living near military airfields and ventricular septal defect, and between mothers living near an incinerator or 'injection well' and obstructive genitourinary defects and possible/probable fetal alcohol syndrome. Because of small numbers of cases in the initial study, the report recommended that a followup case-control study be done using more years of data from the Texas Birth Defects Registry and improving distance measurement from mothers' homes to sites of concern to CFEJ.

In preparation for that followup study, a preliminary study was completed in July 2006. The preliminary study tried to identify all birth defects with a statistically significant elevated prevalence in the original area of concern (most of Nueces County) that also had sufficient numbers of cases for the followup study. It considered all birth defects in the overall ICD-9 category of congenital anomalies; it did this by using the first 4-5 digits of the BPA code (the variation of ICD-9 used by the Texas Birth Defects Registry) for a total of 170 specific types of birth defects. Fifteen birth defects were selected for the followup case-control study. These defects were selected by combining new birth defects that were identified in the preliminary study with the six birth defects listed above and dropping fetal alcohol syndrome (since cases are very poorly captured by the Registry and since overconsumption of alcohol explains most of the cases).

OBJECTIVE

The objective of this case-control study was to measure the association between 15 selected birth defects and proximity to (living near) the sites of concern as listed by

Citizens for Environmental Justice. It was based on mother's residence at the time of birth, as listed in the birth certificate.

METHODS

Design

This was a case-control study, using all live births without birth defects as the comparison group (controls) for all 15 birth defects.

Study Population

Case data were obtained from the Texas Birth Defects Registry database. Cases had to meet the following criteria to be included in this study:

- Be a case in the Texas Birth Defects Registry;
- Have been linked to a birth certificate (99.2% of the potential cases had birth certificates);
- Be delivered in 1996 through 2003;
- Be delivered to mothers who resided in Nueces, San Patricio, or Kleberg Counties at the time of delivery;
- Have at least one of the following 15 birth defects:
    - **Tetralogy of Fallot** (a heart defect consisting of four individual defects: ventricular septal defect, pulmonary valve narrowing or closure, displacement of the aorta to the right, and thickened right ventricle)
    - **Ventricular septal defect** (one or several openings in the wall separating the lower two chambers of the heart, allowing mixture of oxygenated and unoxygenated blood)
    - **Atrial septal defect** (one or several openings in the wall separating the upper two chambers of the heart, allowing mixture of oxygenated and unoxygenated blood)
    - **Anomalies of the pulmonary valve** (malformations of the valve between the right ventricle and the artery leading to the lungs; includes pulmonary valve absence/closure, narrowing, enlargement, dilation, or aneurysm)
    - **Anomalies of the tricuspid valve** (malformations of the valve between the right atrium and the right ventricle; includes tricuspid valve absence/closure, narrowing, enlargement, dilation, or aneurysm)
    - **Congenital insufficiency of the aortic valve** (the valve connecting the left ventricle with the artery going to the body does not close completely, allowing blood to leak back through)
    - **Mitral valve insufficiency** (the valve connecting the left atrium and left vetricle does not close completely, allowing blood to leak back through)
    - **Patent ductus arteriosus** (a blood vessel between the two main vessels leaving the heart (the pulmonary artery going to the lungs and the aorta going to the rest of the body); this can cause abnormal cardiac circulation and pressure in the heart

- **Other anomalies of the aorta** (malformations of the aorta other than patent ductus arteriosus and coarctation or narrowing of the aorta)
- **Anomalies of the pulmonary artery** (malformations of the artery leading from the heart to the lungs)
- **Pyloric stenosis** (narrowing of the pyloric sphincter at the outlet of the stomach; this causes a blockage of food from the stomach into the small intestine)
- **Atresia/stenosis of the large intestine or anus** (closure or narrowing of the large intestine or anal canal)
- **Obstructive genitourinary defects** (narrowing or closure of the urinary tract at any level; urine can accumulate behind the obstruction and damage organs)
- **Anomalies of the diaphragm** (any malformation of the flat muscle separating the chest cavity from the abdominal organs)
- **Gastroschisis** (a congenital opening of the abdominal wall with protrusion of the intestines outside the body).

The first ten birth defects are heart defects. Codes for all birth defects are listed in the appendix.

Comparison babies (controls) were selected using all birth certificates. To be part of this study, controls further had to meet the following criteria:

- Have no birth defect (as documented by the Texas Birth Defects Registry)
- Have a birth certificate
- Be delivered in 1996 through 2003
- Be delivered to mothers who resided in Nueces, San Patricio, or Kleberg Counties at the time of delivery.

Exposure and Other Variables

Sites of concern to CFEJ were address geocoded (assigning the longitude and latitude values to the street address) so that distance from them could be calculated. Some of the sites were very large. Consequently, this study (as an improvement recommended in the previous case-control study) geocoded the boundaries of each site instead of one point as had been done in that previous study. All geocoding was done by the Geographic Information Systems (GIS) group at the Texas Department of State Health Services (DSHS). The geocoding was validated using an iterative process by constructing maps showing the geocoded sites, review of the maps by the CFEJ, revising the maps, and the CFEJ approving the revised maps. The GIS group also geocoded the residence at delivery of each case and control subjects. Residence address was taken from birth certificates.

"Exposure" to potential toxicants at these sites of concern was not directly measured; instead, distance to the nearest boundary of the nearest site of concern within each category was measured in a straight line from the mother's residence at delivery. Sites were categorized as follows (number of sites in brackets):

- Landfills (46)

- Refineries or chemical manufacturing plants (23)
- Military airfields (3)
- Other sites of concern (3: the "old city incinerator", a location described by CFEJ as a "toxic injection well", and a battery recycling site);
- Oso Creek (1).

In other words, each geocoded subject ended up with the following data:

- Distance to the nearest landfill
- Distance to the nearest refinery or chemical manufacturing plant
- Distance to the nearest military airfield
- Distance to the nearest other site of concern
- Distance to Oso Creek.

For all except refineries and chemical manufacturing plants, those distances were then categorized as:

- Less than or equal to ½ mile
- Greater than ½ mile to 1 mile
- 1 mile or less (a combination of the previous two groups)
- Greater than 1 mile (the referent group).

Because refineries and chemical manufacturing plants often have large smokestacks to disperse air emissions, distances to them were categorized as:

- Less than or equal to 2 ½ miles
- Greater than 2 ½ miles to 5 miles
- 5 miles or less (a combination of the previous two groups)
- Greater than 5 miles (the referent group).

Other analyses by the Texas Birth Defects Registry have suggested that hospitals and physicians around the Corpus Christi area may be diagnosing and recording mild cases of several birth defects (particularly heart defects) to a greater degree than is commonly done in the rest of Texas. This would lead to artificially inflated rates in Nueces, Kleberg, and San Patricio Counties. Indeed, that may explain some of the elevations observed in the preliminary study released in 2006. The present study, looking **within** those counties, partly addresses that concern. However, diagnostic practice might still vary within those counties; for example, it may be related to socioeconomic status such that poor women may have less access to medical care. To account for this possibility, the analysis included mother's education level as stated in the birth certificate as a surrogate measure of socioeconomic status.

There are other variables that might partly explain some of the associations observed between proximity to sites and risk of birth defects. For example, gastroschisis occurs more frequently in children of younger mothers. If younger mothers tended to live near landfills, then any association between gastroschisis and landfills might be due to maternal age instead of to site proximity. Therefore, the following variables available from birth certificates were included in this study (where possible):

- Mother's education
- Mother's age at the time of delivery

- Mother's race/ethnic group
- If the mother had diabetes
- Infant sex
- Year of delivery
- Previous live births to the mother
- Plurality of this pregnancy (whether there were twins, triplets, etc.)

Statistical Analysis

Proportions of the study groups with certain characteristics (for example, the proportion of cases that were female versus the proportion that were male) were compared using a chi-squared test.

The information gathered for this study was used to calculate odds ratios to evaluate the association between each specific birth defect (one of fifteen) and residential proximity of the mother to one of the sites in question. For example, an odds ratio of 4.00 for landfills and gastroschisis indicates that mothers of children with gastroschisis are four times more likely to live close to a landfill than mothers of children without any birth defect. Because odds ratios are used to estimate relative risks for rare diseases such as birth defects, this is roughly the same as saying that mothers who live near landfills are four times more likely to have children with gastroschisis than mothers who do not live near landfills. Similarly, an odds ratio of 1.00 for anomalies of the tricuspid valve and refineries indicates that mothers of children with anomalies of the triscuspid valve are as likely to live close to a refinery as mothers of children without any birth defects. All odds ratios in the current study compared mothers living at various distances from sites of concern with mothers living more than one mile away from those sites, with the exception of refineries / chemical manufacturing plants. For those, the odds ratios compared with mothers living more than five miles away. Simple (also called crude) odds ratios and their 95% confidence intervals were calculated using logistic regression.

Statistical significance helps us evaluate the role of chance in our observations. For example, if you flipped an unloaded coin 10 times, you might get 6 heads (60% heads). Flipping it 10 more times you might get 4 heads (40% heads). The variation (40% to 60%) is due to chance. One way to evaluate the impact of that variation is to calculate 95% confidence intervals. We would expect the true probability (50% heads) to be in those confidence intervals 95% of the time; in other words, confidence intervals give us a range for the true value we are trying to find. If the 95% confidence interval does not include 50% for coin flipping, then it is unlikely (that is, 5 times out of 100) that chance alone explains the observed association, and we might feel we have a loaded coin. Similarly in odds ratios, if the 95% confidence interval does not include 1.00 (the null value, or the value at which there is no association between the 'exposure' and the birth defect), then it is unlikely that chance alone explains the observed association. We call that 'statistically significant', and those results are shown in bold in Tables 5-29. Note however that chance is still a valid explanation 5 times out of 100.

Could we eliminate alternative explanations such as age of mothers? Logistic regression was used to calculate both the crude (simple) odds ratios and odds ratios that were adjusted simultaneously for the other factors available from the birth certificate (listed above). Logistic regression was also used to calculate 95% Wald confidence intervals for the crude and adjusted odds ratios. In some situations such as when there were small numbers of cases living near sites and many variables to adjust, the statistical software sometimes could not produce reliable results. In those situations, the analysis was repeated adjusting only for maternal age, race/ethnicity, and education; those situations are indicated by "S" (for short model) in Tables 5-29. For some of the analyses, even this approach did not allow calculation of an odds ratio. In those situations, exact logistic regression was used, indicated by "E" in Tables 5-29. Exact logistic regression was also used in all situations where there were three or fewer cases living near the sites of concern. Because exact regression often exceeded the available computer memory or time, a 10% random sample of controls was selected during each run. Sometimes even the resulting 4,600 controls were too much for the computer to calculate adjusted odds ratios; those situations were indicated as "n/a" in the tables.

Even if an association between a site of concern and a birth defect is statistically significant, it does not mean that living near the site **caused** the birth defect. Statistically significant associations between sites of concern and birth defects are more likely to be causal if the answers to ALL of the following questions are 'yes', especially for the adjusted odds ratios:

- Was the association statistically significant? That is, does the 95% confidence interval exclude 1.00?

- Was the relationship strong? That is, were the crude or adjusted odds ratios much higher than 1.00? That is important since high odds ratios are less likely to be the result of some kind of error or bias. For this report, odds ratios greater than or equal to 1.50 were considered "high"; that corresponds to a 50% increased relative risk.

- Was there a pattern of increasing risk with increasing proximity (a proximity-response relationship)? If living near a landfill for example truly increased risk, one would expect that women living within ½ mile of a landfill would show the highest odds ratios, and women living ½ mile – 1 mile from the landfill would have intermediate odds ratios, when compared with women living more than 1 mile away.

In the tables with odds ratios, "n/a" means the results were not available. This was due in some situations to the statistical software being unable to provide the estimates (e.g. no confidence intervals are provided when there are 0 exposed cases). In other situations, the models did not converge or the results had questionable validity.

Several statistically significant or high odds ratios (the latter arbitrarily defined as greater than or equal to 1.50) were found for five birth defects and women who lived near the three military airfields. Thus supplemental analyses (found in Tables 20-24) were conducted looking at the association between each of those five defects and:

- Distance to Cabaniss airfield
- Distance to Cuddihy airfield
- Distance to Waldron/Roddfield airfield

For the same reason, supplemental analyses (found in Tables 25-29) were conducted looking at the association between five other birth defects and:

- Distance to the old city incinerator
- Distance to the injection well
- Distance to the battery recycling plant.

Data management and statistical analysis were conducted using SAS version 9. Exact logistic regression used LogXact for SAS Procs version 7.

RESULTS AND DISCUSSION

Sample Size and Geocoding Success

There were 2,225 case individuals that were successfully geocoded (Table 1). Because one individual can have multiple birth defects and is included in the analyses for each of those defects, there were effectively 5,613 geocoded cases included in the separate analyses. There were 46,204 geocoded controls. Among all 48,429 geocoded subjects, 79.3% lived in Nueces County, 13.7% in San Patricio, and 7.0% in Kleberg (Table 2).

Overall, 89.4% of the cases and 90.1% of the controls were successfully geocoded (Table 1). These percentages are considered acceptable. The percentages varied slightly by birth defect, ranging from 81.3% for cases with tetralogy of Fallot to 100.0% for cases with gastroschisis.

To help with interpretation of breakdowns by demographic characteristics, Tables 2 and 3 present column percentages. For instance, these tables show information such as what percentage of geocoded subjects (cases and controls) were Hispanic (66.8%, Table 2), or what percentage of geocoded cases were Hispanic (66.1%, Table 3). However, Table 4 presents row percentages, such as the percentage of Hispanics who lived within 1 mile of a landfill (35.4%). For all three tables, statistical significance was based on the combined numbers in the rows and columns.

Among all subjects (Table 2), geocoded mothers were more likely than non-geocoded mothers to:

- be African American or Hispanic
- have either less than or more than a high school education
- have male infants
- live in Nueces County (which is expected since it is more urban), and
- have delivered their infants between 1999 and 2002.

This suggests there were some differences between the geocoded subjects (who make up the remainder of the study) and the tri-county population as a whole. However, because the geocoding rates were high, the impact of those differences is expected to be minimal and the results of this study are thus generalizable to the whole area population.

Potential Confounding Variables

Compared to geocoded controls (Table 3), geocoded case mothers were more likely to be African American, to have less education, and to have diabetes. A greater proportion of case infants were male. Cases tended to come from Nueces County, to have been delivered in the earlier years (1996-2000), and to have been part of a multiple pregnancy.

Among geocoded control subjects, many demographic characteristics were associated with living close to sites of concern (Table 4). Higher percentages of younger and less educated mothers lived near landfills, refineries, and the incinerator/injection well/battery recycling site, whereas higher percentages of older and more educated mothers lived near airfields and Oso Creek. Different race/ethnic groups lived near different site categories. Higher percentages of diabetic mothers than non-diabetic lived near refineries or the incinerator/injection well/battery recycling site. Nueces County had the highest percentage of people living near sites of concern, except for refineries and chemical manufacturing plants; a higher percentage of Kleberg residents lived near sites in that category. The percentage of births to residents near landfills and refineries seemed to decrease gradually over time, but to increase for residents living near Oso Creek. Compared to women with few children, greater percentages of women with many live births lived near refineries and the incinerator/injection well/battery recycling plant. Infant sex and plurality were not associated with living near any of the site categories.

Because all demographic factors measured in this study were either associated with most of the sites or with case/control status, all were adjusted for in the logistic regression models in order to minimize alternative explanations for any associations found. The exception was residence county; that was excluded from adjusted models since it would have overmatched for residential proximity (i.e., interfered with its effect if any).

Associations of Birth Defect Occurrence with Proximity to Sites of Concern

There were 2 independent distance categories times 5 site categories times 15 defects (2 x 5 x 15) for a total of 150 independent comparisons in Tables 5-19 (the basic tables). Thus, using 95% confidence intervals, we would expect (100% – 95%) = 5% x 150, or 7-8 of those comparisons to be 'statistically significant' based on chance alone. Also note that in Tables 5-29, distance category C (less than or equal to 1 mile or 5 miles) is simply the sum of categories A and B. Therefore, the number of cases or controls in categories A, B, and D will add to the total at the top of the column.

In trying to answer the question "Is living near the sites of concern to CFEJ related to having a child with birth defects?", this section casts the net broadly by highlighting associations that met ANY of the following criteria in crude or adjusted odds ratios:

- Statistically significant (95% confidence interval excludes 1.00);
- High odds ratios (greater than or equal to 1.50);
- Proximity-response relationship (for example, the odds ratio for mothers living less than or equal to ½ mile was greater than odds ratio for mothers living more than ½ mile to 1 mile).

Note however, the most compelling evidence for a causal relationship (i.e. answering the question "Do these sites cause birth defects?") arises when ALL of the above criteria are met, especially for adjusted odds ratios that minimize alternative explanations.

Landfills Mothers of children with ventricular septal defect (VSD) lived ½ to 1 mile away from landfills more than did mothers of children without any birth defects (Table 6). That was statistically significant. However, the association was not very strong (crude and adjusted odds ratios of 1.30 and 1.29), and there was no proximity-response relationship (there was not a higher odds ratio for mothers living even closer to landfills).

There were some moderately high odds ratios for landfills with atresia/stenosis of the large intestine and anus (Table 16) and with gastroschisis (Table 19), but those could have arisen by chance (i.e. they were not statistically significant since the 95% confidence intervals included 1.00). Gastroschisis exhibited a proximity-response pattern.

Refineries and Chemical Manufacturing Plants Mothers of children with anomalies of the diaphragm (Table 18) or gastroschisis (Table 19) lived within 2.5 miles of sites within this category somewhat more than did mothers of children without birth defects. The adjusted odds ratios were high and exhibited proximity-response. However those odds ratios could have been due to chance.

Military Airfields Mothers of children with the following birth defects lived closer to one of the three military airfields than mothers of children without birth defects:

- anomalies of the pulmonary valve (Table 8): high crude and adjusted odds ratios in the ½ to 1 mile and less than 1 mile categories, and statistically significant crude odds ratio in the ½ to 1 mile distance category;
- congenital insufficiency of the aortic valve (Table 10) and mitral valve insufficiency (Table 11): both high in the ½ to 1 mile distance category and aortic valve high in the less than 1 mile category, but none statistically significant;
- atresia/stenosis of the large intestine and anus (Table 16): high in the less than ½ mile category and not statistically significant since based on only 1 case;
- anomalies of the diaphragm (Table 18): high in the less than ½ mile and less than or equal to 1 mile categories, not statistically significant, and based on 3 or fewer cases.

Of the five birth defects, only atresia/stenosis of the large intestine and anus, and anomalies of the diaphragm showed proximity-response.

The association of each of these five birth defects was examined individually in relation to proximity to each of the three airfields in Tables 20-24. No mothers of cases with these 5 birth defects lived within 1 mile of Cuddihy. For atresia/stenosis of the large intestine or anus (Table 23) and for anomalies of the diaphragm (Table 24), the very high odds ratios for Cabaniss and Waldron were based on 1 case in each distance category. Because the number of cases in each distance category was very small, it is difficult to determine the meaningfulness of these results.

That left three defects involving heart valves: anomalies of the pulmonary valve (Table 20), congenital insufficiency of the aortic valve (Table 21), and mitral valve insufficiency (Table 22). For congenital insufficiency of the aortic valve, odds ratios were high for Cabaniss airfield but not statistically significant. The other two heart valve defects showed both high and statistically significant odds ratios with Waldron airfield. For all three airfields, high odds ratios were found for the distance of greater than ½ to 1 mile and not within ½ mile. This therefore did not meet the criterion of a proximity-response relationship (higher odds ratios for those living closer to the site of concern).

Incinerator, Injection Well, Battery Recycling Site Mothers of children with the following birth defects lived closer to one of these three sites than mothers of children without birth defects.

- Tetralogy of Fallot (Table 5): high but only for crude odds ratio, not statistically significant, and no proximity-response relationship;
- Ventricular septal defect (Table 6): high and statistically significant crude odds ratios for less than or equal to ½ mile and for less than or equal to 1 mile with a proximity-response relationship; however, the odds ratios were weaker and not significant after adjustment for other variables;
- Atresia/stenosis of the large intestine and anus (Table 16) and obstructive genitourinary defects (Table 17): high and statistically significant crude and adjusted odds ratios for those living ½ - 1 mile or within 1 mile; no proximity-response relationship for either defect;
- Gastroschisis (Table 19): high but not statistically significant crude and adjusted odds ratios for those living ½ - 1 mile away and no proximity-response.

Of the five birth defects, the associations with atresia/stenosis of the large intestine and anus, and obstructive genitourinary defects seemed to be more compelling because of the high odds ratios after adjustment and statistical significance.

The association of each of these five birth defects was examined individually in relationship to proximity to the old city incinerator, the injection well, and the battery recycling site separately in Tables 25-29.

The old city incinerator exhibited high and statistically significant crude and adjusted odds ratios for atresia/stenosis of the large intestine or anus (Table 27), though there was no proximity-response relationship. Odds ratios for obstructive genitourinary defects were high and showed proximity-response (Table 28), but were not statistically significant. The incinerator also showed high crude and adjusted associations with tetralogy of Fallot (Table 25) and gastroschisis (Table 29), but they lacked both statistical significance and a proximity-response pattern.

The injection well was only associated with ventricular septal defect (Table 26), but it was not statistically significant and exhibited no proximity-response.

The battery recycling site showed some high odds ratios with all 5 of the selected birth defects. Adjustment for other variables tended to increase odds ratios except for ventricular septal defect. A proximity-response pattern seemed to be present for ventricular septal defect (Table 26) although adjusted odds ratios were no longer considered high, and obstructive genitourinary defect (Table 28). However, none of the associations for the 5 defects were statistically significant and 3 were based on very few cases living within a mile (tetralogy of Fallot, atresia/stenosis of the large intestine or anus, and gastroschisis).

Oso Creek Very few cases or controls lived near Oso Creek. Mothers of children with anomalies of the pulmonary artery (Table 14) were somewhat more likely to live ½ - 1 mile away from Oso Creek than mothers of children without birth defects. That finding was true only after adjustment for other variables, but could very likely have been due to chance. There was no proximity-response pattern.

Comparison to the Previous Case-Control Study

The current study did not confirm all the results from the previous case-control study. That is a little surprising, since data from the previous study were included in the current study; the previous study examined 5 of the current 15 defects among births in the first 2 of the current 8 years. Specifically, the previous study found that:

- Mothers of children with VSD or obstructive genitourinary defects were more likely to live near airfields, and neither association was observed in the current study;
- Mothers of children with obstructive genitourinary defects were more likely to live near the old city incinerator or the injection well, which was confirmed in the present study.

Comparison to the Scientific Literature

Landfills and Hazardous Waste Sites Several studies have examined risks of having children with birth defects associated with living near hazardous waste sites, which more often than not involve exposures to chemical mixtures. The study results have been inconsistent.

Studies have reported some increased risk of parents living near these sites and total congenital anomalies (Geschwind et al, 1992; Dolk et al, 1998; Dodds and Seviour, 2001; Elliott et al, 2001; Palmer et al, 2005; Gilbreath and Kass, 2006), neural tube defects (NTDs) or nervous system defects (Geschwind et al, 1992; Croen et al, 1997; Marshall et al, 1997; Dolk et al, 1998; Elliott et al, 2001; Orr et al, 2002), total heart defects (Shaw et al, 1992; Malik and Fixler, 2004), conotruncal heart defects (Croen et al, 1997; Dolk et al, 1998; Kuehl and Loffredo, 2003), septal heart defects (Dolk et al, 1998), tracheo-esophageal anomalies (Dolk et al, 1998), musculoskeletal defects (Geschwind et al, 1992), hypospadias (Dolk et al, 1998; Elliott et al, 2001), gastroschisis or omphalocele (Dolk et al, 1998; Elliott et al, 2001), defects of the integument system (Geschwind et al, 1992), and chromosomal anomalies (Vrijheid et al, 2002a).

The current study found little evidence of causal associations between any of the 15 selected birth defects and landfills. This agrees with studies in the literature that have found no association of landfills or hazardous waste sites with total birth defects (Neutra et al, 1991; Boyle et al, 2004), birth defects other than heart defects (Shaw et al, 1992), NTDs (Morris et al, 2003; Suarez et al, 2007), central nervous system defects (Marshall et al, 1997), heart defects (Elliott et al, 2001), oral clefts (Croen et al, 1997; Brender et al, 2006), or musculoskeletal defects (Marshall et al, 1997). Although Dolk et al (1998) found associations of landfills with several birth defects, there wasn't any association with hazard ranking of the landfills (Vrijheid et al, 2002b).

The type of site can make a difference. Where no association with NTDs or conotruncal heart defects was found with all hazardous waste sites, associations were found with National Priority List sites (Croen et al, 1997). On the other hand, this stratification had little impact for NTDs (Suarez et al, 2007) and oral clefts (Brender et al, 2006).

Industrial Facilities A survey of the scientific literature here also yielded mixed results.

NTDs were elevated near industrial facilities that emitted solvents or metals into the air (Marshall et al, 1997). Deaths from heart defects were elevated near industrial facilities (Dummer et al, 2003a). Risk of a type of conotruncal heart defect was higher in regions characterized by release of toxic chemicals into the air (Kuehl and Loffredo, 2003), and hypoplastic left heart malformation was clustered in an area of Baltimore, Maryland with industrial release of solvents, dioxin, and polychlorinated biphenyls (Kuehl and Loffredo, 2006). Heavy lead emissions were associated with increased risks for heart defects, oral clefts, and musculoskeletal defects (Vinceti et al, 2001).

The current study found little evidence of causal associations between any of the 15 selected defects and refineries or chemical manufacturing plants. That agrees with several reports in the literature. No association with total birth defects was found for a factory heavily contaminated with chromium waste (Eizaguiree-Garcia et al, 2000). The same was true for 15 birth defects examined in an area adjacent to a petrochemical plant (Oliveira et al, 2002), for total lethal congenital anomalies in proximity to hazardous industrial facilities (Dummer et al, 2003a), and for total birth defects in an area with dioxin contamination (Mastroiacovo et al, 1988).

Some studies only reported associations in population subgroups for NTDs (older women in Suarez et al, 2007), heart defects (older women in Yauck et al, 2004), and oral clefts (older women in Brender et al, 2006).

Other Sites In the current study, suggestive associations were found between living near the old city incinerator and atresia/stenosis of the large intestine or anus in offspring, and to a lesser extent with obstructive genitourinary defect. Cordier et al (2004) also reported that risk of obstructive uropathies increased with proximity to municipal solid waste incinerators, although other types of birth defects did not show increased risk. Risk of all congenital anomalies may have been associated with solid waste incinerators in Japan (Tango et al, 2004). Lethal cases of spina bifida and heart defects were higher near incinerators (Dummer et al, 2003b). Other studies have been inconclusive or found no association (Cresswell et al, 2003).

There were suggestive associations between living ½ to 1 mile away from military airfields and three heart valve defects in the current study. However, no studies in the literature were found that examined risk of birth defects in relation to airfields.

Living near the battery recycling plant showed high odds ratios for tetralogy of Fallot, ventricular septal defect, atresia/stenosis of the large intestine or anus, obstructive genitourinary defects, and gastroschisis. While no studies in the literature were found that examined risk of birth defects in relation to battery recycling facilities, studies have reported associations between environmental lead exposure and heart defects, oral clefts, and musculoskeletal defects (Grazuleviciene and Dulskiene, 1998; Vinceti et al, 2001) and between exposure to metals and NTDs (Marshall et al, 1997).

Air Pollution Ecologic studies have reported that living in areas with greater industrial pollution was associated with greater total birth defects (Smrcka and Leznarova, 1998) and mutations for 18 specific defects (Antipenko and Kogut, 1993). Environmental lead exposure was associated with heart defects (Grazuleviciene and Dulskiene, 1998). Carbon monoxide was associated with higher risk of septal heart defects, and ozone with conotruncal and other heart defects (Ritz et al, 2002). Gilboa et al (2005) found that carbon monoxide was associated with tetralogy of Fallot (a conotruncal heart defect), and particulates and sulfur dioxide were associated with septal heart defects. A review article included ambient air pollution and chlorinated hydrocarbons among environmental agents associated with heart defects (Kuehl and Loffredo, 2005).

Limitations of This Study

Multiple Comparisons As stated above, we would expect 7-8 of the independent associations with 95% confidence intervals to be ‘statistically significant’ due to chance alone. Looking at the independent proximity categories $\leq$ ½ mile and > ½ mile to 1 mile in Tables 5-19, there were only 5 statistically significant crude or adjusted associations. Thus they all could have arisen by chance and may not reflect true causal relationships.

Number of Cases Although this study examined eight years of data from the Texas Birth Defects Registry, some of the associations were based on a very small number of cases living close to sites of concern in Nueces, San Patricio, and Kleberg Counties. That in turn limits power of the study to detect statistically significant associations. Waiting several more years for even more cases to accrue is probably not productive in this situation. To examine associations with for example, landfills, it is more productive to conduct very large case-control studies such as on a statewide basis. This has been done for neural tube defects and oral clefts in Texas (Brender et al 2006, Suarez et al 2007)**,** and is currently underway with conotruncal heart defects.

Alternative Explanations This study adjusted for a wide variety of potential confounders, but was limited to those that were feasible to examine from the birth certificate. Consequently, it did not consider variables such as diet or medication use. Also, some of the variables that are collected on the birth certificate may have questionable quality (such as presence of maternal diabetes) or only tell part of the story. An example of the latter is that poorer mothers may have less access to prenatal care, be less likely to discover the presence of a birth defect, and be less likely to terminate the pregnancy in a doctor's office if they so choose. That would lead to an artificially high rate of certain birth defects among poor folks. However, the current study did not have income information, and thus used an imperfect substitute, maternal education. So the above bias could be only partly adjusted for.

Using Distance as Proxy for Exposure This study did not measure exposure to particular chemicals. Nor did it consider wind speed and direction, which might be important for estimating airborne exposure. However, there were some advantages to measuring simple distance:

- It answers the question of some residents "Is living near these sites related to having a child with birth defects?" (Note however, that this study is not well suited to answering the question "Do these sites cause birth defects?")
- The highest airborne exposures (if any) probably occur during temperature inversions when the air is still; hence wind speed and directions may be less relevant.
- Any consideration of for example, wind speed and direction, would involve exposure modeling. Such modeling has its own set of assumptions and criticisms, and requires considerable time and expertise.

Definition of Sites of Concern The objective of this study was to examine the association of selected birth defects with sites of environmental concern as defined by CFEJ. DSHS did not validate these sites against for example, federal or state lists of sites of environmental concern. It is possible that some of the sites were no longer active or releasing any toxicants in the time period studied here or in the past. The impact of including such sites would be to bias the odds ratios toward 1.00 (indicating no association). Similarly, the boundaries of the sites were determined iteratively between the DSHS GIS group and CFEJ. Any errors in determining boundaries would potentially misclassify distance for both cases and controls, and could also bias the odds ratios toward 1.00.

Possible County-Wide Exposure This study looked at cases and controls within Nueces, San Patricio, and Kleberg Counties. It would not be able to find associations of birth defects with sites of concern if everyone in that area was exposed to substances from those sites. The alternative is to compare people within that area to people say, in the rest of Texas. That was largely done in the report released in July 2006 which compared Nueces County (79% of the subjects in this study) with the rest of the Texas

Birth Defects Registry. But that in turn was compromised by the observation that physicians and hospitals in the Nueces County area tend to diagnose minor cases of birth defects (especially heart defects) more than physicians in the rest of Texas. Perhaps the best solution to this conundrum is to study something that is not susceptible to variation in diagnostic practice, such as body burden of various chemicals. That study is currently being undertaken in Nueces and other counties by Dr. K.C. Donnelly of Texas A&M University.

Limited Conclusions Regarding Causality

This study was designed to answer the question of some residents "Is living near the sites of concern to CFEJ related to having a child with birth defects?" The Results and Discussion section cast the net broadly by highlighting associations that met ANY of the following criteria in crude or adjusted odds ratios:

- Statistically significant (95% confidence interval excludes 1.00);
- High odds ratios (greater than or equal to 1.50);
- Proximity-response relationship (odds ratio for mothers living less than or equal to ½ mile was greater than odds ratio for mothers living more than ½ mile to 1 mile).

However, the most compelling evidence for a causal relationship (i.e. answering the question "Do these sites cause birth defects?") arises when ALL of the above criteria are met, especially for adjusted odds ratios that minimize alternative explanations. Because none of the associations examined in this report met all of the above criteria, there is little evidence to say that any of these sites caused birth defects.

Strengths of This Study

Number of Cases By looking at eight years of data, there was greater statistical power than the case-control study conducted in the same area several years ago. The size of the current study provided sufficient power to examine and exclude associations for many of the more common birth defects.

Distance Measurement Instead of measuring distance from the mother's residence to one point in a site of concern (such as a landfill) as was done in the previous case/control study, distance was measured to the nearest boundary of the site of concern. That made distance measurement and classification much more consistent between sites, and more relevant as a proxy measure of exposure.

Geocoding Geocoding the mothers' residences and the sites of concern enabled precise distance calculation, an improvement over some previous reports that use zip code or other large areas. Also, the high proportion of residences geocoded imply that these results are generalizable to the whole 3-county population, with little impact of selection bias.

Specific Birth Defects The preparatory study (released in July 2006) examined all birth defects and identified 15 defects that were higher in Nueces County and suitable for the current study. Thus the combination of the two studies ensured that a comprehensive yet focused effort was conducted.

CONCLUSIONS

In this study, there were no compelling associations observed between any of the 15 selected birth defects and proximity of mother's residence to Oso Creek. Gastroschisis exhibited high odds ratios and proximity-response with landfills, but this association was not statistically significant. Similarly, mother's residence near refineries and chemical manufacturing plants showed high odds ratios and proximity-response with anomalies of the diaphragm and gastroschisis, but those associations were not statistically significant.

There were some high and sometimes statistically significant associations between proximity to military airfields and heart valve defects, but those did not show proximity-response.

Maternal residence near the old city incinerator was highly and significantly associated with atresia/stenosis of the large intestine or anus in offspring but there was no apparent proximity-response. Odds ratios for obstructive genitourinary defects were high and showed proximity-response, but were not statistically significant.

The battery recycling site showed some high odds ratios with 5 of the birth defects. A proximity-response pattern seemed to be present for ventricular septal defect and obstructive genitourinary defect. However, none of the associations for the 5 defects were statistically significant.

Because the above associations did not meet all three criteria of high odds ratios, statistical significance, and proximity-response, there is little evidence that maternal residential proximity to those sites actually caused the birth defects examined in this report.

Further studies of the above birth defects especially near military airfields, the old city incinerator, or the battery recycling plant might produce more compelling results if conducted by investigators with the expertise and the time to gather additional data (for example, on operations information, wind speed and direction), conduct detailed exposure assessment, and perform complex analyses, such as the Centers for Disease Control and Prevention (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR), or a university researcher.

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APPENDIX

Codes used to select and categorize birth defects in this study.

Birth Defect Description	**British Pediatric Association (BPA) Codes**
Tetralogy of Fallot	745.200, 745.210, 746.840
Ventricular septal defect	745.400 – 745.490
Atrial septal defect	745.500 – 745.590
Anomalies of the pulmonary valve	746.000 – 746.090
Anomalies of the tricuspid valve	746.100 – 746.105
Congenital insufficiency of the aortic valve	746.400 – 746.490
Mitral valve insufficiency	746.600
Patent ductus arteriosus	747.000
Other anomalies of the aorta	747.200 – 747.290
Anomalies of the pulmonary artery	747.300 – 747.390
Pyloric stensos	750.500 – 750.580
Atresia/stenosis of the large intestine or anus	751.200 – 751.240
Obstructive genitourinary defects	753.200 – 753.290, 753.600 – 753.690
Anomalies of the diaphragm	756.600 – 756.690
Gastroschisis	756.710