ANALYSIS OF BIRTH DEFECT DATA IN THE VICINITY OF THE REDFIELD PLUME AREA IN SOUTHEAST DENVER COUNTY: 1989-1999

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Colorado Responds to Children With Special Needs (CRCSN)
Colorado Department of Public Health and Environment
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Overview: This document is a description of the methods used and summary of the results obtained from the analysis of births defects in live births to residents in the vicinity of the Redfield plume area in Southeast Denver County from 1989 to 1999. Its function is to provide information about the occurrence of birth defects in the study area as part of the public health consultation being conducted by the Environmental Toxicology Section of the Disease Control and Environmental Epidemiology Division of the Colorado Department of Public Health and Environment (CDPHE).

Introduction

- Colorado Responds to Children With Special Needs (CRCSN)

CRCSN is the birth defects monitoring and prevention program at the Colorado Department of Public Health and Environment. CRCSN began collecting data in 1989 under the guidance of an advisory board of parents, physicians, advocates, and representatives from state agencies.

Criteria for inclusion in CRCSN requires that a child must be a Colorado resident diagnosed prenatally to age three years with one of the eligible conditions on the attached list (See Appendix A). Children meeting these criteria are identified from computer linkage of information from hospitals, vital records (birth, death and fetal death certificates), the Newborn Genetic Screening Program, the Newborn Hearing Screening Program, laboratories, physicians, and genetics, developmental and other specialty clinics.

More detailed information about CRCSN, the impact of birth defects and developmental disabilities, specific conditions, and data on birth defects in Colorado are available by contacting CRCSN or at: http://www.cdphe.state.co.us/dc/crcsn/crcsnhome.asp.

- Synopsis of Events

The Redfield Site is approximately an eleven-acre area, which includes one building, in Southeast Denver County. Rifle scopes and binoculars were manufactured at the facility from 1967 through 1998. The Brown Group, Inc. operated the business from 1979 through 1984. In 1984 the business was sold to Redfield Rifle Scopes, Inc. Redfield operated the manufacturing facility until operations were terminated in 1998. Brown Retail currently owns the property and the building. In 1994, an environmental investigation identified the presence of chemicals in the groundwater under the site. The Colorado Department of Public Health and Environment (CDPHE) was notified of the contamination on July 1, 1994. The CDPHE took action by requiring that Redfield Rifle Scopes Inc., install permanent and temporary wells on the property to monitor the groundwater. Continued monitoring of the site indicated that the groundwater contamination concentrations were decreasing, and it was believed that the contamination was confined to the boundaries of the Redfield property.

In January of 1998, samples taken from the groundwater monitoring wells near the northeast corner of the Redfield property indicated that groundwater contamination might be moving off the Redfield Site and into the surrounding neighborhood. In February 1998 an investigation into off-site contamination began, continues to this date and includes groundwater monitoring wells and indoor air testing in homes near the Redfield property.

The CDPHE Environmental Toxicology Section approached the Agency for Toxic Substances and Disease Registry (ATSDR) in September 2001 and requested funding to conduct a public health consultation in the Redfield site area. This request was made in response to the community health concerns about possible increased risks (including birth defects) due to exposures to the chemicals found in the groundwater contamination. The following chemicals have been detected in the indoor air: 1,1,1-trichloroethene, 1,1,1-trichloroethane, perchloroethylene, methylene chloride, 1,1-dichloroethene, and benzene. The most significant of these chemicals is 1,1- dichloroethene (1,1-DCE), also called 1,1 dichloroethylene.

Methods

Objective 1: Establish the rate of birth defects to residents of the study area

1. Selection of geographic boundaries that define the study area

The Environmental Toxicology Section of CDPHE provided the relevant geographic boundaries to CRCSN (See Figure 1.) The boundaries of the study area starting at Colorado Blvd. and Cherry Creek and going clockwise are: Cherry Creek, S. Cherry St., E. Kentucky Ave., Cherry Creek Dr. S., E. Mississippi Ave., Cherry Creek, S. Monaco Pkwy., E. Jewell Ave., S. Oneida St., E. Evans Ave., S. Holly St., E. Louisiana Ave., S. Dahlia St., E. Mississippi Ave., S. Birch St., E. Arizona Ave., and S. Colorado Blvd. The study area includes only residential areas within these boundaries and thus, for example, excludes the commercial areas on the east side of Colorado Blvd. near Mississippi. Questions concerning specific boundary selection should be addressed to the Hazardous Material Section of CDPHE.

2. Identify the number of live births occurring in women residing in the study area

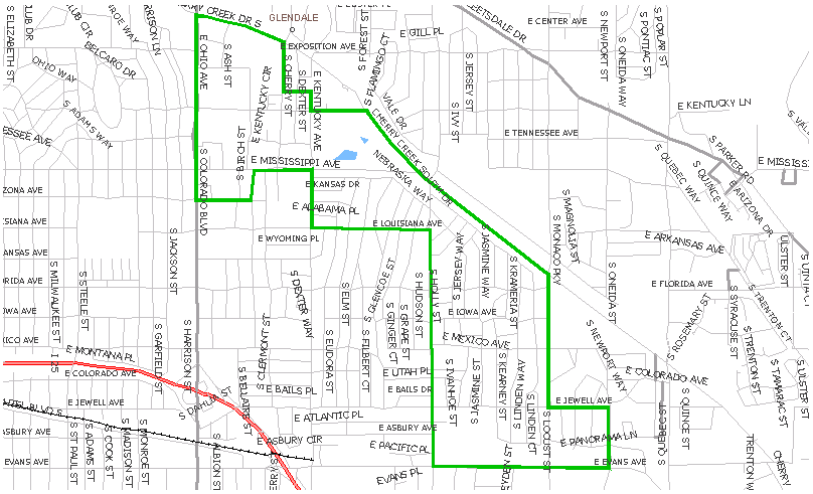
The number of live births in the study area was determined from data maintained by the Health Statistics and Data Management Sections (HSDMS) of CDPHE and was used as the denominator in calculating birth defect rates[1]. HSDMS is responsible for the statewide database of Colorado resident birth certificates.

Specifically, the following resident zip codes were used to select possible study area births: 80222, 80224, 80246, 80231, and 80209. Each address of this subset was electronically geocoded to a longitude and latitude point based on the mother's residence street address reported on her child's birth certificate. Addresses that could not be

[1] The denominator is the total number of live births in the area of interest and allows an estimation of the rate, or frequency, of congenital anomalies within that population. For example, among 322,562 live annual births to Colorado residents in 1989-1994 (the denominator), 14,828 were reported born with major congenital anomalies; for a rate of 459.69 per 10,000 live births, or approximately 5 percent.

electronically geocoded were manually reviewed to determine if the addresses were in the study region. See Table 1.

Figure 1.Map of the Study Area



3. Identifying Birth Defects cases in the study area

All identified live births in the study area (see Figure 1) were matched against the CRCSN database to identify children who have been diagnosed with a birth defect. CRCSN maintains a centralized statewide system for epidemiological monitoring of birth defects and developmental disabilities. Strengths of ascertainment in this program include an extended age range for ascertainment of a condition (up to three years of age), a diversity of reporting sources covering the entire state, and the ability and authority to undertake active case review and surveillance when deemed necessary for special studies.

4. Statistical Analysis of Birth Defects data in the study area

a) Rates of birth defects in the study area were calculated per 10,000 live births for 1989-1999. Similar rate calculations were done for the Denver metropolitan area [excluding the study area] for comparative purposes. The Denver metropolitan area includes the following counties: Adams, Arapahoe, Boulder, Denver, Douglas, and Jefferson. The Environmental Toxicology Section of CDPHE and the CDPHE Cancer Registry previously had selected this area as the appropriate choice for comparison. The statistical test for comparing proportions in independent samples (Snedecor and Cochran 1989) was used to assess statistically significant differences in rates between the study area and the comparison area.

b) A test for trend was conducted on the rates of major congenital anomalies by year using the Cochran-Armitage trend test (Agresti 1990).

c) A space-time analysis was conducted on four major birth defect categories using the SatScan software: 1) Major Congenital Anomalies; 2) Cardiovascular Anomalies; 3) Musculoskeletal Anomalies; 4) Genitourinary Anomalies. SatScan is a software program that has been designed to analyze spatial and temporal data with the *Spatial or Space-time Scan Statistic (* Kulldorff 1997; see also Kulldorff et al, 1997; Kulldorff and Nagarwalla, 1995). The program was used

to: (1) evaluate spatial or space-time disease clusters to see if they are statistically significant, (2) test whether a disease is randomly distributed over space or over space and time. For this analysis, data were aggregated to the census block level.

Results

Table 1 shows the number of live births identified in the study area by year of birth for the time period 1989-1999.

Table 1 Number of Resident Live Births in the Study Area 1989-1999

Year	Live Births
1989	95
1990	103
1991	136
1992	100
1993	118
1994	119
1995	101
1996	133
1997	127
1998	135
1999	133
Total	**1,300**

Table 2 shows the number and rates of birth defects in the study area compared to the comparison area. Ninety-five percent confidence limits are also presented. This range of numbers statistically means that we are 95% sure that the true rate is within the lower and upper limits presented. The rate of total congenital anomalies in the study area was 438.5 per 10,000 live births compared to 545.2 per 10,000 live births in the rest of Denver. The study area rate of major congenital anomalies, [an anomaly is classified as major if it has medical, surgical or cosmetic importance], was 392.3 per 10,000 live births[2] versus 492.0 per 10,000 live births observed in the comparison area. Hip dislocation/dysplasia are the only conditions where the rate was significantly higher in the study area versus the comparison area ($p<.05$).

[2] Among the 1,300 live births to residents of the study area from 1989-1999, 51 were reported born with major congenital anomalies; for a rate of 392.3 per 10,000 live births, or approximately 4 percent.

Table 2. Rates of Birth Defects 1989-1999									
DIAGNOSIS CATEGORY	Study Area					DENVER excluding Study Area			
	Count	Rate	Lower Limit	Upper Limit		Count	Rate	Lower Limit	Upper Limit
TOTAL CONGENITAL ANOMALIES	57	438.46	333.75	564.37		19142	545.18	537.7	552.74
MAJOR CONGENITAL ANOMALIES	51	392.31	293.47	512.61		17275	492.01	484.88	499.22
CENTRAL NERVOUS SYSTEM	3	23.08	4.76	67.29		1028	29.28	27.52	31.12
MICROCEPHALUS	1	7.69	0.19	42.78		243	6.92	6.08	7.85
CONGENITAL HYDROCEPHALUS WITHOUT SPINA BIFIDA	1	7.69	0.19	42.78		287	8.17	7.26	9.18
EYE	2	15.38	1.86	55.46		725	20.65	19.17	22.21
MAJOR EYE	2	15.38	1.86	55.46		531	15.12	13.87	16.47
CARDIOVASCULAR	8	61.54	26.6	120.89		4380	124.75	121.1	128.47
MAJOR CARDIOVASCULAR	7	53.85	21.68	110.63		4024	114.61	111.11	118.18
VENTRICULAR SEPTAL DEFECT	1	7.69	0.19	42.78		1225	34.89	32.97	36.9
OSTIUM SECUNDUM TYPE ATRIAL SEPTAL DEFECT	1	7.69	0.19	42.78		1294	36.85	34.88	38.91
ANOMALIES OF PULMONARY ARTERY	1	7.69	0.19	42.78		418	11.91	10.79	13.1
RESPIRATORY	3	23.08	4.76	67.29		1210	34.46	32.55	36.46
AGENESIS,HYPOPLASIA,DYSPLASIA OF LUNG	2	15.38	1.86	55.46		257	7.32	6.45	8.27
OROFACIAL	1	7.69	0.19	42.78		649	18.48	17.09	19.96
CLEFT LIP WITH/WITHOUT CLEFT PALATE	1	7.69	0.19	42.78		401	11.42	10.33	12.59
GASTROINTESTINAL	7	53.85	21.68	110.63		2033	57.9	55.42	60.47
MAJOR GASTROINTESTINAL	7	53.85	21.68	110.63		1801	51.29	48.96	53.71
TRACHEOESOPHAGEAL FISTULA,ESOPHAGEAL ATRESIA AND STENOSIS	1	7.69	0.19	42.78		163	4.64	3.96	5.41
CONGENITAL HYPERTROPHIC PYLORIC STENOSIS	4	30.77	8.39	78.59		646	18.4	17.01	19.87
ATRESIA,STENOSIS OF THE LARGE INTESTINE,RECTUM,ANAL CANAL	1	7.69	0.19	42.78		201	5.72	4.96	6.57
GENITOURINARY	16	123.08	70.51	199.1		5512	156.99	152.9	161.15
MAJOR GENITOURINARY	16	123.08	70.51	199.1		5492	156.42	152.34	160.58
MUSCULOSKELETAL	16	123.08	70.51	199.1		5078	144.63	140.7	148.63
MAJOR MUSCULOSKELETAL	16	123.08	70.51	199.1		4651	132.47	128.71	136.3
HIP DISLOCATION/ DYSPLASIA*	10	76.92	36.95	141.01		1449	41.27	39.18	43.45
POLYDACTYLY/SYNDACTYLY	1	7.69	0.19	42.78		469	13.36	12.18	14.62
LEG/FOOT LIMB REDUCTION	1	7.69	0.19	42.78		77	2.19	1.73	2.74
REDUCTION DEFORMITY	1	7.69	0.19	42.78		213	6.07	5.28	6.94
CHROMOSOMAL	2	15.38	1.86	55.46		1057	30.1	28.32	31.97

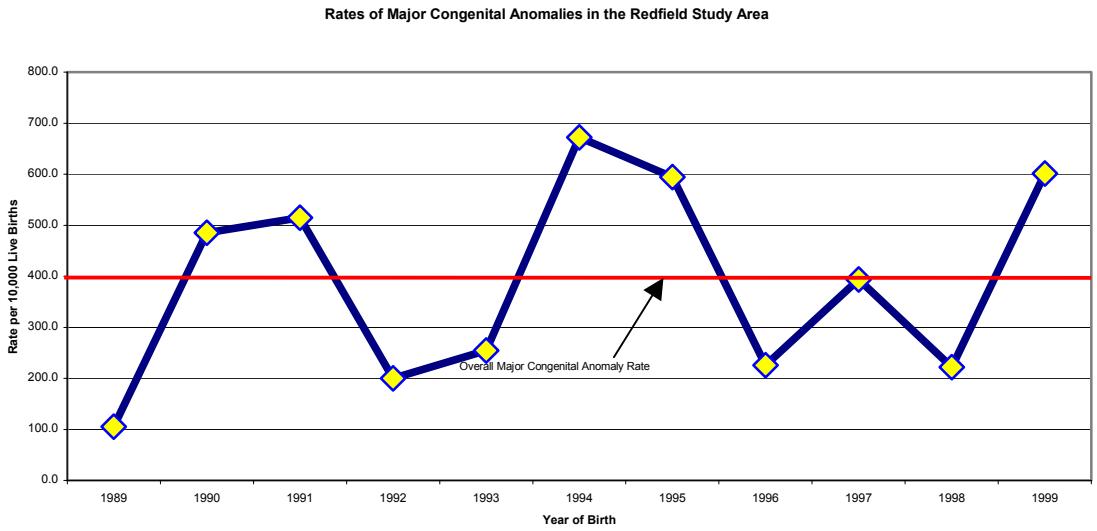
Rates are per 10,000 live births / Lower and upper limits are 95% confidence limits based on a binomial distribution.
Denominator: study area n=1,300 live births, Comparison Area n=351,111
*Statistically Significant (p<. 05)

Fifty-one children born to mothers living in the study area between 1989-1999 were reported to CRCSN having been diagnosed with a major birth defect(s). Table 3 and Figure 3 show the major congenital anomaly rates by year of birth in the study area. These data do not indicate that the rate of major congenital anomalies was increasing over this time period (Cochran-Armitage Trend Test p=0.28).

Table 3. Major Congenital Anomaly Rates Study Area: 1989-1999			
Year of birth	Number of Major Anomalies	Number of Births	Major Congenital Anomaly Rate
1989	1	95	105.26
1990	5	103	485.43
1991	7	136	514.71
1992	2	100	200.00
1993	3	118	254.23
1994	8	119	672.27
1995	6	101	594.06
1996	3	133	225.56
1997	5	127	393.70
1998	3	135	222.22
1999	8	133	601.50
Total	51	1,300	392.31

Rates are per 10,000 live births

Figure 3. Rate of Major Congenital Anomalies



Results of the geographic distribution of cases and live births did not yield any statistical evidence that cases within the study area were geographically clustered in space or space and time other than what would be expected due to a random distribution.

Discussion and Conclusions

In general, at least two of the following three factors are necessary to warrant further action in a disease investigation: 1) a high disease rate, 2) biological plausibility and/or 3) documented exposure (exposure at level above health action levels).

1) Higher Disease rates
In order to determine if a 'high disease rate(s)' had occurred in the study area, statistical comparisons were made with Denver Metro Area Rates excluding the study area. Hip

dislocation/dysplasia was the only birth defect category found to be statistically elevated over the rate estimated in the comparison group (1.9 times increase, p=0.046); however the magnitude of this increase does not meet CRCSN's protocol for further investigation. According to CRCSN protocol, a disease rate must be at least 3 times higher than the comparison area rate, and shown by a statistical hypothesis test to be significantly higher at an alpha level set at 0.05 in order to be considered a "high" rate. This criterion is based on several complex factors, most importantly the likelihood of identifying etiologic information based on the outcome of similar investigations conducted by birth defect surveillance systems across the United States.

Abnormal development of the hip, hip joint instability, and potential dislocation of the hip or femur from the pelvis are often termed developmental hip dysplasia. Clinical studies have shown a familial tendency towards hip dysplasia. The occurrence is also higher in caesarian and breech position births. It has been shown that there is a greater chance for this condition in first-born infants compared to the second or third child. Dislocations generally occur after delivery and are therefore not considered truly congenital in nature. In some cases, an underlying neuromuscular disorder, such as myleodysplasia, arthrogryposis multiplex congentia, or a syndrome complex may be responsible for hip dislocations or dysplasia; however chemical exposure is not known to be related to these conditions.

2) Biological plausibility

The causes of the majority of congenital anomalies are not currently understood. A combination of genetic, biologic or environmental factors is considered to produce many of these conditions. An estimate of the percent of congenital anomalies attributed to each of these factors is shown is Table 4 (Moore, 1993).

Table 4: Causes of major congenital anomalies

Causes	**Percent (%) of Major Anomalies**
Chromosome abnormalities*	6-7
Mutant genes**	7-8
Environmental factors (for example:drugs)	7-10
Multifactorial inheritance (a combination of genetic and environmental factors)	20-25
Unknown causes	50-60

* Chromosome Abnormalities- Chromosomes are structures in the center of our cells, which contain genes. Normally, each cell contains 46 chromosomes. A chromosome abnormality refers to an incorrect number of chromosomes or pieces of chromosomes that are missing or extra.

** Mutant genes- This term refers to a change in genetic (hereditary) material. Genes are instructions that determine how we grow, develop and function. If a gene has a mutation, it may cause serious birth defects.

Biological plausibility refers to a reasonably strong possibility that a defect is associated with exposure to an agent based on information about mechanisms of action, structural and functional relationships, etc. Unfortunately, little is known about the cause of birth defects in relation to particular chemicals. A synopsis of information taken directly from U.S. Department of Health and Human Services individual toxicological profile reports about the agents of concern in this area is included in Appendix B. Copies of information from these reports are available upon request to the CDPHE Environmental Toxicology Section.

3) Documented exposure (exposure level above health action levels).

The methodology used in this investigation is essentially descriptive. A strength of this method is that it can provide evidence to warrant further investigation: e.g., rates higher than expected and statistically significant. A weakness of this analysis is that individual exposure measurements are generally not available and a proxy has to be used, such as geographic region, household, etc. Use of such proxies does not provide evidence for casual conclusions concerning individual exposure and disease occurrence. A weakness inherent in this type of analysis in relation to exposure is that information on potential causes of birth defects, other than the one under investigation (for example, lifestyle behaviors, or genetic predisposition) is lacking or limited.

At the study site, the following chemicals have been detected in the indoor air samples: 1,1,1-trichloroethene, 1,1,1-trichloroethane, perchloroethylene, methylene chloride, 1,1-dichloroethene, and benzene. The most significant of these chemicals is 1,1-dichloroethene (1,1-DCE) because it is found in the greatest concentration in indoor air. Based on all the available data: 1) all chemicals [except 1,1-dichloroethene] detected in indoor air samples are below health action levels and 2) the levels of 1,1-dichloroethene detected above health action levels are negligible.

As seen in Appendix B, there has been one study that suggests oral exposure to 1,1-dichloroethene in humans may be associated with the occurrence of neural tube defects. No information is available concerning reproductive effects in humans following inhalation. In this analysis, no neural tube defects cases occurred in the study area for the time period 1989-1999. The rate of other central nervous system defects reported to CRCSN was not higher than that expected.

Based on the data available at this time, there is no evidence to suggest an elevated occurrence of birth defects in live births attributable to the agents of concern in the study area for the time period 1989-1999.

Recommendations

If continued exposures are anticipated or if prior exposures are found to differ significantly from those that have been reported to CRCSN, we would recommend:

- Continued monitoring and reanalysis of the occurrence of birth defects in this area
- Continued groundwater monitoring in the Redfield site by the Brown Retail Group, Inc.
- Continued regulatory oversight conducted by the CDPHE Hazardous Materials Waste Management Division.

Appendix A. CRCSN Eligibility Criteria

- ✓ **Resident of Colorado**
- ✓ **Diagnosed prenatally to the third birthday**
- ✓ **Diagnosed as having one of the following conditions**

CONGENITAL ANOMALIES

- Central nervous system
- Cardiovascular
- Circulatory
- Respiratory
- Eye, ear and face
- Orofacial
- Gastrointestinal
- Genitourinary
- Musculoskeletal
- Chromosomal abnormalities
- Congenital anomaly syndromes

GENETIC, ENDOCRINE AND METABOLIC DISORDERS

- Newborn Genetic Screening Diagnoses
  - Phenylketonuria (PKU)
  - Congenital hypothryoidism
  - Hemoglobinopathies
  - Galactosemia
  - Cystic fibrosis
  - Biotinidase deficiency
  - Congenital adrenal hyperplasia
- Disorders of amino acid transport and metabolism
- Disorders of carbohydrate transport and metabolism
- Lipidoses
- Disorders of copper metabolism
- Other disorders of purine and pyrimidine metabolism
- Mucopolysaccharidosis

ENVIRONMENTAL RISK FACTORS

- Maternal age 15 years or less
- Maternal education less than 12 years and no prenatal visits

MEDICAL DIAGNOSES AND RISK FACTORS FOR DEVELOPMENTAL DELAY

Birth Outcomes and Perinatal Conditions

- Birth weight less than 1500 grams
- Prematurity less than 32 weeks gestation
- Small for gestational age
- APGAR 3 or less at 5 minutes
- Meconium aspiration syndrome
- Birth trauma
- Intracranial hemorrhage
- Convulsions/seizures
- Drug withdrawal syndrome in the newborn
- Noxious influences affecting fetus
- Fetal alcohol syndrome
- Congenital perinatal infections

Sensory, Development and Growth Conditions

- Hearing loss
- Blindness and low vision
- Retinal degeneration
- Speech and motor delays
- Growth and weight delay
- Mental retardation
- Infantile cerebral palsy
- Dystrophy: muscular and spinal
- Degenerative CNS/Cerebral lipidoses

Other Risk Factors for Developmental Delay

- Encephalitis
- Meningitis
- Injury: head and spinal cord
- Cerebral cysts
- Child maltreatment syndrome
- Chorioretinitis
- Infantile spasms
- Renal tubular acidosis

Appendix B. Synopsis of Reproductive/Developmental Effects Potentially Associated with Redfield Agents of Concern

Information listed is taken directly from the Agency for Toxic Substances and Disease Registry Toxicological Profiles/Department of Health and Human Services

1,1,1-Trichloroethane – No relationship between maternal exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes (spontaneous abortions/congenital malformations) was found in human epidemiology studies (Deane et al. 1989; Linbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al 1991; Wrensch et al. 1990a, 1990b).

Benzene –Epidemiological studies implicating benzene as a developmental toxicant have many limitations, so it is not possible to assess the effect of benzene on the human fetus. The few studies that do exist are limited by a lack of information about end points in control groups, problems in identifying exposed populations, a lack of data on exposure levels, and/or concurrent exposure to multiple substances (Budnick et al. 1984; Forni et al 1971 a; Funes-Carvito et al. 1997; Goldman et al. 1985; Heath 1983; Olsen 1983). Based on available data, other than the possibility of hematological effects in the offspring, it is unlikely that persons living near hazardous waste sites are exposed to levels of benzene in the air, water, or soil high enough to cause fetotoxic effects.

Methylene Chloride- Based on available data, methylene chloride does not appear to pose a hazard to human reproduction and is not likely to cause developmental effects and behavioral changes at levels encountered at hazardous waste sites or in consumer or industrial usage.

1,1-Dichloroethene – The only study reported in humans regarding reproductive effects following oral exposure to 1,1-dichloroethene provides an association with neural tube defects in children (NJDH 1992a, 1992b). However, these data are only suggestive and therefore, should be interpreted with caution. No information is available regarding reproductive effects of 1,1,dichloroethene in humans following inhalation or dermal routes of exposures or in animals following dermal exposure. Only one multigeneration study was identified with rats (Nitschke et al. 1983). This study was conducted by the oral route, and the results were negative. Studies were identified that examined the reproductive effects of 1,1-dichloroethene after acute inhalation in rats (Short, et al. 1997b) and mice (Anderson et al. 1977). No adverse reproductive effects were observed in either of these studies. Available pharmacokinetic data do not suggest route-specific target organs.

Perchloroethylene- Epidemiological studies of women occupationally exposed to perchloroethylene in the dry cleaning industry suggest that they may have an increased risk of adverse reproductive effects, primarily menstrual disorders and spontaneous abortions. (Ahlborg, 1990; Bozo, et al. 1986; Kyyronen et. Al. 1989; Windham et al. 1991; Zielhuis et al. 1989). Interpretation of these studies is complicated by limiting factors, such as small sample populations, failure to account for possible confounding factors, lack of exposure data, and inadequate data collection methods. Other studies have not found an association between perchloroethylene exposure and spontaneous abortions (McDonald et al. 1986; Olsen et al. 1990). Wives of dry cleaners who had significantly more rounded sperm did not have more spontaneous abortions, although there was some evidence that it may take slightly longer for these women to become pregnant (Eskenzai et al. 1991a, 199b). Therefore, it is not possible to speculate on whether adverse reproductive effects could occur in environmentally exposed people.

Studies examining the association between drinking water contamination and birth outcome in humans suggest that there may be an association between birth defects, especially oral clefts, and tetrachloroethylene contamination (Bove et al. 1995; Lagakos et al. 1986). These studies are confounded by more than one contaminant, and the Lagakos et al. (1986) study combined birth defects in the analysis in a manner that has questionable biological relevance.

Trichloroethylene- There is limited evidence that oral exposure to trichloroethylene, in drinking water, may cause birth defects. However, the existing database contains limited positive as well as limited negative reports. Taken together, these data are inconclusive regarding teratogenic effects in humans exposed to TCE.

References

Agresti, A. 1996. *An Introduction to Categorical Data Analysis*, 3rd ed.,
John Wiley & Sons, Inc, U.S.A.

Berhard B.E., Kliegman R.M, Jenson H.B.[editors](2000). *Nelson Textbook of Pediatrics,* 16th ed., W. B. Saunders Company, U.S.A.

Kulldorff M: A spatial scan statistic. *Communications in Statistics: Theory and Methods*, 1997;26:1481-1496.

Kulldorff M, Nagarwalla N. Spatial disease clusters: Detection and Inference. *Statistics in Medicine*, 1995;14:799-810.

Kulldorff M, Feuer E, Miller B, Freedman L: Breast cancer in northeastern United States: A geographical analysis. *American Journal of Epidemiology*, 1997;146:161-170.

Moore, K.L. 1993. *Human Birth Defects. In:The Developing Human.*
W.B. Saunders Company, Philadelphia.

Snedecor G. W. and Cochran W.G. 1989. *Statistical Methods*, 8th ed.,
Iowa State University Press, Iowa.