ITEM 1

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TO : Director, Center for Disease Control

FROM : Cancer and Birth Defects Division
Bureau of Epidemiology

SUBJECT: Congenital Central Nervous System Malformations, Kanawha County, West Virginia

SUMMARY

D[redacted] the Birth Defects Monitoring Program (BDMP) re[redacted], West Virginia--wher[redacted] United States is located--had rates of congenital central [redacted] syst[redacted] rates for those years.

In February 1976 an investigation was undertaken because of the possibility that these higher than expected rates may have been related to parents' occupational or residential exposure to vinyl chloride. The study confirmed that an increase in CNS defect rates had occurred in Kanawha County, and cases clustered primarily in the area east of the plant; however, no relationship between infants with malformations and parents' exposure to vinyl chloride could be established.

INTRODUCTION

Because of continuing concern regarding the possibility that birth defects of the central nervous system (CNS) may be caused by parents' occupational or residential exposure to vinyl chloride, CDC's Birth Defects Branch, Cancer and Birth Defects Division, Bureau of Epidemiology, reviewed 1970-1974 data available through the Birth Defects Monitoring Program (BDMP), a hospital-based system for monitoring the incidence of birth defects and other newborn conditions noted in infants discharged from approximately 1,200 United States hospitals (1). Of the 40 polyvinyl chloride (PVC) production plants in the United States (2), 17 are located in counties which have at least 1 hospital that was participating in the BDMP in 1974 and thus could be included in the review. In 10 of the 17 counties, BDMP data are reported on less than 50% of the total reported births; therefore, even though higher than normal CNS rates were noted in 2 of these counties, they were not included in this study because of the low percentage of total births they represented. [redacted] than national BDMP rates for these years: [redacted] Ohio (Painesville), the site of a previous investigation (3), and Kanawha County, West Virginia.

The Kanawha County findings (Table 1) were discussed with William L. Cooke, M.D., West Virginia State Epidemiologist, and Peter Infante, D.D.S., Dr.P.H., National Institute

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for Occupational Safety and Health (NIOSH), who agreed with the need for further investigation. On February 10, Larry Edmonds, M.S.P.H., and Carol E. Anderson, M.D., met with Dr. Co ke in Charleston, West Virginia, and began an investigation. Others who participated in the investigation and in the preparation of this report included Joseph Carney, Director, and Lucas Neas, Statistician, West Virginia State Department of Health, Division of Vital Statistics; Paul Seekford, M.D., Director, and Edna Smith, R.N., Charleston-Kanawha County Health Department; and Carl Beard, II, Director, West Virginia Air Pollution Control Commission.

BACKGROUND

The principal centers of population in Kanawha County (1970 population 229,113) are Charleston, South Charleston, Dunbar, St. Albans, and Nitro. All are located along the Kanawha River, which flows from southeast to northwest through the valley's hilly terrain.

In 1970 the chemical industry employed 12% of the county's work force. There are 7 major chemical plants and several smaller ones in the Kanawha River Valley within 10 miles of Charleston. Only 1 of these plants produces PVC. This plant, which began production in 1935, uses the solvent, emission, and modified emulsion processes. Vinyl chloride monomer (VCM) is released into the atmosphere as part of the production process.

METHODS

Two data sources were used in this investigation: 1) BDMP listing of infants born with CNS defects from January 1, 1970, through December 31, 1974, and 2) West Virginia Department of Vital Statistics records (birth and fetal death certificates) on infants born with CNS defects from January 1, 1968, through December 31, 1974. Data obtained from these 2 sources were not entirely comparable (4), since BDMP data represented 95% of all hospital births in Kanawha County without regard to parents' residence, and vital statistics records represented only those infants born to county residents. The data were examined separately for trends, and then both sets were combined to determine all CNS defects incidence for 1970 through 1974. A case was defined as a hospital-confirmed CNS defect in an infant born between January 1, 1970, and December 31, 1974, to parents who were residents of Kanawha County at the time of the infant's birth.

We reviewed hospital records to confirm diagnoses, rule out miscoding, and check each mother's place of residence. For each confirmed case, we selected 2 controls from vital statistics records. These controls, all with parents who resided in Kanawha County, were the first liveborn infants without malformations born immediately before and after an infant with a CNS defect and were matched according to the following criteria: 1) month of birth, 2) race, 3) paternal education (number of years: 0-8, 9-12, and 13 and over), and 4) maternal age within 2 years. With the permission of the attending physicians, we interviewed by telephone the families of affected infants and 1 randomly chosen control. The following information was obtained: 1) history of previous pregnancies, including information about miscarriages, stillbirths, and children with malformations in their family, 2) 5-year residential history before and including the year of birth of the child in question, and 3) 5-year occupational history for both parents, including location of work and exposure to chemicals. Case and control families could not be interviewed blindly, since the families often remarked about either the malformation or the normal development of their child. The Kanawha County Health Department and the NIOSH staff assisted in locating families who had changed residences and/or jobs and those who did not have telephones.

RESULTS

Except for 1974, Kanawha County rates shown in the BDMP for total CNS, as well as the particular defects anencephaly and hydrocephaly, were higher than U.S. rates (Table 1). A decline in total CNS defect rates in Kanawha County was noted in both data sets (Tables 1 and 2). In both data sources, the total rates in 1974 were distinctly lower than those in previous years, although the decline was also evident in the 1973 vital records data. Earlier data were available only for 1968 and 1969 from vital records. In both years, there were fewer cases than there were in 1970. The highest BDMP rates for all defects occurred in 1971. Preliminary BDMP data obtained for 1975, the year following the study period, showed that total CNS rates were similar to U.S. rates.

Table 1
Reported Incidence* of CNS Malformations
in Kanawha County, West Virginia, and the United States
Birth Defects Monitoring Program, 1970-1975

	1970		1971		1972		1973		1974	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
Anencephaly										
Kanawha Co.	3	9.0	6	16.3	6	16.6	2	5.2	4	9.6
U.S.		5.6		5.4		4.9		4.9		4.4
Spina bifida										
Kanawha Co.	4	12.0	8	21.8	1	2.8	4	10.5	2	4.8
U.S.		7.2		7.9		7.4		6.4		6.0
Hydrocephalus**										
Kanawha Co.	2	6.0	4	10.9	2	5.5	4	10.5	0	0.0
U.S.		4.8		4.9		4.9		4.5		3.8
Other CNS										
Kanawha Co.	3	9.0	1	2.7	2	5.5	1	2.6	0	0.0
U.S.		4.2		3.9		4.4		4.1		4.2
Total CNS										
Kanawha Co.	12	35.9	19	51.7	11	30.5	11	28.9	6	14.4
U.S.		21.8		22.1		21.6		19.9		18.4

*Rates per 10,000 total births
**Excludes cases with spina bifida

Table 2
Incidence* of CNS Malformations Reported through Vital Records**,
Kanawha County, West Virginia, Residents, 1968-1974

	1968		1969		1970		1971		1972		1973		1974	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
Anencephaly	5	13.6	3	7.6	9	24.1	5	13.2	6	17.5	3	9.0	-	0.0
Spina bifida	6	16.3	3	7.6	5	13.4	4	13.2	2	5.8	-	0.0	1	3.0
Hydrocephalus	2	5.4	2	5.1	2	5.3	3	7.9	5	14.6	2	6.0	-	0.0
Other CNS	-	0.0	-	0.0	-	0.0	1	2.7	-	0.0	-	0.0	-	0.0
Total CNS	13	35.4	8	20.3	16	42.8	13	34.4	13	37.9	5	15.0	1	3.0

*Rates per 10,000 total births
**Birth and fetal death certificates, West Virginia State Department of Health

Combined rates for Kanawha County for the hospital and vital statistics data are given in Table 3. The rates were high from 1970 through 1972, with a decline in 1973 and nly 1 case reported in 1974, giving a 1974 rate well below expected. Forty-seven confirmed CNS defect cases were in infants born to residents of Kanawha County at time of the child's birth. Families of 46 of these infants and of their matched controls were located and interviewed. Five infants' parents were not residents of Kanawha County at the time of conception and were excluded from further analysis. All malformed infants were white, and females predominated (25:16), as usual in anencephaly and spina bifida cases. No seasonal variation was noted in the rates. Of the specific defects, anencephaly had the highest rate.

Table 3
Confirmed Cases and Rates* of CNS Malformations,
Kanawha County Residents, 1970-1974

	1970-1974		1970		1971		1972		1973		1974	
Malformation	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
Anencephaly	23	13.0	9	24.1	5	13.2	6	17.5	3	9.0	-	0.0
Spina bifida	15	8.5	4	10.7	6	15.9	3	8.7	1	3.0	1	3.0
Hydrocephalus	7	4.0	-	0.0	3	8.7	3	8.7	1	3.0	-	0.0
Other CNS	2	1.1	1	2.7	1	2.7	-	0.0	-	0.0	-	0.0
Total CNS	47	26.7	14	37.5	15	39.7	12	34.9	5	15.0	1	3.0

*Per 10,000 total births

Age, Education, and Socioeconomic Index - Close case-control matching was achieved for paternal education, maternal age, and Hollingshead Index, an indicator of socioeconomic status (Table 4). Case and control groups were also comparable regarding maternal education (12.4 and 12.0 years, respectively). Paternal age was slightly older in the case group (27.3 years) than in the control group (25.8 years), but the difference was not statistically significant.

Table 4
Age, Education, and Socioeconomic Index,
CNS Defect Cases and Controls, By Malformation

	Total CNS		Anencephaly		Spina Bifida		Other CNS	
Matching Variables	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Paternal education*	12.6	12.8	12.6	12.2	13.7	14.1	10.9	12.0
Maternal age*	24.3	23.9	24.8	24.4	25.8	25.1	24.3	20.3
Non-matching variables								
Paternal age*	27.3	25.8	26.8	26.4	29.2	26.5	25.4	22.7
Maternal education*	12.1	12.0	11.9	11.9	12.7	12.5	12.1	11.9
Hollingshead Index								
Mean score	47.5	45.5	49.3	48.5	38.9	38.6	58.3	49.4
Class	IV	IV	IV	IV	III	III	IV	IV

*Mean number of years

Generally, cases and controls were similar in the specific defect categories. Among the specific defect categories, parents in the spina bifida group (both case and control) had the highest education and were the oldest; in the "Other CNS" category (mainly hydrocephalus), parents had the least education and were the youngest.

Reproductive History - The total number of previous pregnancies of mothers in the case group (49) was almost the same as that observed for mothers in the control group (48). Other similarities included live births (cases 78%, controls 77%), fetal deaths (cases 22%, controls 23%), and other children with congenital anomalies (1 in each group). The fetal death rates among cases and controls were higher than the rate of 16.1% reported by Warburton and Fraser (5).

A family history of birth defects was reported by 11 of 41 families in the case group but by only 4 of 41 in the control group. Five "case" parents and no "control" parents reported a family history of CNS defects. A possible explanation for the difference is that parental recall is affected by the birth of a child with a congenital malformation (6).

Occupation - Two "case" fathers and 2 "control" fathers were employed in the PVC plant at the time their affected infants were conceived. Fathers of 3 additional controls had worked in the plant on a contract basis for a short time and therefore also had had possible exposures. None of the mothers in either group had ever worked at the PVC plant. One other occupational category is worth noting. In the case group, 2 mothers were employed in dental laboratories when they became pregnant, and 2 fathers had worked in dental laboratories before their infants were conceived.

Parents in the case and control groups were asked about the location of their place of work at the time of their infant's conception. Only parents with a permanent work location were counted, thus excluding workers such as truck drivers and salesmen. The homes of housewives and unemployed parents were considered to be their place of employment. On this basis, distance from work place to the PVC plant was calculated. No difference was observed between case and control groups for either parent regarding distance of work place from the PVC plant.

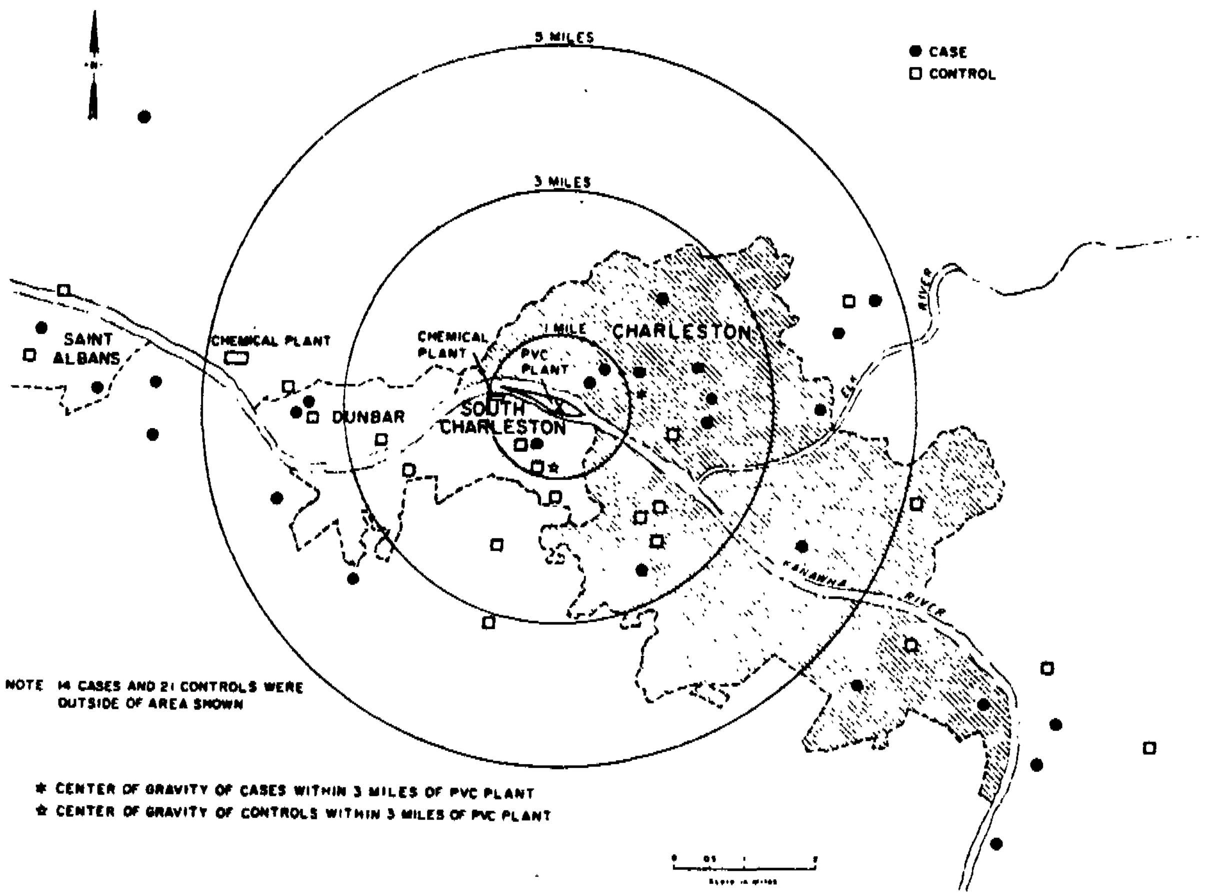
Residence - Parents' place of residence at time of their infant's conception was plotted on county maps, and we then calculated distances from the PVC plant. Table 5 presents the mileage from the plant by 1-mile increments up to 15 miles. Using a chi-square test at 1-mile intervals, we found no significant difference between the 2 groups. Matched pairs of cases and controls were also tested by using the matched pair t-test of significance; no differences were noted.

Table 5
Residential Distance from PVC Plant,
Cases and Controls, By Malformation

Distance from Plant (Miles)	Total CNS		Anencephaly		Spina Bifida		Other CNS	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
≤ 1	3	2	0	0	3	2	0	0
≤ 2	4	4	0	0	3	4	1	0
≤ 3	9	10	1	5	5	4	3	1
≤ 4	14	14	4	6	6	5	4	3
≤ 5	17	15	6	7	7	5	4	3
≤ 6	21	16	9	8	8	5	4	3
≤ 7	23	17	9	8	10	6	4	3
≤ 8	24	22	10	10	10	9	4	3
≤ 9	27	24	12	11	11	9	4	4
≤ 10	30	30	15	13	11	11	4	6
< 15	35	34	19	16	12	12	4	0
TOTAL	41	41	21	21	13	13	7	7

Although no differences were observed in measured distance within concentric circles, within the 3-mile zone of the PVC plant, there were more case family residences in the area northeast of the river and more control family residences in the area south of the river (Figure 1).

Fig. 1 CONGENITAL CNS DEFECTS CASES AND CONTROLS, CHARLESTON-SOUTH CHARLESTON, WEST VIRGINIA, AREA



Using the PVC plant as the origin, we determined x and y coordinates for parents' residence at time of each infant's conception (case and control groups). Four cumulative groups were defined for both cases and controls based on distance of residence from the PVC plant: ≤ 3 miles, ≤ 5 miles, ≤ 10 miles, and the total group.

Case and control groups were then compared for statistically significant differences in their respective centers of gravity (average position), using multivariate extensions of the Wilcoxon matched-pairs signed-ranks test and the Kruskal-Wallis test (7).

The matched-pairs test was used to test the total group (all case-control pairs). Since in the distance-defined groups case-control pairs were split, these 3 groups were analyzed by the (unpaired) Kruskal-Wallis analysis of variance. The only significant difference was for infants in the case and control groups whose families resided within 3 miles of the plant ($p < .02$) (Table 6).

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Table 6
Significance Testing of Differences in
Centers of Gravity, CNS Defect Cases and Controls

Distance from Plant	χ^2 (2 Degrees of Freedom)	Probability
$\leq$3 miles	8.72	<.02
$\leq$5 miles	3.06	>.20
$\leq$10 miles	1.09	>.30
All distances	0.91	>.50

The case and control parents who resided within 3 miles of the PVC plant at their child's conception had a higher socioeconomic status than those who resided more than 3 miles from the plant, as reflected by a class III Hollingshead Index; the remaining group had a class IV. The distribution of this group by date of birth was similar to the remaining group. There were 9 infants in the case group: 5 with spina bifida, 2 with congenital hydrocephalus, 1 with microcephaly, and 1 with anencephaly. In at least 3 cases there was evidence of a familial component to the defect occurrence. One mother gave birth to 2 of the infants: 1 with spina bifida and another with anencephaly. Another case mother reported that her sister had spina bifida, and a third mother had a cousin with a heart defect. Although familial components do not exclude an environmental cause, they do suggest the possibility of genetic causation. There was no difference in previous stillbirths or abortions between case and control parents who lived within 3 miles of the PVC plant or between these parents and those who lived more than 3 miles from the plant. No difference was noted between the mean years of residence of case parents (1.9) and control parents (2.0) who lived within 3 miles of the PVC plant.

Environmental Studies - Atmospheric and environmental data related to VCM and other emissions in Kanawha County are limited. Data on VCM emissions provided by the South Charleston plant at the request of the West Virginia Air Pollution Commission are provided in Table 7. The data included the average amount (pounds per hour) of each year's emissions from 1967 through 1975 and the number of abnormally heavy emissions. On October 1, 1974, after the largest known single emission in the years 1967-1975, measurements were made by plant personnel in the community. The wind was blowing from the southwest, and the highest atmospheric VCM levels (grab samples) were to the northeast (.1 - .2 ppmv). The wind patterns in Kanawha Valley are variable according to the season of the year, time of day, and place of measurement. Monthly wind measurements also made at the plant indicated that the wind was blowing out of the south and west 42% of the time, and north and east 33% of the time during the months the infants with CNS defects were conceived.

Table 7
Annual Average Vinyl Chloride Monomer Emissions,
South Charleston Plant, West Virginia

Year	Emissions (lbs/hr)	Estimated Number of Abnormally Heavy Emissions*
1967	240	
1968	260	
1969	250	
1970	260	28
1971	270	18
1972	235	12
1973	265	5
1974	180	2
1975	76	0

*Amounts ranged from 1,000-8,000 pounds, with an estimated average of 2,000

Source: Polyvinyl chloride plant, at the request of the West Virginia Air Pollution Commission

Should the release of emission coincide with the southwest winds, then one might expect that more emissions could be blown from the plant to the northeast. The West Virginia Air Pollution Control Commission measured suspended and settleable particulate matter, another indicator of wind direction, at various points within the community (Table 8). The reported levels were greater in the southwest, suggesting a prevailing wind from the northeast.

Table 8
Mean Annual Levels of Suspended and Settleable Particulate Matter,
1965-1975

Year	Geometric Mean Suspended Particulate Matter (microgram/cubic meter)		Arithmetic Mean Settleable Particulate Matter (tons/square mile/month)	
	1	2	1	3
1965	205	160	92.2	62.0
1967	171		133.2	68.9
1968			82.3	63.6
1969			68.6	35.4
1970	150	113	47.6	35.9
1971	136	131	30.0	24.0
1972	102	107	24.0	24.0
1973	105	107	18.0	15.0
1974		93		18.5
1975		94		13.3
1970-1973	123.2	114.5		
1967-1973			57.7	38.1

[1] South Charleston High School (southwest)
[2] Federal Building, Quarrier Street (northeast)
[3] North Charleston Fire Department (northeast)
Source: West Virginia Air Pollution Control Commission

DISCUSSION

The investigation in Kanawha County confirmed that an increase had occurred in total congenital CNS malformation rates in 1970-1974. Rates were highest in 1970-1972 and dropped in 1973 to below national rates and in 1974 to only 1 confirmed case. Such a decline was not unique to Kanawha County. A similar, though less marked, trend was also present in BDMP data for other parts of the country. Furthermore, preliminary 1975 BDMP data on CNS defects for the county were higher than 1974 data, suggesting that the apparent low incidence for that year may reflect the variability of small numbers.

As in the Painesville study (3), there were no differences between case and control groups regarding parents' possible occupational exposure to VCM or to other environmental agents at time of their child's conception or for 5 years before conception. On this basis, there was no evidence that the high CNS defect rate in Kanawha County was related to parental occupation in industries producing PVC or other chemicals.

A difference between the locations of residences of the case and control groups within a 3-mile radius of the plant was noted. Although approximately the same number from each group resided within the 3-mile area, those in the case group tended to live east of the plant, and those in the control group lived across the river and south of the plant. Such a pattern might be chance distribution, or it could be related in some way to an environmental exposure limited to the part of the city lying east of the plant. Aside from a slightly higher socioeconomic status, there was nothing to distinguish the families of cases and controls from other families who lived within the 3-mile area. Furthermore, there was no difference in the distribution of the types of defects or the years of birth (or conception).

Since the investigation was undertaken because of a possible association between the high CNS defect rates observed in Kanawha County and the presence of a PVC plant, we gave particular attention to the possibility that the cluster may have been caused by increased VCM emissions.

To explain the case cluster on the basis of a teratogenic effect of atmospheric VCM exposure, one would also expect an approximate correlation between a decrease in atmospheric VCM levels and a fall in CNS defect rates. The decrease in CNS rates which occurred in 1973 preceded the decline in measured VCM emissions and lagged considerably behind the overall decrease in particulates noted in the late 1960s.

This investigation did not reveal an association between the case clustering within 3 miles of the plant and exposure to VCM or other chemicals. Available data suggest that atmospheric and meteorologic conditions along the Kanawha River are variable. To propose that some wind-born teratogen had settled in a particular location in the community, one would have to postulate also the timing of plant emissions with the appropriate wind direction and other atmospheric conditions. No data are available to reconstruct such circumstances.

Furthermore, it must be noted that over 100 compounds other than VCM have been associated with emissions from the plants in the Kanawha Valley area. One study estimated that 52,457 tons of organic compounds, including VCM, were emitted each year by Charleston chemical plants (8). Some of these compounds have been identified as toxic to animals and humans; their individual and combined teratogenic potentials are not known.

Although there was a cluster of CNS defect cases to the east of the PVC plant in Kanawha County, the role of VCM or other compounds in explaining this cluster is conjectural at present.

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