VINYL CHLORIDE

(Teratogenicity)

Supplement to Feb. 3, 1982 Package

References

EPA Project Summary - "Association Between Birth Defects and Exposure to Ambient Vinyl Chloride" - Sept. 1981; pp. 1-6

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Research and Development

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Project Summary

Association Between Birth Defects and Exposure to Ambient Vinyl Chloride

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To better define the association between exposure to vinyl chloride monomer (VCM) and the occurrence of birth defects, this epidemiological study was made in Shawinigan, Quebec, Canada, where a vinyl chloride polymerization plant has operated since 1943. Birth-defect rates in Shawinigan during the last 15 years were compared with rates in three other communities, and seasonal and spatial variations in Shawinigan's birth-defect rate were correlated with estimated VCM concentrations in the environment.

Shawinigan had an excess of birth defects which fluctuated seasonally in a way that could correspond to changes in VCM concentration in the environment. Mothers who gave birth to malformed children were younger on average in Shawinigan than in the comparison communities. However, there was no excess of stillbirths in Shawinigan, the excess in birth defects involved most systems, and variation in birth-defect rates among school districts could not be accounted for by estimates of VCM in the atmosphere.

The occupational and residential histories of parents who gave birth to malformed infants were compared with those of parents of normal infants. The two groups did not differ in occupational exposure or closeness of residence to the vinyl chloride polymerization plant.

This Project Summary was developed by EPA's Health Effects Research Laboratory, Research Triangle Park, NC, to announce key findings of the research report that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

Vinyl chloride monomer (VCM) is carcinogenic in man and other animals and mutagenic in microbial assays, *Drosophila*, yeast, mammalian cells, and man. VCM generates mutations primarily through one of its metabolites, chloroethylene oxide, and with the involvement of liver microsomal enzymes. Although miscarriages and fetal losses among the wives of workers exposed to VCM have been studied, such effects remain undocumented. VCM was found in the fetal and maternal blood and the amniotic fluid of pregnant rats after exposure to air containing VCM; two studies of VCM teratogenicity in animals failed to demonstrate fetal malformations, but showed increased fetal death rates.

At normal temperature and pressure, VCM is a gas; it liquifies at -13° C. It is processed into polyvinyl chloride (PVC; a plastic) through polymerization reactions in autoclaves. The gas is released into the environment during unloading, processing, and autoclave-cleaning operations. The concentration of VCM

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to which people in the community are exposed depends on production rate, wind direction, wind velocity, and distance from the plant.

In Shawinigan (population 27,000), a vinyl chloride polymerization plant (owned by B.F. Goodrich Co., Ltd.) has operated since 1943 and currently produces 25,000 tons/yr of PVC. Ten cases of angiosarcoma of the liver have been reported among workers at this plant. In addition to the PVC plant, Shawinigan has two chemical plants, one aluminum electrolysis plant, one carbide plant, and one pulp and paper mill. A great number of pollutants are discharged into its environment. Furthermore, prevailing winds tend to blow from the pollution sources towards the town's residential areas.

In 1975, a high birth-defect incidence (mostly central nervous system abnormalities) was found in three Ohio towns with PVC plants. However, two subsequent studies failed to find any association between birth defects and either work at or proximity of residence to these plants. In a 1977 study, a higher birth-defect rate was found in Shawinigan than in Drummondville (a town without a PVC plant); the highest rates in Shawinigan were in the vicinity of the plant. The present study was an attempt to associate this high frequency of birth defects with exposure to VCM.

One objective of this study was to establish birth-defect and stillbirth rates in Shawinigan and to compare these rates with those for other communities, in an attempt to confirm the high birth-defect rates previously observed. Another objective was to try to correlate seasonal and spatial variations in the birth-defect rate with variations in VCM concentration in the environment. The final objective was to compare a group of parents who gave birth to malformed infants with a control group of parents of normal children with respect to residential and occupational history and several birth-defect risk factors.

In determining birth-defect rates in Shawinigan, the study included all stillbirths and malformed children born of mothers who resided within the city limits of Shawinigan at the time of delivery and who delivered between January 1, 1966, and December 31, 1979. The case-control study was limited to a shorter period (January 1973 to December 31, 1979), because it required information based on the mothers' recollection of events during their pregnancies. A birth defect was defined as a gross physical or anatomic developmental anomaly present at birth or detected at the hospital during the first days after delivery.

To assess the importance of the excess of birth defects in Shawinigan, three comparison communities were chosen, based on their similarity to Shawinigan in population size and structure, socioeconomic level, and medical-care facilities. To take into account the influence of environmental pollution, one town with an aluminum plant but no VCM-emitting plant (Baie-Comeau—Hauterive) and two towns with neither a VCM nor an aluminum plant (Drummondville and Rimouski) were chosen as control communities.

The Quebec Population Registry provided the annual numbers of births and stillbirths in the communities; as the 1979 data were not available, numbers were estimated from the three preceding years. Birth-defect children and controls were identified and data were collected from several medical files and hospital rosters (delivery-room daybooks, birth-defect rosters, discharge lists, mothers' and children's medical files, and birth rosters). Shawinigan's 14 school districts were used as the unit of spatial distribution of birth defects. For the case-control study, the mothers of affected infants and matched controls were interviewed at home. Cases and controls were matched by maternal age within two years, sex of the infant, and place of residence of the mother.

Two studies were conducted to assess vinyl chloride concentration in the air in Shawinigan. The first was a study of the feasibility of measuring VCM in the air at several locations in Shawinigan using air sampling and analysis techniques (summarized in an appendix to the report of the present study). Its conclusion was that environmental VCM concentrations could be assessed by ambient air sampling at various sites in Shawinigan; depending on location, sampling detected levels up to 45 ppb. During winter, VCM tended to accumulate in the snow in the vicinity of the plant, and VCM concentrations differed between indoor and outdoor samples. The report recommended a continuous one-year sampling program with special attention to meteorologic, topographic, and demographic data to establish the true VCM concentrations to which the Shawinigan population is exposed.

Considering the high cost of such a sampling program, it was decided that for the present study, ambient vinyl chloride concentrations in Shawinigan would be estimated using a dispersion model based on production records and the results of previous air-monitoring activities. This study was conducted by a subcontractor. The dispersion model used the Pasquill-Gifford equation, and its variables included wind direction and velocity, rainfall, humidity, temperature, topography, and estimated VCM production and emissions. The model allowed construction of isopleths of estimated vinyl chloride concentration over Shawinigan.

Results

From January 1966 through December 1979, there were 4534 live births and 33 stillbirths in Shawinigan. Of the live infants, 150 had birth defects, and of the stillbirths, 9 had birth defects. The birth defects reported most frequently were those of the musculoskeletal system, followed by the cardiovascular, central nervous, and urogenital systems. The ages of the mothers did not differ significantly among the various types of birth defect. Defects of the central nervous system (CNS) were particularly frequent among malformed infants with short gestation periods.

The yearly numbers of malformed children per 100 births varied from 1.68 (in 1969) to 6.84 (in 1973), with an overall rate of 3.48. Detailed analysis of the monthly distribution of birth defects and the distribution by affected system for the year 1973 showed no single large increase that could account for the high rate in that year. Nor did the yearly distribution by system show any particular feature that could account for the annual variation in the overall rates. Furthermore, birth-defect rates did not consistently increase or decrease with time.

The observed number of malformed children in Shawinigan was higher than would be expected based on the rate for each comparison community or for all three comparison communities together (see Table 1). The excess birth defects in Shawinigan occurred in the central nervous, cardiovascular, urogenital, and musculoskeletal systems, the eye and ear, and the chest. As the types of defects found in excess in Shawinigan were also the most common types of defects overall, it can be concluded that birth defects in general were in excess in Shawinigan. The proportion of malformed infants was greater in Shawinigan than in the comparison communities in

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Table 1. *Number of Malformed Children Observed in Shawinigan Compared with Expected Numbers Based on Rates for the Comparison Communities (1966-1979)*[a]

Affected System	Observed in Shawinigan	Expected Based on Drummondville	Expected Based on Baie-Comeau—Hauterive	Expected Based on Rimouski	Expected Based on All Comparison Communities
Central nervous	30	19.69*	18.18*	15.33**	17.96*
Cardiovascular	37	19.69**	13.94**	43.06	24.29*
Gastrointestinal	11	9.04	9.70	10.95	9.80
Urogenital	30	19.15*	13.94**	13.14**	15.72**
Musculoskeletal	49	36.71	27.88**	40.14	34.70*
Mouth and upper airways	17	6.92**	13.33	13.14	10.82
Eye and ear	6	1.06**	1.82*	—	1.02**
Chest	3	0.53*	—	0.73	0.41*
Syndromes and other defects	6	6.92	9.70	10.95	8.98
Total	159	102.68**	98.80**	124.08**	107.36**

[a]*Ratio of Poisson variable to its expectation (36); * indicates $p < 0.05$; ** indicates $p < 0.01$.*

all years except 1969 and 1972 (see Table 2).

The number of stillbirths differed only between Shawinigan and Drummondville, where the number of stillbirths was significantly higher. The proportion of malformed children among the stillborn was higher in Shawinigan than in the comparison communities. This is consistent with previous findings of an excess of birth defects in Shawinigan. Mothers who gave birth to malformed children were significantly younger in Shawinigan than in the comparison communities for all malformations combined and for defects of the CNS, mouth and upper airways, and eye and ear. Children in Shawinigan did not differ from those in the comparison communities in mean gestational age at birth, except in the case of chest malformation, for which the sample size was very small.

Figure 1 compares the monthly birth-defect rates for Shawinigan with those for Drummondville and Rimouski. The Shawinigan curve is V-shaped, with the lowest rates in the summer, whereas the curve for the comparison communities is flatter. The seasonal variation in birth-defect rates was statistically significant for Shawinigan, but not for the comparison communities.

The spatial distribution of birth defects in Shawinigan with respect to the PVC plant was analyzed; in no

Table 2. *Distribution of Malformed Children for Each Year (1966-1979)*

Year	Shawinigan	Rate[a]	Comparison Communities	Rates	SH/Comparison Communities[b]	95% Confidence Interval
1966	16	3.54	31	1.82	1.95*	(1.08, 3.52)
1967	13	3.52	33	1.96	1.80	(0.96, 3.39)
1968	8	2.30	24	1.51	1.52	(0.69, 3.34)
1969	6	1.68	27	1.78	0.94	(0.41, 2.18)
1970	15	4.70	24	1.66	2.83*	(1.55, 5.17)
1971	6	2.08	30	2.05	1.01	(0.53, 1.94)
1972	6	2.19	34	2.43	0.90	(0.36, 2.20)
1973	18	6.84	44	3.17	2.16*	(1.28, 3.65)
1974	8	2.97	43	2.81	1.06	(0.48, 2.33)
1975	15	4.40	51	3.10	1.42	(0.81, 2.49)
1976	13	3.98	36	2.20	1.81	(0.93, 3.51)
1977	14	4.56	50	2.76	1.65	(0.93, 2.93)
1978	11	3.33	52	2.88	1.16	(0.61, 2.20)
1979	10	3.11	47	2.69	1.16	(0.60, 2.26)
Total	159	3.48	526	2.35	1.48*	(1.24, 1.75)

[a]*Number of malformed children per 100 births.*
[b]** indicates $p < 0.05$.*

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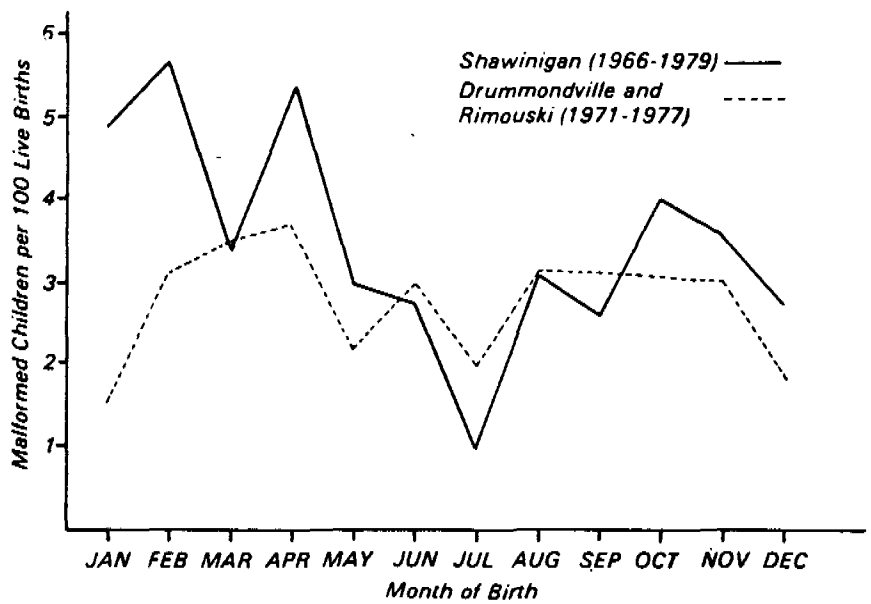

Figure 1. Monthly distribution of birth-defect rates.

school district did the ratio of observed to expected number of birth defects differ significantly from 1. The four districts with the highest rates are located on the north-south axis passing through the vinyl chloride plant; the district in which the plant is located had about the expected number of birth defects. The yearly average concentration of vinyl chloride was estimated for each school district, based on data from a study entitled "Dispersion Patterns of Vinyl Chloride Emitted by B.F. Goodrich Co., Ltd., Shawinigan, Que." (which is appended to the report of the present study). Birth-defect rates did not differ between school districts with high and low VCM exposure, either for all birth defects or for CNS defects (see Table 3). Likewise, school districts adjacent to the plant did not differ from the other school districts in numbers of birth defects (total or CNS), nor did districts differ within and beyond a one-mile radius of the vinyl chloride plant.

For the period January 1973 to December 1979, 68 cases of birth defects were identified in Shawinigan and matched with controls (42 male and 26 female pairs). Five of the cases were stillborn; all of the controls were born alive. There was no significant difference between cases and controls in number of weeks' gestation at delivery. The frequencies of previous birth defects in the families of cases and controls did not differ significantly, nor was there a significant difference between case and control mothers in number of previous pregnancies.

Mothers of malformed infants reported no excess of diseases during pregnancy; however, the following diseases suspected to bear a high risk of birth defect were reported more frequently by case than by control mothers: rubella, hydramnios, epilepsy, nonpsychotic mental disorders, and psychosis. There was no significant difference between case and control mothers in number of previous abortions. There was one previous stillbirth among the control mothers and none for the case mothers; there was one previous malformed child in each of the two groups. There was no significant difference between cases and controls in the father's age. No mother (case or control) was exposed to X-rays during the first trimester of pregnancy, and only one case mother was exposed during the second third of pregnancy; exposure during the third trimester did not differ significantly between case and control mothers.

Table 4 summarizes the mothers' occupations before and during their pregnancies. None of the women were ever exposed to VCM at work before or during pregnancy. The working experiences of the case and control mothers before and during pregnancy did not differ, nor did their smoking habits or alcohol consumption. Two mothers of defective infants reported having used the drug LSD before their pregnancies. There was no significant difference between cases and controls in the father's occupational exposure to chemicals, and no fathers were ever exposed to vinyl chloride (see Table 5). The distance between each mother's place of residence and the VCM plant was measured to ± 100 m, using a map of the city; there was no significant difference between the two groups in distance from the VCM plant.

Discussion

Some observations of this study support the existence of an association between VCM in the air and birth defects in the exposed community,

Table 3. Comparison of Total Birth Defects[a] and CNS Birth Defects[b] Between School Districts with High and Low Atmospheric Vinyl Chloride Concentration

	School Districts With High VCM Levels[c]	School Districts With Low VCM Levels	Total
Births with defects	87	70	157
Births without defects	2285	2125	4410
Births with CNS defects	16	13	29
Births without CNS defects	2356	2182	4538
Total births	2372	2195	4567

[a] $X^2_1 = 0.80$; $p > 0.35$.
[b] $X^2_1 = 0.10$; $p > 0.70$.
[c] School districts nos. 1, 3, 5, 6, 7, and 8.

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Table 4. Distribution of Cases and Controls by Mother's Occupation[a]

Mother's Occupation	Cases		Control	
	Before Pregnancy	During Pregnancy	Before Pregnancy	During Pregnancy
Work outside home without exposure to chemicals	41	22	42	20
Work in VCM industry	0	0	0	0
Work outside home with exposure to chemicals	2	1	2	1
Stay at home	25	45	24	47
Total	68	68	68	68

[a]*Partitioning stay at home vs. work outside home before pregnancy:* $X^2_1 = 0.03$; $p > 0.85$. *Partitioning stay at home vs. work outside home during pregnancy:* $X^2_1 = 0.13$; $p > 0.71$.

while others tend to contradict such an association. High birth-defect rates in Shawinigan were confirmed for a 15-year period, and women who gave birth to malformed children were, on average, younger in Shawinigan than in the comparison communities. These results are consistent with previous findings for three Ohio towns with PVC plants.

The present study revealed seasonal variation in birth-defect rates that could correspond to variation in atmospheric VCM concentrations. VCM could not be measured in air samples during December, January, and February. It is believed that during these months, VCM tends to accumulate near the plant as a liquid, because the outdoor temperature is below its liquefaction point; this VCM would be released into the air in the spring. Birth-defect rates were lowest in September, which is eight months after midwinter, corresponding to the time between the first third of pregnancy and delivery. This observation would tend to support an association between VCM concentration in the air and birth defects in the community. One consultant believed that below its liquefaction point, VCM would remain in the air in droplets, at a concentration similar to that found at higher temperatures. However, because people spend more time indoors during the winter than the rest of the year, winter exposure would tend to be low in any case.

On the other hand, several observations of the present study tend to argue against any association between VCM concentration in the air and birth defects in the community. The spatial distribution of birth defects in Shawinigan cannot be explained on the basis of estimates of VCM concentrations in the community. Malformation rates were not relatively high either near the plant or in the area where VCM concentrations were estimated to be highest, and the school district with the highest birth-defect rate was far from the plant. However, VCM concentrations were not measured directly, but estimated by a theoretical dispersion model based on approximate production and emission values, because the B.F. Goodrich Co. would not release the actual values.

Table 5. Distribution of Cases and Controls by Father's Occupation[a]

Father's Occupation	Cases	Controls
Ever worked in vinyl chloride industry	0	0
Ever worked in industries with exposure to chemicals	20	25
Never worked in industries with exposure to chemicals	43	39
Unknown	5	4
Total	68	68

[a]$X^2_1 = 0.73$; $p > 0.39$.

There was no difference in occupational or residential history between the parents who gave birth to malformed infants and the control parents. Both groups resided at similar distances from the plant, and none of the parents had worked at the plant. Furthermore, all types of birth defects were in excess in Shawinigan, rather than those of any particular system. These results agree with those for the three Ohio cities; however, agents known to be teratogenic in humans and experimental animals have very specific effects, and it seems unlikely that any agent would produce the variety of malformations found in excess in Shawinigan.

Possible explanations of the results as artifactual are not convincing. It is unlikely that Shawinigan's physicians were more inclined to diagnose birth defects than were physicians in the comparison communities. Birth defects were included in this study on the basis of their obviousness, and the birth-defect rates were the same in the three comparison communities. Furthermore, for severe birth defects like those of the CNS, which cannot be misdiagnosed, rates were much higher in Shawinigan than in any of the comparison communities. The method by which the data were collected made it very unlikely that a bias in the quality of the information from the archives of the regional hospitals could have influenced the results.

The possibility remains that pregnant mothers residing outside of Shawinigan who were at risk of having a malformed child migrated to the city for delivery, thereby increasing the birth-defect rate for that town. In the case-control study, six mothers (6.7%) were rejected because they had moved to the city of Shawinigan after the first third of pregnancy, and four more cases were untraceable. Thus, as many as 11% of the birth-defect cases observed in Shawinigan might actually have come from elsewhere, reducing the number of observed cases to 142. However, birth-defect rates would still be significantly higher than in the comparison communities, leading us to believe that the excess noted in Shawinigan was real.

Animal studies have shown that exposure to high levels of VCM during pregnancy results more often in high rates of fetal loss and miscarriage than in birth defects. However, stillbirth rates were no higher in Shawinigan than in the comparison communities, and in the

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case-control study, abortion rates were not higher for case than for control mothers.

Several industries in Shawinigan emit pollutants into the atmosphere, and several of the pollutants may interact to generate potent mutagenic or teratogenic chemicals in the community. The analysis of such an environment and its association with the excess of birth defects was beyond the scope of the present study. However, in the case-control study, there was no difference between the numbers of case and control parents who worked at the aluminum plant, and the comparison community with an aluminum electrolysis plant (Baie-Comeau—Hauterive) had lower birth-defect rates than did Shawinigan. Thus, the aluminum industry probably was not solely responsible for the excess of birth defects in Shawinigan.

Among risk factors (other than occupational or environmental exposure to a pollutant) known to be associated with birth defects, epilepsy and mental disorders before and during pregnancy and the use of the drug LSD before pregnancy were reported more frequently by mothers of malformed children than by control mothers. Drugs prescribed to control epilepsy have been reported to be associated with birth defects and could account for a few birth defects observed in Shawinigan, as could LSD. No other risk factor was reported more frequently by the case than by the control mothers.

An association between VCM in the air and birth defects in the exposed community cannot be substantiated at the present time. If the association exists, it cannot be measured by the methods used in this and in previous studies or in populations of the sizes studied so far.

Conclusions

The conclusions of this study can be summarized as follows:

1. For the years 1966 through 1979, there was an excess of birth defects in the population of Shawinigan, Quebec. This result is similar to the findings for several U.S. cities where vinyl polymerization plants operate.
2. Birth-defect rates underwent a seasonal variation that could correspond to variation in the concentration of VCM in ambient air.
3. Mothers from Shawinigan who gave birth to malformed infants were younger than mothers from the comparison communities who also gave birth to malformed infants.
4. The excess malformations involved not only the central nervous system, but almost all body systems.
5. No correlation was found between the spatial distribution of birth defects in the town and estimates of VCM concentrations in the air. (These estimates were based on approximate data, since information on PVC production and VCM emissions was not available.)
6. Occupational exposure as a causal agent was ruled out, because none of the parents in the study had ever worked at the VCM plant.
7. Cases and controls did not differ in distance of residence from the plant.
8. No excess of stillbirths was observed in Shawinigan, and abortion rates were no higher for mothers of malformed infants than for mothers of normal infants.

Some observations of this study support an association between VCM in the air and birth defects in the exposed community, while others tend to indicate that no such association exists. As the present results are inconclusive, the possibility that VCM generates birth defects in human communities requires further consideration. This would best be accomplished through a program during the next five to ten years to monitor VCM concentration in the air and birth defects in the exposed communities.

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Jeff Beaubier and Gregg Wilkinson are the EPA Project Officers (see below).

The complete report, entitled "Association Between Birth Defects and Exposure to Ambient Vinyl Chloride," (Order No. PB 81-238 883; Cost: $11.00, subject to change) will be available only from:

National Technical Information Service
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Occasional Survey

GENETIC RISKS OF VINYL CHLORIDE

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Summary A study of pregnancy outcome among wives of workers exposed to vinyl-chloride monomer (V.C.M.) indicated that, in comparison with controls, there was a significant excess fetal loss in the group whose husbands had a primary exposure to V.C.M., whereas no differences between the groups were observed before the husbands' exposures. The difference in fetal death-rates for the post-exposure comparisons was a reflection of a greater fetal loss associated with the wives younger-aged husbands. The significant excess did not seem to be the result of bias from interviewers, respondents, nor from women who had experienced chronic abortions weighting the results. These findings, in conjunction with the demonstration of a mutagenic response via microbial test systems and with observations of significant excesses of chromosomal aberrations among workers exposed to V.C.M., raise scientific and public-health concern for the possible genetic risks of V.C.M. to man.

IN the past year, several reports have indicated that vinyl-chloride monomer (V.C.M.) is mutagenic in microbial test systems.[1-3] V.C.M. metabolites also have induced mutations in mammalian cells.[4] Likewise, reports from four countries have shown an excess of chromosomal aberrations in lymphocytes of workers exposed to V.C.M. compared with controls.[5-8] However, Purchase *et al.*[7] have stated (though no animal data were presented), that the mutagenic effects of V.C.M. expressed as chromosomal aberrations in lymphocytes in humans do not occur in germ cells in mice; they concluded that the potential danger of mutagenic effects on the fetus via sperm seemed unlikely to exist. In a study without controls, Selikoff observed fetal death-rates among wives of V.C.M. workers that ranged from 7 to 14 per 100 pregnancies.[9] These rates appear to have been higher than expected.[10]

To develop further data on this question, pregnancy outcome has been studied among the wives of workers exposed to V.C.M. All current V.C.M. polymerisation and polyvinyl-chloride (P.V.C.) fabrication workers were included for study together with a similar number of current rubber workers (8% of all such workers) selected from work areas relatively free from known toxic materials and matched as a group to the V.C.M. workers by age. Group-participation rates ranged from 62 to 77%. Data for the wives of V.C.M. polymerisation workers (primary V.C.M. group) were contrasted with data for the wives of P.V.C. fabrication and rubber workers ("controls"), who were known to have had very low or no V.C.M. exposure, respectively. A total of 95 V.C.M. polymerisation and 158 rubber and P.V.C. fabrication workers were interviewed. Paternal age, pregnancy outcome, and estimates for the time of conception of all pregnancies were ascertained by interview in October, 1974, from males employed at a rubber manufacturing, P.V.C. fabricating, and V.C.M. polymerising facility. As part of a larger survey of worker health, date of first employment in the job categories was determined from company records. Mean paternal age, total number of conceptions, total number of fetal deaths (defined as any product of conception not born alive), and fetal deaths per 100 conceptions were then computed for each group prior to and subsequent to the worker's date of employment. No interviews were conducted with workers' wives and no data were obtained concerning maternal age, except indirectly through paternal age.

Since fetal loss is known to increase with ascending parental age, the fetal death-rates for the primary V.C.M. exposure group were age-adjusted to the control group. Table 1 shows the age-adjusted fetal death-rates for wives of the primary V.C.M. exposure group versus the control group, both prior to and subsequent to each group's respective exposures. Among pregnancies occurring prior to exposure, fetal death-rates were 6·9% for the controls versus 6·1% (age-adjusted) for the primary V.C.M. exposure group. These rates were not significantly different by Mantel-Haenszel Chi-square testing.[12] Among pregnancies occurring subsequent to the husband's exposure, the difference in frequency of fetal deaths between groups was significant at $P<0.05$ ($\chi^2=4.00$, df=1).[12] Although the underlying distributions differed, mean paternal ages were virtually the same—30·4 versus 30·2 years. The significant difference between the groups subsequent to exposure was a reflection of a relatively greater fetal mortality-rate associated with younger-aged husbands in the primary V.C.M. exposure group. Among pregnancies occurring subsequent to exposure, the fetal mortality-rates associated with husbands 30 years of age and older for the primary V.C.M. exposure and control groups were 9/69 (13·0%) and 17/142 (12·0%), respectively; whereas, for

TABLE 1—MEAN PATERNAL AGE, NUMBER OF PREGNANCIES, AND FETAL DEATH-RATES ACCORDING TO HUSBAND'S V.C. EXPOSURE

	"Controls"*	Primary V.C.M. exposure†
Prior to husband's exposure:		
Number of families	95	70
Mean paternal age at conception (yr.)	23·0	26·4
Number of fetal deaths among wives	11	15
Number of pregnancies	159	148
Age-adjusted fetal deaths/100 preg.‡	6·9	6·1
Subsequent to husband's exposure:		
Number of families	113	62
Mean paternal age at conception (yr.)	30·4	30·2
Number of fetal deaths among wives	24	23
Number of pregnancies	273	139
Age-adjusted fetal deaths/100 preg.‡	8·8	15·8§

*Rubber and P.V.C. fabrication workers.
†V.C. polymerisation workers.
‡Rates age-adjusted to "control" group paternal age distribution.
§Subsequent to husband's exposure, the frequency of fetal deaths among wives was significantly greater in the primary V.C.M. exposure group than in the "controls" ($P<0.05$) or in the study group prior to husband's exposure ($P<0.02$ by age-adjusted chi-square testing.[12]

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TABLE II—MEAN PATERNAL AGE, NUMBER OF PREGNANCIES, AND FETAL DEATH-RATES ACCORDING TO HUSBAND'S V.C. EXPOSURE EXCLUDING PREGNANCIES OF WOMEN WITH > 3 FETAL DEATHS

	Controls*	Primary V.C.M. exposure†
Prior to husband's exposure:		
Mean paternal age at conception (yr.)	23·0	26·3
Number of fetal deaths among wives	11	9
Number of pregnancies	159	141
Age-adjusted fetal deaths/100 preg.‡	6·9	3·1
Subsequent to husband's exposure:		
Mean paternal age at conception (yr.)	30·2	30·8
Number of fetal deaths among wives	18	14
Number of pregnancies	265	120
Age-adjusted fetal deaths/100 preg.‡	6·8	10·8

*Rubber and P.V.C. fabrication workers.
†V.C. polymerisation workers.
‡Rates age-adjusted to "control" paternal age distribution.

husbands less than 30 years of age, fetal mortality was 14/70 (20·0%) for the primary V.C.M. exposure group compared with 7/131 (5·3%) for the control group (these data are not shown in tables.)

Furthermore, intragroup comparisons indicated an increase in age-adjusted rates for the primary V.C.M. exposure group from 6·1% before exposure to 15·8% subsequent to the husband's exposure. This difference also was significant, $P<0.02$ ($\chi^2=5.51$, df=1).[12] Similar comparison for rates in the control group, 6·9% versus 8·8%, indicated no significant difference.

To determine whether women who had chronically experienced abortions might have weighted the results in favour of a higher fetal death-rate in the primary V.C.M. group subsequent to husband's exposure, pregnancies of women who had more than two abortions were eliminated from the analyses and the data were recalculated to determine whether or not the trend was maintained. The decision to exclude all pregnancies among families associated with more than two abortions was made without prior knowledge of how these families were distributed among the exposure categories. The data in table II show that the trend was maintained. Prior to exposure, the fetal death-rates in the control and primary V.C.M. exposure groups were 6·9% and 3·1% (age-adjusted), respectively, whereas, after exposure, the rates were 6·8% and 10·8%, respectively. Subsequently, data were eliminated for pregnancies of women who had experienced, firstly, more than one abortion, and, secondly, more than three abortions, and each time the trend was maintained. No changes in rates for controls were observed, whereas a 2–3-fold increase was observed in the primary V.C.M. group subsequent to exposure.

To determine whether differences in fetal loss might have been the result of one or two interviewers weighting the results, the data were analysed by individual interviewer. The results demonstrated a general trend for each interviewer to report a higher ascertainment among V.C.M. polymerisation workers than among the control group.

Further, the possibility was entertained that the interval between the date of interview and the date of fetal loss might have influenced the results through differences in recall. The interval, however, was estimated to have been about two years less for controls, suggesting that, if a bias did exist, it would have been towards a greater ascertainment in the control group. In some cases, the worker failed to indicate the ages of his children and in other cases he was unable to recall the approximate time of his wife's abortion; therefore, the data were analysed to determine the distribution of fetal death-rates among the respondents in each occupational group who did not complete the interview properly. The difference in fetal death-rates between groups was very slight.

Finally, the workers may have been subject to bias resulting from prior knowledge of known hazards of vinyl chloride. However, the workers themselves did not always know into which of our employment categories they were being allocated. For example, several P.V.C. fabrication workers who were included in the control group thought that they had a primary V.C.M. exposure as a fabrication worker. In addition, the questions regarding pregnancy outcome were contained in a much larger interview-questionnaire, the results of which demonstrated very few significant differences with no consistent bias for the parameters ascertained between the workers with a primary V.C.M. exposure, and the other groups. This observation as well as several others presented above tend to support the validity of the study.

In summary, a significant excess of fetal loss was observed among wives of workers following exposure to V.C.M. The excess did not appear to be the result of bias from interviewers or respondents, nor from women who experienced chronic abortions weighting the results. Several mechanisms by which such fetal loss may arise are suggested. Either fetal or maternal toxicity or germ-cell mutagenesis in the mother through indirect V.C.M. exposure from the father might be considered, although these mechanisms seem highly unlikely in view of the highly volatile nature of V.C.M.[13] When the findings of the present study are taken in conjunction with the prior demonstration of a mutagenic response via microbial test systems and observations of significant excesses of chromosomal aberrations among workers exposed to V.C.M., the leading possibility is germ-cell damage in the father through direct V.C.M. exposure. The increased fetal mortality among wives of workers subsequent to V.C.M. exposure now raises serious scientific and public-health concern for the possible genetic risks of vinyl chloride to man.

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was used after 1963. In particular, the incidence of convulsions recorded for 1965 was more than double the 1963 figure. I find difficulty in grasping how such evidence indicates an association between removal of adjuvant and disappearance of serious reactions. Even Dr Tiru, whom he cites, seems far from sure.

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NOEL W. PRESTON

SIR,—The merits of whooping-cough vaccination will never be settled by a series of letters in *The Lancet*, but I feel nevertheless that I must correct two of the statements made by Dr Basuli and Professor Stewart in their letter of May 15 (p. 1074). In the first place, Sako did publish clinical observations on vaccinated and control subjects, taking careful note of exposure: 30 cases in 159 exposed vaccinated *vs.* 137 cases (with 13 deaths) in 149 exposed unvaccinated infants or young children. This is detailed in the reference cited, and further details can be found in a later paper.[1] But others did far more carefully designed studies than Sako, and obtained similar answers; the work of Silverthorne, Miller, Kendrick, Singer-Brooks, Coppolino, Bell, and others is liberally cited in the literature and I will not take up space by detailed references here. One cannot, however, overlook the masterful studies by the British Medical Research Council,[2] and the fact is that, with three exceptions, every properly controlled study on whooping-cough vaccine has shown it to be moderately to highly effective. It is, of course, possible to prepare a poor vaccine and, conceivably, a good vaccine that is irrelevant because of differences in serotype. But these problems have been corrected in the U.K., and Dr Fraser's analysis (May 1, p. 969) suggests that, with a little more attention to the younger infants, whooping-cough vaccine in Glasgow might prove satisfactory to all.

My second point concerns alum. In the first place its use has not "long been discontinued" as a component of vaccines; at least four U.S. manufacturers still use it and it is included in one of the most widely used forms of diphtheria-tetanus-pertussis vaccines. However, its use is diminishing since it is thought to be less effective as an adjuvant than the other salts of aluminium. Yet this very fact renders Sako's results more, rather than less, impressive.

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GEOFFREY EDSALL

GENETIC RISKS OF VINYL CHLORIDE

SIR,—Dr Paddle (May 15, p. 1079) asks us to specify the method of data collection used in our study (April 13, p. 734) and to show a tabulation of the data before age adjustment.

As mentioned several times, the data were obtained by interview with the workers. The range for response-rates, which were similar for the study and control groups, were also included. As we stated, the questions about pregnancy outcome were contained in a much larger interview questionnaire which was the initial item of a cross-sectional health survey that included a physical examination, X-rays, and laboratory tests. The results of the survey demonstrated very few significant differences, and no consistent bias toward a higher prevalence for the indices measured in either the study or control group. The interview protocols were administered by six interviewers (two successive teams of three interviewers) from the Center for Disease Control, each with experience in field health surveys. Each interview took 15–30 min, and was carried out in a mobile van interview booth. The interviewers had participated in a formal review of the questionnaire before the study. In addition, a physician member of the survey team reviewed positive responses immediately after the interview and, where appropriate, sought further elaboration from the interviewee.

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PATERNAL AGE DISTRIBUTION FOR FETAL DEATHS ACCORDING TO HUSBAND'S V.C. EXPOSURE

Paternal age (yr)	"Controls"		Primary exposure	
	Pregnancies	Fetal deaths	Pregnancies	Fetal deaths
Before exposure:				
<20	31	2 (6·5%)	7	0
20–24	80	4 (5·0%)	44	2 (4·5%)
25–29	38	4 (10·5%)	56	7 (12·5%)
30–34	6	1	27	5 (18·5%)
>35	4	0	14	1
All ages, crude rate	159	11 (6·9%)	148	15 (10·1%)
Mean paternal age at conception	23·0 yr.	. .	26·4 yr.	. .
Age-adjusted rate*	. .	. . (6·9%)		(6·1%)
After exposure:				
<20	1	0	0	. .
20–24	43	4 (9·3%)	22	3 (13·6%)
25–29	87	3 (3·4%)	48	11 (22·9%)
30–34	87	7 (8·0%)	36	3 (8·3%)
>35	55	10 (18·2%)	33	6 (18·2%)
All ages, crude rate	273	24 (8·8%)	139	23 (16·5%)
Mean paternal age at conception	30·4 yr.	. .	30·2 yr.	. .
Age-adjusted rate*	. .	. . (8·8%)	. .	. . (15·8%)

* Fetal mortality-rates for primary v.c. exposure group are direct age adjusted to the paternal age distribution of the pregnancies in the control group.

The table shows data for age-specific fetal mortality-rates before age adjustment, for both time periods (i.e., before and after the husband's exposure).

Before the husband's exposure, the crude fetal mortality-rates are 10·1% for the study group and 6·9% for the control group. However, after direct age adjustment the study-group rate became 6·1%. This is the result of a younger paternal age for pregnancies in the control group. For example, pregnancies to wives of men less than 30 years of age made up 93·7% (149/159) of the control-group pregnancies as compared to 72·3% (107/184) of the study-group pregnancies. Our paper indicated this difference in age between the groups for before exposure comparisons. Table 1 in that paper showed that the mean paternal ages were 23·0 years for the control group and 26·4 years for the study group.

As shown here in the table, subsequent to husband's exposure, the crude fetal mortality-rates were 8·8% and 16·5% for the control and study groups, respectively. With direct age adjustment the 16·5% was reduced to 15·8%. Age adjustment for the subsequent to exposure comparisons resulted in little change in the rates because the age distributions for pregnancies in both the study and control groups after exposure were similar. For example, pregnancies to wives of men younger than 30 years of age made up 48·0% (131/273) of the control-group pregnancies and 50·4% (70/139) of the study-group pregnancies.

We hope this explanation of the age-adjustment procedure is now clear. It is the fact that the two standard age distributions derive from the control group's populations of pregnancies, rather than of persons (whether fathers or not) that probably accounts for the numerical behaviour that Dr Paddle finds "misleading".

In the subsequent to husband's exposure comparisons, the significant difference in fetal mortality-rates was a result of pregnancy outcome associated with husbands younger than 30 years of age. This difference was significant at $P<0.001$ ($\chi^2=10.52$, D.F.=1). If vinyl chloride (V.C.) is indeed related to this observed difference, the excessive fetal mortality at these ages could, in theory, be a reflection of placing newly hired personnel, with little or no seniority, in exposure categories that had relatively worse environmental exposures.

In our paper of April 3 we cited eight references which have demonstrated that V.C. had elicited a positive response in microbial test systems and had been associated with significant excesses of chromosomal aberrations in lymphocytes of workers occupationally exposed to it. Three additional studies which also have demonstrated a positive mutagenic response to

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v.c., have been drawn to our attention recently; in two of these studies, the microbial test system was used,[1,2] while in the third, *Tradescantia* was used.[3] Therefore, we do not agree with Dr Paddle's statement that this is an "isolated" question.

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PLASMA-GLUCAGON AFTER PANCREATECTOMY

SIR,—Dr Barnes and Dr Bloom (Jan. 31, p. 129 reported no circulating immunoreactive glucagon (I.R.G.) in both the basal state and after arginine stimulation in five pancreatectomised patients. Dr Gerich and his colleagues (April 17, p. 855) have made similar observations in another patient. We have evaluated I.R.G. dynamics in a totally pancreatectomised patient, with results quite different from those cited above. Because of the heterogeneity of I.R.G. species measured by antiserum 30K, we assay before and after acetone extraction. The post-extraction assay measures predominantly I.R.G. of <9000 daltons (S-I.R.G.), and subtracting S-I.R.G. from total plasma-I.R.G. (unextracted) allows quantification of the larger molecular weight I.R.G. species (L-I.R.G.).

A 30-year-old male, member of a multiple endocrine adenoma type 1 family, underwent a total pancreatectomy, hemigastrectomy, and duodenectomy in 1967 for removal of an insulinoma. He has remained free of disease subsequently. Further evidence of total pancreatectomy was afforded by essentially unmeasurable basal levels of C peptide with failure to rise during an arginine infusion (by A. Rubenstein, University of Chicago). His basal, fasting concentrations of S-I.R.G. and L-I.R.G., before an arginine infusion, 24 h after receiving his standard insulin dose (21 units lente and 10 units semilente) were 35 pg/ml and 104 pg/ml, respectively. These values are within normal limits for our laboratory. The accompanying table depicts the plasma levels of small and large molecular weight I.R.G., glucose, and C peptide during the administration of arginine (500 mg/kg/30 min). The arginine infusion produced a small but definite rise in S-I.R.G. with no change in L-I.R.G. In addition, a 50 mg/dl increase in plasma-glucose concentration occurred concurrently with the increase in S-I.R.G.

Several factors may be involved in the difference between our observations and those of Dr Barnes and Dr Bloom. Unger et al., using antiserum 30K, failed to demonstrate I.R.G. in the plasma of pancreatectomised dogs;[4] subsequently several investigators[5–8] have observed circulating I.R.G. (30K) in pancreatectomised dogs (and other species) when they are deprived of insulin for several days, demonstrating the sensitivity of extrapancreatic alpha cells to inhibition by insulin. Because of ethical considerations achieving this degree of insulin deficiency may not be appropriate in man, but our patient may have been more insulin deficient than those previously reported. Although alpha cells indistinguishable from pancreatic alpha cells have been reported in the stomach of man,[9] earlier work by Muller et al.[10] failed to demonstrate a rise in I.R.G. (30K) with arginine infusion in two pancreatectomised patients. However, these patients did have significant plasma-I.R.G. levels in the basal state. Plasma contains several different molecular weight species that are measured as I.R.G. (30K).[11–13] Therefore, it is possible that the antiserum used by Dr Barnes and Dr Bloom does not react with all the I.R.G. plasma components measured in assays using antiserum 30K. In addition, the partial gastrectomy and duodenectomy that is usually done in conjunction with a total pancreatectomy in man may result in at least partial removal of the source of extrapancreatic glucagon and may vary in different patients depending upon the extent of the surgery.

GLUCOSE, I.R.G., AND C PEPTIDE CONCENTRATIONS DURING ARGININE INFUSION

Time (min)	Glucose (mg/dl)	S-I.R.G. (pg/ml)	L-I.R.G. (pg/ml)	C-peptide (ng/ml)
Control	224	35	104	0·7
10	238	57	103	..
20	242	74	101	..
25	..	..	..	0·7
30	253	91	99	0·7
35	..	..	..	0·7
45	265	77	98	..
60	272	68	92	..
90	274	51	99	..

While our patient is potentially unique in being a member of a family with multiple endocrine neoplasia, we feel that on the basis of his results we can only conclude that: (1) in this pancreatectomised man, I.R.G. (30K) of both large and small molecular weight(s) circulates in the basal state, and that at least the small-molecular-weight fraction shows a rise with arginine; (2) the increase in plasma-glucose that accompanied the S-I.R.G. rise suggest that this S-I.R.G. is biologically active; and (3) the existence of an extrapancreatic source of biologically active glucagon in man has not been excluded.

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SIR,—We read with interest the article by Dr Bloom and Dr Barnes (Jan. 31, p. 219) on the absence of pancreatic glucagon-like immunoreactivity (I.R.G.) in the plasma of pancreatectomised man. The data generated diametrically opposed views on the diabetogenic role of pancreatic glucagon by Dr Gerich and his colleagues on the one hand (April 17, p. 855) and Dr Donowitz and Dr Felig on the other (April 17, p. 855). We wish to add information which may help to resolve these contradictory views.

In contrast to the findings of Bloom and Barnes, we[13] found high levels of "pancreatic" I.R.G. in the plasma of a pancreatectomised patient, as did Muller et al.[14] in two other patients. Although 50% of the pancreatic I.R.G. could be accounted for by factors in plasma which interfere with the assay[15] the rest appeared immunometrically as pancreatic I.R.G. and presumably derived from an extrapancreatic source. In contrast to I.R.G. in porcine duodenal extracts,[16] which closely resembles true pancreatic I.R.G., the I.R.G. in pancreatectomised human plasma is dissimilar in physicochemical properties (gel electrophoresis), is not stimulated by arginine, insulin hypoglycaemia, or tolbutamide, or suppressed by glucose, and has no apparent role in blood-glucose regulation.[13] We have previously[17] referred to the various forms of gastrointestinal pancreatic I.R.G. found

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ONCOGENIC AND MUTAGENIC RISKS IN COMMUNITIES WITH POLYVINYL CHLORIDE PRODUCTION FACILITIES *

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Much attention has been focused on the relation between vinyl chloride exposure and angiosarcoma of the liver.[1-4] Studies also have indicated that vinyl chloride produces cancers of multiple sites in laboratory animals[5] and perhaps in humans.[6] Little information, however, is available regarding the relation between vinyl chloride exposure and the developmental status of products of conception among women associated with such exposure. In a study of stillbirths and miscarriages among wives of vinyl chloride workers in two plants, Selikoff[13] observed rates of 140/1,000 pregnancies in one population and 72/1,000 in a second population. Although there has been no explanation of these findings, a comparison of these data with those for the state of Georgia, which records all products of conception, results in rates that are two to four times greater than the rate in Georgia.[7] Miscarriages and stillbirths from the latter source,[7] however, might still be underreported, especially in the first trimester of pregnancy. Because data on a national basis for miscarriages of all products of conception are lacking, it is difficult to determine whether the rates in the wives of these workers were actually higher than expected or whether they were the result of differences in case ascertainment.

Ducatman and coworkers[9] also have observed a significantly greater number of chromosomal breaks in lymphocytes among workers exposed to vinyl chloride as compared to controls; these findings have been duplicated in Sweden.[10] The relation of chromosomal breaks in plant employees to mutagenesis and birth defects in their children, however, has not yet been studied. In view of these observations, an epidemiologic study of the distribution of congenital anomalies in Ohio residents living in the three communities that have polyvinyl chloride production facilities was undertaken. Since the study by Tabershaw and Gaffey[11] had shown an excess number of deaths from cancer of the central nervous system, leukemia, and lymphomas among vinyl chloride workers, data from state vital statistics records for these neoplasms were also analyzed.

MATERIALS AND METHODS

The three Ohio communities that have polyvinyl chloride production facilities lie in the northeastern part of the state. Two cities, Painesville and Ashtabula, are situated about five miles from the coast of Lake Erie; the third, Avon Lake,

* This study was initiated at the request of the Industrial Union Department of the AFL-CIO.

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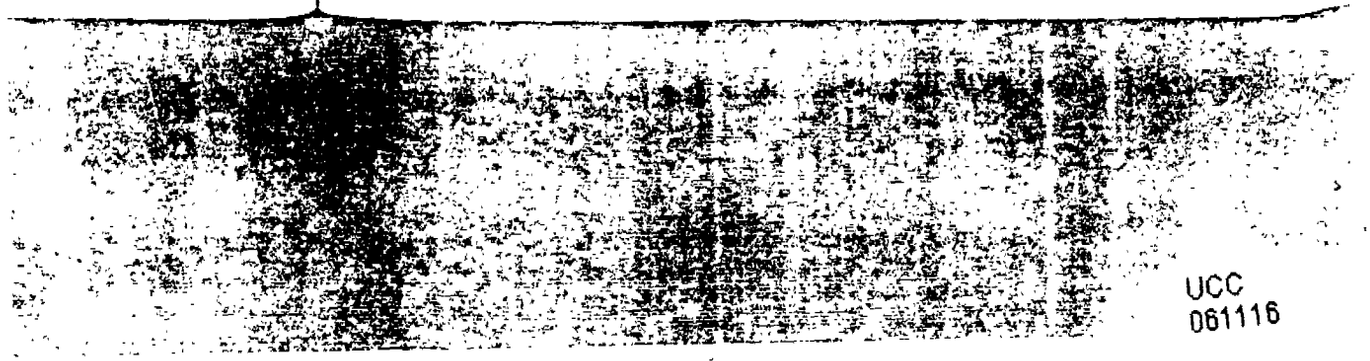

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is located on the lake. Painesville is about thirty miles to the west of Ashtabula, and Avon Lake lies about fifty miles west of Painesville. The population of the three communities ranges from 24,000 in Ashtabula to 12,000 in Avon Lake. The polyvinyl chloride production facility in Ashtabula began operations in 1954; the one in Avon Lake began in 1946. Two plants are located in Painesville; one began operation in 1946 and the other began in 1967. Between the two census years 1960 and 1970, the population of Avon Lake increased by thirty percent, whereas the populations in the other two communities have remained about the same. The median family income in Painesville is equal to that of the state as a whole, the median income in Ashtabula is below the state median, and the income in Avon Lake is above it.

Since 1968, information for specific congenital malformations in Ohio residents has been recorded on birth certificates.[10] Since 1970, this information has been coded according to the International Classification of Diseases, 8th Revision, as adapted for the United States (Codes 740–759).[11] Any information recorded under the congenital anomalies section of the certificate that did not fit into these codes was omitted from the analyses. Thus, data for conditions such as prematurity and hyaline membrane disease, and so on, were eliminated. Data for deaths resulting from cancer of the central nervous system, leukemia, and lymphomas in the adult population aged 45 years and older were also analyzed. For lymphomas, data for mycosis fungoides from 1958 to 67 were not included in the analyses.

Results

For the four-year period 1970–73, the numbers of children with congenital malformations and rates per 1,000 resident live births were computed separately for each of the three cities as well as for the entire state. These data are shown in Table 1. For the entire state, the rate of malformations per 1,000 live births was 10.14. The rates in the three index cities ranged from 17.37 in Ashtabula to 20.33 in Avon Lake. If malformations had occurred in the three cities at the expected rate based on the state average (10.14/1,000 live births), the total expected number of children with malformations in each of the three cities would have ranged from 19.27 in Ashtabula to 7.48 in Avon Lake. As shown in Table 1, the differences between the observed and expected numbers of malformations in each city were significant at the $p < 0.01$ level by the χ^2 test. With data for all three of the cities combined, the occurrence of malformations was much greater than expected ($\chi^2 = 27.13$, $p < 0.001$).

Malformations at birth in these three cities were then compared to congenital malformations for residents living in the balance of the three counties in which the cities were located. As shown in Table 2, the differences in the frequency of malformations were significantly greater in two cities versus the remainder of the counties. With data for all three cities combined and data for all three counties combined, the difference in the number of malformations per 1,000 live births between the cities and the balance of the counties was highly significant ($p < 0.001$). To maximize sample size, data for the three index cities were combined and the rates of malformations were computed for each year and compared to the rates for the balance of the counties and for the entire state. As shown in Figure 1, the rates for the balance of the counties and for the entire state appear to be about the same, whereas the rate in the three index

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s to the west of Ashtabula, lle. The population of the to 12,000 in Avon Lake. ibula began operations in ants are located in Paines- gan in 1967. Between the Avon Lake increased by two communities have re- in Painesville is equal to shtabula is below the state

alformations in Ohio resi- ce 1970, this information sification of Diseases, 8th -759).[1] Any information he certificate that did not Thus, data for conditions id so on, were eliminated. nervous system, leukemia, ears and older were also es from 1958 to 67 were

children with congenital were computed separately le. These data are shown ions per 1,000 live births from 17.37 in Ashtabula red in the three cities at 000 live births), the total h of the three cities would von Lake. As shown in spected numbers of mal- .01 level by the χ^2 test. irrence of malformations).

n compared to congenital three counties in which erences in the frequency ies versus the remainder d and data for all three nalformations per 1,000 unties was highly signifi- r the three index cities computed for each year unties and for the entire of the counties and for e rate in the three index

TABLE 1

RESIDENT BIRTHS, MALFORMATION RATE PER 1,000 LIVE BIRTHS IN OHIO AND IN THREE SELECTED COMMUNITIES AND OBSERVED VS. EXPECTED NUMBERS OF MALFORMATIONS IN EACH CITY: YEARS COMBINED, 1970–73

Area	Births	Malformations * Rate	Number Observed	Number Expected †	χ^2
Ohio	719,287	10.14	7,295	—	—
Ashtabula	1,900	17.37	33	19.27	9.78 ‡
Painesville	1,381	18.10	25	14.00	10.29 ‡
Avon Lake	738	20.33	15	7.48	7.56 ‡
All three communities	4,019	18.16	73	40.75	27.13 §

* Malformations are based on codes 740–759 of the International Classification of Diseases, Eighth Revision, 1968.
† Expected numbers are based on state rate/1,000 live births.
‡ $p < 0.01$.
§ $p < 0.001$.

cities is about twice as great and appears to be increasing to a slightly greater degree with time. With regard to race, ten percent of the births during the period under study were among black women and ten percent of the children with birth defects indicated were also black. In addition, mothers in the three index communities who gave birth to children with malformations were, on the average, one year younger than mothers in the balance of the counties who

TABLE 2

NUMBER OF BIRTHS AND MALFORMATIONS AND RATES FOR THREE SELECTED CITIES IN COMPARISON TO OCCURRENCE IN THE BALANCE OF THE COUNTIES IN WHICH THE INDEX CITIES ARE LOCATED: YEARS COMBINED, 1970–73

	Births	Malformations N	Rates/1,000 Live Births	χ^2
Ashtabula	1,900	33	17.37	
Balance of Ashtabula County	4,821	68	14.10	0.96
Painesville	1,381	25	18.10	
Balance of Lake County	11,842	84	7.09	18.27 *
Avon Lake	738	15	20.33	
Balance of Lorain County	18,544	222	11.97	4.03 †
All three cities	4,019	73	18.16	
Balance of all three counties	35,207	374	10.62	18.21 *

* $p < 0.001$.
† $p < 0.05$.

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delivered children with congenital anomalies. Thus, race and maternal age did not appear to be related to the observed differences. In the three index cities, the malformation rates at the hospital where most of the area children were born were consistently greater for the city children than for children from the balance of the counties born at these same hospitals. Therefore, differences in reporting attributable to specific hospitals did not appear to be a factor.

On the basis of population size, three other county-city combinations were then matched to each of the study area county-city combinations and malformation rates were computed for each city and balance of the county, as done previously for the study areas. The differences in the frequency of malformations between the balance of the counties and the cities were not significant.

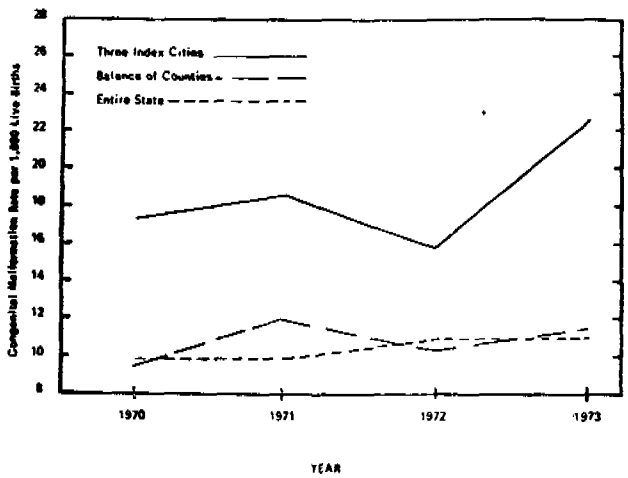

FIGURE 1. Congenital malformations in Ohio residents in rates per 1,000 live births in the three index cities combined, in the balance of the counties in which these cities are located, and in the entire state, 1970–73. (ICD, 8th Revision Codes 740–759).

Malformation rates were then computed for nine cities in the vicinity of the index communities that were most similar in size to the index communities. In the surrounding cities, two of nine had significantly greater numbers of malformations than expected. One community, Geneva, which is twelve miles from Ashtabula, and a second community, North Ridgeville, eight miles from Avon Lake, had rates of 25 and 27 malformations/1,000 live births, respectively. These data are shown in TABLE 3. Since North Ridgeville was proximate to Avon Lake, data for the former were combined with those from the three primary cities being studied, and the occurrence of specific malformations was compared to the expected, which was based on the state average over the period 1970–73. TABLE 4 shows data for observed versus expected defects and relative risks for specific malformations. Significant excesses were observed for defects

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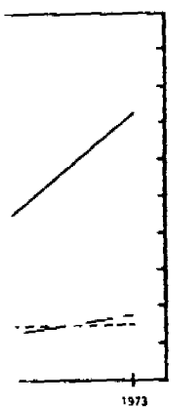

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TABLE 3

COUNTY AND CITY POPULATION AND NUMBER OF BIRTHS, MALFORMATIONS AND MALFORMATION RATE PER 1,000 LIVE BIRTHS FOR THE THREE OHIO CITIES WHERE POLYVINYL CHLORIDE IS MANUFACTURED AND FOR 10 CITIES SURROUNDING THE INDEX CITIES: YEARS COMBINED, 1970–73

County	County Population *		City	Population *	Births	Malformations Indicated	Rate/1,000
Ashtabula	98,237	1.	Conneaut	14,522	996	12	12.05
		2.	Geneva	6,449	433	11	25.40
			Ashtabula †	24,313	1,900	33	17.37
Lake	197,200	3.	Mentor	36,912	2,767	20	7.23
		4.	Willoughby	18,634	1,459	3	2.06
		5.	Eastlake	19,690	1,618	10	6.18
		6.	Wickliffe	21,354	1,077	7	6.50
		7.	Willowick	21,231	841	4	4.76
			Painesville †	16,536	1,381	25	18.10
Lorain	256,843	8.	North Ridgeville	13,152	1,174	32	27.26
		9.	Lorain City	78,185	6,345	71	11.19
		10.	Elyria	53,427	4,811	46	9.56
			Avon Lake †	12,261	738	15	20.33

* County and city population figures are based on estimates of 1972 population.
† City with polyvinyl chloride manufacturing facility.

TABLE 4

OBSERVED VS. EXPECTED AND RELATIVE RISK FOR SPECIFIC CONGENITAL ANOMALIES IN INDEX AREAS: 1970–73

Defect Category	Number of Cases		RR *
	Observed	Expected	
Central nervous system (470–749)	17	5.62	3.02
Eye (744)	0	0.58	0.00
Ear, face, neck (745)	2	1.35	1.48
Heart (746)	3	2.32	1.29
Other circulation (747)	1	0.48	2.08
Respiratory system (748)	2	0.57	3.51
Cleft palate and lip (749)	10	6.54	1.53
Other upper alimentary tract (750)	12	2.33	5.15
Other digestive system (751)	4	1.90	2.11
Genital organs (752)	16	8.40	1.90
Urinary system (753)	0	0.56	0.00
Clubfoot (754)	23	8.23	2.79
Other limbs (755)	13	11.10	1.17
Other musculoskeletal (756)	1	1.88	0.53
Skin, hair, and nails (757)	5	2.78	1.80
Other unspecified (758)	2	0.54	3.70
Multiple systems (759)	3	3.63	0.83

* RR (relative risk) = observed/expected.

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of the central nervous system, upper alimentary tract, genital organs, and club-foot. Because of the severity of the defects involved, the greatest cause for concern appears to be defects of the central nervous system. These were anencephaly, spina bifida, and hydrocephalus. Since state records indicated that two-thirds of the children with anencephaly are found among stillbirths, observed versus expected anomalies of the central nervous system were computed for stillbirths and live births of residents in the three communities with polyvinyl chloride production facilities, plus North Ridgeville, which was located proximate to Avon Lake. With all communities combined, the data in TABLE 5 show that there were significantly greater numbers of central nervous system defects than expected, both among stillbirths and live births. Among stillbirths and live births combined, there were 25 CNS defects observed versus 8.42 expected. More than half the cases occurred in Painesville and six each occurred in North Ridgeville and Ashtabula, whereas none were observed in Avon Lake. There were 8 CNS anomalies versus 2.8 expected among stillbirths and 17 versus 5.6 expected among live births. Of the eight stillbirths, four had anencephaly, three had spina bifida with hydrocephalus, and one had hydrocephalus only. All four of the stillbirths with anencephaly occurred in Painesville.

Since the report by Tabershaw and Gaffey[4] has shown an excess of deaths from CNS tumors, leukemia, and lymphomas among workers exposed to vinyl chloride, observed deaths from these cancers were compared to the expected number for the white population ages 45 years and older for the period 1958–73. Since there were no deaths reported in blacks for any of these cancers, data are shown only for whites. The risk of death from these cancers in the community is expressed as a Standardized Mortality Ratio (SMR),[12] which is the ratio of the number of observed to expected deaths based on a standard population times 100. The Ohio white population over the same period was used as the standard population. With the data for all four communities combined, TABLE 6 shows there were 38 deaths from CNS tumors versus 24 expected, significant at $p < 0.01$ by χ^2-testing. The greatest contribution to the excess CNS tumors

TABLE 5

OBSERVED AND EXPECTED ANOMALIES OF THE CNS AND RELATIVE RISK AMONG LIVE AND STILLBIRTHS IN THE INDEX AREA COMMUNITIES: 1970–73

	Among Stillbirths		Among Live Births		Live and Stillbirths Combined	
	Observed/ Expected	RR *	Observed/ Expected	RR	Observed/ Expected	RR
Ashtabula	2/1.03	1.95	4/2.05	1.95	6/3.08	1.95
Painesville	5/0.75	6.70	8/1.49	5.36	13/2.24	5.80
Avon Lake	0/0.40	0.00	0/0.80	0.00	0/1.20	0.00
N. Ridgeville	1/0.63	1.58	5/1.27	3.94	6/1.90	3.16
Communities Combined	8/2.81	2.85	17/5.61	3.03	25/8.42	2.97 †

* RR = relative risk.
† $p < 0.001$.

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...S AND RELATIVE RISK
COMMUNITIES: 1970–73

	Live and Stillbirths Combined	
R	Observed/ Expected	RR
95	6/3.08	1.95
16	13/2.24	5.80
00	0/1.20	0.00
04	6/1.90	3.16
13	25/8.42	2.97 †

TABLE 6

OBSERVED AND EXPECTED CANCER DEATHS AND STANDARDIZED MORTALITY RATIOS FOR RESIDENTS 45 YEARS AND OLDER IN INDEX COMMUNITIES BY SEX: 1958–73 *

Communities	Males Obs./Exp.	Males SMR	Females Obs./Exp.	Females SMR	Sexes Combined Obs./Exp.	Sexes Combined SMR
CNS (191–192)						
Ashtabula	7/6.90	101	6/4.74	127	13/11.64	112
Painesville	12/4.26	282	2/3.14	64	14/7.40	189
Avon Lake	2/1.68	119	1/1.05	95	3/2.73	110
N. Ridgeville	6/1.43	420	2/0.87	230	8/2.30	348
Communities combined					38/24.07	158 †
Leukemia and Aleukemia (204–207)						
Ashtabula	13/12.63	103	11/9.38	117	24/22.01	109
Painesville	8/7.47	107	7/6.34	110	15/13.81	109
Avon Lake	1/2.70	37	5/1.84	272	6/4.54	132
N. Ridgeville	2/2.47	81	0/1.68	0	2/4.15	48
Communities combined					47/44.51	106
Lymphomas (200–203)						
Ashtabula	18/14.77	122	14/12.29	114	32/27.06	118
Painesville	12/8.88	135	4/8.25	48	16/17.13	93
Avon Lake	4/3.50	114	5/2.53	198	9/6.03	149
N. Ridgeville	3/3.07	98	1/2.25	44	4/5.32	75
Communities combined					61/55.54	110

* ICD 8th Revision Codes.
† $p < 0.01$.

deaths was from male residents of Painesville. If these were eliminated from the analyses, the differences between expected and observed deaths would not have been significant. Although the numbers are small, the data also show an excess of CNS tumor deaths in North Ridgeville males, who had an SMR of 420. If these findings are compared to the data in TABLE 5, it may also be observed that the same communities had the greatest excess of CNS anomalies among stillbirths and live births, especially Painesville.

Deaths attributed to leukemia and aleukemia (Codes 204–207) and to lymphomas (Codes 200–203) in the communities appeared to be about the same as the expected. For the balance of the counties, mortality from CNS tumors and leukemia was not significantly different from the expected. These data are shown in TABLE 7. Deaths from lymphomas, however, were significantly lower among white males in the balance of Lorain County and among white females in the balance of Ashtabula County.

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Discussion and Summary

The results of the findings suggest that mothers living in communities with PVC-production facilities gave birth to an excess number of children with congenital malformations as compared to the expected based on the state average or based on the experience in the balance of the counties in which these cities are located. Other county-city combinations matched by population size showed no significant differences in incidence of congenital malformations. Maternal age, race, and possible differences in hospital reporting were not considered factors accountable for the observed differences. With regard to specific malformations, anomalies of the central nervous system appear to be of the greatest concern. An excess number of central nervous system defects was observed among stillbirths and live births from the index cities, with the exception of Avon Lake. Most of the excess, however, was attributable primarily to Painesville and secondarily to a community located proximate to Avon Lake, North Ridgeville. Deaths from central nervous system tumors in adult male residents of Painesville and North Ridgeville were also significantly greater than expected. On a community basis, excess deaths from the other cancers were not apparent.

Since many underlying factors could be responsible for the mutagenic and/or teratogenic and carcinogenic mechanisms involved, these preliminary findings obviously do not link polyvinyl chloride production with the increased occur-

Table 7

Observed and Expected Cancer Deaths and Standardized Mortality Ratios for Residents 45 Years and Older in Balance of Counties, by Sex: 1958–73

Balance of County	Males Obs./Exp.	Males SMR	Females Obs./Exp.	Females SMR	Sexes Combined Obs./Exp.	Sexes Combined SMR
CNS (191–192)						
Ashtabula	19/21.42	89	11/13.26	83	30/34.68	87
Lake	32/34.78	92	19/21.41	89	51/56.19	91
Lorain	50/50.89	98	39/31.95	122	89/82.84	107
Leukemia and Aleukemia (204–207)						
Ashtabula	44/38.15	115	24/26.30	91	68/64.45	106
Lake	49/50.55	97	39/35.56	110	88/86.11	102
Lorain	91/83.37	109	53/59.54	89	144/142.91	101
Lymphomas (200–203)						
Ashtabula	39/45.05	87	16/34.32	47 †	55/79.37	69 †
Lake	78/64.76	120	50/48.37	103	128/113.13	113
Lorain	78/101.60	77 *	74/78.76	94	152/180.36	84 *

* $p < 0.05$.
† $p < 0.01$.

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others living in communities with excess number of children with spected based on the state average he counties in which these cities atched by population size showed genital malformations. Maternal l reporting were not considered es. With regard to specific mal-

STANDARDIZED MORTALITY RATIOS E OF COUNTILS, BY SEX: 1958–73

nales		Sexes Combined	
ap.	SMR	Obs./Exp.	SMR
6	83	30/34.68	87
1	89	51/56.19	91
5	122	89/82.84	107
emia			
0	91	68/64.45	106
6	110	88/86.11	102
4	89	144/142.91	101
2	47 †	55/79.37	69 †
7	103	128/113.13	113
6	94	152/180.36	84 *

tem appear to be of the greatest is system defects was observed ix cities, with the exception of attributable primarily to Paines- roximate to Avon Lake, North tumors in adult male residents nificantly greater than expected. ther cancers were not apparent. nsible for the mutagenic and/or ved, these preliminary findings ction with the increased occur-

rence of congenital malformations and central nervous system tumors, but indicate the need for further study of possible contributing factors. Possible relations between central nervous system tumors in adults and CNS defects among live and stillbirths in other populations might also be given consideration.

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