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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 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

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 $p < 0.05$.*

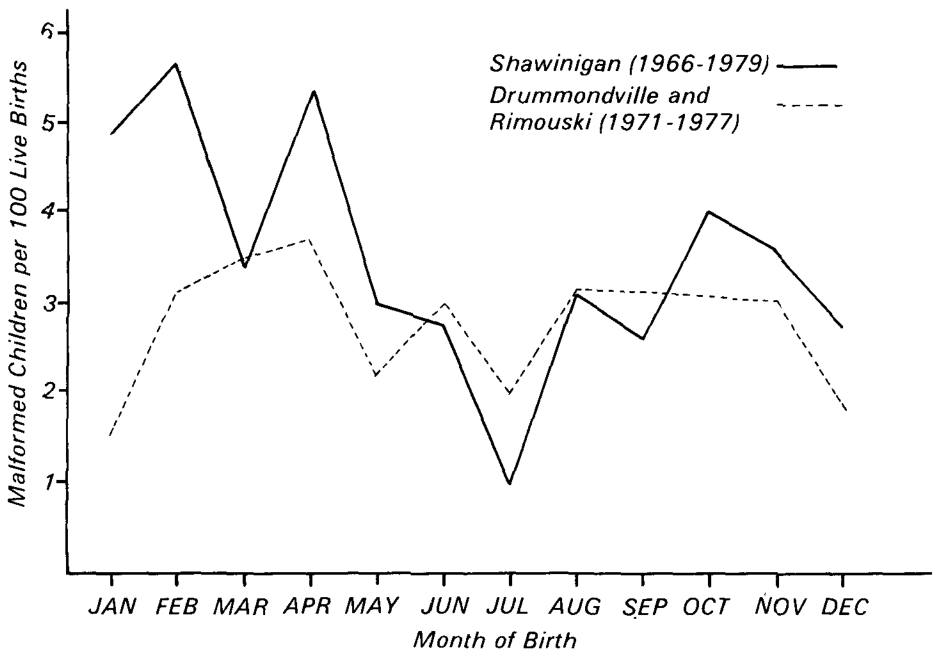

Figure 1. *Monthly distribution of birth-defect rates.*

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 abcut 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.

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 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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