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October 30, 1975

A. R. Adams, General Manager
Tel: (215) 687-6150
Twx:

Mr. John Oakes, Editor
The New York Times Company
229 West 43rd Street
New York, New York 10036

Dear Mr. Oakes:

On Saturday, October 25, the New York Times published a news story from Los Angeles under the caption "U.S. Official Links Polyvinyl Chloride to Birth Defects." It is regretful that a newspaper such as the New York Times, which enjoys a reputation for publishing news that is "fit to print", continues to malign polyvinyl chloride; let alone check the correctness of a highly technical report. Perhaps the utterance of a federal official such as Dr. Wagoner makes the report credible.

In the first place, there is not one scintilla of evidence that links polyvinyl chloride (a plastic) with birth defects. Secondly, Dr. Wagoner does not provide the basis for his assertion that "birth defects are up to three times higher than normal among babies born in three Ohio towns where polyvinyl chloride, a cancer causing chemical, is manufactured." I must assume that this assertion is derived from an ill-conceived study by Dr. Peter Infante. After careful research, the Center for Disease Control (CDC), reference Vol. 24, No. 29, Week Ending July 19, 1975, reports that "it could not establish any association between cases and vinyl chloride exposure."

What earthly purpose this news release has accomplished I do not know, other than to burden the lay public with morbid conclusions irresponsibly derived and, once given credence by the press, never to be removed from public opinion.

Very truly,

A. R. Adams

A. R. Adams

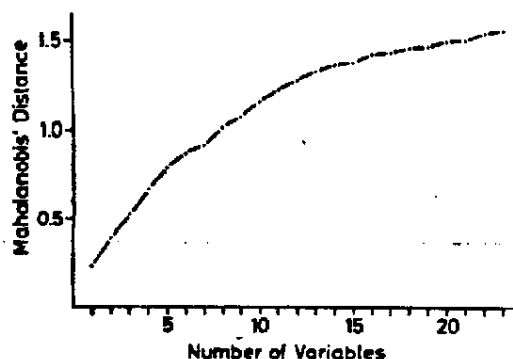
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Enclosures:

New York Times Article

CDC Report VI. 24, No. 29

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the discrimination of vector of means can be tested for significance.

A high discrimination between the malformation group and its matched controls appeared within the first 10 of the 24 variables (see accompanying figure). Even with 8 variables a significant discrimination of both groups at 1% level was found. The discrimination of both groups was also possible without the two factors "abortions/stillbirths in mothers family" and "hours of daily work".

So, even in a sample with factors each not discriminating significantly between both groups, the linear discriminance analysis makes it possible to discriminate between the malformation group and the matched controls. This might mean that the malformations in our sample can be explained as caused by the combination of many minor factors (extrinsic and intrinsic).

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J. KLEINFELDT
K.-H. DIEGMARDT

CONGENITAL MALFORMATIONS AND VINYL CHLORIDE

SIR.—In March, 1975, a significantly increased rate of central-nervous-system (C.N.S.) malformations was reported in 3 Ohio communities where polyvinyl chloride (P.V.C.) polymerisation plants are located;¹ the increase was not uniform and appeared more prominent in the Painesville area. There are two P.V.C. plants in Painesville, one of which began operation in 1949 and the other in 1967. The birth-defect rates were computed from birth-certificate data for 1970-73 and were compared with similar data for the entire State of Ohio. This study suggested a relationship between the higher rates of C.N.S. malformations and the increased risk of exposure to vinyl chloride in these communities.

By analysing data collected through the Center for Disease Control's hospital-based birth defects monitoring programme (S.D.M.P.),² we examined this relationship. Two hospitals participating in the S.D.M.P. are located in cities with polymerisation plants: one is in Pennsylvania, the other in Painesville, Ohio. C.N.S.-malformation rates for white infants born in these two hospitals in 1970-74 were compared with the rates for white infants in each State. No increase was seen in the Pennsylvania hospital, but an increase, primarily in anencephaly and spina bifida, was noted in the Painesville hospital for the total time 1970-74 (see table).

ANENCEPHALUS AND SPINA BIFIDA IN OHIO STATE AND IN PAINESVILLE HOSPITAL, OHIO

Year	Anencephalus				Spina bifida			
	Painesville		State		Painesville		State	
	No. of cases	Rate*	No. of cases	Rate	No. of cases	Rate	No. of cases	Rate
1970	0	0.0	26	5.0	3	31.2	58	11.1
1971	1	10.3	38	7.3	3	30.9	44	8.5
1972	3	35.6	31	6.3	0	0.0	47	9.6
1973	2	24.9	27	5.4	2	24.9	46	9.2
1974	0	0.0	22	4.5	1	15.1	29	6.0
1970-1974	6	14.1	144	5.7	9	21.2	224	8.9

* Per 10 000 total white births.

The S.D.M.P. hospital data for Painesville were compared with birth-certificate data from the Ohio department of health, and 1 additional case not included in the S.D.M.P. report was added, bringing the total to 15. 30 controls, the first normal white infant born before and after each case, were selected from the hospital birth registry. Medical records for cases and controls were reviewed to confirm the diagnosis and to obtain, among other data, the parents' occupation and residence at the time of the infant's birth. In addition, parents of 14 of the affected children were interviewed about previous occupations and residences.

The study revealed that none of the interviewed parents of affected infants had ever worked at either of the two P.V.C.-polymerisation plants in Painesville (1 set of parents could not be located, but records show that they did not work at these plants at the time of their infant's birth); 2 of the fathers of controls had worked at one of the plants at the time of their infants' births. None of the parents in either group lived within 2 miles of the two plants. The chi-square test of significance was used in comparing the distances from residence and work-place of mothers and fathers to the P.V.C. plants for cases and controls. Comparisons were made at distances of 1 to 10 miles, in 1-mile increments. A significantly larger proportion of control mothers than case mothers worked (including housewives) within a 10-mile radius of the P.V.C. plant, at the 95% confidence level. This is probably a chance occurrence among multiple comparisons.

Vinyl chloride is a known carcinogen,³ and concern has arisen over its possible teratogenic effects. This concern stems from recent studies which have shown (a) an increase in mutagenicity in bacterial assay systems⁴ and (b) increased breakage in chromosomes of P.V.C.-polymerisation workers.⁵ The Ohio Department of Health study¹ is the only report that has suggested that vinyl chloride causes birth defects in man. Although the follow-up study reported here confirmed a moderate increase in C.N.S. malformations in Painesville, Ohio, no association was found with vinyl-chloride exposure.

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LARRY D. EDMONDS,
HENRY FALK
JACK E. NISSIN

LATE COMPLICATIONS OF TUBAL LIGATION

SIR.—Unlike Mr Darwish and Dr Saafan (Nov. 15, p. 975), we are uncertain as to the aetiology of the late sequelae of female sterilisation, which they refer to as menstrual irregularity, but in our study it will be noted we looked specifically at menorrhagia and dysmenorrhoea. It seems unlikely that a psychosomatic cause could be present when two different tech-

1. Infante, P. in Proceedings of the Conference on Occupational Carcinogenesis at the New York Academy of Science, 23 March, 1975, New York (in the press).

2. Center for Disease Control. Congenital Malformations Surveillance Annual Summary 1974. Atlanta, 1975.

3. Center for Disease Control. Morbidity and Mortality Weekly Report, Feb. 9, 1974, p. 49.

4. Kawanishi, T., Johansson, A., Ramek, C., Wachsmuth, C. A. *Am J Hyg.* 1974, 3, 194.

5. Finner-Crawford, P., Lambert, R., Lindsten, J. *Lancet*, 1975, i, 459.

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RESEARCH & DEVELOPMENT

JAN 22 1976

W. M. SMITH

THE EFFECTS OF MATERNALLY INHALED VINYL CHLORIDE ON
EMBRYONAL AND FETAL DEVELOPMENT IN MICE, RATS AND RABBITS

BY:

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K.D. Nitschke, H.D. Haberstroh, F.J. Murray
H.F. Balmer and P.J. Gehring

REVIEWED BY:

P. J. Gehring

December 19, 1975

Toxicology Research Laboratory
Health and Environmental Research
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This study was funded by the companies supporting the vinyl chloride
projects being administered by the Manufacturing Chemists Association,
Washington, D.C.

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rabbits at a significantly different incidence from controls. Among litters of rabbits exposed to 500 ppm vinyl chloride, the incidence of delayed ossification of the 5th sternebra was increased whereas that of the 6th sternebra was decreased. Delayed ossification of sternebrae did not occur at a higher incidence than control among litters of rabbits exposed to 2,500 ppm vinyl chloride alone or in combination with 15% ethanol in the drinking water.

DISCUSSION

The results of these studies indicate that exposure of pregnant mice, rats or rabbits to vinyl chloride by inhalation at concentrations sufficiently high to cause maternal toxicity was not teratogenic in any of the three species. The responses of mice, rats and rabbits are summarized in Table 11. Less maternal toxicity was observed among rats and rabbits than mice during exposure or at the time of cesarean section. Among rats one maternal death and an increase in liver weight was observed at 2,500 ppm while only a slight decrease in maternal weight gain was observed at 500 ppm. Among rabbits, one maternal death was observed at 2,500 ppm and there was a decrease in food consumption at 500 ppm. In comparison, 500 ppm was quite maternally toxic to mice as evidenced by the significantly decreased weight gain and food consumption and by the occurrence of a number of maternal deaths.

Exposure to vinyl chloride was not consistently embryotoxic in the three species studied. A significant increase in the percent resorptions was observed among mice exposed to 500 ppm vinyl chloride, but not among rats or rabbits exposed to 500 ppm or 2500 ppm vinyl chloride. Some decreases in fetal body weight and crown-rump length were observed in rats and mice but not rabbits. A teratogenic response to maternally inhaled vinyl chloride was not observed in mice, rats or rabbits. With the exception of unilateral and bilateral dilated ureter among litters of rats exposed to 2500 ppm vinyl chloride, no external or soft tissue anomalies were observed at an incidence significantly higher than control in any of the three species. Examination of the skeletons revealed only minor skeletal variants; no skeletal malformations were found at an incidence significantly greater than in the control groups.

Ingestion of 15% ethanol in the drinking water enhanced some of the effects of inhaled vinyl chloride. In each of the three species tested, maternal weight gain and food consumption was lower than among animals exposed to vinyl chloride alone. The percent resorptions was slightly increased among mice and significantly increased among rabbits exposed to vinyl chloride in combination with 15% ethanol in the drinking water. Fetal body measurements were lower among litters of

mice and rats which received ethanol and vinyl chloride compared to vinyl chloride alone. Certain malformations were observed among litters of mice, rats and rabbits which also received ethanol but their incidence was not statistically different than control litters. The effect of simultaneous ingestion of ethanol on the disposition of vinyl chloride in these animals seemed to enhance maternal toxicity to an extent greater than embryotoxicity.

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In summary, the results of these studies indicate that exposure of pregnant mice, rats and rabbits to vinyl chloride by inhalation was not teratogenic at the concentrations tested. Mice were more susceptible to the toxic effects of vinyl chloride than either of the other two species. Simultaneous exposure to vinyl chloride by inhalation and 15% ethanol in the drinking water resulted in toxic effects greater than those associated with exposure to vinyl chloride alone in the three species. Neither exposure to vinyl chloride alone or in combination with 15% ethanol in the drinking water caused a significant teratogenic response in mice, rats or rabbits.

SEP 23, 1980

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 : ADAMS, W. G. F.
 TITLE : CHROMOSOMAL ANALYSES IN VINYL CHLORIDE-EXPOSED WORKERS
 PUBLICATION SOURCE : MUTAT RES 57:325-334, 1978
 LANGUAGE : ENG
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*Mutagenesis
 Occupational
 VC
 Epidemiology
 Human*

***** EXPERIMENTAL DESIGN *****

PERIPHERAL BLOOD LYMPHOCYTES WERE COLLECTED FROM 57 VC/PVC WORKERS; 19 ON-SITE CONTROLS AND 5 OFF-SITE CONTROLS; AND 48 OR 72 HR. CULTURES WERE PREPARED AND SCORED FOR CHROMOSOMAL ABERRATIONS (CLASSIFIED ACCORDING TO BUCKTON AND PIKE: B, C₁, C₂ CELLS). FIFTY CELLS FROM EACH CULTURE/INDIVIDUAL WERE SCORED BLINDLY. SUBJECTS WITH RECENT HISTORY OF EXPOSURE TO X-RAYS; PROLONGED DRUG TREATMENT OR RECENT VIRAL INFECTIONS WERE EXCLUDED FROM THE STUDY. EXPERIENCE OF VC ODOR DETECTION AND THE DESCRIPTION OF VC EMPLOYMENT WERE RECORDED. THE VC/PVC WORKERS WERE CLASSIFIED INTO 6 GROUPS: GROUP 1; 17 PVC AUTOCLAVE WORKERS; GROUP 2; 10 PACKERS AND DRYERS OF PVC POWDER; GROUP 3; 7 VC PRODUCTION WORKERS; GROUPS 4 AND 5; CONSISTED OF ENGINEERING MAINTENANCE MEN FOR PVC (11 MEN) AND VC (7 MEN) EQUIPMENT AND PLANT; GROUP 6; 5 MEN WITH OCCUPATIONS OTHER THAN PROCESS OPERATORS IN THE VC/PVC PLANT. THERE WAS NO SIGNIFICANT DIFFERENCE FOUND BETWEEN ON-AND OFF-SITE CONTROLS; THEREFORE THE 24 MEN WERE COMBINED INTO ONE CONTROL GROUP. THE AUTOCLAVE WORKERS ARE CONSIDERED TO HAVE THE HIGHEST EXPOSURE TO VC AND THE HISTORIC AVERAGE EXPOSURE LEVELS ARE GIVEN: 1945 - 1955 APPROXIMATELY 1000 PPM; 1955 - 1960 APPROXIMATELY 400 - 500 PPM; 1960-1970 APPROXIMATELY 300-400 PPM; MID 1973 APPROXIMATELY 15 PPM AND 1975 APPROXIMATELY 5 PPM. THE SMOKING HISTORY ON THESE INDIVIDUALS WAS COLLECTED 18 MONTHS AFTER THE BLOOD SAMPLES WERE TAKEN. LIVER FUNCTION TESTS INCLUDING BILIRUBIN, ALANINE TRANSAMINASE, ASPARTATE TRANSAMINASE, ALKALINE PHOSPHATASE, GAMMA-GLUTAMYL TRANSPEPTIDASE AND PLATELET COUNTS WERE PERFORMED ON VC EXPOSED WORKERS AND ON-SITE CONTROLS.

THE AVERAGE DURATION OF EXPOSURE IN EXPOSED GROUPS AND AVERAGE AGE OF ALL GROUPS WERE GIVEN: GROUP 1 - 10.7 YEARS EXPOSURE AND 41 YEARS OF AGE; GROUP 2 - 12.7 YEARS EXPOSURE AND 42 YEARS OF AGE; GROUP 3 - 6.3 YEARS EXPOSURE AND 44 YEARS OF AGE; GROUP 4 - 15.5 YEARS EXPOSURE AND 47 YEARS OF AGE; GROUP 5 - 6.1 YEARS EXPOSURE AND 36 YEARS OF AGE; GROUP 6 - 8.6 YEARS EXPOSURE AND 40 YEARS OF AGE; CONTROLS - 44 YEARS OF AGE.

***** KEYWORDS *****

VINYL CHLORIDE; HUMAN STUDY; OCCUPATIONAL EXPOSURE; VC WORKERS; PVC WORKERS; CHROMOSOME ABERRATIONS; DURATION OF EXPOSURE; SMOKING HISTORY; BILIRUBIN; PLATELETS; ALKALINE

PHOSPHATASE; ALANINE TRANSAMINASE; ASPARATE TRANSAMINASE;
EXCURSION LEVELS; PERIPHERAL BLOOD LYMPHOCYTES; B CELLS; C
CELLS; JOB CLASSIFICATION; AUTOCLAVE OPERATORS; DRYING;
PACKING; PVC POWDER; VC PRODUCTION; MAINTENANCE; Cs; Cu;
RINGS; DICENTRICS; FRAGMENTS; CHROMATID BREAKS; CHROMATID
GAPS; CHROMOSOME BREAK; CHROMOSOME GAPS; INVERSIONS;
TRANSLOCATIONS; MUTAGENICITY.

***** ABSTRACTS *****

IN THE ANALYSES OF CHROMOSOMAL DAMAGE IN VC/PVC WORKERS THE DATA FROM 48 AND 72 HOUR CULTURES HAVE BEEN POOLED. THE NUMBER AND PERCENTAGE OF CHROMOSOMAL ABERRATIONS ARE HIGHER IN THE EXPOSED GROUPS COMPARED TO CONTROLS; EXCEPT FOR CHROMOSOME GAPS, WHERE THE CONTROL VALUE IS RELATIVELY HIGH, AND FOR FRAGMENTS, WHERE THE CONTROL VALUE IS HIGHER THAN THE VALUE OF GROUP 6 (0.00). THE AUTOCLAVE WORKERS (GROUP 1) HAVE THE HIGHEST SIGNIFICANT INCREASE ($P < 0.01$) OF TOTAL B TOTAL Cu AND TOTAL C CELLS, COMPARED TO THE CONTROL POPULATION. VC MAINTENANCE WORKERS (GROUP 5) HAVE THE NEXT HIGHEST VALUES, AND PVC LABORATORY WORKERS AND MANAGERS (GROUP 6) HAD THE LOWEST WITH CHROMATID GAPS OCCURRING SIGNIFICANTLY MORE FREQUENT THAN IN THE CONTROLS ($P < 0.05$). GROUPS 2, 3, AND 4 HAVE VALUES BETWEEN GROUPS 5 AND 6. HISTORY (1973-1974) OF RECENT EXPOSURE CORRELATED WITH A HIGHER PERCENTAGE OF ABNORMAL CELLS (CHROMATID GAPS, TOTAL C CELLS, AND FRAGMENTS). CHROMATID GAPS, TOTAL C CELLS AND FRAGMENTS ARE CONSIDERED THE MOST SUGGESTIVE INDICATOR OF CHROMOSOMAL ABNORMALITIES, SINCE THEY HAVE THE HIGHEST CORRELATION BETWEEN LENGTH OF EMPLOYMENT (AT A 1% SIGNIFICANCE). LIVER FUNCTION TESTS WERE SHOWN TO HAVE A NEGATIVE CORRELATION WITH CHROMOSOMAL ABERRATIONS (AT EITHER 5% OR 10% SIGNIFICANCE LEVEL.) THERE WAS FOUND A POSITIVE SIGNIFICANT CORRELATION BETWEEN PRESENT SMOKERS AND TOTAL C CELLS ($P = 0.0259$) AND WITH TOTAL Cu CELLS ($P = 0.05$). PRESENT SMOKERS, LENGTH OF EMPLOYMENT AND EXPERIENCE OF HIGHER SHORT TERM EXPOSURE CORRELATED WITH THE PERCENTAGE OF C CELL ABNORMALITIES.

THESE RESULTS INDICATE 4 FACTORS INFLUENCE THE INCREASE OF CHROMOSOMAL ABERRATIONS IN VC/PVC WORKERS: THE JOB CATEGORY, THE LENGTH OF EMPLOYMENT AND RECENT EXPOSURE TO SHORT-TERM EXCURSION LEVELS OF VC AND SMOKING HABITS. THE DIFFERENCE SEEN IN CHROMOSOMAL ABNORMALITIES IN GROUP 1 (THE HIGHEST) AND GROUP 6 (THE LOWEST) IMPLIES THAT THE OVERALL EXPOSURE LEVEL TO VC HAS AN INFLUENCE ON CLASTOGENIC EFFECT. THE AUTHORS SUGGEST USING THE VALUE OF TOTAL C CELL ABNORMALITIES AS AN INDICATOR OF CHROMOSOMAL ABERRATIONS IN FUTURE STUDIES.

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 138 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.¹¹ 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†
<i>Prior to husband's exposure:</i>		
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
<i>Subsequent to husband's exposure:</i>		
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.

†P.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.¹¹

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†
<i>Prior to husband's exposure:</i>		
Mean paternal age at conception (yr.)	23.0	26.3
Number of fetal deaths among wives	11	9
Number of pregnancies	139	141
Age-adjusted fetal deaths/100 preg.‡	6.9	3.1
<i>Subsequent to husband's exposure:</i>		
Mean paternal age at conception (yr.)	30.7	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 v.c.m. fabrication workers.

†v.c.m. 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 dif-

ferences 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 v.c.m. 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.

Requests for reprints should be addressed to P.F.I., N.I.O.S.H., Post Office Building, Room 515, Cincinnati, Ohio 45262, U.S.A.

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GENETIC RISKS OF VINYL CHLORIDE

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In the past year, several reports have indicated that vinyl chloride monomer (VCM) is mutagenic in microbial test systems.¹⁻³ VCM 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 VCM as compared to controls.⁵⁻⁸ However, Purchase et al.,⁷ have stated recently, though no animal data were presented, that the mutagenic effects of VCM expressed as chromosomal aberrations in lymphocytes in humans do not occur in germ cells in mice; they concluded that the potential for mutagenic effects on the fetus via sperm seemed unlikely. In a study without controls, Selikoff observed fetal death rates among wives of VCM workers that ranged from 7-14 per 100 pregnancies.⁹ These rates appear to have been higher than expected.¹⁰

To develop further data on this question, a study of pregnancy outcome was made among the wives of workers exposed to VCM. All current VCM polymerization and polyvinyl chloride (PVC) 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 VCM workers by age. Group participation rates ranged from 62-77 percent. Data for the wives of VCM polymerization workers (primary VCM exposure group) were contrasted with data for the wives of PVC fabrication and rubber workers ("controls"), who were known to have had very low or no VCM exposure, respectively. A total of 95 VCM polymerization and 158 rubber and PVC 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, PVC fabricating and VCM polymerizing 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 VCM exposure group were age-adjusted to the control group. Table I shows the crude and age-adjusted fetal death rates for the wives of the primary VCM 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 VCM 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 VCM exposure group. Among pregnancies occurring subsequent to exposure, the fetal mortality rates associated with husbands 30 years of age and older for the primary VCM exposure and control groups were 9/69 (13.0%) and 17/142 (12.0%), respectively; whereas,

for husbands less than 30 years of age, fetal mortality was 14/70 (20.0%) for the primary VCM exposure group as compared to 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 VCM 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 if women who had chronically experienced abortions may have weighted the results in favor of a higher fetal death rate in the primary VCM 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 VCM 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 VCM group subsequent to exposure.

To determine whether differences in fetal loss may have been the result of one or two interviewers weighting the results, the data were analyzed by individual interviewer. The results demonstrated a general trend for each

interviewer to report a higher ascertainment among VCM polymerization workers as compared to the control group.

Further, the possibility was entertained that the time interval between the date of interview and the date of fetal loss might have influenced the results through differences in recall. The time interval, however, was estimated to have been about two years less for controls, suggesting that if a bias did exist, it would have been toward 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 analyzed 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 minimal.

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 PVC fabrication workers who were included in the control group thought that they had a primary VCM 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 VCM exposure as compared to 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 VCM. The excess did not appear to be the result of bias from interviewers, 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 VCM exposure from the father might be considered, although these mechanisms seem highly unlikely in view of the highly volatile characteristic of VCM.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 VCM, the leading possibility is germ cell damage in the father through direct VCM exposure. The increased occurrence of fetal mortality among wives of workers subsequent to VCM exposure now raises serious scientific and public health concern for the possible genetic risks of vinyl chloride to humans.

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TABLE I
MEAN PATERNAL AGE, NUMBER OF PREGNANCIES AND FETAL DEATH RATES
ACCORDING TO HUSBAND'S VC EXPOSURE

	<u>"CONTROLS"</u> ⁺	<u>PRIMARY VCM EXPOSURE</u> ¹
PRIOR TO HUSBAND'S EXPOSURE		
NUMBER OF FAMILIES	95	70
MEAN PATERNAL AGE AT CONCEPTION (YEARS)	23.0	26.4
NUMBER OF FETAL DEATHS AMONG WIVES	11	15
NUMBER OF PREGNANCIES	159	148
AGE-ADJUSTED FETAL DEATHS/100 PREG. ⁰	6.9	6.1
SUBSEQUENT TO HUSBAND'S EXPOSURE		
NUMBER OF FAMILIES	113	62
MEAN PATERNAL AGE AT CONCEPTION (YEARS)	30.4	30.2
NUMBER OF FETAL DEATHS AMONG WIVES	24	23
NUMBER OF PREGNANCIES	273	139
AGE-ADJUSTED FETAL DEATHS/100 PREG. ⁰	8.8	<u>15.8</u> [*]

⁺ RUBBER AND PVC FABRICATION WORKERS.

¹ VC POLYMERIZATION WORKERS.

⁰ 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 VCM EXPOSURE GROUP AS COMPARED TO THE "CONTROLS" ($P < 0.05$) OR TO THE FREQUENCY IN THE STUDY GROUP PRIOR TO HUSBAND'S EXPOSURE ($P < 0.02$) BY AGE-ADJUSTED CHI-SQUARE TESTING.¹²

TABLE II
 MEAN PATERNAL AGE, NUMBER OF PREGNANCIES AND FETAL DEATH RATES
 ACCORDING TO HUSBAND'S VC EXPOSURE
 EXCLUDING PREGNANCIES OF WOMEN WITH ≥ 3 FETAL DEATHS

	<u>"CONTROLS"</u> ⁺	<u>PRIMARY VCM EXPOSURE</u> [¶]
<u>PRIOR TO HUSBAND'S EXPOSURE</u>		
MEAN PATERNAL AGE AT CONCEPTION (YEARS)	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
<u>SUBSEQUENT TO HUSBAND'S EXPOSURE</u>		
MEAN PATERNAL AGE AT CONCEPTION (YEARS)	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 PVC FABRICATION WORKERS.

[¶] VC POLYMERIZATION WORKERS.

[°] RATES AGE-ADJUSTED TO "CONTROL" PATERNAL AGE DISTRIBUTION.

1. The original "fetal wastage" data which resulted from the Pottstown NIOSH/URW/UNC/FPC quadripartite agreement was first disclosed in a May, 1975 meeting in Akron.
2. The "data" was not considered at that time to be statistically significant. Therefore, did not become an issue.
3. The basic data itself was developed via the initial "personnel questionnaire" which was administered to all our clockcard employees in October, 1974.
4. Dr. Infante joined NIOSH in August of 1975 and felt he was poorly "briefed" as to the quadripartite relationship.
5. Dr. Infante felt, and still does obviously, that the "fetal wastage" data while not conclusive definitely does require publication if in fact the proper disclaimers were present-- that is, the limitations of this information.
6. Nobody could disagree that the information was significant enough to be reported in Lancet as long as again the limitations of the validity of the data were identified.

Conclusion

Further publicity dealing with the Pottstown study should involve the total quadripartite group and the "fetal wastage" data while being published will clearly identify the limitations and statistical reliability inherent in the data.

The net conclusion should be that further studies including greater numbers of workers is justified, but until this is accomplished the "fetal wastage" data from Pottstown cannot be considered absolute.

Dr. Bernstein, NID

Separate -

See p 2 & 3.

Table I - In sig 5% level. Table II
dpts - marginally!

Table III

mean - not sig
dpts - not sig

Entire anal not valid
Small sample size!
med 10/1000.