

Occasional Survey

GENETIC RISKS OF VINYL CHLORIDE

PETER F. INFANTE JOSEPH K. WAGONER
 ANTHONY J. MCMICHAEL RICHARD J. WAXWEILER
 HENRY FALK

Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, and Bureau of Epidemiology, Center for Disease Control; and School of Public Health, University of North Carolina

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 ^a	Primary v.c.m. exposure ^a
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 pregnancies	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 pregnancies	8.8	15.8

^aRubber and p.v.c. fabrication workers.

^bv.c.m. polymerisation workers.

^cRate age adjusted to "control" group paternal age distribution.

^dSubsequent 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

TABLE II—MEAN PATERNAL AGE, NUMBER OF PREGNANCIES, AND FETAL DEATH-RATES ACCORDING TO HUSBAND'S V.C.M. 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	159	141
Age-adjusted fetal deaths/100 preg.‡	6.9	3.1
<i>Subsequent to husband's exposure:</i>		
Mean paternal age at conception (yr.)	30.2	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.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 enumerated 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 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.

Requests for reprints should be addressed to P.F.I., N.I.O.S.H., Post Office Building, Room 515, Cincinnati, Ohio 45202, U.S.A.

REFERENCES

1. Bartsch, H., Malavielle, C., Montesano, R. *Int. J. Cancer* 1975, 15, 429.
2. Iqbal, N., Hara, R., Varoncelli, S., et al. *Mutation Res.* in the press.
3. Rannug, U., Johansson, A., Ramel, C., Wachmeister, C. *A. Ambio* 1974, 3, 194.
4. Huberman, E., Bartsch, H., Sachs, L. *Int. J. Cancer*, 1975, 16, 639.
5. Ducatman, A., Hirschhorn, K., Seikoff, I. *J. Macromol. Rev.* 1975, 31, 163.
6. Fenech, J., Lambert, B., Lindsten, J., Ehrenberg, L., Natarajan, A. T., Osterman-Liikari, S. *Lancet*, 1975, i, 459.
7. Purchase, I. F. H., Richardson, C. R., Anderson, D. *ibid* 1975, ii, 410.
8. Hillstad, L., Thue-Evensen, E. (unpublished).
9. Seikoff, I. J., N.I.H. H.S. Conference on Public Health Implications of Components of Plastics Manufacture, Pinehurst, North Carolina, July, 1974.
10. Infante, P. F. *Ann. N.Y. Acad. Sci.* in the press.
11. Shapiro, S., Jones, L. A., Hansen, P. M., Muehle, Q. 1962, 40, 7.
12. Mantel, N., Haenszel, W. *J. Natl. Cancer Inst.* 1959, 22, 209.
13. United States Environmental Protection Agency, sampling and analysis of select toxic substances, toxic III vinyl chloride. Contract no. 68-01-2640 Jan. 20, 1976.

COPIED BY MCA FOR DISTRIBUTION TO THE VINYL CHLORIDE
TECHNICAL PANEL, AUGUST 27, 1976, MR. M. FREIFELD

1079

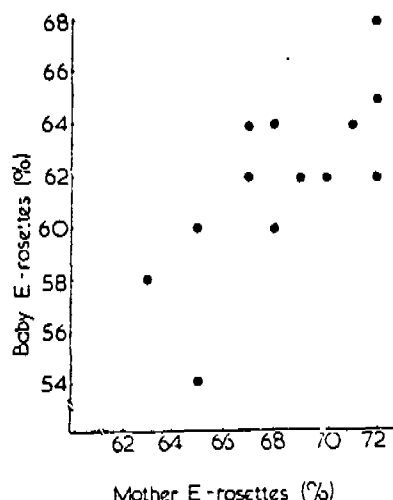


Fig. 2—E-rosetting cells in 13 mother-baby pairs.

$p < 0.001$, paired t test). For the E-rosetting cells the mean for the mothers was 68.3% (s.d. 2.9%) and for the babies 61.9 (s.d. 3.7%). This difference too is significant ($p < 0.001$) and the correlation coefficient is also significant ($r = 0.74$, $p < 0.005$) (fig. 2).

The E-rosettes in the mothers ranged from 63% to 72%. We had no counts of less than 50% and cannot speculate in the same way as Halbricht and Kompe, but our counts for the babies ranged from 58% to 65% which is higher than their figures and nearer the mean of 58% reported by Campbell et al.² and Steel et al.³

There is considerable variation in E-rosette counts due to technique. We used the method described by Sternsward et al.⁴ In testing each mother and baby's cells together, however, variation due to technique should not greatly affect the ratios.

The normal range of T cells in newborns is probably wide. However, our findings suggest that there is a direct relationship between the number of E-rosetting cells in some mothers and their babies. Since these cells are the major subpopulation of peripheral-blood lymphocytes, it is likely that the correlation between the total blood-lymphocyte counts is largely due to the correlation between the E-rosetting cells (T cells). This raises the possibility that these cell populations in the fetus are regulated by maternal factors.

Bomb Hall Children's Hospital,
Manchester M19 2AA

Post. Mat. Gen. Hospital,
London SE1 6JH

Christie Hospital and Holt
Radium Institute,
Manchester M20 9BX

D. L. K. EVANS

N. VYRAMUTHU

M. PALMER

GENETIC RISKS OF VINYL CHLORIDE

SIR,—The assertion in the paper by Dr Intime and his colleagues (April 3, p. 734) that "a significant excess of fetal loss was observed among wives following exposure to V.C." is such as to have justified much more complete presentation. Any assertion of such importance should at least be supported by a specification of the methods of data collection, and a tabulation of the raw data before analysis.

1. Campbell, B. A. C., Wilson, C., Wood, L., Arnold, Green, A. A., & Cunniff, J. (1974), *Br. J. Obstet. Gynaecol.*, **81**, 469.

2. Steel, C. M., Evans, J., Smith, M. A., & Jones, 1975, *ibid.*, **81**, 914.

3. Sternsward, U., Jonvall, M., Vankar, L., Wager, H., & Svalby, K. (1972), *ibid.*, **79**, 1452.

The subject being spontaneous abortion, the use of a questionnaire, and the ensuing low response-rates, can be viewed sympathetically, but must detract from the accuracy of the study. The data are presented only after an age-adjustment procedure which behaves very misleadingly. A crude percentage of 10.1 for a sample whose average age is 26.4 is adjusted violently downwards to 6.1, while a figure of 16.5 for a sample of average age 30.2 is only reduced marginally to 15.8. Presumably the adjustment is being done within the study and the small sample size is the cause of this anomaly. It would have been better to have adjusted all the figures in accordance with national figures, but perhaps, in such a delicate area, such statistics are not available or are unreliable.

It is to be hoped that the complete study will be published without delay, with the above omissions rectified, so that it will be possible to put this, at present isolated, question in context.

Central Medical Group,
Imperial Chemical Industries,
Widnes, Cheshire SK9 1QB

G. M. PADDIE

SOCIAL STIGMA AND TUBERCULOSIS

SIR,—You have stated¹ that "Within the U.K. tuberculosis is no longer feared. It is widely known to be curable with little inconvenience to the patient and it carries little, if any, social stigma". Personal experience in Belfast showed that fear still existed in some patients before their disease was explained to them. Because of this we have tried to find out if social stigma still exists.

We asked 32 patients with pulmonary tuberculosis and 31 controls with other chest diseases of similar age, sex, and social background, about their attitudes towards their disease. In the tuberculosis group only 2 of the 13 with a family history of tuberculosis and 7 of the 19 without such a history knew that it was still possible to develop the disease in Belfast. In fact, there are at present about 100 new cases notified each year in a population of 600 000.

Only 17 of the 32 patients with tuberculosis knew that their disease was infectious. 2 university students were among the group who did not know. A similar proportion thought the disease was in some way related to an inherited weakness of the chest.

Both the tuberculosis group and the control group were asked if they had any sense of shame or similar emotional feelings because of their illness. 5 of the 31 control patients expressed feelings of inferiority, shame, embarrassment, and a sense of social isolation. These were all related to specific physical disabilities such as cough, sputum, or dyspnoea. 12 of the 32 tuberculosis patients described feelings of shame, inferiority, and a fear of social ostracism. None of these attitudes were related to specific physical complaints. The interview with another patient was cancelled due to obvious embarrassment and shame about discussing the disease. An additional 4 from the group of tuberculosis patients although not suffering from a direct social stigma about the disease expressed a sense of guilt and shame at the reflection of their life style. These patients were males who had been heavy drinkers with families, although none were alcoholics.

Improved social conditions here in the past helped to reduce the incidence of pulmonary tuberculosis. However, in many large cities there is increasing alcoholism, overcrowding, squatting, and drug taking, as well as an increase in the numbers of old people. Such features may arrest the downward trend in notifications of the disease. If the lack of knowledge about tuberculosis and the continued social stigma not just in elderly patients exist in other areas of the U.K. then perhaps now is the time to increase public education about a preventable and curable disease.

Forster Green Hospital,
Belfast, BT8 4HD

JOHN COMPTON
FRID STANFORD

1. *Lancet*, 1975, **ii**, 993

PLASTICS DIVISION
LIBRARY
THE FIRESTONE TIRE & RUBBER CO.

BFS

005225