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, data on 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 the 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 I 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 ($P<0·05$ ($\chi^2=4·00$, 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 is 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 17/139 (13·0%) and 17/142 (12·0%), respectively; whereas

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

	"Controls"*	Primary V.C.M. exp...
Prior to husband's exposure:		
Number of families	95	70
Mean paternal age at conception (yr.)	23·0	26·...
Number of fetal deaths among wives	11	15
Number of pregnancies	159	148
Age-adjusted fetal deaths/100 preg.‡	6·9	6·...
Subsequent to husband's exposure:		
Number of families	113	67
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·...

*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... 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 ($P<0·...$ age-adjusted chi-square testing.[12]

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TABLE II—MEAN PATERNA... DEATH-RATES ACCORDING... PREGNANCIES O...

Prior to husband's exposure:
Mean paternal age at conception (yr.)
Number of fetal deaths among wives
Number of pregnancies
Age-adjusted fetal deaths/100 preg.‡
Subsequent to husband's expos...
Mean paternal age at conception (yr.)
Number of fetal deaths among wives
Number of pregnancies
Age-adjusted fetal deaths/100 preg.‡

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

husbands less than 3(
14/70 (20·0%) for th
compared with 7/13
these data are not sho

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%), respectively; whereas,

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O HUSBAND'S V.C. EXPOSURE

	"Controls"*	Primary V.C.M. exposur
		70
	23·0	26·4
	11	15
	159	148
	6·9	6·1
		62
	30·2	30·2
	24	23
	23	139
	6·8	15·8

normal age distribution.
frequency of fetal deaths among w
V.C.M. exposure group than in the "
ure to husband's exposure ($P<0.02$

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 DEATH'S

	"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.
‡Mean 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 6·8%, 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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