Vinyl Chloride Cytogenetics

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This report presents cytogenetic findings from a group of 209 workers employed for up to 28 years in the manufacture of vinyl chloride monomer at the Texas Division of Dow Chemical U.S.A. Cytogenetic evaluation results from this group were compared to results found in examination of individuals being considered for employment. Statistical analyses were performed on a group basis for chromatid aberrations, chromosome aberrations and proportion of abnormal cells; no statistical difference of significance was found between the two groups. Comparison of these results with reported studies suggests that the level of cytogenetic aberrations in vinyl chloride workers is probably related to the length and level of exposure, and that risk of adverse genetic effect can be avoided in controlled, minimal-exposure environments.

Vinyl chloride (VC) has been reported to be carcinogenic in animals[1,2] and human beings[3] and mutagenic in bacterial test systems.[4,5,6] There have been reports of increased frequencies of chromosomal aberrations in workers exposed to vinyl chloride at polyvinyl chloride (PVC) facilities.[7,8,9] Similar increases were not found upon cytogenetic evaluation of German PVC workers[10] nor in our own preliminary investigation of a group of American VC workers.[11] One study based on interviews with male employees has indicated an increased rate of fetal wastage among wives of VC-exposed workmen involved in polymerization operations.[12]

We have recently completed cytogenetic evaluation of all currently-employed workers exposed to vinyl chloride at the Dow (Freeport) Texas Division. Both vinyl chloride and vinylidene chloride are produced in this plant. Vinylidene chloride has also been reported as mutagenic in bacterial test systems.[13] However, while these Dow workers are involved with the production of both compounds, the degree of contact with vinylidene chloride is far less than the exposure to vinyl chloride.

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Vinyl chloride monomer has been produced at the Texas Division of Dow Chemical U.S.A. since 1948. There are no vinyl chloride polymerization operations. Average exposure levels, as is the case for almost all vinyl chloride monomer plants, have been generally lower than those reported for facilities involved in polymerization operations.[14] Although the threshold limit values for vinyl chloride had been 500 parts per million (ppm) until 1974, Dow had established a goal of 50 ppm or below in 1959.[15] The current Occupational Health and Safety Administration (OSHA) standard for vinyl chloride is one ppm as a time-weighted-average over an eight-hour workday. We have found that the TWA concentration of vinyl chloride for all VC-related job classifications was approximately 5 ppm from 1968 to 1973; in 1974, TWA concentrations were 1 to 2 ppm. Since 1975, average levels of exposure have been lowered to less than 1 ppm. Estimates of average exposure levels for the years prior to 1968 are less reliable. For the purposes of this study, estimates of exposure were calculated for specific job classifications, based on records of both personnel and area monitoring (Table 1). However, actual exposure may vary from individual to individual within the same job classification and accidental, short-term exposures of some workers to concentrations in excess of the standard probably occur from time to time. Documentation of such incidents is difficult.

Methods

Our study group was composed of 209 workers who had worked in the vinyl chloride plant for periods ranging between one and 332 months (average, 48.3 months) at the time of this investigation. As part of the medical surveillance program for this group, peripheral blood samples were obtained, and evaluation of lymphocyte chromosomes was performed. Lymphocytes were cultured using a modification of the Moorhead technique.[16] Standard procedures, as previously described,[17] were used for incubation, processing, and analysis.

Findings were compared to cytogenetic data from a group of 295 "preemployment examinees" who had chromosome evaluation done as part of routine preemployment examination and who, at that time, had no known exposure to chromosome-break-

Table 1. — Estimated Exposure to Vinyl Chloride (VC) for Vinyl Chloride-Related Job Classifications.

Job Classification	Estimated Exposure in Parts per Million, as Time-Weighted Average 1973-1974	1960-1972	Before 1960
Supervisor	1.7	4.4	8.2
R&D Engineer	1.7	4.4	8.2
Plant Engineer	1.7	4.4	8.2
Technical Specialist	0.5	0.5	0.5
Development Lab (Lab Staff)	1.2	3.9	7.7
Quality Control Lab	5.7	11.4	15.2
Instrument Man	1.3	4.0	7.8
Electrician	1.3	4.0	7.8
Coverer (Insulation)	0.3	0.3	0.3
Painter	0.7	0.7	0.7
Pipefitter	0.9	0.9	0.9
Machinist	2.4	5.1	5.9
Welder (Boilermaker)	0.6	0.6	0.6
Maintenance (Utility Man)	1.3	4.0	7.8
Material Handler	0.5	0.5	0.5
Production Foreman	1.3	4.0	7.8
Shift Foreman	4.4	7.1	10.9
Control A Op (VC & Chlorine)	5.3	7.9	11.7
Control A Op (E & DI)	0.9	0.9	0.9
Control A Op (Vinyl)	2.8	5.5	9.3
Control A Op (Chlorination)	2.3	5.0	8.0
Control B Op (Clay & Chloride)	0.7	0.7	0.7
Control C Op (Chloride & Vinyl)	4.8	7.3	11.1
Control C Op (Chlorination)	2.6	5.3	9.1
Class 1 Op	5.3	8.0	11.8
Class 1 Op (Pairs)	0.5	0.5	0.5
Class 3 Op	2.6	5.3	9.1
Production Clerk	0.7	0.7	0.7
Unit Manager	0.7	0.7	0.7

ing agents. The records selected for inclusion in the control group were matched to those of the study group, insofar as possible, for sex, number of cells analyzed, and time period during which the culture was initiated.

Age variation between the two groups could not be completely eliminated: the average age of the vinyl chloride workers was 39.5 years (range, 18 to 67 years), and the average age of the preemployment control group was 25.1 years (range 18 to 50 years).

Results

As shown in Table 2, data from both groups — vinyl chloride workers and preemployment controls — were scored and compared on the basis of chromatid breaks; chromosome breaks; rings, dicentrics, and exchange figures; and the proportion of abnormal cells. The proportion of abnormal cells was calculated to show the overall frequency of aberrant cells, that is, the ratio of cells with at least one aberration to the total number of cells examined. Results, expressed in terms of the mean percentage for these categories of aberration, showed no major differences between the two groups for any of the classifications.

Using Chi-square analysis, it was decided to see if differences in various aberration rates could be detected within the two groups. Accordingly, both groups were divided into those showing zero-to-five percent aberrations and those showing greater-than-five

Table 2. — Cytogenetic Study of 209 Workers Exposed to Vinyl Chloride.

	Workers	Controls
No. of cultures	209	295
No. of cells	10,453	14,761
Chromatid breaks	2.4%	3.6%
Chromosome breaks	1.0%	1.1%
Rings, dicentrics, and exchanges	0.4%	0.2%
Abnormal cells	3.7%	4.5%

percent aberrations, and the vinyl chloride workers were separated into those with estimated TWA exposure levels of less-than-1 ppm, from 1-to-5 ppm, and greater-than-5 ppm. The estimated exposure levels were based on calculations for specific job classifications to which members of the vinyl chloride study group were assigned. Three categories of aberration were chosen for this analysis: chromatid breaks, chromosome breaks, and the proportion of abnormal cells.

As shown in Table 3, no significant differences were found when these groupings were compared on the basis of chromatid aberrations. Results from those workers with estimated exposures of greater than 5 parts per million are almost identical to those of the control group.

Similar conclusions were reached upon evaluation of the data for chromosome breaks (Table 4) and the proportion of abnormal cells (Table 5). In all three cases, most of both groups were found to have zero-to-five percent aberrations, and the vinyl chloride workers with the highest level of estimated exposure showed aberration rates not significantly different than those of the control group. Findings for both groups, workers and controls, are considered to be within the range of normal variation as seen in this laboratory.

Discussion

The reports that have appeared, to date, concerning chromosome aberrations in vinyl chloride workers have not been in agreement. This conflict may be due either to the small number of workers studied or to differences in exposure levels, or both. The Swedish group studied by Funes-Cravioto et al[14] was composed of seven PVC workers who had been exposed for nine to 29 years and who were found to have an increased frequency of chromosome breakage. The level of exposure for this group was

Table 3. — Distribution of Chromatid Aberrations Related to Vinyl Chloride (VC) Exposure.

	No. in Group	% of Group with 0-5% Aberrations	% of Group with >5% Aberrations
Exposure to VC*	209		
<1 ppm	70	90%	10%
1-5 ppm	98	77	23
>5 ppm	41	80	20
Controls	295	75	25

$\chi^2_{(3)} = 7.75$ $P = 0.051$

*Exposure levels are estimates based on calculations for specific job classifications; prior exposure for individuals may have been higher or lower; exposure levels for individuals are known to vary within job classifications.

Table 4. — Distribution of Chromosome Aberrations Related to Vinyl Chloride (VC) Exposure.

	No. in Group	% of Group with 0-5% Aberrations	% of Group with >5% Aberrations
Exposure to VC	209		
<1 ppm	70	96%	4%
1-5 ppm	98	94	6
>5 ppm	41	95	5
Controls	295	94	6

$\chi^2_{(3)} = 0.355$ ($P = 0.95$)

Table 5. — Distribution of Abnormal Cells Related to Vinyl Chloride (VC) Exposure.

	No. in Group	% of Group with 0-5% Aberrations	% of Group with >5% Aberrations
Exposure to VC	209		
<1 ppm	70	84%	16%
1-5 ppm	98	71	29
>5 ppm	41	73	27
Controls	295	70	30

$\chi^2_{(3)} = 5.37$ ($P = 0.12$)

reported to have continuously decreased over a period of years until immediately prior to the study when VC concentrations in the polymerization department were estimated to be 20 to 30 ppm.

The U.S. group of 11 PVC workers surveyed by Ducatman et al[19] was also reported to show an increased rate of chromosome breakage following exposures estimated to have been in excess of 500 ppm at times. The group of ten German workers investigated by Fleig and Thiess[20] worked with either VC or PVC or both for periods ranging between six and 34 years and with exposures estimated to have decreased from greater than 500 ppm in 1945 to between 10 and 25 ppm in 1974. Evaluation of this group for increased aberration rates was negative.

The study of British PVC workers by Purchase et al.[21] concluded that the frequency of cytogenetic aberrations was increased in 56 exposed workers as compared to 24 nonexposed individuals. Estimates of the levels of exposure were not given in this report. The medical director of the surveyed group, however, has informed us that while further analyses of the data confirmed the findings of increased aberrations in workers exposed to "higher" levels of vinyl chloride, no differences between worker and control groups were detected upon evaluation of the data for workers exposed to "lower" levels.

An earlier report from our laboratory[22] concluded that there were no cytogenetic differences of statistical significance between a group of 121 workers exposed to vinyl chloride and a 75-person control group. As in the work reported here, there was a discrepancy in the age composition of the two groups, because applicants seeking employment tend to be younger than those already settled into jobs. We do not believe, however, that this difference is a confounding factor in our comparison since the difference is not great and because it has been shown[23] that the cytogenetic change most often associated with aging is chromosome loss, rather than chromosome breakage.

On the basis of our negative findings and the conflicting findings reported by others, we believe that the level of chromosome aberrations in workers exposed to vinyl chloride is probably related to the length and level of exposure and that the risk of adverse cytogenetic effects can be avoided in controlled, minimal-exposure environments. Cytogenetic dose-response curves, similar to that suggested here, have been reported for x-irradiated ankylosing spondylitics,[24] A-bomb survivors,[25] radium dial painters,[26] persons exposed to Thorotrast,[27] and workers exposed to lead.[28] It has also been noted that the groups exposed to radiation later demonstrated significant increases in neoplastic incidence. A-bomb survivors, for example, have shown increased rates of leukemia and thyroid carcinoma;[29] radium dial painters were found to be at increased risk of osteogenic sarcoma;[30] and thorium dioxide-exposed persons have an increased rate of liver tumors.[31] This relationship between chromosomal breakage and neoplasia strongly suggests that cytogenetic analyses may be a useful tool for detecting environmental situations which may be associated with increased cancer risks to the workers.

The present study is one of several involving Texas plant employees to investigate the possibility that increased rates of fetal loss or birth defects in offspring are experienced by wives of vinyl chloride workmen and to determine the morbidity-mortality experience of all past and present VC workers. A search has been made for cases of angiosarcoma of the liver; none have been found in our study group (533 individuals) which includes all past and present VC workers. Current workers are also being monitored as part of the continuing medical surveillance program.

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