

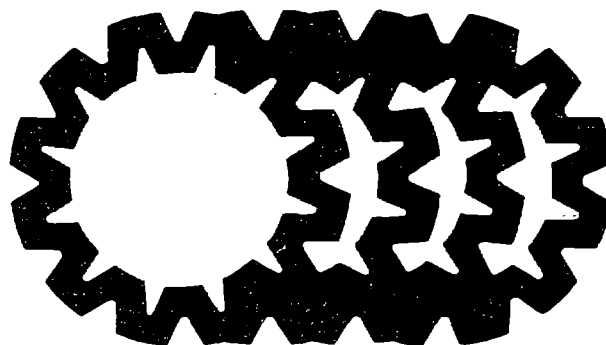
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A CROSS-SECTIONAL EPIDEMIOLOGIC SURVEY OF VINYL CHLORIDE WORKERS



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A CROSS-SECTIONAL EPIDEMIOLOGIC SURVEY OF VINYL CHLORIDE WORKERS

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ABSTRACT

A considerable number of studies have associated occupational vinyl chloride monomer (VCM) exposure with a variety of adverse health effects. The extent to which VCM induces these abnormalities in the workforce is not well defined. This cross-sectional medical survey of 433 predominantly white male employees, divided into four VCM exposure groups (never, light, heavy, former), determined the prevalence of illnesses and abnormalities based on data gathered by interview, medical examination, blood and pulmonary function tests, liver scans, and hand and chest x-rays. Age-adjusted analyses indicated that hepatomegaly, central nervous system symptoms, diastolic hypertension, and spouses' fetal wastage (the latter two statistically significant at $p < 0.05$) were more prevalent among past or present VCM exposed workers than among controls. Although VCM-related respiratory system problems, acroosteolysis, Raynaud's phenomenon, and chromosome aberrations have been identified by other investigators, no excessive prevalence of these toxic effects was found in this population compared with industrial worker controls.

CONTENTS

Abstract	iii
Acknowledgement	vii
Introduction	1
Methods	2
Discussion	9
References	15
Tables	18
Appendices	33

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INTRODUCTION

The causal relationship between occupational exposure to vinyl chloride monomer (VCM) vapor and the development of liver angiosarcoma is now well established. Following the first cluster of VCM-induced human cases of liver angiosarcoma discovered by Creech and Johnson (1), there have been a number of corroborative findings, including animal bioassay tests (2,3), additional case reports of VCM-induced liver angiosarcoma (4), and formal epidemiologic studies (5-7).

Available evidence also indicates that VCM can induce nonmalignant liver alterations (9-15), portal fibrosis in particular, long before the development of clinically manifest liver malignancy. Furthermore, pathophysiologic effects do not appear to be limited to the liver. For example, experimental animal research (2,18), as well as clinical (17) and epidemiologic (5,7,8,16,19) studies of workers exposed to VCM and polyvinyl chloride (PVC) dust, indicate a toxic effect on the respiratory system. Some of these same studies have also found increased risk of hematopoietic and central nervous system tumors. Microbial test system studies (20-22) and cytogenetic studies of VCM-exposed workers (23-26) indicate possible genetic effects. The anesthetic properties of vinyl chloride monomer (14) have been implicated as causing numerous central nervous system symptoms, such as headaches, dizziness, and fainting, in exposed workers (27).

The extent to which VCM induces clinically detectable abnormalities among workers occupationally exposed has not yet been well defined. Consequently, in order to determine the range of health effects associated with VCM, the National Institute for Occupational Safety and Health (NIOSH) and the Bureau of Epidemiology of the Center for Disease Control (CDC), in collaboration with the Occupational Health Studies Group (OHSG) of the University of North Carolina, conducted a cross-sectional medical survey at a chemical plant in Pottstown, Pennsylvania, which has a PVC polymerization operation, a PVC fabrication operation, and a rubber tire production operation. The specific objectives of the survey were: 1) to compare the prevalence of liver abnormalities and liver disease in VCM-exposed workers and appropriately selected control workers at the plant; and (2) to identify those tests best suited for detection of other illnesses and abnormalities in these groups of workers.

METHODS

The plant selected is one of the older PVC polymerization plants in the United States, having operated continuously since 1948. The plant thus provided a favorable research opportunity, since sufficient time had elapsed for the appearance of VCM-induced chronic effects. In addition, the plant provided the unique situation where a PVC polymerization ("chemical") plant, a PVC fabrication ("plastics") plant, and a non-VCM plant (a rubber tire operation) were located next to each other within one large corporate facility, although the individual plants were physically distinct from one another. Further, selection of non-VCM-exposed controls was facilitated because the University of North Carolina had conducted prior industrial hygiene surveys within these plants as part of an ongoing, joint company-union research project.

Shown in Table 1 are the four groups of hourly (production) employees who were requested to participate in the study. The first three groups are ordered by current VCM exposure. The first group consisted of a 9% sample of the 2400 rubber workers in the plant who were not exposed to VCM. These workers were age-frequency matched to the VCM-exposed chemical workers, and were chosen from departments in the plant identified as having the least exposure to other potentially confounding toxins such as solvents, dusts, and fumes.

The second group, the plastics workers, included everyone currently working in the PVC fabrication operation who had never worked in the chemical polymerization operation. Since these men were working with solid PVC plastic, their 8-hour time-weighted average exposure to VCM was probably below 10 ppm prior to this survey. However, for the third group listed, the chemical workers, the VCM exposure before 1974 was considered to be very much higher than in the plastics area. Every employee working in the chemical plant at the time of this survey was included in this group. All former chemical workers working elsewhere in the plant made up the fourth group surveyed. Participation rates of those requested to participate varied from a low of 62% in the rubber workers to a high of 77% in the chemical workers.

Using these four groups, two etiologic models were designed for classifying subjects in the analysis of the relationship of health status to VCM exposure. The first, the Acute Exposure Model, reflects the above-mentioned sampling design, and is based on the subject's job at the time of participation in this health survey. The former chemical workers were treated as a separate group for this analysis, regardless of their current jobs, since, under an assumption of acute exposure etiology, their past VCM exposures,

however brief, might be associated with some residual health effects. A second etiologic model, a Cumulative Exposure Model, based on each worker's entire work history at the plant, afforded no meaningful comparisons because of the extremely high correlation between age and dose, which precluded any legitimate age adjustment. Data presented here are therefore confined to the cross-sectional ("Acute Exposure") comparisons.

The health testing program, as outlined in Appendix A, consisted of a comprehensive 210 item questionnaire, including the Rose cardiovascular and British Medical Research Council respiratory symptom (BMRC) questions, administered to participants by trained medical interviewers; a thorough physical examination performed by NIOSH and CDC physicians; pulmonary function tests; chest x-rays, and a series of laboratory tests, including a complete blood count, platelet count, urinalysis, liver function, serum protein electrophoresis, hepatitis antigen, and sputum cytology. In addition, all study subjects who had been chemical workers for at least 10 years underwent liver-spleen scans with lead markers and hand x-rays performed at a nearby hospital. Cytogenetic studies were carried out on a very small sample of workers (Appendix B) (39).

Participants from all three shifts were tested, during the shift they worked, during the month of October, 1974. All physicians, interviewers, and technicians were blind to the occupational status of each worker; occupational status was determined independently, by use of the company's personnel records.

Individual consent was obtained from each participating worker. Results of testing were released only to the participant himself and to the physician(s) designated by each worker. Detailed medical reports on all of the questionnaire and physical examination findings, as well as most of the laboratory findings, were sent to the designated physicians within 2 months of the examination. Summary letters of these findings were sent to all the workers at the same time. Meetings were held with study participants before, during, and after the medical examination to discuss procedures as well as findings.

The United Rubber, Cork, Linoleum, and Plastics Workers of America and the local union (URW Local #336) Health and Safety Committee at the Pottstown plant provided considerable support in obtaining participation of workers in the study. Almost all examinations were performed during working hours, and the plant personnel department and local union safety representatives assisted in the examination scheduling.

Similarity of the groups was measured in terms of age, race, sex, alcohol consumption, and cigarette smoking. All of the study subjects were male, except for two plastics workers. Eleven (3%) of the study subjects were black and were distributed fairly evenly over the four occupational groups. All sex-race groups were included in the analysis. The age distributions of the current chemical workers and rubber worker controls

were similar, since they had been group-matched on age initially. However, when all four occupational groups were considered, the age distributions were significantly different (Table 2). Therefore, age adjustment of all test results was carried out using the direct method with the age distribution of the entire 411 persons as the standard.

Analysis of daily alcohol consumption, based on current drinking habits, showed that the four groups were nearly identical; thus, no adjustment for alcohol consumption was deemed necessary (Table 3). Although there were no statistically significant differences in smoking habits, the distributions did vary sufficiently for pulmonary function testing and respiratory symptom results to be smoking-adjusted.

Liver

Only one person, a chemical worker, gave a history of cirrhosis. Approximately 3% of those interviewed in each occupational group gave a positive history of gall bladder disease, whereas hepatitis (Table 4) was slightly more prevalent among persons who had been exposed to vinyl chloride.

The four liver function tests used (serum glutamic oxaloacetic transaminase (SGOT), total bilirubin, lactic dehydrogenase (LDH), and alkaline phosphatase) were analyzed by comparison of mean value, and by prevalence and severity of abnormals (Table 4).

In the total study population reported herein, 21% had an abnormal SGOT, 5% an abnormal total bilirubin, 4% an abnormal LDH, and 13% an abnormal alkaline phosphatase. For the most part, similar abnormality prevalences were found in each of the occupational groups, the major exception being abnormal LDH levels in 11.8% of the former chemical workers. Neither the overall mean values nor distribution of the abnormals by severity differed notably among the occupational groups.

Two methods were employed to detect hepatomegaly: physical examination (measured by both palpation and percussion) and liver scan. The liver scan procedure, described in Appendix A, consisted of six pictures with lead markers to aid in liver size determination. However, when the liver size measurements from the scans were tested for inter-reader variation, it was found that reader number one averaged 3 centimeters in height and 2.4 centimeters in width greater than reader number two. These differences were statistically significant ($p < 0.001$) in a matched pairs t-test. Standardization of measuring techniques among the readers was therefore deemed insufficient for their use in the analysis of hepatomegaly.

Hepatomegaly, as measured by palpation or percussion, is somewhat subjective. To determine whether one physician might have been overzealous in diagnosing hepatomegaly, thus possibly biasing the results, prevalence of palpated hepatomegaly by individual physician was calculated. No statistically significant difference was observed. Of the two measurements on physical examination, palpation (as defined by palpable liver) appeared to be the more sensitive, diagnosing 11% of the total population as having

hepatomegaly compared with 6% by percussion (≥ 11 centimeters) (Table 5). The good consistency between the two techniques for determining hepatomegaly was demonstrated by agreement in over 90% of the cases diagnosed by percussion.

One of the more interesting findings in this study was the Relationship Between Hepatomegaly and VCM Exposure. Current chemical workers had almost twice the age-adjusted prevalence (13.22%) of palpated hepatomegaly as did rubber workers (7.1%) and plastics workers (7.3%). A gradient in the same direction from chemical workers to plastics workers and rubber workers also existed when hepatomegaly was diagnosed by percussion alone (5.2%, 5.0%, 3.4%), and by both percussion and palpation (4.6%, 3.5%, 0.8%). However, no differences were found between current chemical workers in high, medium, and low-exposure jobs (not shown).

Two of the eleven people with hepatomegaly by percussion and palpation were heavy drinkers, and one of these two also had a history of hepatitis. To investigate the occurrence of liver problems evidenced by combinations of abnormalities, cases were analyzed that had two or more of the four liver function tests abnormal and hepatomegaly by both percussion and palpation. All 4 cases that met these criteria had been exposed to VCM. One was a former chemical worker and the other three were current chemical workers. All of them had an elevated SGOT.

Of the 123 liver scans performed on long-term VCM-exposed workers (a few salaried and hourly employees not in the four major occupational groups were included in this number), 94 were read as normal by all three nuclear medicine specialists, independently. Of the 29 scans read as abnormal, only 4 were read as abnormal by two reviewers and none were read as abnormal by all three reviewers. One reviewer read a total of two scans as abnormal, and the other two read 13 and 18 scans, respectively, as abnormal (Table 6).

The four cases read as abnormal by two readers included: 1) a 33-year old salaried process control engineer (not a member of the four occupational groups) whose LDH was elevated, 2) two chemical workers who worked as polymer reactor cleaners (the job associated with the highest VCM exposure in the chemical plant) aged 44 and 47, both of whom were light drinkers and had no abnormal liver function tests, and 3) a 52-year old former polymer reactor cleaner, now working elsewhere in the chemical plant, who was a greater-than-moderate drinker and had no abnormal liver function tests.

Other Abnormalities

There were no significant differences between groups for symptoms suggestive of Raynaud's phenomenon (Table 7). In addition, there was no difference between groups for the presence of an abnormal Allen Test (which has been suggested as an indicator for acroosteolysis).

Twenty-two of the 207 hand x-rays taken were read as abnormal for some state of acroosteolysis by at least one of the two independent radiologists. Most of the abnormal findings reported were from Reader #2. All but two of the abnormalities related to damage to the tufts of the cortex, a less

severe state of acroosteolysis, and many were possibly related to other causes, such as trauma. Although the other two x-rays showed possibly more severe changes of the shaft, they were only read as positive by one reader. One of the two cases had worked since 1952 in the chemical plant, while the other, a maintenance man since 1964, had worked intermittently in the chemical plant.

Central nervous system symptoms elicited during the interview (Table 8) showed that severe, persistent headaches were slightly more prevalent among chemical and plastics workers, compared to rubber and former chemical workers. A history of having ever lost consciousness on the job was less common in the rubber workers. On neurologic examination, the four occupational groups were found to be similar, with the exception of slightly diminished reflexes in the chemical group.

Since some of the known effects of VCM on humans (angiosarcoma, acroosteolysis, and Raynaud's phenomenon) involved the circulatory system, there was a specific interest in the results relating to the cardiovascular system. No noticeable differences among the occupational groups were found for prevalence of angina pectoris, as measured by the Rose Questionnaire, but a much higher prevalence of systolic hypertension ($> 140\text{mm}$) in the former chemical workers, and a higher prevalence of diastolic hypertension ($> 90\text{mm}$) in all three VCM-exposed groups compared to rubber workers, were seen (Table 9). Current and former chemical workers also had an increased history of having been told of hypertension in the past by a physician, and an increased history of having taken either "water pills" or blood pressure medication in the past, compared to rubber workers. Furthermore, the age-adjusted (by analysis of covariance) mean diastolic blood pressures were significantly different among the four groups ($p < 0.05$).

Tables 10 and 11 present prevalences of Pulmonary Function (PF) impairment among job groups. In Table 10, smoking, age, and height differences between study subjects were automatically controlled by comparing actual PF value with expected PF value derived from the appropriate smoking category of the total plant population. In Table 11, the actual PF values of study subjects in each job group and smoking category were compared to expected values derived from the literature, and the prevalence reported in other VCM workers. FEF₅₀/FVC and FEF₇₅/FVC impairment cut-off points have been shown to be effective in distinguishing normal subjects from those with obstructive lung disease (33).

There was no difference between job or smoking groups in the prevalence of volume impairment (FVC). Flow impairment was not consistently associated with any job group. For example, the former chemical workers had the highest prevalence of impaired FEF₂₅₋₇₅, FEV₁/FVC (nonsmokers), FEF₅₀/FVC and FEF₇₅/FVC (smokers), and FEV₁ (smokers). Present chemical workers had the lowest prevalence of impairment of airflow (FEF₂₅₋₇₅, FEV₁/FVC, FEF₅₀/FVC), but highest prevalence for FEV₁ (overall) and FEV₁ (nonsmokers). Rates of

airflow impairment $\geq 10\%$ of lowest rates were observed in nonsmoking former chemical workers (42%) compared to hourly chemical workers (22%) for FEV₁/FVC, and smoking former chemical workers (65%) compared to rubber (50%), plastics (56%), and hourly chemical (51%) for FEF₇₅/FVC. With regard to FEF₇₅/FVC, rates of impairment were consistently high for all groups. Nearly half of the study subjects had small airways obstruction to which this test pertains. Former chemical workers also had the highest prevalence of CV/VC impairment, and rubber workers the lowest prevalence. The greatest and most consistent effects were those of smoking. Except for FVC, smokers had consistently higher prevalence of impairment by all PF tests.

Because of the possibility of more recent, or more subtle, exposure effects among workers in this study population, before-and-after shift PF tests were carried out on a sample of 56 of the participating workers (Figure 1). Since there was a higher proportion of smokers within the subset of chemical workers, compared to the rubber and plastics subsets, results are presented separately for smokers and nonsmokers.

Smokers, overall, had statistically significant reductions for all seven PF tests. Nonsmokers, however, showed little reduction, with the most obvious being for flow rates at low lung volumes, FEF₅₀ and FEF₇₅ (measuring small airways performance). Chemical workers who were smokers had significant reductions for five of the seven tests, predominantly reflecting small airways obstructive change. However, both the plastics and rubber workers who smoked showed reductions of similar magnitude, although the smaller number of plastics smokers precluded their attaining statistical significance. The other two respiratory system health tests, sputum cytology and chest x-rays, showed minor interoccupational group differences. No sputum cytology findings revealed more than moderate atypia. Mild and moderate atypia age-adjusted prevalence rates were 26%, 29.4%, 33.3%, and 17.9% for the four groups, respectively. When the chest x-rays were read by three radiologists by the UICC/ILO criteria for pneumoconiosis, only one definite case was detected, and he was a former silica worker.

The health questionnaire incorporated the British Medical Research Council's chronic respiratory system questionnaire (see Appendix A). A comparison of age- smoking-adjusted respiratory symptom prevalence rates in the 4 occupational categories is presented in Table 12. For 3 of the 4 symptoms analyzed, the current hourly chemical workers had symptom rates slightly higher than those of the rubber worker control group. The plastics workers and former chemical workers, however, had rates substantially higher than the rubber workers.

Information on the pregnancy outcomes of the workers' wives, gathered as part of the questionnaire, were analyzed by age of father at time of conception, both before and after exposure at the plant. Since the number of pregnancies was so small, all workers in the chemical and former chemical

groups were included in the primary VCM exposure group; and since the two other groups did not differ by fetal wastage either before or after employment, they were combined in this analysis as a control group. Paternal age-specific fetal death rates are given in Table 13.

Pre-exposure fetal death rates did not differ between the two groups when adjusted for age (6.9% versus 6.1%). However, subsequent to the husband's exposure, the primary VCM exposed group had a statistically significant higher fetal death rate ($p < 0.05$) than the control group after age adjustment (15.8% versus 8.8%). Although not discussed here, this difference persists even when pregnancies of women considered to be chronic aborters are excluded from the analysis (28).

Cytogenic studies of peripheral blood lymphocytes, carried out on a small subsample of the workers, indicated VCM exposed workers had a slightly higher proportion of chromosome breakage than rubber workers (Table 14). The plastics workers, with presumed lower VCM exposure than the chemical workers, had a slightly higher breakage proportion than all other groups. None of these intraplant differences were statistically significant. Each of the three groups studied at the plant had a higher breakage rate than a non-industrial set of controls drawn from CDC personnel of approximately the same ages (see, also, Appendix B).

DISCUSSION

None of the liver function tests showed striking interoccupational group differences, with one exception. LDH abnormalities were found in only 2-4% of three of the work groups, but in 12% of the former chemical workers, including three persons with values greater than 250. Other studies done on populations of active and retired VC workers (29,30) with lower mean ages found approximately 2% with LDH abnormalities, which is consistent with most groups in this study. Since the results are age-adjusted, age can be ruled out as being responsible for this excess in the former chemical workers. (However, since the current chemical workers include only 3.6% with abnormal LDH, and since there is no dose-response gradient in the chronic model, self-selection out of the chemical area related to symptoms of associated abnormalities may be taking place.) Prevalence of alkaline phosphatase and total bilirubin abnormalities are also similar to, but slightly lower than, in the two other studies. With respect to SGOT, Wyatt's study (29) found approximately 8% abnormal in VCM exposed workers and 14% in unexposed workers, both of which are substantially lower than our figure. Lilis et al. (30), using a more restrictive abnormality criterion for SGOT (≥ 50 is defined as abnormal rather than ≥ 40), found 6% abnormal. Using this criteria, 4.9%, 3.1%, 6.1%, and 7.2% abnormalities were found in the 4 groups, respectively. It is particularly noteworthy that all 3 studies have shown over 10% of VCM exposed workers with elevated alkaline phosphatase, since the laboratories set the demarcation point for abnormality as the upper 5% tail in the general population. The fact that all four work groups display this high prevalence of alkaline phosphatase abnormality in this study could possibly be explained by either demographic (e.g., age) differences between the study populations and the laboratory reference population, or by the existence of some unidentified plant-wide hepatotoxin(s).

The most numerically impressive test difference between VCM-exposed and non-VCM-exposed workers is hepatomegaly. Despite the acknowledged imprecision of determining hepatomegaly by physical examination, the consistency of the results seen here is striking. Hepatomegaly prevalence followed a weak dose-response gradient to VCM exposure from the chemical workers to the plastics workers to the rubber workers when measured by palpation, percussion, or both; degree of hepatomegaly followed the same exposure gradient. A gradient of hepatomegaly prevalence by duration of VCM exposure, unadjusted for age, has been reported elsewhere (3).

The liver scan appears to be of doubtful value as a screening test to detect possible early liver damage, not only because of the radiation exposure, inaccessibility of equipment, and high cost, but also because of the difficulty of standardizing reported findings when dealing with minimal

or early changes. It is possible, however, that with continued collaboration in an ongoing testing program, these problems could be overcome. The divergent liver scan results reported by our 3 readers could be secondary to a number of factors: a) differences in procedures between the center where the scans were performed and the respective institutions of the 3 reviewers, despite a major effort on our part to standardize techniques before the study started, b) different standards for the interpretation of normal and abnormal by the 3 reviewers, and c) the possibility that a number of these scans represent truly equivocal findings, i.e., changes that are minimal or borderline and for which agreement or diagnosis would be difficult to attain. The latter interpretation is supported by the fact that many of the reported findings were in the possible or probable categories, rather than the definite category.

There were only four workers who were judged as having hepatomegaly and who also had 2 or more abnormal liver function tests (one of which was always the SGOT). In addition, liver scans of 4 other workers were read as abnormal by 2 readers. The fact that all 8 were exposed to VCM suggests the possibility that such screening tests, separately or jointly, are detecting early VCM-induced liver disease. Only by following this, and other populations, prospectively, would it be possible to fully assess the predictive value of any of these tests for detecting VCM-induced disease.

Splenomegaly and decreased platelet counts, 2 findings which have been noted in earlier studies of VCM-exposed workers (30,13), were not seen in this study. The extent to which these VCM-associated changes are related to primary disease in the spleen, or are secondary to portal hypertension, is not entirely clear, but this study does suggest that these screening tests may be related to a slightly more advanced stage of the disease than might have existed in this survey.

Other previously recognized health effects due to vinyl chloride exposure were not very frequent in this population. Prevalence of symptoms of Raynaud's phenomenon were not increased, and Allen Test abnormalities were no more common among VCM-exposed than nonexposed workers. Although indications of acroosteolysis were seen in over 10% of the hand x-rays, poor interobserver reliability among the x-ray readers, the fact that most of the x-ray changes noted were for the earlier stages of acroosteolysis, and the absence of increased symptoms or physical findings suggestive of acroosteolysis indicate that this disease is not a major problem at the plant now. (A review of serial x-rays taken in prior years would provide a clearer picture for the development of this disease over time.) A history of central nervous system symptoms, expected from the anesthetic effect of vinyl chloride, was found more often in vinyl chloride-exposed workers. This is consistent with an earlier study by Spirtas et al. (27) of the same plant. Because of changing working conditions over time, it is quite possible that many of the central nervous system symptoms reported in the medical history occurred well in the past, and although no neurologic abnormalities were noted during this cross-sectional examination, one should

not rule out the possibility that such abnormalities might have been present at a time when central nervous system symptoms were more prevalent. Overall, there is little proof that current VCM exposures are high enough to induce these VCM-related central nervous system health effects.

The substantially lower prevalence in the rubber workers of diastolic hypertension, measured as greater than 90mm Hg, is difficult to explain. The excess hypertensives in the other three groups are all in the 90-105mm Hg range. While the anxiety levels may have been higher in workers currently or formerly exposed to VCM (since most of them were aware of its carcinogenic potential), if such emotions were responsible for the differential prevalence of diastolic hypertension, one would expect a concomitant differential prevalence of systolic hypertension - which did not exist, except in the former chemical workers. Additionally, pulse rates were similar in the four groups, which argues against an anxiety etiology. More chemical and former chemical workers reported previously diagnosed hypertension than rubber workers, and there was also an increased history for having taken water pills or anti-hypertensive medication in the past; however, it was impossible to tell from interview data whether their exposures or hypertension came first. The increased prevalence in former chemical workers of systolic hypertension, if due to VCM, would also be expected in the current chemical workers, unless the systolic hypertension temporarily follows a diastolic hypertension-induced selection out of the chemical area. Such a hypothesis, although very tenuous, would be consistent with Table 9.

While these cardiovascular findings may be unrelated to VCM exposure, VCM has definite, known vascular effects, such as angiosarcoma, acroosteolysis, and Raynaud's phenomenon. Therefore, it is plausible, at least by analogy, that VCM in some way is responsible for the hypertension. Although there was a random allocation of subjects to the various examining physicians, it is well known that a single blood pressure reading is a somewhat unreliable finding in epidemiologic studies, and the relationship noted here between systemic hypertension and VCM exposure warrants more detailed investigation.

Experimental studies and case histories suggest that VCM acts as a lung irritant at high exposure levels (10,13,14). The reported epidemiologic study of VCM-PVC workers tends to support this literature (19). This study suggests no difference in PF on respiratory symptoms related to VCM exposure. Former chemical workers tended to have higher rates of impairment, but this could be due to exposure in their non-VCM jobs, or could reflect some self-selective migration away from that work area by individuals most prone to develop symptoms in response to exposure to the chemical plant environment. However, in the absence of information on jobs held subsequent to chemical plant jobs, no conclusions can be made.

The environmental factor having the greatest effect on baseline lung function was smoking. Smokers in all job groups had higher rates of flow impairment when compared to nonsmokers. This was a consistent finding, and the impairment was of greater magnitude than any differences observed between job groups.

The interval age- height- and smoking-adjusted comparisons between job groups in Tables 10 and 13 suggest no apparent effect of VCM exposure on either PF or respiratory symptoms. An external comparison relates impairment prevalence of this population to the findings of Miller et al. in another population of current and former VCM-PVC workers (Table 11). Using their criteria for impairment, their rates for volume impairment (FVC) are slightly lower than this study. This may be due, however, to their excluding any individual with flow impairment ($FEV_1 < 75\%$ of FVC).

Former chemical workers who also smoked had flow impairment (FEV_{75}/FVC) prevalence of 65%, a rate 10-15% higher than the other job groups, and the same prevalence as Miller et al. (19) found in their study. This was the highest prevalence of impairment in any of the job groups, and for any PF parameter. Nonsmokers in each job group had roughly comparable prevalence of FEV_{75}/FVC impairment.

Impairment rates for FEV_{75}/FVC may be elevated in the Miller et al. (19) study because 41% of the group from which flow-volume curves were obtained were selected because of abnormal spirometric findings. Prevalence of FEV_1/FVC impairment in this study was elevated, perhaps because there was no corresponding reduction in FVC. At least 2 reports in the literature (13,17) describe restrictive changes in the lung in PVC workers. In this study, the baggers (chemical workers) and banbury operators (plastics) have the greatest exposure to PVC dust. However, they comprise less than 10% of each job group, and so volume impairment in these workers alone is unlikely to affect the results of the entire job category.

FEV_1 impairment, an indicator of larger airways obstruction, was not elevated when compared to cotton textile (34) or hemp workers, and was comparable to nonexposed populations (35-38). FEV_{75} , a sensitive test for small airways obstruction, revealed a high prevalence ($>50\%$) of impairment. Prevalence of impaired FEV_{50} , also a sensitive indicator of small airways obstruction, was similar to FEV_1 . Unfortunately, the significance of the cutoffs for FEV_{50} and FEV_{75} (expressed as a percentage of FVC) has not been fully evaluated. Prevalence of impaired CV/VC, also an indicator of small airways function, was intermediate between the flow rate (FEV_{50} , FEV_{75}) impairments.

Flow impairment prevalence in this study does not appear elevated when compared to other working populations. For about one of every five workers to have some impairment is too high; however, this high prevalence of PF impairment, and the absence of differences in either respiratory function or symptoms among the job groups, suggests that all of the workers may be experiencing significant exposures. Indeed, for several of the PF tests, the chemical workers had better results than the other job groups.

To assess the possibility of the current exposure hazard, before- and after-shift tests were carried out on some workers. Any reduction in PF over the shift suggests the likelihood of some harmful exposure. Smokers, overall, had significant reductions in PF, most obviously for flows at low lung volume. Nonsmokers showed little reduction. Smokers in all job groups experienced reductions of similar magnitude, supporting the idea that all job groups face some respiratory insult.

While the increased frequency of chromosomal aberrations among the different occupational groups, compared with controls from outside the plant, may be due to exposure to VCM and/or other plant-wide chemicals, the results reported in Table 14 might also be due, at least partially, to age or socioeconomic status differences. Additionally, it should be noted that, although the magnitude of the differences between the occupational groups studied at the plant do not support other investigations associating VCM exposure with chromosomal aberrations (23-26), there are differences among these various studies in the composition of the populations under study which might make direct comparison somewhat difficult, and the sample size in this study was small.

The significant excess of fetal loss experienced by the wives of workers subsequent to their husband's VCM exposure must be assessed against the weaknesses inherent in a questionnaire survey. These weaknesses have been discussed elsewhere (28), lending credence to the belief that these findings are not spurious. This excess is biologically consistent with the previously demonstrated mutagenic response to VCM in microbial test systems (20-22), and the increased frequencies of chromosomal aberrations in VCM-exposed workers found by other investigators (23-26). This evidence mandates further research into this new adverse health consequence of VCM and additional agents found to be mutagenic in laboratory test systems and which are in broad use in the plastics and rubber industries.

Finally, while no cases of hepatic angiosarcoma, far advanced liver disease, or cancer of other sites were detected by the study among those currently employed, this should not be misconstrued with regard to the recent, extensive documentation of VCM liver carcinogenicity and toxicity; nor does it preclude the existence of such VCM-related conditions within this study population. In fact, liver angiosarcoma has been found previously at this VCM polymerization plant, and with a short period of time elapsing between earliest clinical manifestation and death. Hence, only a small proportion with such silent and difficult-to-diagnose diseases could be expected to be found in a cross-sectional medical survey.

It should be pointed out that there are differences between plants with respect to work practices, production techniques, working conditions, composition of workforce - in the presence or absence of various associated toxins - and other factors. This potential diversity of exposure within the PVC industry cautions against drawing general conclusions from this single study, about the hazards of VCM exposure, and the usefulness of screening tests in general VCM-exposed working populations. It is, therefore, necessary to put these into perspective alongside those reported from other plants, both in this country and elsewhere. Nevertheless, there are some tentative conclusions based on our findings which merit further evaluation.

Finally, with regard to the currently recommended liver screening procedures, the apparent low specificity of the liver function tests as a screening procedure, taken together with their unknown sensitivity and predictive value, emphasize the generally perceived need for a more specific test for detecting early liver damage in VCM exposed workers. Simultaneously, the true, early screening value of these standard liver function tests used in this study needs to be determined by a longitudinal medical surveillance program of the workers.

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TABLE 1
Subgroups of Workers Included in Survey

VCM Exposure	Occupational Group (N)	Sample Sought	# Participants (Participation Rate)
None	Rubber (2400)	9%	134 (62%)
Lightly Exposed	Plastics (105)	All	80 (76%)
Exposed	Chemical (164)	All	126 (77%)
Past Exposure	Former Chemical (101)	All	71 (70%)

TABLE 2
Age Distrubution of the Four Occupational Groups

<u>Age</u>	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>	<u>Total</u>
15-29	36 (27%)	19 (24%)	26 (21%)	12 (17%)	93 (23%)
30-39	23 (17%)	7 (9%)	13 (11%)	13 (18%)	56 (14%)
40-49	34 (25%)	12 (15%)	47 (36%)	29 (41%)	122 (30%)
<u>≥</u> 50	41 (30%)	42 (51%)	40 (32%)	17 (24%)	140 (35%)
Total	134 (100%)	80 (100%)	126 (100%)	71 (100%)	411 (100%)
Mean Age	40.3	44.4	42.3	42.4	42.1

chi square = 29.83 p = <0.01

TABLE 3
Alcohol Consumption by Occupational Group

<u>Alcohol Score*</u>	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>	<u>Total</u>
0	31 (23%)	13 (16%)	26 (21%)	14 (20%)	84 (20%)
.01 to .74	35 (26%)	24 (30%)	36 (29%)	18 (25%)	113 (28%)
.75 to 3.75	58 (43%)	37 (46%)	58 (46%)	35 (49%)	188 (46%)
>3.75	10 (8%)	6 (8%)	6 (5%)	4 (6%)	26 (6%)
Total	134 (100%)	80 (100%)	126 (100%)	71 (100%)	411 (100%)

* Equivalent ounces of pure alcohol per day
 $\chi^2 = 2.54$ ($p > 0.05$)

TABLE 4
Severity of Liver Function Abnormalities

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
SGOT (>39 Abnormal)				
Mean	31.6	32.1	32.6	34.5
Total Abnormal	22	19	25	19
40-49	16	16	17	14
>49	6	3	8	5
Prevalence*	17.1%	22.8%	19.8%	26.9%
Total Bilirubin (>1 Abnormal)				
Mean	.69	.63	.64	.63
Total Abnormal	8	5	4	4
1.01-1.40	6	4	4	3
>1.40	2	1	0	1
Prevalence*	5.4%	5.4%	3.5%	4.8%
LDH (>225 Abnormal)				
Mean	171	174	170	185
Total Abnormal	2	4	4	8
226-250	1	3	2	5
>250	1	1	2	3
Prevalence*	1.8%	4.2%	3.6%	11.8%
Alkaline Phosphatase (>85 Abnormal)				
Mean	67	66	66	69
Total Abnormal	18	10	16	11
86-115	15	8	15	8
>115	3	2	1	3
Prevalence*	13.1%	11.9%	12.5%	15.6%
History of Hepatitis				
Number	3	1	5	4
Prevalence *	1.9%	0.8%	3.7%	5.6%

*Directly Age-Adjusted

TABLE 5
Prevalence of Hepatomegaly

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
Palpation				
Number	9	8	17	10
Prevalence*	7.1%	7.3%	13.2%	13.0%
Percussion				
Number	4	5	7	1
12-13 cm	3	4	4	1
>13 cm	1	1	3	0
Prevalence*	3.4%	5.0%	5.2%	0.8%
Both Palpation and Percussion				
Number	1	3	6	1
Prevalence*	0.8%	3.5%	4.6%	0.8%

* Directly Age-Adjusted

TABLE 6
Liver Scan Results

Total number of liver scans performed in study: 123
 Normal to all 3 readers: 94
 Abnormal to 1 reader only: 25
 Abnormal to 2 readers: 4
 Abnormal to all 3 readers: 0

<u>Reader</u>	<u>Definitely Abnormal</u>	<u>Probably Abnormal</u>	<u>Focal Defect</u>	<u>Diffuse Disease</u>	<u>Other</u>
#1	-	13	2	7	4
#2	2	16	9	13	-
#3	-	2	2	-	-
Total	2	31	13	20	4

TABLE 7
Prevalence* of Raynaud's Symptoms

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
Had attacks of numbness, cold, blue coloration in fingers				
a. Unilateral	4.5%	2.0%	4.1%	5.8%
b. Bilateral	2.4%	3.8%	3.1%	1.8%
c. Such attacks precipitated by cold	4.1%	1.5%	3.8%	6.9%
d. Such attacks precipitated by emotional upset	0.6%	0%	0.6%	2.5%

*Age-Adjusted

TABLE 8
Prevalence* of Central Nervous System Symptoms

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
History of:				
Severe, Persistent Headaches	8.6%	12.7%	13.7%	6.4%
Losing Consciousness or Fainting on the Job	2.1%	5.2%	6.3%	5.8%

*Directly Age-Adjusted

TABLE 9
Severity of Hypertension

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
Systolic				
Number Hypertensive (≥ 140 mm Hg)	40	31	48	31
140-160 mm Hg	32	22	41	22
161-180 mm Hg	8	6	3	7
>180 mm Hg	0	3	4	2
Prevalence*	36.6%	32.5%	37.5%	45.6%
Mean*	132.4	135.7	134.9	137.2
Diastolic				
Number Hypertensive (> 90 mm Hg)**	31	33	51	26
90-94 mm Hg	17	14	25	17
95-105 mm Hg	10	12	21	5
>105 mm Hg	4	7	5	4
Prevalence*	24.3%	39.9%	39.4%	41.0%
Mean*	82.0	86.1	85.7	84.4
History of taking water pills or blood pressure medication	4.7%	11.5%	9.7%	16.0%
Previously told of high blood pressure by a physician*	19.6%	20.5%	25.7%	24.7%

* Age-Adjusted

** Rubber vs χ^2 (Mantel-Haenszel) significant ($p < 0.05$)

TABLE 10
Prevalence of Pulmonary Function (PF) Impairments*
Among Job Groups Adjusted for Age, Height, and Smoking

PF	<u>% Impairment</u>			
	Rubber	Plastics	Hourly Chemical	Former Chemical
FEV1 < 0.80 predicted	9.8	3.8	10.4	8.5
FVC < 0.80 predicted	4.5	8.8	6.4	5.6
FEF ₂₅₋₇₅ < 0.80 predicted	16.5	21.3	17.6	25.4
CV/VC > 1.20 predicted	17.6	26.6	24.8	30.0

* Expected values based on total worker population categorized by smoking

TABLE 11
Prevalence of Pulmonary Function (PF) Impairment
Among Occupational Groups by Smoking Category

PF	<u>% Impairment</u>				
	Rubber	Plastics	Chemical	Former Chemical	Miller et al.
FEV ₁ /FVC < 0.75					
Nonsmokers	31.4	37.8	22.2	41.9	32
Smokers	44.4	53.5	41.3	47.5	48
All	39.9	46.3	34.4	45.1	45
FEV ₁ < 0.80 Predicted*					
Nonsmokers	8.2	8.1	11.1	9.7	--
Smokers	13.9	14.0	18.8	20.0	--
All	11.3	11.3	16.0	15.5	--
FVC < 0.80 Predicted					
Nonsmokers	8.2	5.4	6.7	12.9	3.9
Smokers	6.9	11.6	8.8	7.5	4.7
All	7.5	8.8	8.0	9.9	4.6
FEF ₅₀ /FVC < 0.56					
Nonsmokers	4.9	10.8	2.2	3.2	--
Smokers	18.1	18.6	10.0	20.0	--
All	12.0	15.0	7.2	12.7	--
FEF ₇₅ /FVC < 0.30					
Nonsmokers	39.3	46.0	42.2	48.4	44
Smokers	50.0	55.8	51.3	65.0	63
All	45.1	51.3	48.0	57.8	60
CV/VC > 1.20 Predicted**					
Nonsmokers	6.8	10.8	15.6	16.1	--
Smokers	25.0	35.7	35.0	38.5	--
All	16.8	24.1	28.0	28.6	--

* Based on regressions from Ref. 31

** Based on regressions from Ref. 32

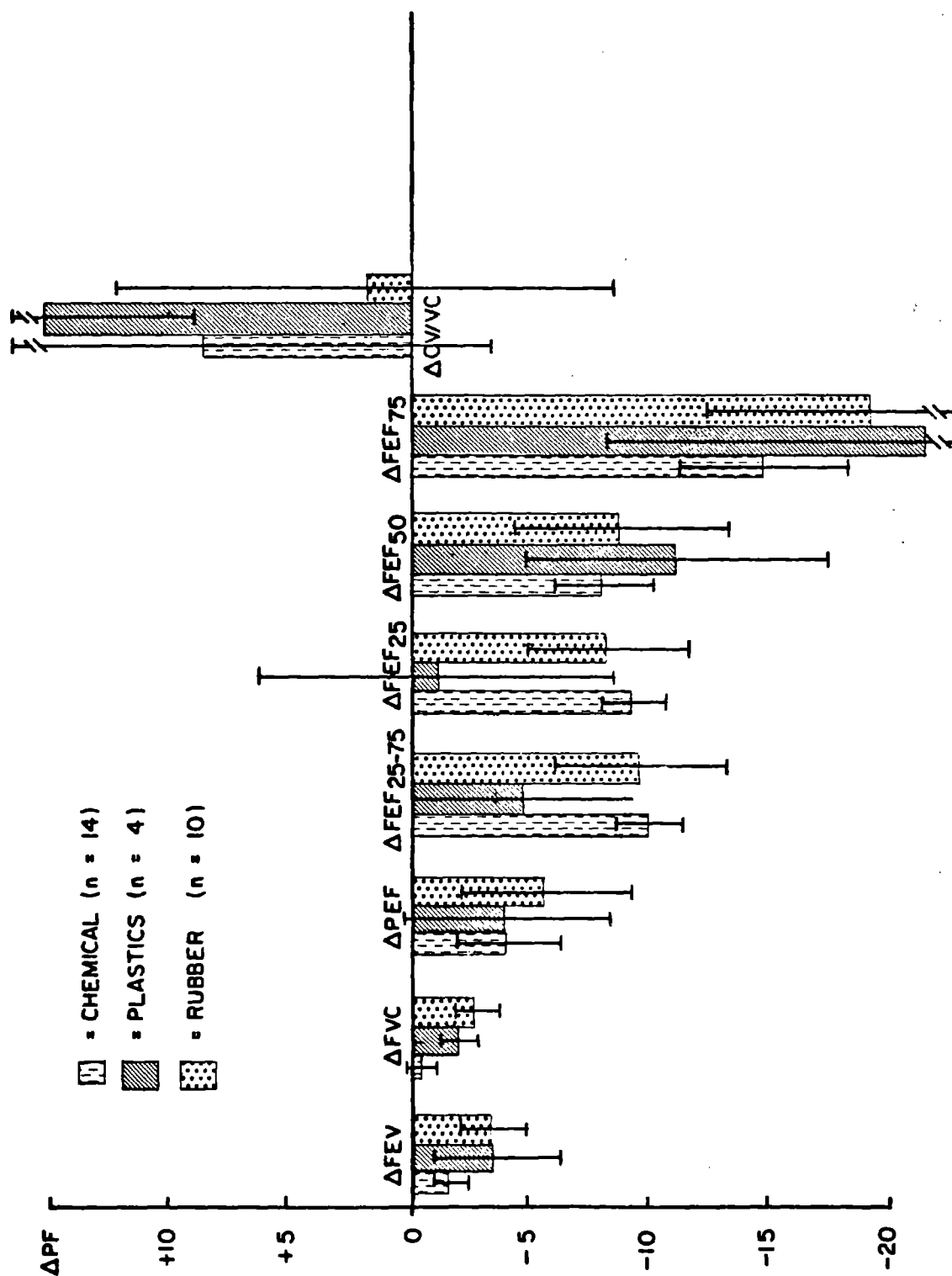


Figure 1. Mean percent change in pulmonary function (ΔPF) of smokers in chemical, plastics, and rubber group (with standard error).

TABLE 12
Age- and Smoking-Adjusted Prevalence Rates
of Respiratory Symptoms

<u>Symptom</u> +	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
Cough 1 and 2	10.0*	21.0	15.7	13.7
Phlegm 1 and 2	16.8*	26.5	14.8	28.0
Persistent Cough and Phlegm	6.8*	13.5	7.9	9.8
Breathlessness (Grade 2,3,4)	19.8**	20.4	22.3	25.7*
N	133	80	126	71
Age (years)	40.31 (12.8)*	44.4 (13.7)	42.1 (13.2)	42.2 (11.0)
Height (inches)	69.8 (3.4)*	69.2 (2.4)	69.5 (2.2)	69.6 (2.8)

* = 1 missing

** = 3 missing

+ Scored according to BMRC criteria

TABLE 13

Paternal Age Distribution for Fetal Deaths
According to Husband's VC Exposure

Paternal Age Group (Years)	<u>"Controls"</u>			<u>Primary VC Exposure</u>		
	<u>Pregnancies</u> (N)	<u>Fetal</u> (N)	<u>Deaths</u> (%)	<u>Pregnancies</u> (N)	<u>Fetal</u> N	<u>Deaths</u> (%)
Prior to Husband's Exposure						
<20	31	2	6.5	7	0	0.0
20-24	80	4	5.0	44	2	4.5
25-29	38	4	10.5	56	7	12.5
30-34	6	1	16.7	27	5	18.5
<u>>35</u>	4	0	0.0	14	1	7.1
ALL AGES	159	11	6.9	148	15	10.1
AGE-ADJUSTED			6.9			6.1
Subsequent to Husband's Exposure						
<20	1	0	0.0	0	0	0.0
20-24	43	4	9.3	22	3	13.6
25-29	87	3	3.4	48	11	22.9
30-34	87	7	8.0	36	3	8.3
<u>>35</u>	55	10	18.2	33	6	18.2
ALL AGES	273	24	8.8	139	23	16.5
AGE-ADJUSTED			8.8			15.8*

* Mantel-Haenzel χ^2 significant at $p < 0.05$ for the comparison of the two post exposure groups

TABLE 14
CYTOGENETIC STUDIES

<u>Exposure</u>	<u>Number of Subjects</u>	<u>Average Age</u>	<u>Average Months Worked</u>	<u>Number of Metaphases Scored</u>	<u>Number With Breakage</u>	<u>Percent With Breakage</u>
Chemical	14	49.4 (44-65)	291.1 (215-346)	1105	74	6.7
Plastics	4	52.5 (46-58)	315.8 (261-341)	180	14	7.8
Rubber	17	48.5 (31-58)	305.8 (114-357)	1306	77	5.9
Controls*	4	44.3 (37-51)	-	586	21	3.6

* CDC male employees not exposed to laboratory chemicals

APPENDIX A

TEST PROCEDURES

I. Medical Questionnaire

Administered by trained medical interviewers (PHS Venereal Disease Representatives), the questionnaire contained sections on demographic information, a past history with complete review of systems and emphasis on prior drug use, a family history with special emphasis on liver diseases, a respiratory symptom questionnaire based on the British Medical Research Council Questionnaire, and a cardiovascular symptom questionnaire (the Rose Questionnaire). Specific questions relating to potential VCM-induced effects, such as Raynaud's phenomenon, were included. In addition, a section related to the occurrence of stillbirths, miscarriages, and birth defects in offspring of workers was included.

II. Physical Examination

A general, thorough physical examination was given by CDC physicians, including tests chosen a priori for their relevance to possible vinyl chloride induced disease, such as the Allen Test, liver examination by both palpation and percussion, a careful neurologic examination, and a gum guaiac stool examination.

III. Hematologic Test

Ten milliliters of blood was drawn. A smear was made immediately for a qualitative platelet estimation and the remainder was refrigerated and sent to Upjohn Laboratories in King of Prussia, Pennsylvania, where hemoglobin hematocrit, white blood cell count, and platelet count were performed within 4 hours of the time the blood was drawn.

IV. Serologic Procedures

Thirty milliliters of blood was drawn, centrifuged, and the serum pipetted off and refrigerated immediately at the test site. (Sera for the sorbitol dehydrogenase procedure was immediately frozen in dry ice.) At the end of each 8-hour testing session, the serum was transported by direct auto courier to National Health Laboratories in Alexandria, Virginia, for a standard SMA-12 run, including total bilirubin, alkaline phosphatase, lactic dehydrogenase, serum cholesterol, serum glutamic oxaloacetic transaminase, total protein, albumin, blood urea nitrogen, glucose, inorganic phosphate, calcium, and uric acid. Additionally, serum protein electrophoresis, hepatitis antigen, sorbitol dehydrogenase, and ornithine carbamyl transferase were run.

V. Urinalysis

Each subject had a routine urinalysis with microscopic examination performed by Upjohn Laboratories in King of Prussia, Pennsylvania. Specimens were transported together with the hematologic specimens.

VI. Sputum Cytology

Each subject was given a 10% propylene glycol mist and asked to cough into a jar of carbowax solution. At the end of each week, the samples were sent to Dr. Geno Saccomano's laboratory in Grand Junction, Colorado, for analysis.

VII. Chest X-Ray

For persons who had received a chest x-ray within the last 6 months, that x-ray was obtained and used for our review. All other people in the study were given 14 x 17 posterior-anterior x-rays on a mobile unit at 70-80 KV by a licensed x-ray technician. Films were developed on site and quickly read by a physician for quality and problems requiring immediate medical attention. Later, all films were sent to three UICC/ILO certified radiologists: Dr. Benjamin Felson at the University of Cincinnati, Dr. Martin Donner at Johns Hopkins Hospital, and Dr. M. Dennis at the University of Maryland, who read them according to the 1970 UICC/ILO criteria for pneumoconiosis and other chest diseases.

VIII. Hand X-Rays

For a number of study participants, hand x-rays that had been previously taken by the company within the last 6 months were used. The rest of the subjects were given routine hand x-rays (45 KV, 90 MAS, with cardboard holders) at Pottstown Memorial Medical Center by their staff. The hand-x-rays were then sent, along with the attached forms, to Dr. Martin Donners and Dr. Walter Whitehouse at the University of Michigan Hospital for reading.

IX. Liver Scan

Five people had previous, recent liver scans done at the request of the plant administration at the Pottstown Memorial Medical Center and these scans were used. The other 118 people were also scanned at the Pottstown Memorial Medical Center using a diverging collimator (gamma camera). One milliliter of Technicium 99 Sulfur Colloid was injected into patients 10 to 15 minutes before scanning. A lead marker was placed on the right costal margin to aid in liver size determination. Six pictures, including anterior-posterior and lateral views of the spleen and liver, were taken. A standard reading form was developed

by Dr. Mallov in conjunction with the three nuclear medicine specialists who later read the films: Dr. Edward Silberstein at the University of Cincinnati, Dr. Mansfield at the Jefferson Medical Center, and Dr. T.P. Haynie at the University of Indiana.

X. Pulmonary Function Testing

All workers performed the pulmonary function tests seated and with a noseclip. At least 5 forced exhalations were obtained. The equipment used was Model 220 waterless spirometer and Model 750 Recorder, made by Cardio Pulmonary Instruments, Houston, Texas. For spirometry and flow volume parameters, the following procedure was followed: 1) several relaxed breaths, 2) inhale to about 2/3 full capacity, 3) forcibly exhale to RV, 4) inhale to full capacity, 5) forcibly exhale to RV. Three curves for calculations were selected on the following basis: 1) FVC and FEV₁ within 10% of each other and 2) appearance of curve - if it were possible to have a choice between curves, they were selected on the basis of: a) partial exhalation between 60 and 75% of FVC, b) initial forced expiration done with full force and without hesitation, and c) similarity in the shape of the curves. Calculations of flow are expressed as percent of FVC exhaled.

At least three single-breath nitrogen (SBN₂) maneuvers were performed, with inhaled and exhaled N₂ differences less than 5%. Exhaled flow from full vital capacity was maintained below 0.4 liters/sec. The criteria for selection of two curves were that VC be within 10% of each other, and exhaled flow rate was not greater than 0.7 liters/sec. for longer than 1/2 second. Individuals having less than two acceptable curves were not recorded. Closing volume (CV) was determined by drawing a straight line by eye along the latter part of the alveolar plateau. The volume between the first convincing point of departure from this line and the full VC was recorded as CV.

APPENDIX B

CHROMOSOMAL DAMAGE IN MEN OCCUPATIONALLY-EXPOSED TO VINYL CHLORIDE MONOMER AND OTHER CHEMICALS

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Introduction

Data from various sources suggest that the biologic effects of vinyl chloride monomer (VCM) include mutagenicity as well as oncogenicity. Pertinent studies include observations concerning the mutagenic effects of VCM in bacterial test systems (Rannug et al. 1974; Bartsch, Malaveille, and Montesano, 1975), mutagenicity of VCM metabolites in mammalian cells (Huberman, Bartsch, and Sachs, 1974), and cytogenetic studies of polyvinyl chloride (PVC) polymerization workers (Ducatman, Hirschhorn, and Selikoff, 1974; Funes-Cravioto et al. 1975; Kilian, Picciano, and Jacobson, 1975; Purchase, Richardson, and Anderson, 1974). Also relevant may be observations suggesting increased fetal loss in families of PVC workers (Infante et al., 1976). Among the several cytogenetic studies reported, three have suggested increased chromosomal breakage among polymerization workers (Ducatman, Hirschhorn, and Selikoff, 1975; Funes-Cravioto et al., 1975; Purchase, Richardson, and Anderson, 1975), and one has not (Kilian, Picciano, and Jacobson, 1975). This report concerns cytogenetic analyses conducted on workers employed at a rubber and plastics plant, some exposed to VCM and others not.

Materials and Methods

The work described here was part of a cross-sectional study designed to provide multiphasic medical screening data on the health status of men employed at a large rubber and plastics plant. The overall study was conducted jointly by the Center for Disease Control (CDC) (National Institute for Occupational Safety and Health and Bureau of Epidemiology) and the Occupational Health Studies Group of the University of North Carolina, in cooperation with the Firestone Corporation and the United Rubber Workers. Results of the entire study, together with a detailed description of the study's design and methodology, will be published separately.

Cytogenetic analyses, primarily designed to measure frequencies of chromosomal breakage, were performed on peripheral blood lymphocytes from 35 men; specimens were obtained from 18 men in October 1974, and from 19 men in January 1975; two specimens were taken on both occasions). Subjects were restricted to men primarily or exclusively employed for 10 years or longer in three different employment categories: 14 in PVC polymerization (presumed high exposure to VCM, intermittent or sustained), 4 in PVC processing (presumed low exposure to VCM), and 17 in rubber tire manufacture (industry controls, presumed negligible exposure to VCM). Work history details were obtained by interview and confirmed by review of company records.

Initially, the study was designed to compare breakage frequencies in workers exposed to VCM with frequencies in other workers. However, when initial analyses showed no significant differences among worker groups, a control group was selected (April 1975) consisting of four male employees at CDC not exposed directly to any laboratory chemicals.

Material for cytogenetic analysis was prepared in the same manner with the same reagents as the earlier material from workers at the plant. To assess comparability in microscopic reading of slides between April 1975, and the earlier dates, previously-read slides from the high VCM and industry control groups were blindly interspersed among the CDC workers slides. Breakage frequency recorded on the second reading of high VCM/industry control slides (6.0% of 150 scored metaphases) did not differ significantly from the first reading. Cytogenetic material was processed using standard procedures (Moorhead et al., 1960). Cells were cultured for 72 hours in the presence of phytohemagglutinin. Giemsa staining was used without banding.

Results

Frequency levels of chromosomal breakage in each group are shown in Table 1. Levels of breakage in all three industry groups, whether exposed to VCM or not, were significantly increased over the CDC control level, the high VCM group at the $p < 0.01$ level, the low VCM and industry control groups at the $p < 0.05$ level. At the same time, no significant differences were noted between the three industry groups themselves. Groups were comparable in terms of age and number of months worked. Breakage frequencies for individual subjects within groups did not vary significantly one from another.

An effort was made to relate levels of breakage to duration of employment and, hence, extent of potential toxic exposure (Table 2). While a significant gradient was seen for industry controls, interpretation is uncertain because of small numbers and because the mean age of subjects increased with employment duration. No gradient was seen for the high VCM group, whether in terms of total employment or of employment in contact with VCM. The low VCM exposure group was too small to permit analysis by exposure duration.

Chromatid gaps comprised the majority (86%) of aberrations seen (Table 3). Similar types of aberrations were seen with similar frequencies among all four groups.

Discussion

When reviewed in terms of comparisons between worker and nonworker groups, the present observations are not inconsistent with prior studies suggesting that industrial exposure to VCM is associated with an approximately two-fold increase in levels of chromosome breakage as measured in culture of peripheral blood lymphocytes. In contrast with at least one prior report (Huberman, Bartsch, and Sachs, 1975), however, breakage consisted mostly of simple chromatid gaps rather than more complex forms.

The fact that overall breakage levels were similar in workers exposed heavily, lightly, or negligibly to VCM may imply, in this particular work setting at least, the presence of agents other than VCM capable

of inducing chromosome breaks. Because of the wide range of chemicals to which rubber workers at this plant were exposed (primarily solvents of various kinds), it was impossible to relate any particular agents to the abnormal effects observed. No clear-cut pattern was seen to relate degree of breakage to duration of exposure.

Summary

Measurements of chromosomal breakage were made in peripheral blood lymphocytes from workers exposed heavily, lightly, or negligibly to VCM at a large rubber/plastics plant. Breakage levels in all three groups were significantly increased over levels in nonindustrial controls. Breakage consisted mostly of simple chromatid gaps. The results suggest that other agents, in addition to VCM, may cause cytogenetic damage in workers employed in the rubber/plastics industry.

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Table 1
LEVELS OF CHROMOSOMAL BREAKAGE BY EXPOSURE GROUP

Exposure	Number of Subjects	Average Age (Range)	Average Number of Months Worked (Range)	Metaphases		
				Number Scored	Number With Breakage	Percent With Breakage*
High VCM	14	49.4 (44-65)	291.1 (215-346)	1,105	74	6.7
Low VCM	4	52.5 (46-58)	315.8 (261-341)	180	14	7.8
Industry Controls	17	48.5 (31-58)	305.8 (114-357)	1,306	77	5.9
CDC Controls	4	44.3 (37-51)	--	586	21	3.6

* Levels of statistical significance: High VCM vs. CDC Control $\chi^2 = 7.09$ $p = < 0.01$
Low VCM vs. CDC Control $\chi^2 = 4.64$ $p = < 0.05$
Industry Control vs. CDC Control $\chi^2 = 3.95$ $p = < 0.05$
High VCM vs. Low VCM $\chi^2 = 0.18$ $p = > 0.05$
High VCM vs. Industry Control $\chi^2 = 0.81$ $p = > 0.05$

Table 2
LEVELS OF CHROMOSOMAL BREAKAGE IN RELATION TO EXPOSURE DURATION

Exposure	Months Worked	Number of Subjects	Average Age	Average Number Of Months Worked	Number Scored	Metaphases	
						Number With Breaks	Percent With Breaks
High VCM (Total Employment)	100-199	0	-	-	-	-	-
	200-299	8	47.4	264.6	700	49	7.0
	300-399	6	52.2	326.5	405	25	6.2
$\chi^2(1 \text{ D.F.}) = 0.16 \quad p > 0.05$							
High VCM (VCM Employment)	100-199	2	60.0	179.0	100	7	7.0
	200-299	9	47.7	252.3	755	53	7.0
	300-399	3	47.7	318.3	250	14	5.6
$\chi^2(2 \text{ D.F.}) = 0.58 \quad p > 0.05$							
Industry Controls	100-199	2	31.0	132.5	100	0	0
	200-299	2	44.5	265.5	76	1	1.3
	300-399	13	51.8	338.6	1,130	76	6.7
$\chi^2(2 \text{ D.F.}) = 9.91 \quad p < 0.01$							

Table 3

TYPES OF CHROMOSOMAL ABERRATIONS OBSERVED

Chromosomal Aberration	High VCM		Low VCM		Industry Controls		CDC Controls	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Chromatid Gaps	59	5.3	12	6.7	74	5.7	18	3.1
Isochromatid Gaps	7	0.6	0	0	6	0.5	1	0.2
Chromatid Breaks	2	0.2	0	0	2	0.2	2	0.3
Isochromatid Breaks	5	0.5	2	1.1	9	0.7	1	0.2
Isochromatid Fragments	3	0.3	0	0	0	0	0	0
Exchange Figures	1	0.1	0	0	0	0	0	0
Ring Chromosomes	1	0.1	0	0	0	0	0	0
Total Breakage	78	7.1	14	7.8	91	7.0	22	3.8
Total Cells with Breakage	74	6.7	14	7.8	77	5.9	21	3.6
Hypodiploid Cells	121	11.0	33	18.3	155	11.9	61	10.4
Hyperdiploid Cells	2	0.2	0	0	3	0.3	1	0.2
Total Cells Scored	1,105	-	180	-	1,306	-	386	-

