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REPORT ON A CASE CONTROL STUDY
COVERING WHITE FEMALE EMPLOYEES
OF PVC FABRICATORS

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Organization Resources
Counselors, Inc.

*Copy to Dr. E. Zwickler
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BACKGROUND

In January 1974, B. F. Goodrich Chemical Company disclosed that angiosarcoma of the liver was the cause of death of three employees at that company's Louisville, Kentucky plant. The Goodrich disclosure suggested the possibility of a new occupational disease and showed a need to reevaluate the standard of the Occupational Safety and Health Administration (OSHA) for occupational exposure to vinyl chloride. At that time, there were no data from which to determine the prevalence of angiosarcoma of the liver in the plastics industry. On further investigation other cases of the disease were found in the industry, but the pattern of occurrence suggested that they were associated with those processes which involved high concentration of vinyl chloride monomer which had not been converted in the polymerization process. Thus, there was a question of whether adverse effects were possible for employees who had been engaged in fabrication in situations where potential exposures were thought to be low and to result only from the release of unreacted monomer trapped in the resin.

Representatives of the PVC producers who were members of the ORC Occupational Safety and Health Standards Group questioned Leo Teplow, Special Consultant to ORC, on the feasibility of a study of the health risks to employees who were working with vinyl chloride and polyvinyl chloride. When it was learned that the National Institute

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for Occupational Safety and Health (NIOSH) was engaged in conducting a mortality study of employees in vinyl chloride and resin producing plants, the scope of the proposed study was limited so that it included only employees engaged in the fabrication of finished products, using PVC resins. The objective of the study would be to determine the facts and cause involved in the deaths of employees in 17 PVC fabricators in the period from 1964-1973. Of specific interest would be whether any case of angiosarcoma of the liver had occurred, such information to be based on an analysis of death certificates. Once these figures were extracted and the distribution of causes determined, they were to be compared with published mortality tables.

Industry decided that such a study had merit and agreed to finance it. ORC then contacted Dr. Leonard Chiazze, Director of the Division of Biostatistics and Epidemiology, Department of Community Medicine and International Health of Georgetown University, who designed the protocol, developed a records system, and interpreted the results. The ORC staff served as the interface with industry, and was responsible for field work. ORC issued "Report on a Mortality Study Covering Employees of PVC Fabricators" in February 1976, and at the time copies were submitted to OSHA and NIOSH. On June 16, 1976, there was a discussion of the findings among representatives of OSHA, NIOSH, Dr. Chiazze, participating companies, and ORC.

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The ORC study identified 44 deaths among white women in which the underlying cause of death was cancer of the breast. The 44 deaths attributed to cancer of the breast occurred among women who were employees of eight of the participating companies (Table 1). On the basis of a Proportional Mortality Ratio analysis, the number of deaths due to breast cancer appeared to be somewhat greater than had been anticipated, with the expected number being based upon the distribution of deaths, by cause, among all U.S. white women.

The study did not reveal any case of angiosarcoma of the liver among employees of the fabricators under study. There were, however, some possible excesses identified in the Proportionate Mortality Ratio analysis, and these are summarized in Table 2. The findings also indicated that there was a need to do further research to determine the feasibility of analyzing work histories. During the fall of 1976 there were discussions of alternative follow-up studies.

DEVELOPMENTS IN THE SCIENTIFIC LITERATURE

Concurrent with discussions concerning a follow-up study, Dr. Cesare Maltoni, whose research in Italy played an important role in the development of the OSHA Standard for Occupational Exposure to Vinyl Chloride, released interim results of a study on rats exposed to low levels of vinyl chloride monomer. His preliminary findings,

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shown in Table 3, suggested the possibility of a dose response relationship at low levels of exposure between vinyl chloride and mammary tumors. In an NIH Symposium in January 1977, Dr. Joseph Wagoner of NIOSH commented on the Maltoni results (Table 3) and the Chiazze/ORC results (Table 2). The implications of the two studies were obvious. Exposure to vinyl chloride—whether as a result of direct inhalation of the monomer under controlled conditions or as a result of the occasional release of unreacted monomer entrapped in the resin—might induce tumors.

In December 1976, Dr. Chiazze and ORC recommended that a case control study be conducted to determine the work histories of the white female employees in the study whose death certificates indicated breast cancer as the underlying cause of death. Only white females were studied, as no breast cancer deaths were found among males in the original study and the number of nonwhite females (23 deaths from all causes) was too small for further analysis.

ORGANIZATION OF THE STUDY

After a discussion of the merits of a follow-up study, the eight companies decided to proceed with a case control study and agreed to finance it.

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Data Collection

William E. Nichols, Ph.D., and ORC Consultant, was responsible for the design of the questionnaire used to elicit work histories and for auditing for accuracy the personal data entries on the death certificates. He also scheduled the necessary plant visits and supervised the data collection team. The plant visits were made by William E. Nichols; G. John Tysse, ORC Consultant; Carolyn Sutherland, ORC Staff Associate; and Maha Shakhashiri, Georgetown University, Research Associate. The field work was conducted between February 25 and March 28, 1977.

Data Interpretation

Leonard Chiazze, Sc.D., Associate Professor and Director, Division of Biostatistics and Epidemiology, Georgetown University School of Medicine, was responsible for designing the protocol, verifying the field reports, providing for data processing, and interpreting the results.

DESCRIPTION OF PARTICIPATING FABRICATORS

Geographic Distribution of Breast Cancer Deaths

The 44 breast cancer cases occurred in 19 locations of eight of the 17 companies that were included in the original study. Twelve locations with 23 of the deaths were in the East, and seven locations with 21 of the deaths were in the Midwest. It is interesting

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to note that 40 of the 44 decedents worked in plants north of the Ohio River and east of the Mississippi River, where there is a deficiency of selenium in the soil.¹

Three of the 44 breast cancer deaths occurred in offices physically located in separate cities but treated administratively as a part of plant employment. Another eight deaths occurred in a general office located in the same city as a major plant. The remaining 33 deaths occurred in plants that ranged in size from 300 to 7,000 employees.

Sex and Ethnic Mix

Work populations in the 19 locations reported in this study were predominantly male during the study period 1964-1973 and seem to be consistent with the ratio of deaths (85.4 percent male) found in the analysis of death certificates on which the original study was based. There has been an increase in female employment in recent years, and the ratio for the study period years is not representative of current employment.

Similarly, the ethnic mix in the 19 locations during the study period was predominantly white (88.3 of the deaths in the original study were known to be white). All but two of the plants reported that

1

See "Studies Firm Up Some Metals' Role in Cancer," Chemical and Engineering News (January 17, 1977), pp. 35-37; Birger Jansson et al., "Gastrointestinal Cancer: Its Geographic Distribution and Correlation to Breast Cancer," Cancer (December 1975), p. 2373.

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nonwhite employment has been increasing. The two exceptions are located in isolated communities in the Midwest where the nonwhite population is small.

Turnover Rate

Most of the plants report an overall low turnover rate because the wage levels in these companies tend to be higher than for other employers in the area, and because the work is relatively light. Turnover appears to be lower in rural areas than in urban areas, and lower in small plants than in large. The turnover that does occur is predominately among short-service employees.

Extent of Unionization

All but two of the plants are organized, and a variety of unions, both independent and with international affiliation, are represented.

Use of PVC Resins

Histories of use of PVC varied widely among the plants, and at the time of the study period varied from over 20 years to less than five. Moreover, the form in which PVC was a raw material ranged from resins delivered in bulk by railroad cars to a raw material that was considered a fabricated product as defined by OSHA

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and was extruded at the plant.² An example of intermediate state includes pellets with color added by the PVC resin producers.

JOB CONTENT AND EXPOSURE POSSIBILITIES

A multitude of jobs were held by the breast cancer cases, ranging from office and clerical worker (10) and outside salesperson (1) to production jobs such as bench inspector, press operator, trimmer, assembler, and sweeper. Such a wide range of job content and location made it impossible to determine precisely whether there was PVC exposure in every case. Therefore, it was necessary to develop a subjective ranking system.

McMichael et al.³ developed a system of Occupational Titles in which jobs in the rubber industry were grouped together on the basis of operation (type of machine and/or process) and materials handled. Their study was in a homogeneous industry with emphasis on tires, tubes, flaps, and bladders. However, in the ORC study

2

"Fabricated product" means a product which is made wholly or partly from polyvinyl chloride, and which does not require further processing at temperatures, and for times, sufficient to cause mass melting of the polyvinyl chloride resulting in the release of vinyl chloride (29 CFR 1910.1011 (a) (6)).

3

A. J. McMichael, M.D., Ph.D.; R. Spirtas, Dr. P.H.; J. F. Gamble, Ph.D.; and P. M. Tousey, B.S.N., "Mortality Among Rubber Workers: Relationship to Specific Jobs," Journal of Occupational Medicine (March 1976).

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there was insufficient compatibility of job tasks, machinery, material, and products to permit the use of such a sophisticated format.

B. F. Goodrich Chemical Company developed a subjective rating scale for jobs at the Louisville, Kentucky plant as a part of its continuing study of health hazards in the polymerization stage. The exposure to chemicals (including vinyl chloride) in the Louisville plant was classified into six stages ranging from "no exposure" to "intimate contact—skin or high inhalation." The rating program spanned approximately seven months.⁴

Consequently, for purposes of this study, PVC exposure potential was categorized into five classes—"no exposure," "improbable exposure," "possible exposure," "definite exposure," and "unknown exposure"—as shown below. The distribution of cases and controls by these categories is given in Table 4. Below, in tabular form, is a presentation of the various categories of exposure potential through employment, and examples of each.

Classification of
Exposure Potential

Examples

No exposure

Employment terminated before
PVC use
PVC processed in a separate
building from decedents' work
station

⁴

Paige E. Mosser, "Industrial Data Bank—Work and Exposure Data," paper delivered at University of Louisville Seminar on Medical Surveillance in an Industrial Setting, April 21, 1977.

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Classification of
Exposure Potential(continued)

Examples (continued)

	PVC processed in the same building but removed from decedents' work station
Improbable	Decedent handled only fabricated products
Possible	Work station in vicinity of PVC resins; periods of no monitoring or with no detectable level of VCM.
Definite	Direct work with PVC resins Monitoring indicated a detectable level of VCM
Unknown	Employment records not complete enough to determine potential for exposure

MONITORING HISTORY

There was little history of monitoring among fabricators prior to the Goodrich disclosure, as VCM levels were well below the TLV of 500 ppm which was established by ACGIH and adopted in May 1971 by OSHA in its initial package of health standards. Following the Goodrich disclosure, and the subsequent development by OSHA first of an emergency temporary standard and ultimately of a permanent standard, monitoring was carried out, and the levels of exposure at jobs classified as "improbable," "possible," and "definite" and previously occupied by decedents, are well below the permissible levels promulgated by OSHA; in fact, almost all show no detectable level.

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THE CONTROL GROUP

A series of controls was used which matched for ages (plus or minus five years) and company of employment (plant, if possible). Eligible to be used as members of the control group were employees whose deaths were from diseases of the circulatory system (ICDA 390-458, Eighth Revision) and accidents (ICDA-E800-E999). Unfortunately, not every breast cancer death had at least one matching control, and it was necessary to exclude nine deaths from analysis, leaving 35 deaths with matched controls.

FIELD WORK

In planning the field work, emphasis was placed on obtaining employment histories on the 35 cases with matched controls. However, it was also possible to obtain such information on five of the nine unmatched cases, and the information suggested that their exposure histories were generally similar to the 35 matched cases. The exposure information on the nine deaths excluded from further analysis is summarized as follows:

- 4 deaths with no information (010052, 010256, 010279, 120382)
- 5 deaths with some exposure information (020001, 030006, 060094, 070281, 080019):
 - 2 deaths with no PVC exposure,
 - 2 deaths with PVC exposure improbable,
 - 1 death with no record of the individual having worked in the plant. Possibly employed in a retail outlet.

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Table 5 presents the distribution by company of the 35 breast cancer deaths (hereafter called cases) and the 134 controls matched for age which were available for analysis. Mean age at death of the cases and controls was compared as a check on the matching procedure. Average age at death for the 35 deaths attributed to breast cancer was 62.6 (standard error = 2.26) compared with an average of 65.0 (standard error = 0.99) for the controls. Although controls are slightly older on the average, the difference is not significant when the standard errors are taken into account. Comparison of cases and controls using a variety of other variables—including length of employment, continuous vs. intermittent employment, ever married vs. never married, and childbearing history—reveals no significant differences between cases and controls for any of these variables (Table 6-9).

STATISTICAL PROCEDURES

After matching by age and company, 31 matched sets of cases and controls were developed from the 35 cases and 134 controls. There are fewer matched sets than cases because, in four instances, there were two cases of similar age. The Mantel-Haenszel procedure was used to derive a measure of relative risk and to test for significant departures from unity. In this procedure, each of the 31 sets can be viewed as a 2 x 2 contingency table, as follows:

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	PVC EXPOSURE		
	YES	NO	TOTAL
Cases	A_i	B_i	N_{1i}
Controls	C_i	D_i	N_{2i}
TOTAL	M_{1i}	M_{2i}	T_i

The relative risk is the ratio of the probability of developing the disease among women with PVC exposure to the probability among women not exposed, and is calculated as:

$$R = \frac{\sum_i \frac{A_i D_i}{T_i}}{\sum_i \frac{B_i C_i}{T_i}}$$

To assess whether an observed relative risk may have occurred by chance, a Chi-Square test is performed. As detailed by Mantel and Haenszel, a summary one degree of freedom Chi-Square corrected for continuity is computed by the formula:

$$\chi^2_{MH} = \frac{(|\sum_i A_i - \sum_i E(A_i)| - \frac{1}{2})^2}{\sum_i V(A_i)}$$

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The calculated Chi-Square must be 3.84 or larger in order to conclude with 95 percent assurance that the observed relative risk did not occur by chance alone.

Combining the five exposure categories into two may be accomplished in a variety of ways resulting in several possible relative risk measures. For example:

1. YES = Yes only

NO = No only

(ignore improbable, possible, unknown)

$$R = 1.87 \quad \chi^2_{MH} = 0.0298$$

2. YES = Yes + improbable + possible + unknown

NO = No

$$R = 0.9541 \quad \chi^2_{MH} = .0049$$

3. YES = Yes + possible

NO = No + improbable + unknown

$$R = 0.337 \quad \chi^2_{MH} = 0.217$$

4. For Cases: YES = Yes + possible + unknown

NO = No + improbable

For Controls: YES = Yes + possible

NO = No + improbable + unknown

$$R = 5.1065 \quad \chi^2_{MH} = 1.8871$$

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Note that in example 4, unknowns are treated as YES for cases and as NO for controls. This represents an extreme although highly unlikely possibility.

None of the above calculated relative risks, including example 4, are statistically significant; that is, they may have occurred by chance alone. Similar analyses were carried out on a company-by-company basis. None of the relative risks so calculated is significantly different from unity. Furthermore, the absolute magnitude of the highest relative risk achieved for any company in the most extreme case (example 4) was 1.75 ($\chi^2_{MH} = 0.498$).

INTERPRETATION OF RESULTS

A great deal of caution must be exercised in the interpretation of these relative risks. While they do not prove that there is no excess risk of death from breast cancer among women employees with PVC exposure, they do suggest that no overwhelming excess risk exists. On the other hand, considering that the proportion of controls which was exposed, or was possibly exposed, was 7.5 percent, it would have been necessary to have more than 200 cases and 200 controls in order to detect a substantially large increase in risk, twofold, for example, with 95 percent assurance that a risk of such magnitude, if observed, did not occur by chance, and 80 percent probability of observing a twofold risk if, in fact, it did exist. In order to achieve 90 percent

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probability of detecting a true twofold risk, it would be necessary to have available about 400 cases and 400 controls. Given the percentage of controls in this study with PVC exposure (7.5 percent), a percentage which was unknown at the beginning of the study, it would not be possible to detect small increases in relative risk. However, it is clear that no overwhelming excess risk does exist. It is likely that if an excess risk does exist, it is relatively small. Perhaps of greater importance, and based upon these data, is the suggestion that the proportion of women employees in these companies who had a history of PVC exposure is substantially smaller than had been anticipated.

OBSERVATIONS

Recordkeeping

The records of the participating companies were sufficiently complete in most cases to permit classification into the subjective categories. If one devotes sufficient time, it is possible to reconstruct reasonably complete work histories.

Exposure Records

Because of the TLV level for vinyl chloride prior to the Goodrich disclosure, it is impossible to estimate either duration or level of exposures on those jobs where decedents had the potential for direct contact with PVC resins. Similar studies in the future, whether on vinyl chloride or other substances, may encounter the same difficulty

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for pre-OSHA years. The less harmful the substance was considered, the greater the difficulty will be in determining exposures.

Conflict with other Regulations

Compliance with EEO regulations regarding entries denoting race, national origin, place of birth, or preexisting conditions may hamper legitimate epidemiological research in the future. Old employment applications and personal records contain entries that aid in current research, but are prohibited in today's records.

Both sex mix and ethnic mix in the work force are changing drastically, and the researcher in the future must be sensitive to the shifting patterns in the work population under study.

Errors in Work Force Estimation

Estimates of the number of employees engaged in PVC fabrication and the percentage of employees with direct exposure to PVC resins seem to have been overestimated by both OSHA and employers during the deliberations that led to the OSHA permanent standard for occupational exposures to vinyl chloride.

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Table 1
Distribution of Deaths Attributed to Breast Cancer
Among Eight PVC Fabricators by Company, 1964 - 1973
(White Females Only)

<u>Company</u>	<u>Number of Deaths</u>
01	14
02	1
03	1
06	16
07	4
08	3
10	4
12	1
Total	44

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Table 2
Observed and Expected Deaths Due to Selected Causes
Among Employees of 17* PVC Fabricators, 1964-1973

Cause of Death	Observed	Expected	PMR ^a
WHITE MALE			
ALL CANCERS	665	562.814	1.18
SELECTED TYPES OF CANCER			
Buccal Cavity and Pharynx	15	16.898	0.89
Digestive (including Liver)	210	162.373	1.29
Liver	8	4.192	1.43
Respiratory	205	176.899	1.16
Breast	..	..	..
Genitals	42	57.981	0.72
Urinary	36	33.178	1.09
Lymphatic (including Leukemia)	61	55.837	1.09
Leukemia	19	23.408	0.81
DIABETES	43	49.676	0.87
DISEASES OF CIRCULATORY SYSTEM	1,933	1,835.244	1.05
CIRRHOSIS OF LIVER	42	62.947	0.67
WHITE FEMALE			
ALL CANCERS	179	135.933	1.32
SELECTED TYPES OF CANCER			
Buccal Cavity and Pharynx	3	1.872	1.60
Digestive (including Liver)	53	34.929	1.52
Liver	..	0.827	..
Respiratory	12	11.715	1.02
Breast	44	31.907	1.38
Genitals	19	22.971	0.83
Urinary	11	4.487	2.45
Lymphatic (including Leukemia)	10	12.481	0.80
Leukemia	1	4.951	0.20
DIABETES	10	15.274	0.65
DISEASES OF CIRCULATORY SYSTEM	277	305.578	0.91
CIRRHOSIS OF LIVER	3	12.136	0.25

^aPMR = ratio of Observed to Expected where the expected number is calculated on the basis of the 1968 U.S. white male (or female) distribution of deaths specific for cause and age.

*Data submitted by one company were excluded because it was not possible to identify cause of death.

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Table 3
 Maltoni Experiment B1 15 (October 1976)
 Exposure for 52 Weeks, 4 Hours/Day, 5 Days/Week for 1 Year
 Results After 87 Weeks — Sprague-Dowley Rats

Concentration ppm	Number	Survivors	Zimbal Glan Carcinoma	Nephro- blastoma	Number of Animals with Tumors				
					Angiosarcoma		Mammary Tumors		Other
					Liver	Other	Carcinoma	Carcinosarcoma	
25	120	45	3	..	3	..	9	1	7
10	120	51	1	..	..	..	11	1	5
5	120	62	..	..	..	..	13	..	5
1	120	49	..	..	..	..	7	1	4
0	120	49	..	..	..	..	4	..	4
Total	600	256	4	..	3	..	44	3	25

Table 4
Distribution of 35 Cases and 134 Matched Controls
By Exposure Category

<u>Exposure Category</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Number</u>	<u>Percent</u>	<u>Number</u>	<u>Percent</u>
Definite exposure	2	5.7	6	4.5
No exposure	25	71.4	97	72.4
Improbable exposure	4	11.4	17	12.6
Possible exposure	..	..	4	3.0
Unknown exposure	4	11.4	10	7.5
Total	35	100.0	134	100.0

Table 5
Distribution by Company of 35 Cases and
134 Matched Controls Available for Analysis

<u>Company</u>	<u>Cases</u>	<u>Controls</u>
01	11	37
02	..	..
03	..	..
06	15	65
07	3	2
08	2	4
10	4	26
12	..	..
Total	35	134

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Table 6
Average Years Employed for Cases and Controls
With Known Length of Employment

Study Group	Number	Years Employed	
		Average	Standard Error
Cases	31	26.53	2.37
Controls	117	25.60	1.08

Table 7
Distribution of Cases and Controls
by Continuous or Intermittent Employment

Type of Employment	Cases		Controls	
	Number	Percent	Number	Percent
Continuous	13	37.1	31	23.1
Intermittent	9	25.7	32	23.9
Unknown	13	37.1	71	53.0
Total	35	100.0	134	100.0

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Table 8
Distribution of Cases and Controls by Marital Status

Marital Status	Cases		Controls	
	Number	Percent	Number	Percent
Ever married	25	71.4	110	82.1
Never married	10	28.6	24	17.9
Total	35	100.0	134	100.0

Table 9
Distribution of Cases and Controls by Childbearing History

Children	Cases		Controls	
	Number	Percent	Number	Percent
Yes	11	31.4	64	47.8
No	4	11.4	6	4.5
Unknown	20	57.1	64	47.8
Total	35	100.0	134	100.

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