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AMERICAN JOURNAL OF EPIDEMIOLOGY Vol. 114, No. 5

Printed in U.S.A

POWER CONSIDERATIONS IN EPIDEMIOLOGIC STUDIES OF VINYL CHLORIDE WORKERS

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Beaumont, J. J. (NIOSH, Cincinnati, OH 45226) and N. E. Breslow. Power considerations in epidemiologic studies of vinyl chloride workers. *Am J Epidemiol* 1981;114:725-34.

Nine retrospective mortality studies of workers exposed to vinyl chloride were reviewed to determine whether differences in their hypothesis testing results might be due to differences in statistical power. Where possible, the power of each study was calculated for cancer of the lung, brain and liver. When power was taken into consideration, the results for liver and brain canc r were found to be consistent with an etiologic role for vinyl chloride. For lung cancer, the data were not consistent with an etiologic role, in that two studies with very high power yielded negative results.

epidemiologic methods; respiratory tract neoplasms; brain neoplasms; liver neoplasms; vinyl chloride

The nine mortality studies of workers exposed to vinyl chloride that have been completed to date disagree in their hypothesis testing results for some causes of death, and for those causes it is difficult to draw conclusions about excess risk (1–12). The studies that are negative for a cause of death are especially difficult to interpret, since they may or may not have had the statistical power to detect an excess risk if, in fact, one existed. To aid in the interpretation of the studies, their statistical power with respect to three sites of cancer—liver, brain and lung—was calculated, and their hypothesis testing results, positive or negative, were considered in the context of power.

METHODS

Power calculations

Statistical power is the probability of not overlooking an excess risk, i.e., of not making a Type II statistical error. To aid in the interpretation of this frequently confusing subject, a brief review of Type I and Type II errors follows.

Investigators are most familiar with Type I errors. If the true state of nature is the null hypothesis (no increase in risk), then a Type I error is wrongly rejecting the null hypothesis and declaring that there is an increase in risk. The probability of a Type I error is known as alpha, or more commonly, the "level of significance." For example, when an investigator finds an excess and declares it "significant at the 0.05 level," in a sense what he or she is saying is that there is less than a 5 per cent chance of having made a Type I error.

Type II errors are less familiar but,

Received for publication November 14, 1980, and in final form April 13, 1981.

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The authors thank Jay Lubin, Richard Waxweiler, Thomas Fischbach, Noel Weiss and William Halperin for their valuable advice. Their special thanks go to Philip Landrigan for encouraging this approach.

This paper was presented at the Conference to Re-evaluate the Toxicity of Vinyl Chloride, Polyvinyl Chloride and Structural Analogues, Rockville, MD, March 20–21, 1980.

nevertheless, very important (13). Underlying this concept is the fact that when the true state of nature is the alternative hypothesis (increased risk), the research goal is to detect it (i.e., reject the null hypothesis). Suppose one has specified an alpha level (0.05, for example) for testing a null hypothesis of no increased risk for a particular exposure. If an exposure is harmful with a relative risk of R, then not rejecting the null hypothesis (i.e., wrongly accepting the exposure as harmless) is called a Type II error. The probability of a Type II error is usually denoted beta (β). Conversely, the probability of correctly rejecting the null hypothesis and therefore of detecting the excess risk is called the power and is equal to $1 - \beta$. Thus, power quantifies the ability of a particular study to detect an excess risk that truly exists. It is intuitively clear that with a fixed amount of data there is a greater likelihood of detecting a large excess risk. Similarly, an increase in the amount of data increases the chance of observing a given risk, i.e., increases the power.

The approximate power $1 - \beta$ of the vinyl chloride studies to detect a relative risk R at the alpha level of significance was calculated from the following formula, which uses the fact that the square root transformation stabilizes the variance of the Poisson distribution (see the statistical appendix):

$$Z_{1-\beta} = Z_\alpha - 2(\sqrt{R} - 1)(\sqrt{E})$$

Here Z_α denotes the upper 100_α percentile of the standard normal distribution and E the expected number of cancer deaths based on general population rates. This approximation agrees well with exact power calculations based on Poisson probabilities made by Cutler et al. (14, 15). When the discreteness of the exact test based upon Poisson probabilities is accounted for, the approximate and exact power curves are virtually identical.

A family of power curves based upon the approximation is shown in figure 1, where each curve is for a different relative risk. It can be seen that as the assumed relative risk increases for a given number of expected deaths, the power also increases. Similarly, as the expected number of deaths increases for a given relative risk, the power also increases.

Application to vinyl chloride literature

The assumed relative risks for the power calculations were the median (approximate) standardized mortality ratios reported for each cancer site in the vinyl chloride literature. Power calculations are usually performed with a somewhat arbitrarily chosen relative risk, but since relative risk information was available from the vinyl chloride studies, it was thought best to make use of these data. Separate assumptions were made for analyses considering all person-years at risk and for analyses considering only person-years after a minimum latency (time since first exposure), because in the former case the risk was diluted by the 10 to 20 years that are often required for cancer to develop after exposure to a carcinogen. The median reported mortality ratio was not used in one instance: for overall lung cancer, where the median was 1.03, essentially no excess risk. Since some risk needs to be assumed to calculate power, the arithmetic mean (approximately 1.5) was used.

The statistical powers of mortality studies of workers exposed to vinyl chloride were calculated with respect to three sites of cancer: liver, brain and lung. These three sites were chosen because they have been the subject of most of the discussion of causality in the vinyl chloride literature. The powers of the studies were subsequently plotted on power curves for two purposes: to show the variability in powers, and to relate positive and negative findings to power. For the purposes of this review, a positive finding was defined as an excess risk for a

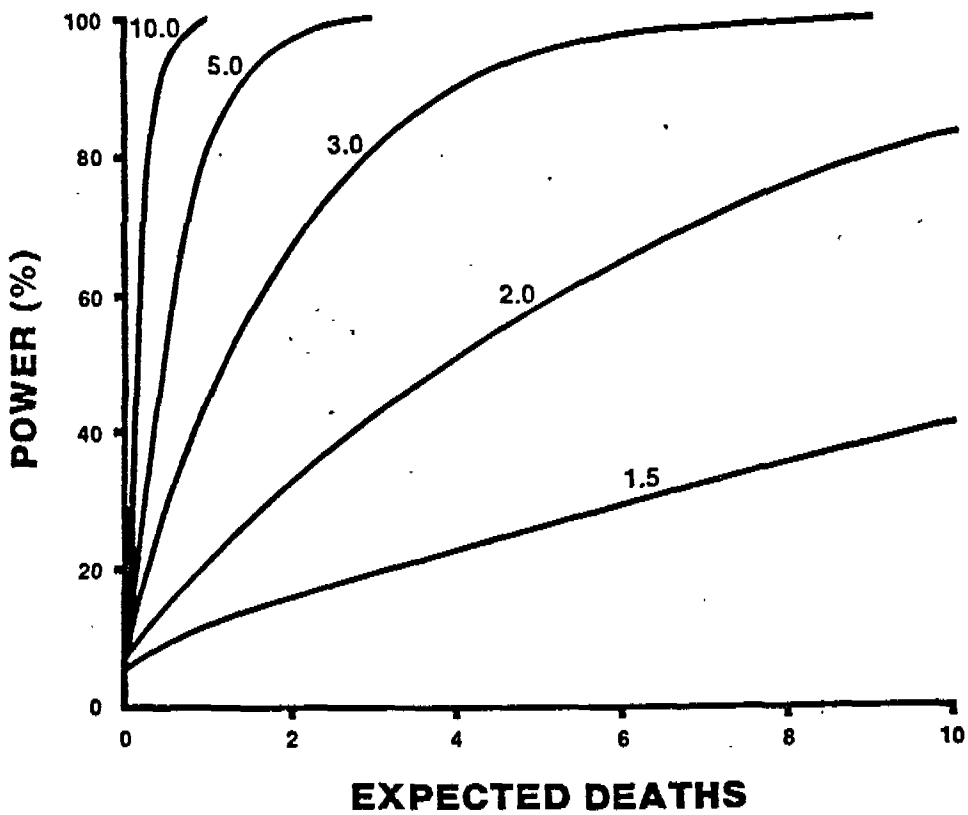

FIGURE. 1. Approximate power curves for various assumed relative risks in standardized mortality ratio studies (for one-sided comparisons with alpha = 0.05).

particular cancer with statistical significance at the 0.05 level, using a one-sided Poisson test.

It was expected that if vinyl chloride was carcinogenic for an organ site, there should be a pattern: the studies with high power should, in general, be positive, and the studies with low power should, in general, be negative. This assumed that exposure would result in a constant value of R across the various populations. The assumption was somewhat tenuous because, as discussed below, the populations differed in a number of respects.

RESULTS

The historical prospective studies of vinyl chloride exposed workers are listed in table 1. The sizes of the study populations varied considerably, from 255 in the study by Nicholson et al. (3) to 9677 in the Equitable Environmental Health study (6, 7). The reports were not entirely independent; for example, many of the workers in the study by Ott et al. (10) were included in the Equitable Environmental Health study, and there was an overlap of about 800 workers in the studies by Waxweiler et al. (4) and Waxweiler (5).

It should be noted that the studies were dissimilar in many other ways. As can be seen in table 1, a minimum exposure of 1–5 years was required in some studies, while others required only one day. Some studies reported findings based upon all person-years at risk, some included person-years at risk only after a minimum time since first exposure, and some reported both types of analysis. The control (standard) populations used were different: four of the five American studies

TABLE 1

Historical prospective (standardized mortality ratio) studies of vinyl chloride exposed workers

Study	Year	Cohort size	Exposure minimum (years)	Person-years considered		Cancer ratios reported		
				All	Minimum latency	Lung	Brain	Liver
Fox and Collier (1, 2)	1976, 1977	7717	>0	X	X	X	X	X
Nicholson et al. (3)	1975	255	5		X			
Waxweiler et al. (4)	1976	1294	5		X	X	X	X
Waxweiler (5)*	1978	4806	>0	X	X	X	X	X†
Equitable Environmental Health (6, 7)	1974, 1978	9677	1	X	X	X	X	
Reinl et al. (8)	1978	7021	>0	X		X	X	X
Buffler et al. (9)	1979	464	>0	X	X	X		
Ott et al. (10)	1975	522	>0	X		X		
Byren et al. (11)	1976	750	>0	X	X	X	X	X
Duck et al. (12)	1975	2120	>0	X		X		

* One of four plants in 1976 study.

† Liver cancer not reported (Waxweiler, personal communication, 1980).

used United States rates, the fifth used Texas rates; and the British, Swedish and German studies used their respective national rates. There were also minor differences in the International Classification of Diseases codes included for the specific cancers. Finally, there were probably differences in age composition which could be important if an effect were dependent upon age. While it was felt that none of these dissimilarities was important enough to prevent comparison of statistical powers, it should be noted that factors other than power could have had a bearing on the ability of the studies to detect excess risk.

Liver cancer was reported in the four studies listed in table 2 and graphically presented in figure 2. When the results were tested for statistical significance with a one-sided Poisson test, it was found that three of the four studies showed significant excesses (4, 5, 8, 11). The powers were all very high, despite the fact that the expected numbers of deaths were in all instances small. The small expected numbers would normally have led to low statistical powers, but the high estimated relative risks had a large effect on the calculations. The powers of the studies are shown in two columns in table 2 and on two lines in figure 2 because the calculations assumed different relative risks for analyses considering all person-years at risk and for analyses considering only person-years after a minimum latency (relative risks of 5 and 10, respectively, were assumed for liver cancer).

The results for brain cancer (table 3) were more variable, in that three of five studies had statistically significant findings (5–7, 11), and that the powers ranged from 12 per cent to a maximum of approximately 80 per cent. In figure 3, the range of powers is presented graphically. It can be seen that, in general, the studies with high power had positive findings and those with low power had negative findings.

Of the eight studies of lung cancer, only

TABLE 2

Liver cancer: results and powers of epidemiologic studies of vinyl chloride

Author	Observed deaths	Expected deaths	Mortality ratio	Excess $p < 0.05$?	Power (%) If $RR = 5.0$	Power (%) If $RR = 10.0$
Fox and Collier (1, 2)	4	1.6	2.44	–	93	
Waxweiler (5)	10	2.3	4.27	+	98	
(10+ latency)	8	0.5	15.09	+		92
Waxweiler et al. (4) (15+ latency, 5+ exposure)	7	0.4	16.08	+		86
Byren et al. (11)	4	1.0	4.13	+	80	
(10+ latency)	4	0.7	5.89	+		98
Reinl et al. (8)	12	0.9	15.23	+	76	

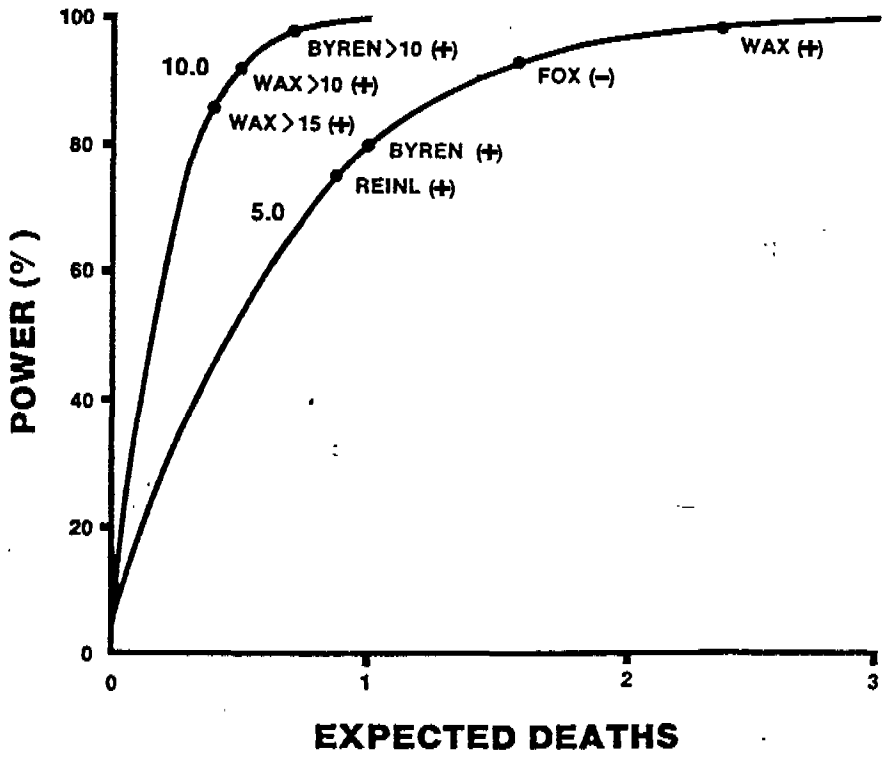

FIGURE 2. Approximate powers of vinyl chloride studies reporting results for liver cancer: 10.0 = assumed relative risk after a minimum latency, 5.0 = assumed relative risk overall. REINL = Reinl et al. (8); BYREN = Byren et al. (11); FOX = Fox and Collier (1, 2); WAX = Waxweiler et al. (4) and Waxweiler (5).

two yielded statistically significant results (4, 5, 9) (table 4 and figure 4). Again, there was a wide range of powers, from 14 per cent to almost 100 per cent, but here the studies with very high power were

gative, an unlikely occurrence if vinyl chloride is indeed a human lung carcinogen.

DISCUSSION

The data regarding liver cancer in vinyl chloride exposed workers suggested

TABLE 3

Brain cancer: results and powers of epidemiologic studies of vinyl chloride

Author	Observed deaths	Expected deaths	Mortality ratio	Excess $p < 0.05$?	Power (%)	
					If RR = 2.0	If RR = 3.0
Fox and Collier (1, 2)	2	3.7	0.55	–	48	
Waxweiler (5)	9	4.3	2.09	+	53	
(10+ latency)	8	3.1	2.56	+		82
Waxweiler et al. (4)						
(15+ latency, 5+ exposure)	3	0.9	3.29	–		40
Equitable Environmental Health (6, 7) (1+ exposure)	12	5.9	2.03	+	64	
Byren et al. (11)	2	0.3	6.12	+	12	
Reinl et al. (8)	2	1.3	1.62	–	24	

strongly that the chemical is carcinogenic for the liver. Three of the four studies reported statistically significant excess risks (4, 5, 8, 11), and the nonsignificant study (1, 2) reported a small excess (4 observed, 1.6 expected). The statistical powers of the studies were high (all above 75 per cent) due to the high observed relative risk. Even without knowledge of the animal studies, and without knowledge that angiosarcoma of the liver is extremely rare, one might conclude from these data that vinyl chloride is carcinogenic for the liver.

The powers of the studies that reported brain cancer ranged from 12 per cent to 80 per cent. The expected trend for a causative association was seen, in that the studies with high power were statistically significant and the studies with low power were, with one exception, nonsignificant. The most reasonable interpretation, therefore, is that the data are consistent with an etiologic hypothesis for vinyl chloride and cancer of the brain.

Only two of eight studies reporting lung cancer results showed significant excesses (4, 5, 9). While some of the negative results could be explained by low statistical power, two studies that were negative had very high power (1, 2, 6, 7). The lack of trend is evidence that vinyl chloride may not be a lung carcinogen, or that the actual relative risks were much lower than the assumed values of 1.5 and 2.0, in which case the powers were also much lower. It should be noted that one of the two negative studies with high power (by Fox and Collier (1, 2)) was also negative for liver cancer. Since it is generally accepted that vinyl chloride is a liver carcinogen, it may be that the exposures in that study were minimal. The other negative study with high power (Equitable) did not report liver cancer results, but did find a significant excess of brain cancer, which may constitute evidence of substantive exposure.

Examination of "positive" and "nega-

FIGURE 3.
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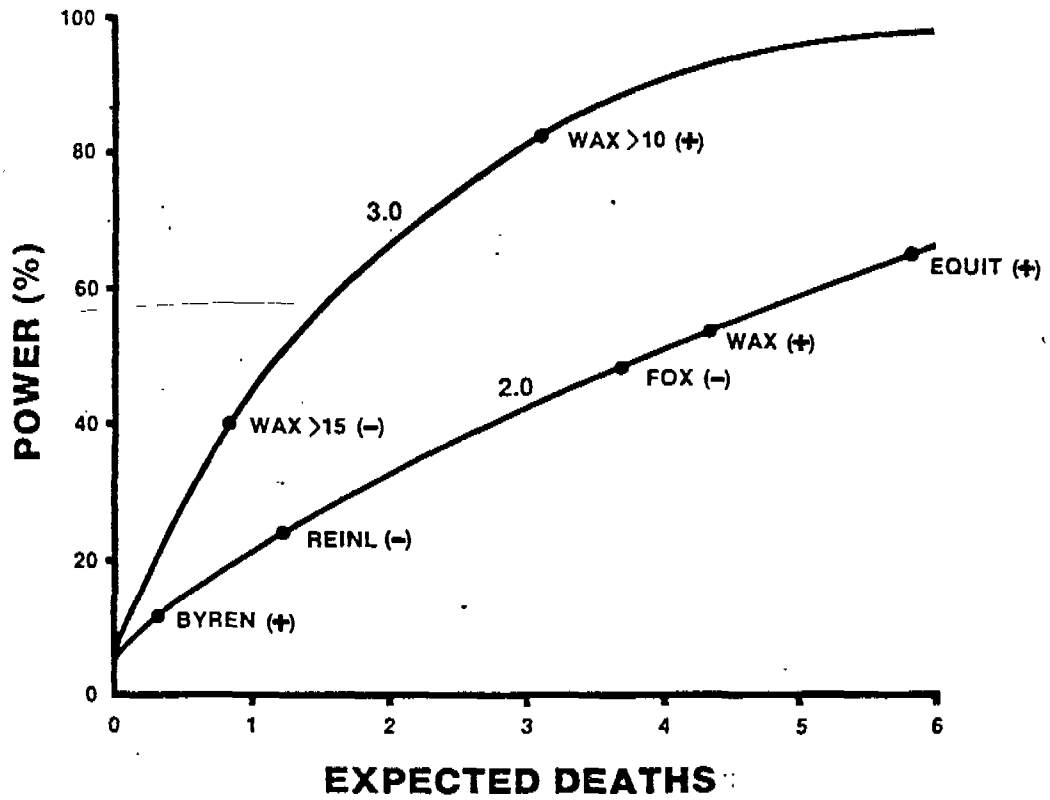

FIGURE 3. Approximate powers of vinyl chloride studies reporting results for brain cancer: 3.0 = assumed relative risk after a minimum latency, 2.0 = assumed relative risk overall. BYREN = Byren et al. (11); REINL = Reinl et al. (8); FOX = Fox and Collier (1, 2); WAX = Waxweiler et al. (4) and Waxweiler (5); EQUIT = Equitable Environmental Health (6, 7).

tive" hypothesis testing results in the light of statistical power is only one of several approaches to reviewing the evidence of carcinogenicity for a substance. For example, one can compute a combined relative risk for each cancer site (by combining the observed and expected numbers from the studies), and then, with the help of homogeneity testing, determine which studies are compatible with the combined risk estimate (see the Appendix for the homogeneity test). Liver cancer in the present review has a combined overall relative risk of 5.17 ($p < 0.00001$), and also a significant ($p = 0.002$) result in homogeneity testing, largely due to the Reinl (8) relative risk of 15.23. The combined relative risk for overall brain cancer is 1.74 ($p < 0.01$); here the results are more homogeneous ($p = 0.10$), although Byren (11) is somewhat of an outlier with a relative risk of 6.12. Finally, the combined relative risk for overall lung cancer is 1.06 (nonsignificant), with some evidence (homogeneity $p = 0.06$) that the results from Waxweiler (4, 5) and Buffler (9) are out of step with the others (relative risks of 1.49 and 2.89, respectively).

Close examination of the individual studies can also be helpful in searching for reasons for differing results. For example, the expected number of deaths from liver cancer in the Byren study (11) is unusually large relative to the expected numbers for brain and lung. Detailed examination of this anomaly might be informative. There are other consid-

TABLE 4

Lung cancer: results and powers of epidemiologic studies of vinyl chloride

Study	Observed deaths	Expected deaths	Mortality ratio	Excess $p < 0.05$?	Power (%)	
					If RR = 1.5	If RR = 2.0
Fox and Collier (1, 2)	46	51.2	0.90	–	94	
(15+ latency)	28	26.0	1.08	–		100
Waxweiler (5)	42	28.2	1.49	+	77	
(10+ latency)	39	24.9	1.56	+		99
Waxweiler et al. (4)						
(15+ latency, 5+ exposure)	11	5.7	1.94	+		63
Equitable Environmental Health						
(6, 7) (1+ exposure)	45	44.3	1.02	–	91	
(15+ latency, 1+ exposure)	41	39.2	1.05	–		100
Buffler et al. (9)	5	1.7	2.89	+	14	
(5+ latency, 2.29+ exposure)	4	1.0	3.81	+		21
Byren et al. (11)	3	1.8	1.68	–	15	
Duck et al. (12)	16	15.5	1.03	–	55	
Reinl et al. (8)	22	24.6	0.95	–	75	
Ott et al. (10)	4	5.2	0.77	–	27	

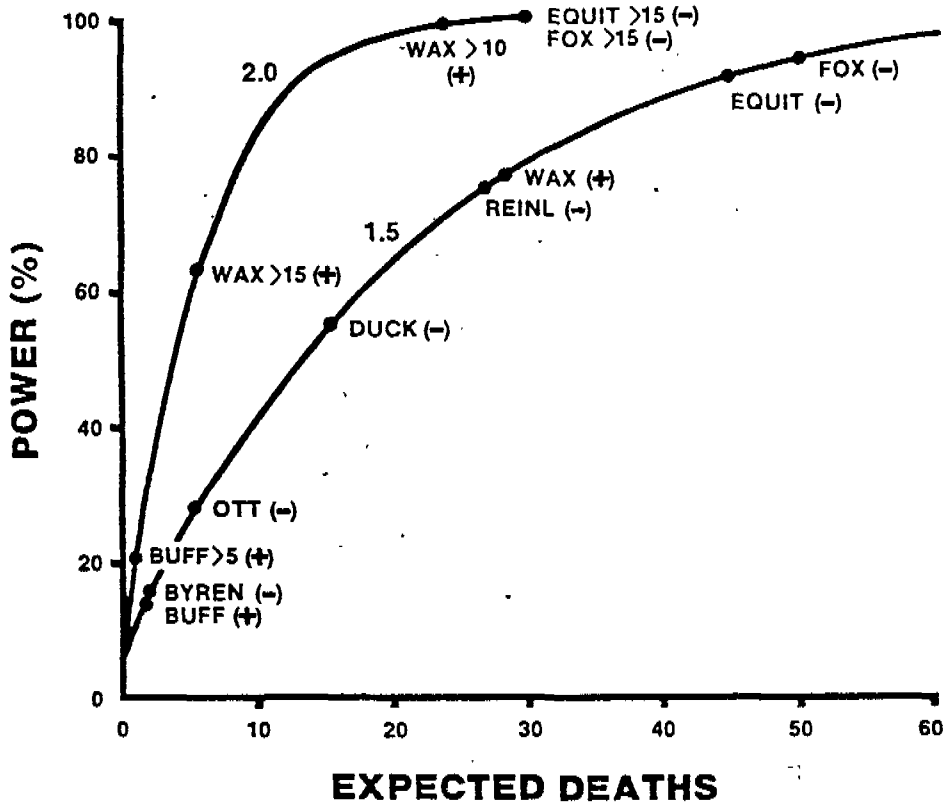

FIGURE 4. Approximate powers of vinyl chloride studies reporting results for lung cancer: 2.0 = assumed relative risk after a minimum latency, 1.5 = assumed relative risk overall. BUFF = Buffler et al. (9); BYREN = Byren et al. (11); OTT = Ott et al. (10); DUCK = Duck et al. (12); REINL = Reinl et al. (8); WAX = Waxweiler et al. (4, 5); EQUIT = Equitable Environmental Health (6, 7); FOX = Fox and Collier (1, 2).

erations, such as dose-response, degree of exposure, concomitant exposures, and confidence limits for risk ratios, that also need to be kept in mind. While consideration of statistical power cannot provide a complete answer, it is one more useful way of looking at epidemiologic evidence.

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Appendix

The approximate power formula assumes that the observed number of deaths from the cause of interest follows a Poisson distribution with mean RE, where E is the expected number based on standard population rates and R is the ratio of rates (relative risk) for the study as opposed to the standard population. It follows that for large values of RE, the square root of the observed deaths is approximately normally distributed with mean $\sqrt{RE}$ and variance ¼ (16). Now, if a random quantity has a normal distribution with mean μ and variance σ^2, its power $1 - \beta$ to reject the null hypothesis $\mu = \mu_0$ at the α level of significance is given by

$$Z_{1-\beta} = Z_\alpha - \frac{\mu - \mu_0}{\sigma}$$

Substitution of $\mu = \sqrt{RE}$, $\mu_0 = \sqrt{E}$, and $\sigma = ½$ into this expression yields the required result.

The homogeneity test for the combined relative risk uses the chi-square distribution with $n - 1$ degrees of freedom. The equation is

$$\chi^2_{(n-1)} = \sum_{i=1}^{n} \frac{(O_i - \hat{\theta}E_i)^2}{\hat{\theta}E_i}$$

where n = the number of studies,
O_i = the observed deaths from the ith study,
E_i = the expected deaths from the ith study,
and $\hat{\theta}$ = $\sum O_i / \sum E_i$, the combined relative risk estimate.

The Role of Human Genetic Monitoring in the Workplace

Betty J. Dabney, Ph.D.

The history and current state of some newer short-term tests for occupational genetic monitoring are reviewed. These are: cytogenetics, sister chromatid exchange, body fluid analysis, tests utilizing sperm, and detection of somatic cell variants. Occupational studies on benzene, vinyl chloride monomer, and epichlorohydrin are critically discussed from the standpoints of design and interpretation. It is concluded that these tests are not appropriate for risk assessment at the present time. Their clinical relevance, if any, is unknown. Proper validation and standardization have not been done, and design problems have often clouded the results of previous studies. There is a critical need for further research in the area of occupational genetic monitoring. Future applications should include integration with prospective morbidity and mortality studies, standardization of design and statistical methods, and development of new tests with genetically relevant endpoints.

The question of whether or not occupational exposure to mutagens may pose a genetic risk to future generations is one of both public and scientific concern. Reliable short-term tests are desirable to define potential genetic problems and to assist in preventing their occurrence in the work force. Several recent publications have reviewed the subject of estimating induced genetic effects in man.[1-5] All of these reviews convey the same message: that no chemical or physical agents are known to cause mutations in man. Even the extensive genetic studies on survivors of the atomic bomb attacks in Japan and their offspring have failed to demonstrate any induced mutations in that population.[6] However, one cannot assume that exposure to mutagens in the workplace would have a similar lack of effects.

In the light of growing interest in occupational genetic monitoring, it is timely to review the history and current state of this field. These comments are based only upon evaluation of the scientific merit of the proposed tests, and do not attempt to resolve ethical, moral, or legal questions arising from human genetic monitoring.

For the purpose of this discussion, several terms need be defined. Genetic "screening" refers to a one-time test for known heritable diseases, such as sickle cell anemia. Genetic "monitoring" will describe a program of repeated short-term tests on an individual or group to determine possible genetic damage in somatic or germ cells, damage which is not necessarily heritable. A "mutation" is defined as a heritable change in a cell or individual, in distinction to "genetic damage," which shall refer to any structural or functional disruption of the genetic apparatus. Genetic damage is not necessarily equivalent to a mutation, since it may either be correctly repaired, or be lethal to a cell, instead of giving rise to a heritable change.

This discussion is concerned with genetic monitoring. In this context, genetic monitoring is designed to detect effects brought on by occupational exposures. It has been proposed that genetic monitoring techniques should be used as a biological dosimeter for employees working with, or exposed to, suspected mutagens. The proposals also suggest that monitoring techniques could be used to identify individuals in that group who may be unusually susceptible to those agents. As an "early warning system," genetic monitoring would be used to identify groups or individuals at risk for possible clinical effects before other clinical signs are apparent.

It is extremely important to understand that all of the genetic monitoring tests to be discussed here are still in the developmental stage and are not yet useful as predictive tools. Consequently, the tests should not be considered part of a routine industrial medical surveillance program, nor should they be used for risk assessment at this time. These concerns are substantiated for the following reasons: (1) the clinical implications, if any, of abnormal results in these tests are not yet clear; and (2) the intrinsic variability of the tests and the multiplicity of external factors affecting their results, and most importantly, previous experiences from occupational studies utilizing cytogenetic monitoring bear out these conclusions. These points will be expanded later in this paper.

Description of Tests

Cytogenetics, the study of numerical and structural chromosome aberrations, is distinguished here from classical clinical cytogenetics, which detects heritable chromosome abnormalities present in every somatic cell of an individual. In occupational cytogenetics, a positive test refers to detection of a significant increase in the frequen-

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cy of damaged chromosomes in samples from a group of individuals over a detectable frequency in a properly selected control group. Generally, cultured lymphocytes are used. From five- to tenfold variations in the normal or control group lymphocyte chromosome breakage frequencies, with unexplained seasonal peaks, have been reported in different studies.[7,8,9] In most of the occupational studies, less than a twofold elevation in chromosome breakage frequencies usually is found. One of the great difficulties in interpreting results of cytogenetics studies arises from the wide variation in chromosome aberration frequencies found within replicate studies of an individual and among individuals within a study group.

Some of this variation can be attributed to the use of different culture media,[10,11] to recent viral infection in the subjects,[12] to the staining procedure used to visualize the chromosomes,[13] to the use of whole blood vs. washed lymphocytes,[14] or to smoking or recent alcohol consumption.[15] Intra- and inter-scorer and inter-laboratory variations in scoring criteria may also come into play, particularly when dealing with the problem of whether or not to count achromatic lesions (gaps). The scoring criteria recommended by the World Health Organization,[16] which do not include gaps, are used by many laboratories, but there is an ongoing dialogue among scientists concerning the most relevant criteria for scoring chromosome aberrations.

The major strength of cytogenetics for occupational studies is that there is a far larger data base for this test than for any of the others discussed here. In addition to the occupational studies, there is considerable literature on in vitro and on animal studies. Major limitations for cytogenetics are the high degree of skill required on the part of the scorer and the limited capacity for handling additional cases in existing laboratories, such that any industry-wide general monitoring program would be impossible at the present time.

Sister chromatid exchange (SCE) is a related test in which dividing cells incorporate 5-bromodeoxyuridine into DNA during two consecutive rounds of replication, causing the two chromatids in each chromosome to take up stain differentially. This procedure allows easy visual detection of crossover events and exchanges between the sister chromatids. The number of these SCEs per cell increases in whole animal and in vitro cell culture studies after sufficient exposure to mutagens. Details of this procedure as it relates to testing chemicals for mutagenic potential have recently been the subject of a number of review articles, such as the one by Latt.[17]

The SCE techniques have also had limited use in genetic monitoring programs. Usually lymphocyte cultures obtained from the study groups are processed to reveal chromatid exchanges in the same manner used for the experimental cell culture systems. An excellent example of using the technique is a study conducted to evaluate chronic effects in patients treated with arsenic.[18] Elevated frequencies of SCEs were reported to persist for many years in the arsenic-treated patients, but it is not known if this is generally true. At the present time the use of SCE for occupational monitoring should be regarded as highly exp rimental. Some occupational studies describing the use of SCE will be discussed further in this paper.

Body fluid analysis is a microbial cell mutagenicity assay used to detect mutagenic activity in urine, blood or feces of exposed individuals. This test has been used on individuals involved in acute exposures, with somewhat varying results.[19] Samples from normal unexposed individuals are sometimes positive, because of cigarette smoke metabolites[20] or possibly of metabolites of certain foods.[21] Other tests utilizing genetic endpoints in the host's cells may be easier to interpret from the standpoint of risk assessment. However, thoroughly validated body fluid analysis techniques might some day prove to be useful for determining whether individuals are at risk from occupational exposures to certain types of chemicals. Further research and comparison with other tests need to be completed before any judgment can be made on the general utility of body fluid analysis.

Other tests are being developed which may ultimately be useful for occupational studies. Several of these newer systems utilize sperm, thus providing an advantage over the tests using somatic cells when searching for potentially heritable effects. Animal models suggest that mutagen-induced heritable changes in sperm shape may prove useful in the future.[22,23] The animal tests include studies on the loss of sperm enzymes as detected by cytological staining procedures.[24,25]

The human YFF sperm cell test has been used by Kapp et al[26] in an occupational study. In this test a positive effect is indicated by a significant elevation in the frequency of sperm containing two or more fluorescent bodies. These bodies are presumed to be revealing the presence of multiple Y-chromosomes produced by nondisjunctions occurring during meiosis. The YFF test needs further development, particularly to minimize false positives due to fluorescence of non-Y chromosomes.

None of these tests on sperm have endpoints proven to be of genetic significance (i.e., associated with heritable disease states). Until validation is accomplished, these tests should be regarded purely as experimental systems.

Other tests under development examine the frequency of somatic cells lacking certain enzymes, the best of these taking advantage of the fact that cultured lymphocytes deficient in the enzyme hypoxanthine guanine phosphoribosyl transferase are not killed by 6-thioguanine.[27] This test is particularly promising because it studies a recognized genetic endpoint in the individual's cells, and is relatively simple and rapid to perform. Its use, though still quite limited, has been compared to both chromosome aberrations and SCE. In untreated psoriasis patients, there was a significant elevation in the frequency of 6-thioguanine-resistant lymphocytes, while SCE and chromosome aberration frequencies were normal.[28,29,30] Other potentially promising single-cell variant assays are also being intensely studied.[24] Further developments in genetic monitoring may include automation and flow cytometry techniques to facilitate chromosome and mutant cell analyses, but at the present time these methods are not practical for general use.[31]

History of Genetic Monitoring in the Workplace

The use of short-term tests for genetic damage in occupational studies is a fairly recent practice, with the majority of studies having been published by European laboratories over the past 15 years. Most of the occupational

studies have looked for structural chromosome damage (e.g., breaks, dicentrics, exchanges) or for aneuploidy (abnormal number of chromosomes). A description of an industrial monitoring program is given by Kilian and Picciano.[32] The subject of chromosome studies on industrial populations has been reviewed recently by Purchase.[33]

A relationship between relatively high occupational exposures and increased frequencies of chromosome aberrations has been implicated for several chemicals in previously published studies. Those which are most representative have been chosen for further elaboration in this paper.

Benzene has the largest literature of occupational exposure associated with chromosome aberrations. In their early studies Forni et al selected subjects with histories of high occupational exposures and clinical hemopathies. A representative study by Forni et al[34] included subjects with a variety of work and clinical histories. Approximately 100 cells from each culture were scored according to the "Cu-Cs" system of Buckton et al.[35] "Cu cells" consist of cells with chromosome breaks, dicentrics, and rings, and "Cs cells" are those containing chromosome exchanges and inversions. The 25 patients with past benzene hemopathy and with 1 to 18 years since occupational exposure to benzene averaged 1.89% Cu cells and 1.22% Cs cells. The matched controls averaged 0.49% and 0.04%, respectively. Statistical analysis (χ^2) revealed a significant difference between workers and controls, but no trends were seen with respect to severity of hemopathy or to age. (However, other studies, such as those of Tough et al,[36] have identified an age-related trend among exposed benzene workers.) Two of three subjects with documented acute exposures to high concentrations of benzene exhibited elevated frequencies of chromosome aberrations three to four years after exposure, while a third subject was within the control range.

This study has several merits, including the practice of repeated samplings. It also attempts to document exposures to benzene and other chemicals, and uses age- and sex-matched controls. While the studies of Forni et al are commendable in the sense that they followed the precepts of epidemiology in their design and established the association between chromosome aberrations and benzene-induced hemopathies, they cannot be used to address the question of the utility of genetic monitoring as a dosimeter or as a predictor of clinical risk. The use of subjects only with previously established clinical findings precluded the possibility of establishing any temporal or causal relationship between chromosome aberrations and disease. Unfortunately, in the case of benzene the persistence of and increase of chromosome aberrations correlated with time after of exposure make it impossible to establish a relationship between the duration of exposure and induction of chromosome aberrations.

The most recent occupational cytogenetics study on benzene is that of Picciano.[37] This study included two groups of workers totaling 52 individuals and 44 controls selected during preemployment examinations and matched as closely as possible for age, sex, and date of testing. Exposures to benzene for the worker groups averaged about 2 ppm (time-weighted average) over the preceding four-year period. No information on possible peak exposures was given. From an evaluation of 200 cells per person, no significant difference was found between worker and control groups with respect to abnormal cells (1.6% vs. 1.4%) or to chromatid breaks (1.0% vs. 1.1%), but frequencies of chromosome breaks (0.67% vs. 0.35%) and of "marker" chromosomes comprised of rings, dicentrics, and exchanges (0.19% vs. 0.06%) were shown by χ^2 analysis to be significantly elevated in the worker groups. In contrast to the findings of other studies,[36] no trend was seen with age, but there was an unavoidably large age difference between the worker and the control groups (39 vs. 27 years average).

The Picciano study illustrates several recurrent problems in structuring and interpreting occupational cytogenetic studies. Firstly, it is not clear if external variables which might have influenced the results (smoking, recent viral infection or drug use, nonoccupational exposure to chemicals and radiation, occupational exposure to chemicals other than benzene, presence of interfering disease states) were adequately controlled in structuring both the worker and the control groups. Secondly, while the difference in chromosome aberration frequencies for some categories was statistically significant, the overall frequencies were quite low and would be considered in the normal range in most laboratories. Thus, the biological or clinical significance of the elevated frequencies is debatable. Repeat studies were not reported, making it unclear if the small differences between groups were sustained with time. Thirdly, the failure to include information on peak exposures makes it impossible to determine if the small elevations could be explained by chronic exposures to low concentrations, or by high acute exposures. Finally, there is still some question of the most meaningful parameter for expressing the chromosome aberration frequencies found in the study. The current trend seems to be toward using the percentage of abnormal cells, rather than isolating individual categories of aberrations for analysis, but this issue is far from being resolved.

Elevated frequencies of chromosome aberrations have also been reported to be associated with occupational exposure to vinyl chloride monomer (VCM). Since the original study by Ducatman et al[38] in 1975, several laboratories have followed chromosomal changes in occupational groups exposed to VCM. Illustrative of this are two ongoing studies of recent reports.

In the first of these studies, one by Kucerova et al,[39] nine workers exposed to relatively high concentrations of VCM (20 to 150 ppm) were evaluated over a two-year period for chromosome aberrations and also for SCE at the time of the final sampling. A control group of eight age- and sex-matched individuals was sampled concurrently with the final worker study. Smoking, drinking, diagnostic radiation, and drug usage patterns were documented for both the controls and the third sampling of the workers. Statistical analysis (t-test) was done only on the third sampling, where control values were available. The results showed significant elevations in the percent of cells containing chromosome aberrations in the worker group compared with the controls (5.2% vs. 1.8%) and also for SCEs (13.8/cell vs. 9.4/cell). There was no apparent effect of smoking or of lifestyle.

Evident in the study by Kucerova et al are several prob-

lems in interpretation. Firstly, there was a wider range in values within individuals sampled at different times (11% maximum) than there was between controls sampled at the same time (3%). It is unclear if this temporal variation was due to laboratory artifacts or to true biological differences. Thus it is difficult to determine the significance of the findings in the first two worker samplings, where no concurrent controls were used. This illustrates that such group studies are best done as cross-sectional studies, utilizing concurrent matched controls, rather than longitudinal ones, utilizing previous values from an individual as his own control. Another problem with this study is the small group size of only nine persons. It is important to consult with a statistician at the design stage in order to ascertain if the group and sample sizes are sufficiently large to permit desired limits of sensitivity to be detected.

The second ongoing occupational study on VCM is that of Hansteen et al,[40] in which 39 VCM workers and 16 community controls were originally sampled in 1974. All but two of the workers and 32 matched controls were studied three years later. Initially chromosome breakage frequencies were elevated in the worker group compared with the controls (3.4% vs. 1.8%). The difference was significant by the Wilcoxon two-sample ranking test. Values from heavily exposed workers were slightly higher than those of the other workers (3.9% vs. 3.15%). Documented exposures to VCM were reduced considerably during the interval between the two samplings, with final exposures averaging 1 ppm. Samples from the follow-up study showed no significant difference between workers and controls for chromosome breakage frequencies (1.25% to 1.91% for workers vs. 2.33% for matched office worker controls). Frequencies of SCE for 16 of the workers and their matched controls at the time of the final sampling were similar, averaging 7.6 vs. 7.5 SCE/cell. Chromosome breakage frequencies were not significantly different between the two control groups composed of different individuals (1.79% in 1974 vs. 2.33% in 1977).

This study by Hansteen et al is valuable in that it illustrates the importance of continued exposure monitoring for the duration of any such study. It also suggests that chromosome aberrations associated with exposure to VCM may be less persistent than those found with benzene exposure.

A third chemical implicated in elevating chromosome breakage frequencies as a result of occupational exposure is epichlorohydrin (ECHH). Two relevant studies which follow are presented in detail in this paper. The first, an ongoing study by Sram et al,[41] follows 28 workers, 23 of whom were first reported in 1977. This study is of interest because it utilized two control groups, one age-, sex-, and lifestyle-matched from within the same or nearby factories, and the second from the general population. Over a period of four years the frequencies of abnormal cells among the worker group increased with duration of employment (1.37%, 1.91%, 2.69%, and 3.02% with 0, 1, 2, and 4 years of employment, respectively). Matched factory worker controls for the final sampling averaged 2.06% abnormal cells, compared with 1.33% from a general population sample also taken at the time of the final sampling. There were significant differences between the final worker samples and the matched controls, and between control groups as well.

In this study are presented several additional problems with occupational genetic monitoring. The first problem is in choosing a proper control group, there being a significant difference between control groups. Since the significance of findings in a worker group is dependent upon findings in an appropriate control group, the definition of an appropriate control group needs to be clear-cut before the study is undertaken. In view of the lack of concurrent controls for the first two samplings, and the temporal variability problem discussed previously, one cannot conclude with a high degree of certainty that the increasing frequencies of chromosome aberrations were due to occupational exposure to ECHH. Another problem illustrated in this study is the relatively small distinction between groups. This type of difficulty tends to cloud any biological relevance of the results.

A second occupational study where elevated frequencies of chromosome aberrations were attributed to occupational exposure to ECHH is that of Picciano.[42] In this study 93 epoxy resin workers were compared with 75 preemployment individuals. The durations and actual or relative exposures levels of the workers were not reported. Chromosome aberration frequencies were shown to be significantly greater in the worker group compared to the preemployment group by χ^2 analysis (4.25% vs. 2.38%).

This study has serious flaws which are not readily apparent. Considerations of epidemiology similar to those which were discussed in relation to the study by Picciano should apply to this study design. Secondly, and more importantly, unreported subsequent sampling of the abnormally high cases showed significant reductions in frequencies of chromosome aberrations.[43] Several types of culture media had been used over a period of months. Most of the high frequencies in the initial sampling could be attributed to one type of culture medium in both worker and control groups.[43] Failure to adequately control the many variables in this study rendered the results uninterpretable.

These studies on workers exposed to ECHH illustrate the importance of carefully controlling laboratory variables and applying the precepts of epidemiology in any such group study. As a result, the question of whether or not occupational exposure to ECHH can induce chromosome breaks is still unresolved.

Other studies of chromosome aberrations in lymphocytes have been reported for groups of workers exposed to pesticides, arsenic, styrene, mercury, lead, and cadmium. These studies generally suffer from defects in their experimental design and interpretation similar to those discussed earlier. In these cases the information available is too sparse to allow for any general conclusions on the validity of the current observations.

Only one occupational study, that by Kapp et al,[26] has been published, in which germ cell effects were examined in a monitoring system. In this study occupational exposure to 1,2-dibromo-3-chloropropane was associated with increased frequencies of nondisjunction in sperm, as determined by the YFF test. Eighteen persons comprised the worker group, and 15, the control group. However, no details were given concerning the latter group. Frequencies of sperm containing two fluorescent bodies were found to be 3.8% for the workers and 1.2% for the controls. These values were found to be significantly differ

by χ^2 analysis. This group of workers needs to be followed in a reproductive epidemiology study, and further studies need to be conducted with the YFF test, before it can be determined if abnormal results in th s test are associated with an increased risk for siring aneuploid offspring.

It is evident from these occupational studies that there exist many problems confounding the interpretation of their results. As has been discussed in this paper, different laboratories have used different statistical analyses. It is concluded, therefore, that appropriate and consistent statistical methods need to be developed for these types of studies. By necessity, many studies are conducted over a period of months or years. Given the great influence of laboratory variables on the results, and the impossibility of controlling them over the long run, one wonders if the small group differences reported in these studies were real. The problem of variability in chromosome aberration frequencies is so great that often two laboratories cannot agree on a definition of the normal range of values. Compounded with these problems is the unanswered question of whether or not the small differences seen, and even the endpoints themselves in chromosome aberrations or SCE, are genetically or clinically relevant.

Of the studies performed on clinically normal subjects, there has often been no apparent purpose in the studies other than for determination of the chromosome aberration or SCE frequencies. Unless these results are related to other clinical findings and the individual cases are followed in prospective epidemiology studies (morbidity, mortality, and reproductive effects), the clinical significance of the short-term tests may never be known.

Indeed, with the interpretive and technical problems of cytogenetics discussed here, one wonders how useful this test can ever be for risk assessment. Fifteen years of its development in occupational monitoring have so far not contributed much to understanding genetic risk in the workplace. Perhaps the researcher's time would be better spent developing other tests which are not subject to these problems.

Common Considerations

There are some important considerations which apply to all short-term tests for genetic monitoring. A major difficulty lies in the lack of experience in designing and performing the studies. A second concern is that the majority of the tests are using readily accessible somatic cells. It is often impractical or impossible to determine if comparable genetic damage or mutations occur in other body tissues, because testing of those tissues cannot be adequately performed with existing techniques. A third and practical concern is cost of testing and the limited capacity of existing laboratories. Therefore, tests should be performed on exposed occupational groups only where there are prior positive findings in some animal system such as those described by Brewen.[44] Finally, all of these tests are relatively new, indicating that not enough time has elapsed since their inception to allow for determination of what long-term effects, if any, are associated with positive findings. Thus, *all* of these short-term tests must be nsidered *research tools*. They are *not* established clini- l tests. When used in an occupational group study, they should be part of a well-structured research program, which includes ongoing epidemiological studies.

Guidelines for Genetic Monitoring

As research tools, these tests should be part of a well-designed protocol for occupational study. Assistance of epidemiologists and statisticians, as well as of laboratory scientists, industrial hygienists and physicians, should be enlisted at the design stage. To facilitate comparisons, different facilities conducting these studies should use a consistent experimental design. The core of this design should include a basic questionnaire for recording family and personal work, health, lifestyle and reproductive histories and for the updating of forms to follow up changes in health or work status as the study progresses. Population size should be sufficient to allow for detection of predetermined limits of sensitivity. Before any workers are sampled, a stable unexposed comparison group should be developed initially, with repeated samplings done to establish the expected range of normal values, and to directly examine possible confounding variables. Repeated samplings should be taken on the worker group at specified intervals, with comparison control group samplings performed at the same times. Workers and controls with known significant exposure to potential mutagens outside of the exposures expected to be encountered in the normal course of the study should be excluded. Reliable exposure estimates prior to and during the study are extremely important in establishing cause and effect. Longitudinal studies are not recommended until factors influencing the variability of these tests can be identified and controlled in the design of the study. As a rule, recognizable factors with unknown but potentially confounding influences should be controlled in the design of the study. Samples should be coded and scored blind to minimize scoring bias.

Clearly positive findings in an occupational group, confirmed by repeated samplings at more than one time, should be an indication for further clinical studies which might include formal reproductive epidemiology and prospective morbidity and mortality studies. Such populations should be carefully monitored for any clinical effects. Further actions on an individual basis should lie in determining more precisely any potentially mutagenic exposures either on or off the job, and to reduce such exposures where appropriate. Subsequent genetic monitoring should then be conducted. Individuals with persistently abnormal findings should be referred to a medical specialist in genetics for further evaluation.

Summary and Conclusions

There are still many unknown factors in human genetic monitoring. Because few adequate studies have been performed on workers in well-defined industrial settings, and because these have not always been performed in conjunction with other clinical studies, the predictive value of short-term genetic tests has not been established, and these tests should be regarded as research tools still in the development stage. More occupational group studies with follow-up clinical evaluations and proper epidemiological design need to be performed before the clinical value of these tests can be established. It is imperative, therefore, that future studies of this type be carefully planned to produce meaningful results. The greatest need is in developing and validating rapid tests with clearly genetic endpoints indicating unequivocal clinical rele-

vance. Until that goal is accomplished, genetic monitoring should not be used to set standards for safe exposures, or to establish conditions for the prevention of occupational disease.

The author acknowledges and appreciates the support of the American Industrial Health Council in the preparation of this paper.

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LEGISLATION

DENMARK

FOOD ADDITIVES

Promulgation order no.65 of 20 February 1981 contains general regulations concerning the use of additives in foods. It also contains new regulations on the labelling of food products with information on the additives used.

PESTICIDES

Promulgation order no.410 of 17 September 1980 lays down rules concerning the classification, packaging, labelling and registration of pesticides.

DANGEROUS SUBSTANCES*

Notice no.408 of 17 September 1980 from the Danish Ministry of the Environment lays down rules concerning the classification, packaging, labelling, sale and storage of dangerous substances and products. The alphabetical list of chemicals that have already been classified as dangerous substances which is referred to in Annex VI of the notice, has since been replaced by a new list (in Danish) published in Notice no.147 of 16 March 1981.

EUROPEAN ECONOMIC COMMUNITY

ANALYSIS OF VCM IN FOOD*

The official method of analysis for the control of vinyl chloride released by materials and articles into foodstuffs has now been published as Commission Directive 81/432/EEC of 29 April 1981 (Off. J. Europ. Commun. 1981, 24 (L167), 6). Member States are required to enforce this method of analysis by 1 October 1982.

*Further details of this document and of other items of legislation similarly marked may be obtained from the BIBRA Information Section.

Original Articles

JOM
October 1981 Vol. 23 No. 10

Cancer Mortality of a Group of Canadian Workers Exposed to Vinyl Chloride Monomer

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The present study was undertaken to find out whether there was an excess of cancer mortality from causes other than angiosarcoma of the liver among a group of workers heavily exposed to vinyl chloride monomer (VCM). The mortality of 451 workers exposed to VCM for more than five years was compared with that of 870 workers from the same company who had not been exposed to VCM. The relative risk for digestive cancer was significantly higher than 1 (6.25, confidence interval 2.69 to 14.52) in the exposed group. The standardized mortality ratio (SMR) for digestive cancer was also higher (SMR 259.26 $p < 0.01$) than that of the general population. No other cancer was in excess. Since the exposed workers are known to have had a cigarette smoking experience similar to that of those who were not exposed, it is concluded that the association between lung cancer and VCM exposure, if present, is indeed rather small.

Several studies have demonstrated that vinyl chloride monomer (VCM) produces angiosarcoma of the liver among people exposed at work.[1-7] There is, however, much controversy about the capability of VCM to generate other types of cancer in man. One author,[8] using a proportional mortality ratio technique, described excesses of lung cancer (observed, 13; expected, 7.9; obs/exp 1.6) and brain cancer (observed, 5; expected, 1.2; obs/exp 4.2) in a group of 161 workers from two vinyl chloride plants.[8] Another author,[9] who studied the mortality of a group of 1,294 American workers exposed to VCM, reported excesses of lung cancer (observed, 11 expected, 7.5; SMR 194, $p < 0.05$) and brain cancer (observed, 3; expected, 0.6; SMR 498, $p < 0.05$) among men who had had their first exposure more than 15 years before their death. While most authors have not been able to document a significant excess of any other cancer in their studies, they have noted that such an excess may exist.

In order to better document the cancer mortality associated with exposure to VCM, the present study of the workers of the Shawinigan vinyl chloride polymerization plant was undertaken.

The main objectives of the study were (1) to compare mortality among vinyl chloride workers with the mortality of workers from a nearby industrial complex; and (2) to compare the mortality of the VCM workers with that of the general population. The Shawinigan vinyl chloride plant opened in 1943 as an independent company which produced both VCM and PVC (polyvinyl chloride). In 1958, it was merged into an industrial complex (to be used as the comparison group) of which it became the Canadian Resins Division. In the late 1960s, the VCM production ceased and only the polymerization process continued operation. In 1972, this division was sold and again became an independent plant. Over the years, the VCM and PVC productions fluctuated. The average annual work force at the plant was 225 men. In 1965, VCM production was estimated at 90 million pounds and PVC at 60 million pounds.[10] In 1977, PVC production was 22.3 million pounds.[11] Since several episodes of unconsciousness among workers were reported, the level of VCM in the air at the workplace is believed to have been high during this period. Ten cases of angiosarcoma of the liver have been reported since then.[7]

The industrial complex from which the comparison group was drawn comprises several divisions: a carbide division which produces calcium carbide and acetylene black; a chemicals division which produces several chemicals derived from acetylene: acetone, chloral, butanol, acetic acid, acetaldehyde, several acetates, solvents and resins; a stainless steel division which consisted of a small foundry and a division formed in 1957, which produced

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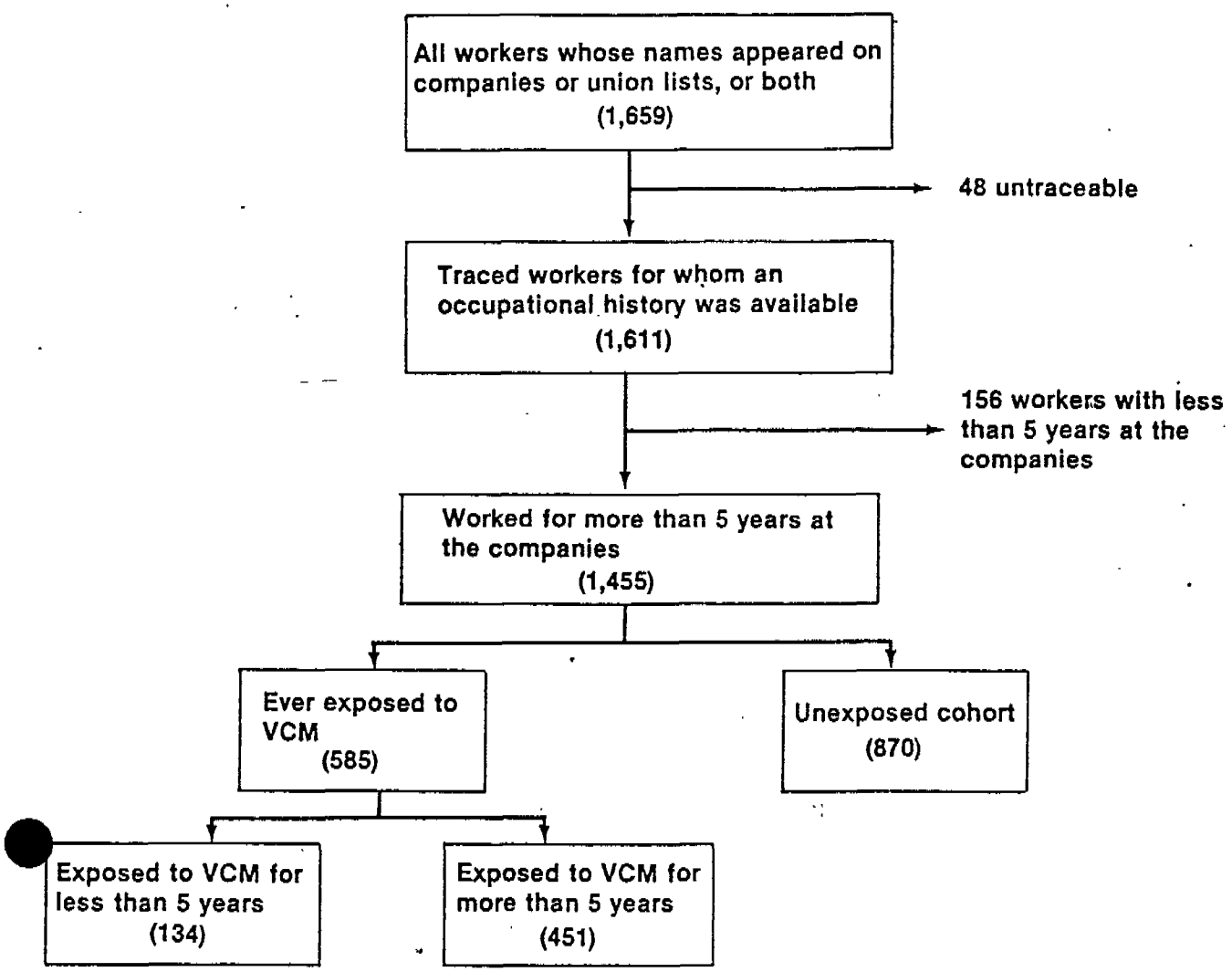

Fig 1. — Population under study.

sulfuric acid, chlorine and cyanide. This complex started operations in 1927; some of its divisions opened at a later date; others closed in the late 1960s or early 1970s. The annual number of male workers averaged 1,000.[12]

Methods

Population Under Study. — All production workers whose names appeared on the unions' lists or the companies payrolls of the VC plant and the industrial complex between January 1, 1948, and December 31, 1972, constituted the population under study. Several methods (old addresses, telephone books, Quebec motor vehicles bureau, inquiries with fellow workers and families, searches in homes for retired persons) were used to trace these men, 18% of whom were still working for the same companies. Once identified, the worker himself or his next of kin (spouse, child or close relative) was questioned at home or at work by a trained interviewer. The questions permitted the reconstruction of a detailed occupational history within and outside the companies under study. Questions were also asked regarding smoking habits. For each deceased person believed to have been exposed to VCM, the occupational history was confirmed with the help of a fellow worker.

The men whose number of years of work for these companies, as established through occupational histories, did not exceed five were removed from the study. The remaining population was then subdivided into three groups. The first group (known as the unexposed cohort) consisted of men who stated they had not been involved with the production of VCM or PVC, or both, for a period greater than five months. The second group (constituting the exposed cohort) comprised men who declared they had worked on the production of VCM-PVC for more than five years. Finally, the third group consisted of the men who had worked on the production of VCM-PVC for a period of six months to five years. This group was excluded from analysis because it neither fulfilled the definition of the exposed nor the unexposed cohort.

Data Sources. — The vital status of these men was established as of December 31, 1977. Causes of death were determined from death certificates. They were coded according to the 8th revision (ICDA) by one of the authors, who was unaware at the time of the coding as to which group the man belonged. For cancer cases, a histopathological confirmation was sought on autopsy, biopsy or cytology reports contained in the medical files at the hospital. Information on Quebec's population and mor-

Table 1. — Age Distribution of the Men in the VCM-Exposed and Unexposed Cohorts as of December 31, 1977 (Deceased Excluded).

Age	Exposed No.	Exposed %	Unexposed No.	Unexposed %
25-29	0	—	1	0.2
30-34	0	—	3	0.5
35-39	1	0.3	6	0.9
40-44	28	7.1	45	7.1
45-49	75	19.1	55	8.6
50-54	96	24.5	84	13.2
55-59	102	26.0	112	17.6
60-64	53	13.5	110	17.3
65-69	30	7.7	113	17.7
70-74	6	1.5	65	10.2
75 +	1	0.3	43	6.7
Total	392	100.0	637	100.0

tality by cause, age and sex was secured from Statistics Canada for the year 1971. In order to ensure the validity of the results, only the causes of death which appeared on the death certificates were used in the comparisons.

Statistical Analysis. — The results were analyzed using the "man-years at risk" method as described by Hill.[13] The number of person-years of observation was established for each five-year age group and for each five-year period between 1948 and 1977.

The mortality in the exposed cohort was compared with that in the unexposed cohort according to the method of relative risk. The tests of significance used were those of Mantel, Haenszel[14,15] and Miettinen.[16,17] The observed mortality was also compared with the mortality expected from the population of the Province of Quebec according to the method of the standardized mortality ratio (SMR).[18] The test of significance used was the one described by Bailar and Ederer.[19]

Quality Control Procedures. — A thorough occupational history was developed for workers who were exposed within the VC plant. The questionnaires presented a detailed profile of the plant while specifying possible jobs within its major units. Before the beginning of the study, it was pre-tested with former employees.

Interviewers who contacted the workers had received training by the same person and were supervised during the entire study. The completed questionnaires were reviewed weekly by one of the authors and missing information was sought by telephone. Data entered in the computer were systematically checked against the original questionnaires.

Results

As shown in Fig 1, the population under study originally comprised 1,659 workers. Of these, 48 men were untraceable, leaving the number in the study population at 1,611 (or 97.1% of the original number). After the removal of the 156 men who had worked at the companies for a period not exceeding five years and the 134 men who had been exposed to VCM for a perod extending from six months to five years, the exposed cohort comprised 451 men and the unexposed one, 870 men. In the exposed cohort, the proportion of men who responded to the questionnaire for themselves was 84.3%. In the unexposed cohort, this proportion was somewhat lower at 68.2%.

The age distributions of the workers in the exposed and unexposed cohorts as of December 31, 1977, reveals that workers in the unexposed cohort (Table 1) were somewhat older. Since the industrial complex had been in operation for several years when the VC plant opened, the finding of older people in the latter cohort was predictable.

Table 2 shows the distribution of the exposed workers according to their length of exposure and their observation period (time between first employment and end of follow-up). Among these, 81% (365 out of 451) had an observation period of 15 years or more. For 23% of them, the time elapsed between first exposure and the end of the follow-up period exceeded 29 years. The mean observation period for the exposed cohort was 22.6 years.

Table 3 gives the diagnosis at death and the diagnosis after histopathological review of all the cancer cases found in the exposed group. On the death certificates, eight cancers of the liver were reported. The histopathological review rejected one of them as being a cancer of the sigmoidal flexure of the colon, but added another as an incorrectly diagnosed cancer of the peritoneal cavity. All eight cancers of the liver turned out to be angiosarcoma of the liver. It is noted that two more angiosarcomas of the liver were certified as cirrhosis on the death certificates and were considered as such throughout this study.

Table 4 compares the mortality of the exposed workers with the mortality of the unexposed workers. The confidence interval (95%) of the relative risk indicates that there is a significant excess of mortality due to cancers of the digestive system in the exposed group (RR 6.25, confidence interval 2.69 to 14.52). There is no excess in the other causes of death.

Table 5 shows the standardized mortality ratios (SMRs) for the exposed workers in comparison with the entire population of the Province of Quebec. The SMR for all causes is 83.02, thereby showing no excess of death in the exposed cohort. Although the SMRs for all cancers, respiratory system diseases and digestive system diseases ex-

Table 2. — Distribution of Exposed Workers by Length of Exposure and Observation Period.

Exposure (Years)	Observation Period (Years) 5-9	10-14	15-19	20-24	25-29	30 +	Total
5- 9	30	28	7	40	2	4	111
10-14	—	28	26	19	17	5	95
15-19	—	—	17	35	19	8	79
20-24	—	—	—	22	24	15	61
25-29	—	—	—	—	34	33	67
30+	—	—	—	—	—	38	38
Total	30	56	50	116	96	103	451

Table 3. — Age at Death, Diagnosis on Death Certificate and Diagnosis on Histological Review of the 20 VCM-Exposed Workers Who Died of Cancer.

Case Number	Death Certificate	Histological Review	Age at Death (Years)	Total Exposure (Years)	Latency Period (Years)
1	Cancer of the liver	Cancer of the sigmoid flexure of the colon	73	15	28
2	Cancer of the intestine	Metastatic cancer of the colon	56	16	17
3	Carcinoma of the trachea	Carcinoma of the trachea	50	15	15
4	Angiosarcoma of the peritoneal cavity	Angiosarcoma of the liver	41	11	11
5	Cancer of the lung	(no review)	54	16	16
6	Cancer of the liver	Angiosarcoma of the liver	42	19	19
7	Cancer of the liver	Angiosarcoma of the liver	57	17	23
8	Cancer of the prostate	Cancer of the prostate	64	26	29
9	Angiosarcoma of the liver	Angiosarcoma of the liver	62	18	23
10	Cancer of the pancreas	Epithelioma of the head of the pancreas	40	8	13
11	Adenosarcoma of the intestine	Adenosarcoma of the intestine	53	25	28
12	Hepatoma	Angiosarcoma of the liver	53	24	24
13	Cancer of the liver	Angiosarcoma of the liver	53	22	23
14	Cancer of the pancreas	Anaplastic epithelioma of the pancreas	59	29	30
15	Chondrosarcoma	Chondrosarcoma	43	7	10
16	Hepatoma	Angiosarcoma of the liver	48	22	22
17	Primary cancer of the liver	Angiosarcoma of the liver	53	5	12
18	Cancer of the digestive track	Cancer of the cecum	52	26	26
19	Cancer of the biliary ducts	Cancer of the head of the pancreas	54	12	12
20	Lymphoid leukemia	Lymphoid leukemia	48	21	21

ceed 100, they are not statistically significant. On the other hand, deaths by accident and violence are significantly lower ($p < 0.01$). As for specific cancer deaths, a significant excess is noted for cancer of the digestive system only. This excess is accounted for exclusively by cancer of the liver (8 cases observed versus 0.14 expected, SMR 5,714.29). No other cancers are in excess.

The cancer mortality among the workers who were still alive 15 years after their first exposure shows the same results as the mortality in the entire group, namely that only cancers of the digestive system are in excess in the exposed cohort (Table 6).

Discussion

Difficulties encountered in comparing the mortality of a group of workers with the mortality of a whole population are well documented. They are termed: "healthy population selection effect," "survivor population effect,"[20] "ethnic/cultural/social characteristics." They are believed to underestimate the actual mortality of a group of workers and therefore to underscore the effects of the risks to which these individuals are being exposed at work. There are no easy ways to avoid such difficulties. One method would be to compare a group of workers with another group of workers with the same characteristics except for the exposure to the risk under study. The problems encountered in so doing are no easier. Although the group most similar to industrial workers is probably another group of industrial workers from the same town, it is almost impossible to think of a group of industrial

Table 4. — Deaths Observed in the VCM-Exposed and Unexposed Cohorts, Age-Adjusted Relative Risks and Confidence Intervals of the Relative Risk.

Cause of Death		No. of Cases Exposed	No. of Cases Unexposed	Relative Risk	95% Confidence Interval of the Relative Risk
All cancers	(140-209)	20	52	1.48	0.84- 2.61
Mouth and pharynx	(140-149)	0	2	—	—
Digestive	(150-159)	14	9	6.25	2.69-14.52*
Respiratory	(160-163)	2	20	0.36	0.08- 1.58
Bone, skin, connective	(170-173)	2	2	1.67	0.21-12.99
Urogenital	(185-189)	1	7	0.83	0.10- 7.10
Eye, CNS	(190-192)	0	2	—	—
Leukemia	(200-209)	1	4	1.15	0.07-17.80
Other cancers		0	6	—	—
Cardiovascular	(390-458)	25	124	0.80	0.47- 1.36
Respiratory	(460-519)	6	15	0.81	0.44- 9.35
Digestive	(520-577)	4	12	1.44	0.49- 4.25
Accidents and violence	(800-899)	2	15	0.51	0.21- 1.24
Others		2†	15	0.57	0.14- 2.39
Total		59	233	1.07	0.79- 1.45

*Significant according to Miettinen's test[17]
†One cause unknown

Table 5. — Observed and Expected* Numbers of Deaths in the VCM-Exposed Cohort and Standardized Mortality Ratios (SMRs).

Cause of Death		Observed	Expected	SMR
All cancers	(140-209)	20	16.37	122.17
Mouth and pharynx	(140-149)	0	0.64	—
Digestive	(150-159)	14	5.40	259.26†
Respiratory	(160-163)	2	5.78	34.60
Bone, skin, connective	(170-173)	2	0.38	526.32
Urogenital	(185-189)	1	1.33	75.19
Eye, CNS	(190-192)	0	0.60	—
Leukemia	(200-209)	1	1.67	59.88
Other cancers		0	0.54	—
Cardiovascular	(390-458)	25	31.67	78.94
Respiratory	(460-519)	6	3.21	186.91
Digestive	(520-577)	4	3.85	103.90
Accidents and violence	(800-999)	2	10.58	18.90†
Others		2‡	5.40	37.03
Total		59	71.07	83.02

*Expected numbers obtained from 1971 males Quebec death rates applied to person-years in each age group
†$p < 0.01$[19]
‡One cause unknown

workers not exposed to some kind of carcinogenic risks. In the present study, the authors decided to compare the exposed workers with both the general population and a group of unexposed workers. It must be noted that among the unexposed workers, no causes of death were found to be in excess when their mortality was compared with that of the general population.

The comparison of the mortality of the exposed and the unexposed workers gave results similar to the one reached by the comparison with the general population. The number of cancer of the digestive system was significantly higher in the exposed cohort. No other cancer was in excess and there even seemed to be a deficit (not statistically significant) in respiratory cancers.

Considering the fact that animals experimentally exposed to VCM have developed not only angiosarcomas of the liver but also malignant tumors of several organs (skin, lung, bone, Zimbal glands, kidneys, mammary glands)[21 22 23] and since several epidemiological studies on VCM-exposed workers have found an excess of lung cancer,[24] the results of this study of heavily exposed men are surprising. Three questions can be raised. One concerns the ascertainment of the population. In retrospective studies conducted from old company or union records it sometimes happens that records of people who die or leave get lost. These losses could account for the low cancer rates observed. But this is a remote possibility, since the approach followed was a historical-prospective retrospective one, which began with old lists of workers composed in 1948 and 1952 and followed almost everyone through time, adding new workers as they first appeared on more recent lists. This was done without knowledge of exposure to VCM.

A second reason for low lung cancer rates could be a bias in the classification of persons as exposed or not exposed. The classification was made essentially on the basis of personal recollection for living persons and by family members with confirmation by co-workers for deceased persons. To minimize such bias, much attention had been given to the occupational history (with indication of the buildings the subject had worked in) and workers with VCM exposure shorter than five years were rejected. There remains the possibility that some of the men who died of liver cancer, had they lived longer, might have developed lung cancer.

The small size of the population under study increased the probability of not detecting an excess that was actually present. This was a case where "the number of person/years at risk may be too small to detect an increased risk of cancer."[25] It was particularly true for rare cancers such as cancer of the brain and cancer of the lymphatic system. Inasmuch as cancer of the lung was concerned,

Table 6. — Relative Risks and SMRs for Cancer Deaths Among Men Having an Observation Period of 15 Years and More.

Cancers		No.	Relative Risk	95% Confidence Interval of the Relative Risk	SMR
All cancers	(140-209)	15	1.30	0.97- 1.74	129
Mouth and pharynx	(140-149)	0	—	—	—
Digestive	(150-159)	11	5.68	2.72-11.58	281*
Respiratory	(160-163)	2	0.35	0.25- 4.73	47
Bone, skin, connective	(170-173)	0	—	—	—
Urogenital	(185-189)	1	0.82	—	—
Eye, CNS	(190-192)	0	—	—	—
Leukemia	(200-209)	1	0.59	—	—
Other cancers		0	—	—	—

*$p < 0.01$[19]

the situation was somewhat different. When one applies the Quebec lung cancer death rate after adjustment for age to the exposed cohort, the probability of finding an excess twice as high as in Quebec was 73%. This probability would have been 99% had the excess been three times as great in the exposed group.[25]

In view of the fact that the smoking experience of the exposed workers was similar to that of the unexposed and considering that the subjects in this study are believed to have been heavily exposed to VCM, it seems reasonable to conclude that the excess of lung cancer associated with VCM exposure, if present, is indeed rather small.

The authors wish to express their gratitude to the following who contributed to this study: workers, union representatives and management personnel of the companies Canadian Resins and Chemicals, Shawinigan Chemicals, B.F. Goodrich and Gulf Canada, Drs. H Iturra and J Fabia, epidemiologists, and Dr. F Delorme, pathologist, for their help and advice; the several hospitals contacted, and the several persons who assisted with the collection of information and the writing of this article

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Reducing Financial Risks

There is too little evidence that the nuclear industry, which was never very good at calculating its own interest, is seriously contemplating the effect of another Three Mile Island on its future — or its fortunes. The industry has already returned to complaints that the safety bureaucracy is nitpicking it to death, running up construction costs and delaying licenses. The latest complaint is that, in the aftermath of the TMI accident, NRC diverted safety reviewers to deal with operating reactors and fell behind in approving new licenses.

There is a kind of tunnel vision in the failure to see the connection between safety and the special financial risk involved in nuclear investment. To use the current energy crisis to avoid safety requirements is to ignore the fact that safety is essential to protecting the heavy investment in nuclear power. Some hope lies in the fact that, although the industry thinks safety requirements are a pain in the neck, they may be forced to look at them as an investment in financial public relations to alleviate the bankers' skepticism.

— Victor Gilinsky, Commissioner, the Nuclear Regulatory Commission, as quoted in "Notable and Quotable," in *The Wall Street Journal*, May 21, 1981.

JOM
October 1981 Vol. 23 No. 10

Cancer Mortality of a Group of Canadian Workers Exposed to Vinyl Chloride Monomer

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The present study was undertaken to find out whether there was an excess of cancer mortality from causes other than angiosarcoma of the liver among a group of workers heavily exposed to vinyl chloride monomer (VCM). The mortality of 451 workers exposed to VCM for more than five years was compared with that of 870 workers from the same company who had not been exposed to VCM. The relative risk for digestive cancer was significantly higher than 1 (6.25, confidence interval 2.69 to 14.52) in the exposed group. The standardized mortality ratio (SMR) for digestive cancer was also higher (SMR 259.26 $p < 0.01$) than that of the general population. No other cancer was in excess. Since the exposed workers are known to have had a cigarette smoking experience similar to that of those who were not exposed, it is concluded that the association between lung cancer and VCM exposure, if present, is indeed rather small.

Several studies have demonstrated that vinyl chloride monomer (VCM) produces angiosarcoma of the liver among people exposed at work.[1-7] There is, however, much controversy about the capability of VCM to generate other types of cancer in man. One author,[8] using a proportional mortality ratio technique, described excesses of lung cancer (observed, 13; expected, 7.9; obs/exp 1.6) and brain cancer (observed, 5; expected, 1.2; obs/exp 4.2) in a group of 161 workers from two vinyl chloride plants.[8] Another author,[9] who studied the mortality of a group of 1,294 American workers exposed to VCM, reported excesses of lung cancer (observed, 11 expected, 7.5; SMR 194, $p < 0.05$) and brain cancer (observed, 3; expected, 0.6; SMR 498, $p < 0.05$) among men who had had their first exposure more than 15 years before their death. While most authors have not been able to document a significant excess of any other cancer in their studies, they have noted that such an excess may exist.

In order to better document the cancer mortality associated with exposure to VCM, the present study of the workers of the Shawinigan vinyl chloride polymerization plant was undertaken.

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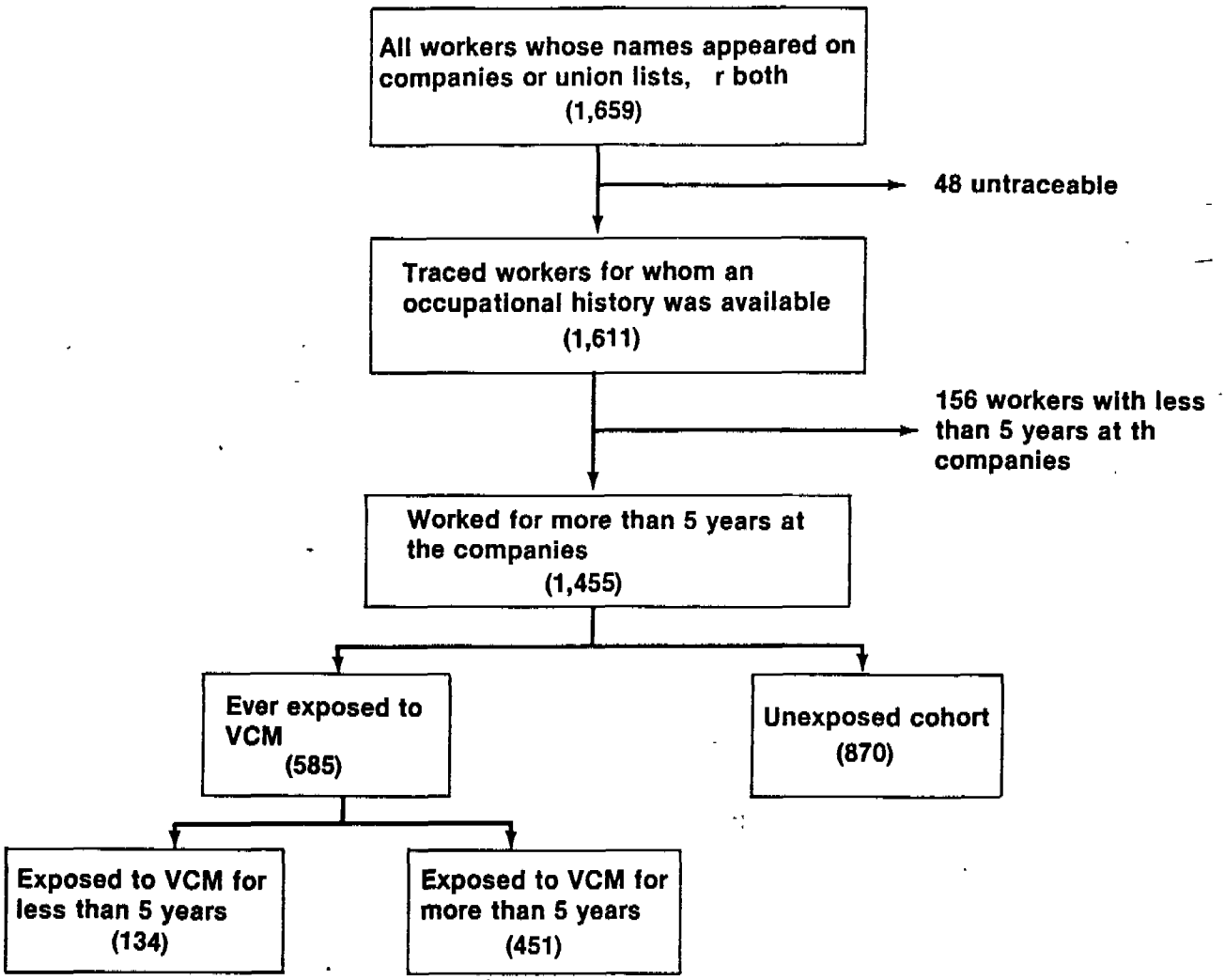

Fig 1. — Population under study.

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Population Under Study. — All production workers whose names appeared on the unions' lists or the companies payrolls of the VC plant and the industrial complex between January 1, 1948, and December 31, 1972, constituted the population under study. Several methods (old addresses, telephone books, Quebec motor vehicles bureau, inquiries with fellow workers and families, searches in homes for retired persons) were used to trace these men, 18% of whom were still working for the same companies. Once identified, the worker himself or his next of kin (spouse, child or close relative) was questioned at home or at work by a trained interviewer. The questions permitted the reconstruction of a detailed occupational history within and outside the companies under study. Questions were also asked regarding smoking habits. For each deceased person believed to have been exposed to VCM, the occupational history was confirmed with the help of a fellow worker.

The men whose number of years of work for these companies, as established through occupational histories, did not exceed five were removed from the study. The remaining population was then subdivided into three groups. The first group (known as the unexposed cohort) consisted of men who stated they had not been involved with the production of VCM or PVC, or both, for a period greater than five months. The second group (constituting the exposed cohort) comprised men who declared they had worked on the production of VCM-PVC for more than five years. Finally, the third group consisted of the men who had worked on the production of VCM-PVC for a period of six months to five years. This group was excluded from analysis because it neither fulfilled the definition of the exposed nor the unexposed cohort.

Data Sources. — The vital status of these men was established as of December 31, 1977. Causes of death were determined from death certificates. They were coded according to the 8th revision (ICDA) by one of the authors, who was unaware at the time of the coding as to which group the man belonged. For cancer cases, a histopathological confirmation was sought on autopsy, biopsy or cytology reports contained in the medical files at the hospital. Information on Quebec's population and mor-

Table 1. — Age Distribution of the Men in the VCM-Exposed and Unexposed Cohorts as of December 31, 1977 (Deceased Excluded).

Age	Exposed No.	Exposed %	Unexposed No.	Unexposed %
25-29	0	—	1	0.2
30-34	0	—	3	0.5
35-39	1	0.3	6	0.9
40-44	28	7.1	45	7.1
45-49	75	19.1	55	8.6
50-54	96	24.5	84	13.2
55-59	102	26.0	112	17.6
60-64	53	13.5	110	17.3
65-69	30	7.7	113	17.7
70-74	6	1.5	65	10.2
75 +	1	0.3	43	6.7
Total	392	100.0	637	100.0

tality by cause, age and sex was secured from Statistics Canada for the year 1971. In order to ensure the validity of the results, only the causes of death which appeared on the death certificates were used in the comparisons.

Statistical Analysis. — The results were analyzed using the "man-years at risk" method as described by Hill.[13] The number of person-years of observation was established for each five-year age group and for each five-year period between 1948 and 1977.

The mortality in the exposed cohort was compared with that in the unexposed cohort according to the method of relative risk. The tests of significance used were those of Mantel, Haenszel[14,15] and Miettinen.[16,17] The observed mortality was also compared with the mortality expected from the population of the Province of Quebec according to the method of the standardized mortality ratio (SMR).[18] The test of significance used was the one described by Bailar and Ederer.[19]

Quality Control Procedures. — A thorough occupational history was developed for workers who were exposed within the VC plant. The questionnaires presented a detailed profile of the plant while specifying possible jobs within its major units. Before the beginning of the study, it was pre-tested with former employees.

Interviewers who contacted the workers had received training by the same person and were supervised during the entire study. The completed questionnaires were reviewed weekly by one of the authors and missing information was sought by telephone. Data entered in the computer were systematically checked against the original questionnaires.

Results

As shown in Fig 1, the population under study originally comprised 1,659 workers. Of these, 48 men were untraceable, leaving the number in the study population at 1,611 (or 97.1% of the original number). After the removal the 156 men who had worked at the companies fo period not exceeding five years and the 134 men who had been exposed to VCM for a perod extending from six months to five years, the exposed cohort comprised 451 men and the unexposed one, 870 men. In the exposed cohort, the proportion of men who responded to the questionnaire for themselves was 84.3%. In the unexposed cohort, this proportion was somewhat lower at 68.2%.

The age distributions of the workers in the exposed and unexposed cohorts as of December 31, 1977, reveals that workers in the unexposed cohort (Table 1) were somewhat older. Since the industrial complex had been in operation for several years when the VC plant opened, the finding of older people in the latter cohort was predictable.

Table 2 shows the distribution of the exposed workers according to their length of exposure and their observation period (time between first employment and end of follow-up). Among these, 81% (365 out of 451) had an observation period of 15 years or more. For 23% of them, the time elapsed between first exposure and the end of the follow-up period exceeded 29 years. The mean observation period for the exposed cohort was 22.6 years.

Table 3 gives the diagnosis at death and the diagnosis after histopathological review of all the cancer cases found in the exposed group. On the death certificates, eight cancers of the liver were reported. The histopathological review rejected one of them as being a cance the sigmoidal flexure of the colon, but added anothe an incorrectly diagnosed cancer of the peritoneal cavity. All eight cancers of the liver turned out to be angiosarcoma of the liver. It is noted that two more angiosarcomas of the liver were certified as cirrhosis on the death certificates and were considered as such throughout this study.

Table 4 compares the mortality of the exposed workers with the mortality of the unexposed workers. The confidence interval (95%) of the relative risk indicates that there is a significant excess of mortality due to cancers of the digestive system in the exposed group (RR 6.25, confidence interval 2.69 to 14.52). There is no excess in the other causes of death.

Table 5 shows the standardized mortality ratios (SMRs) for the exposed workers in comparison with the entire population of the Province of Quebec. The SMR for all causes is 83.02, thereby showing no excess of death in the exposed cohort. Although the SMRs for all cancers, respiratory system diseases and digestive system diseases ex-

Table 2. — Distribution of Exposed Workers by Length of Exposure and Observation Period.

Exposure (Years)	Observation Period (Years) 5-9	10-14	15-19	20-24	25-29	30 +	Total
5- 9	30	28	7	40	2	4	111
10-14	—	28	26	19	17	5	95
15-19	—	—	17	35	19	8	79
20-24	—	—	—	22	24	15	61
25-29	—	—	—	—	34	33	67
30+	—	—	—	—	—	38	38
Total	30	56	50	116	96	103	451

Table 3. — Age at Death, Diagnosis on Death Certificate and Diagnosis on Histological Review of the 20 VCM-Exposed Workers Who Died of Cancer.

Case Number	Death Certificate	Histological Review	Age at Death (Years)	Total Exposure (Years)	Latency Period (Years)
1	Cancer of the liver	Cancer of the sigmoid flexure of the colon	73	15	28
2	Cancer of the intestine	Metastatic cancer of the colon	56	16	17
3	Carcinoma of the trachea	Carcinoma of the trachea	50	15	15
4	Angiosarcoma of the peritoneal cavity	Angiosarcoma of the liver	41	11	11
5	Cancer of the lung	(no review)	54	16	16
6	Cancer of the liver	Angiosarcoma of the liver	42	19	19
7	Cancer of the liver	Angiosarcoma of the liver	57	17	23
8	Cancer of the prostate	Cancer of the prostate	64	26	29
9	Angiosarcoma of the liver	Angiosarcoma of the liver	62	18	23
10	Cancer of the pancreas	Epithelioma of the head of the pancreas	40	8	13
11	Adenosarcoma of the intestine	Adenosarcoma of the intestine	53	25	28
12	Hepatoma	Angiosarcoma of the liver	53	24	24
13	Cancer of the liver	Angiosarcoma of the liver	53	22	23
14	Cancer of the pancreas	Anaplastic epithelioma of the pancreas	59	29	30
15	Chondrosarcoma	Chondrosarcoma	43	7	10
16	Hepatoma	Angiosarcoma of the liver	48	22	22
17	Primary cancer of the liver	Angiosarcoma of the liver	53	5	12
18	Cancer of the digestive track	Cancer of the cecum	52	26	26
19	Cancer of the biliary ducts	Cancer of the head of the pancreas	54	12	12
20	Lymphoid leukemia	Lymphoid leukemia	48	21	21

ceed 100, they are not statistically significant. On the other hand, deaths by accident and violence are significantly lower ($p < 0.01$). As for specific cancer deaths, a significant excess is noted for cancer of the digestive system only. This excess is accounted for exclusively by cancer of the liver (8 cases observed versus 0.14 expected, SMR 5,714.29). No other cancers are in excess.

The cancer mortality among the workers who were still alive 15 years after their first exposure shows the same results as the mortality in the entire group, namely that only cancers of the digestive system are in excess in the exposed cohort (Table 6).

Discussion

Difficulties encountered in comparing the mortality of a group of workers with the mortality of a whole population are well documented. They are termed: "healthy population selection effect," "survivor population effect,"[20] "ethnic/cultural/social characteristics." They are believed to underestimate the actual mortality of a group of workers and therefore to underscore the effects of the risks to which these individuals are being exposed at work. There are no easy ways to avoid such difficulties. One method would be to compare a group of workers with another group of workers with the same characteristics except for the exposure to the risk under study. The problems encountered in so doing are no easier. Although the group most similar to industrial workers is probably another group of industrial workers from the same town, it is almost impossible to think of a group of industrial

Table 4. — Deaths Observed in the VCM-Exposed and Unexposed Cohorts, Age-Adjusted Relative Risks and Confidence Intervals of the Relative Risk.

Cause of Death		No. of Cases Exposed	No. of Cases Unexposed	Relative Risk	95% Confidence Interval of the Relative Risk
All cancers	(140-209)	20	52	1.48	0.84- 2.61
Mouth and pharynx	(140-149)	0	2	—	—
Digestive	(150-159)	14	9	6.25	2.69-14.52*
Respiratory	(160-163)	2	20	0.36	0.08- 1.58
Bone, skin, connective	(170-173)	2	2	1.67	0.21-12.99
Urogenital	(185-189)	1	7	0.83	0.10- 7.10
Eye, CNS	(190-192)	0	2	—	—
Leukemia	(200-209)	1	4	1.15	0.07-17.80
Other cancers		0	6	—	—
Cardiovascular	(390-458)	25	124	0.80	0.47- 1.36
Respiratory	(460-519)	6	15	0.81	0.44- 9.35
Digestive	(520-577)	4	12	1.44	0.49- 4.25
Accidents and violence	(800-899)	2	15	0.51	0.21- 1.24
Others		2†	15	0.57	0.14- 2.39
Total		59	233	1.07	0.79- 1.45

*Significant according to Miettinen's test[17]
†One cause unknown

Table 5. — Observed and Expected* Numbers of Deaths in the VCM-Exposed Cohort and Standardized Mortality Ratios (SMRs).

Cause of Death		Observed	Expected	SMR
All cancers	(140-209)	20	16.37	122.17
Mouth and pharynx	(140-149)	0	0.64	—
Digestive	(150-159)	14	5.40	259.26†
Respiratory	(160-163)	2	5.78	34.60
Bone, skin, connective	(170-173)	2	0.38	526.32
Urogenital	(185-189)	1	1.33	75.19
Eye, CNS	(190-192)	0	0.60	—
Leukemia	(200-209)	1	1.67	59.88
Other cancers		0	0.54	—
Cardiovascular	(390-458)	25	31.67	78.94
Respiratory	(460-519)	6	3.21	186.91
Digestive	(520-577)	4	3.85	103.90
Accidents and violence	(800-999)	2	10.58	18.90†
Others		2‡	5.40	37.03
Total		59	71.07	83.02

*Expected numbers obtained from 1971 males Quebec death rates applied to person-years in each age group
†$p < 0.01$[19]
‡One cause unknown

workers not exposed to some kind of carcinogenic risks. In the present study, the authors decided to compare the exposed workers with both the general population and a group of unexposed workers. It must be noted that among the unexposed workers, no causes of death were found to be in excess when their mortality was compared with that of the general population.

The comparison of the mortality of the exposed and the unexposed workers gave results similar to the one reached by the comparison with the general population. The number of cancer of the digestive system was significantly higher in the exposed cohort. No other cancer was in excess and there even seemed to be a deficit (not statistically significant) in respiratory cancers.

Considering the fact that animals experimentally exposed to VCM have developed not only angiosarcomas of the liver but also malignant tumors of several organs (skin, lung, bone, Zimbal glands, kidneys, mammary glands)[21 22 23] and since several epidemiological studies on VCM-exposed workers have found an excess of lung cancer,[24] the results of this study of heavily exposed men are surprising. Three questions can be raised. One concerns the ascertainment of the population. In retrospective studies conducted from old company or union records it sometimes happens that records of people who die or leave get lost. These losses could account for the low cancer rates observed. But this is a remote possibility, since the approach followed was a historical-prospective retrospective one, which began with old lists of workers composed in 1948 and 1952 and followed almost everyone through time, adding new workers as they first appeared on more recent lists. This was done without knowledge of exposure to VCM.

A second reason for low lung cancer rates could be a bias in the classification of persons as exposed or not exposed. The classification was made essentially on the basis of personal recollection for living persons and by family members with confirmation by co-workers for deceased persons. To minimize such bias, much attention had been given to the occupational history (with indication of the buildings the subject had worked in) and workers with VCM exposure shorter than five years were rejected. There remains the possibility that some of the men who died of liver cancer, had they lived longer, might have developed lung cancer.

The small size of the population under study increased the probability of not detecting an excess that was actually present. This was a case where "the number of person/years at risk may be too small to detect an increased risk of cancer."[25] It was particularly true for rare cancers such as cancer of the brain and cancer of the lymphatic system. Inasmuch as cancer of the lung was concerned,

Table 6. — Relative Risks and SMRs for Cancer Deaths Among Men Having an Observation Period of 15 Years and More.

Cancers		No.	Relative Risk	95% Confidence Interval of the Relative Risk	SMR
All cancers	(140-209)	15	1.30	0.97- 1.74	129
Mouth and pharynx	(140-149)	0	—	—	—
Digestive	(150-159)	11	5.68	2.72-11.58	281*
Respiratory	(160-163)	2	0.35	0.25- 4.73	47
Bone, skin, connective	(170-173)	0	—	—	—
Urogenital	(185-189)	1	0.82	—	—
Eye, CNS	(190-192)	0	—	—	—
Leukemia	(200-209)	1	0.59	—	—
Other cancers		0	—	—	—

*$p < 0.01$[19]

the situation was somewhat different. When one applies the Quebec lung cancer death rate after adjustment for age to the exposed cohort, the probability of finding an excess twice as high as in Quebec was 73%. This probability would have been 99% had the excess been three times as great in the exposed group.[25]

In view of the fact that the smoking experience of the exposed workers was similar to that of the unexposed and considering that the subjects in this study are believed to have been heavily exposed to VCM, it seems reasonable to conclude that the excess of lung cancer associated with VCM exposure, if present, is indeed rather small.

The authors wish to express their gratitude to the following who contributed to this study: workers, union representatives and management personnel of the companies Canadian Resins and Chemicals, Shawinigan Chemicals, B F Goodrich and Gulf Canada. Drs. H. Iturra and J Fabia, epidemiologists, and Dr F Delorme, pathologist, for their help and advice; the several hospitals contacted, and the several persons who assisted with the collection of information and the writing of this article.

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Reducing Financial Risks

There is too little evidence that the nuclear industry, which was never very good at calculating its own interest, is seriously contemplating the effect of another Three Mile Island on its future — or its fortunes. The industry has already returned to complaints that the safety bureaucracy is nitpicking it to death, running up construction costs and delaying licenses. The latest complaint is that, in the aftermath of the TMI accident, NRC diverted safety reviewers to deal with operating reactors and fell behind in approving new licenses.

There is a kind of tunnel vision in the failure to see the connection between safety and the special financial risk involved in nuclear investment. To use the current energy crisis to avoid safety requirements is to ignore the fact that safety is essential to protecting the heavy investment in nuclear power. Some hope lies in the fact that, although the industry thinks safety requirements are a pain in the neck, they may be forced to look at them as an investment in financial public relations to alleviate the bankers' skepticism.

— Victor Gilinsky, Commissioner, the Nuclear Regulatory Commission, as quoted in "Notable and Quotable," in *The Wall Street Journal*, May 21, 1981.

Exposure Indices for Epidemiological Surveillance of Carcinogenic Agents in an Industrial Chemical Environment

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A prospective system for establishing chemical exposure indices was developed and implemented for 22 chemicals used at a Louisville chemical plant. Validation of the indices was done statistically using industry-related cancer (liver angiosarcoma) and worker-matched controls. A rank ordered system for exposures was used to identify a relationship between the occurrence of disease and the presence of a suspect chemical used in the industrial environment.

A major difficulty in the epidemiology of occupational carcinogenesis is obtaining accurate exposure data, especially if the data must be procured after cancer develops. While epidemiological investigations of outbreaks of disease, infectious or chronic, are always retrospective, the long latent period between exposure to a causative factor and the occurrence of cancer complicates this problem. Routine continuous recording of exposure to possible carcinogens is an ideal goal. Unfortunately, this is not practical for most chemicals in a modern industrial setting. What is eminently practical, however, is a system utilizing rank ordering of exposures for highly suspect chemicals.

The B. F. Goodrich Louisville Chemical plant developed such a system in 1974 in response to the discovery of cases of hepatic angiosarcoma.[1-5] This system was the basis of the initial reports. It was extensively modified during a prospective medical screening program established by the University of Louisville under contract NO1-CN-55212 with the cancer control program of the National Cancer Institute.[6,7] The authors are unaware of other similar existing data sets. Occupational studies are usually based on group, rather than individual, exposures. An excellent review of the literature is given by Gamble et al.[8] A recent discussion of a computerized system is given by Kerr.[9]

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The system for establishing exposure indices on an ongoing basis was developed through employee work histories and rank ordered job exposure categories. All jobs are classified uniquely by both area location and work description by means of area-description (A-D) codes which identify employment occurring in a particular building or area, independent of job; in a particular job, independent of building or area; or by both area and description.

The exposure index combines two components, i.e. work history and job exposure category, by utilizing the A-D code. The chemical exposure rating is an ordered, six-category ranking assigned to each A-D number for each calendar year, as follows:

Rating	Level of Exposure
0	Absent from Environment (on leave, furlough, layoff, etc.)
1	Lowest Exposure (includes exposure up to somewhere near one hour per day)
2	Minimal Exposure to Low Levels (chemical in building — not handled; low vapor pressure and dust level; individual probably works on different floor)
3	Moderate Exposure (works around the chemical, but exposure is minimal; individual is frequently exposed to little spills or leaks and infrequently — less than once per month — to large spills or leaks)
4	Works in Area Subject to High Occupational Exposures (normally exposure is minimal, but large spills or leaks occur once per month or more)
5	Works in Areas Where Level is High (exposure levels in area are frequently high; might consider that some risk is involved if the chemical is very toxic)
6	Intimate Contact — Skin or High Inhalation (includes individuals with daily and direct contact with the chemicals, such as poly cleaner in the old days and those who handled slurry)

Table 1. — Detailed Work and Exposure History.

	1A Work History			1B Exposure Rank for Each Chemical				
Year	A Building	D Job	No. Months	Vinyl Chloride	2*	3*		22*
1944	000	576	6	2	1	1	.....	4
1945	000	576	5	2	1	1	.....	4
1945	111	194	7	5	1	1	.....	1
1946	111	194	12	6	4	1	.....	1
1947	111	194	12	6	4	3	.....	1
1948	111	194	8	5	4	3	.....	1
1948	121	192	4	4	3	1	.....	1
1949	121	192	4	4	3	1	.....	1
1949	112	253	8	2	6	3	.....	2
1949	112	253	8					
1949	112	253	8					
1949	112	253	8					
1957	121	235	12	4	3	1	.....	1
1957	121	235	12					
1957	121	235	12					
1957	121	235	12					
1972	117	573	5	1	2	1	.....	1
1972	000	574	7	2	1	1	.....	4
1973	000	574	12	2	1	1	.....	4
1974	000	574	8	2	1	1	.....	4
1974	Terminated							

*Other chemical

Twenty-two chemicals from two distinct manufacturing processes, one related to synthetic rubber and the other to plastics, were selected for rating. The ratings were assigned by panels of chemical exposure judges. The full six-point scale was not utilized for all chemicals. Although it would have been ideal to have a quantitative, continuous scale of actual exposure to parts per million, this was not available for all B. F. Goodrich employees for all chemicals (nor is it likely to be available in any other industry). In order to overcome the subjectivity inherent in this exposure rating system, knowledgeable people from each area of the plant were selected to serve as that area's chemcal exposure judges. The primary criterion for their selection was experience in the given area. As a rule, production foremen and technical people (i.e., chemical engineers) were in the majority among each area's panel of judges. The area production foremen were especially invaluable as they are experienced in and knowledgeable of all jobs performed in their areas. Most valuable, however, were those individuals who had been at the plant since its inception, or shortly thereafter. The chemical exposure judges met as a group and agreement was by consensus.

Table 1A gives the work history for a hypothetical individual. Note that each job is identified for each year indicating both the A-D number and the number of months worked during the year. This individual, therefore, began work in 1944 and worked for six months on A-D number 000576. He worked an additional five months on this number during 1945. He completed the last seven months in 1945 working at A-D number 111194. Table 1B identifies the exposure rating assigned to each of the 22 monitored chemicals for each A-D number for each year. For instance, the first row indicates the exposure ratings assigned in 1944 to A-D number 000576. In 1945 these remained unchanged. The third row indicates the exposure ratings for A-D number 111194 during 1945. The information in Tables 1A and 1B is combined to give cumulative exposure rank months (CERM) and average exposure ranks (AER). In this example, this individual in 1944 would have had 12 CERM for vinyl chloride in 1944, having worked six months at an exposure rank of 2 during the year. During 1945, this individual would have had CERM to vinyl chloride of (5 x 2) plus (7 x 5) or 45. He would have worked a total of 12 months and would have had an AER (45 ÷ 12) equal to 3.75. The assumption is made that the CERM can be used as a rank order statistic. The assumption is empirically validated later in this paper. The CERM cannot be considered as representing interval data and no such use of it is intended. The results given here are based on revised work histories and A-D codes developed during the NCI contract period. These same codes are now applied to the individual monitoring of all employees.

The data are accurately obtained in a prospective manner. Work histories are obtained on an ongoing basis. Each time an employee changes jobs, the change is identified by a payroll change card indicating the last A-D number, the new A-D number and the date of change. In addition, the rating of exposures by A-D number is now done on an annual basis using auxiliary information available about the A-D number including individual and area monitoring pertinent to the particular A-D number. Thus far this is available for only three chemicals and only since 1974. The rating of exposures is now obtained from chemical exposure judges consisting of representatives of both labor and management. This process takes about two weeks annually.

In order to determine whether such a system could work retrospectively, work histories were abstracted by A-D numbers from payroll records for all employees who worked on or after January 1, 1974, from records dating back to the opening of the plant in 1942. Payroll records

Table 2. — Standard Normal Deviates Comparing Exposure Ranks of Angiosarcoma Cases with the Average Exposure of Matched* Controls (by Selected Chemicals).

Chemical	Group 1 (23 Controls)	2 (29 Controls)	3 (36 Controls)	4 (4 Controls)
1	−1.43	2.32	−0.66	−2.20
2	−2.13	−0.93	−2.00	−0.53
3	−3.54	−2.16	−3.16	−1.50
4	−3.31	−1.79	−0.06	−1.76
5	3.97	0.84	5.08	1.11
6	−2.01	−2.58	−1.59	—
7	−2.33	−2.59	−1.93	−1.50
8	0.29	−0.47	1.56	—
9	−3.92	−0.27	6.44	−2.28
10	−0.76	3.64	0.17	−0.71
11	11.27	7.59	0.93	5.08
12	−1.69	−1.35	0.45	−1.00
13	−1.78	−1.41	5.95	0.00
14	−2.41	−2.91	−2.35	−0.85
15	−1.87	−1.63	0.40	−1.21
16	5.13	3.12	5.77	2.55
17	−0.77	−3.43	5.53	−1.50
18	1.55	−1.45	5.68	1.07
10	2.56	−4.36	4.64	−0.83
20	9.11	2.65	3.72	2.60
21	−3.87	−2.39	−2.91	−1.31
22	6.55	2.34	2.36	2.85

*Matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974

did not have the A-D numbers that were subsequently developed; these older records referred to many jobs which no longer existed, and to some which were performed in buildings long since torn down. However, a staff of knowledgeable employees matched the jobs listed on these payroll records with current A-D numbers. Final determination for controversial work records was made, wherever possible, by an individual employee's review. The chemical exposure judges, who were assigning ordered rating exposures to A-D numbers for each year, faced these same problems. They used, in addition to their memory, whatever records of chemical processes and procedures that were available. (The company maintains a file on all products ever produced and all processes ever used at the plant.)

This system of determining work exposure data was *validated empirically* in the following manner: The incidence of hepatic angiosarcoma at the B. F. Goodrich plant since January 1, 1974, presented in four subjects. Each of the four subjects was matched by exact year of birth, by sex and race (white or non-white), by exact year of employment, and by continuing employment at the B. F. Goodrich plant through January 1, 1974. All matches are included in the subsequent analysis. Each of the angiosarcoma subjects and the corresponding matched group were compared on CERM separately for each calendar year. The results were then ranked within each calendar year and the ranks were summed over the calendar years. If the work histories and the ordered rating exposures were no better than random assignments, one would expect a uniform distribution of ranks within each year and independence from year to year. Otherwise, rank order exposures should demonstrate higher exposure to vinyl chloride in those individuals with hepatic angiosarcoma.

Table 2, which gives standard normal deviates, was calculated from the observed sum of ranks, the expected sum of ranks, and the theoretical standard error (conditional on the observed pattern of tied ranks) of the expected sum of ranks. Sums were over years. The results show a very clear pattern of high exposure to chemical number 16, vinyl chloride. This is to be expected a priori if the work history data and the exposure rank data are valid. A second finding of importance is that all four angio-

Table 3. — Comparison of Frequency of Observed and Expected Excess Exposure to Selected Chemicals.

Number of Angiosarcomas Showing Excess Exposure	Expected* Proportion	Observed Frequency	Expected Frequency	Contribution to Chi Square
0	1/16	6	1.25	18.05
1	4/16	6	5.00	0.20
2	6/16	2	7.50	4.03
3	4/16	1	5.00	3.20
4	1/16	5	1.25	11.25
Total		20	20.00	$36.73 = X^2$, $p < 0.001$

*Calculated from the binomial distribution with $n = 4$ and $p = 1/2$

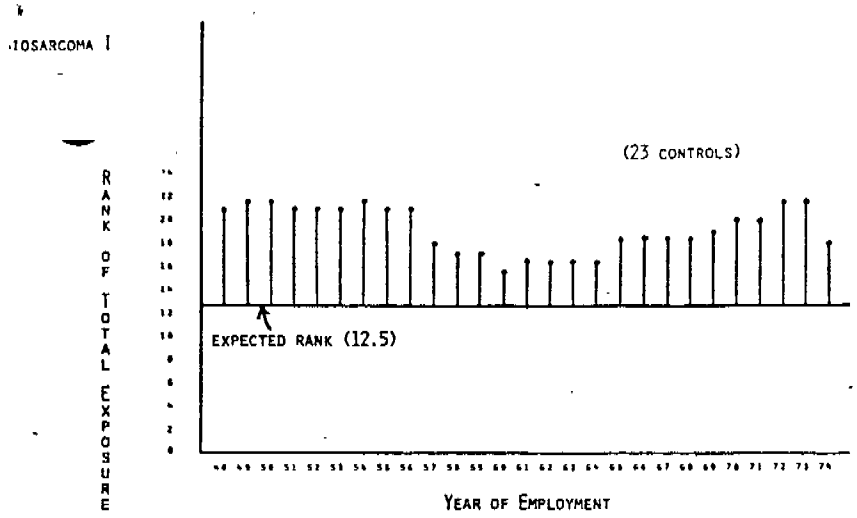

Fig. 1 — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

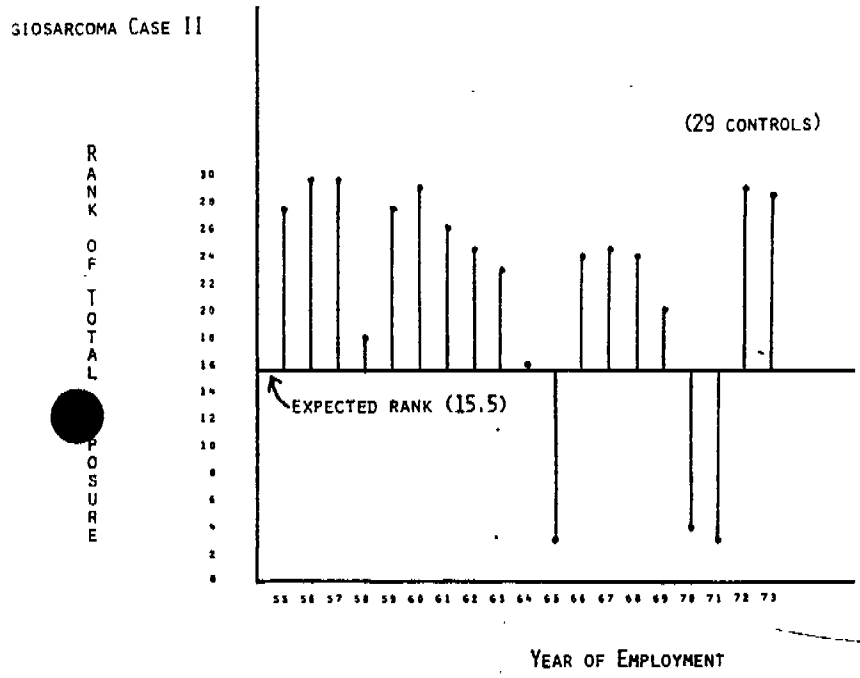

Fig 2. — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

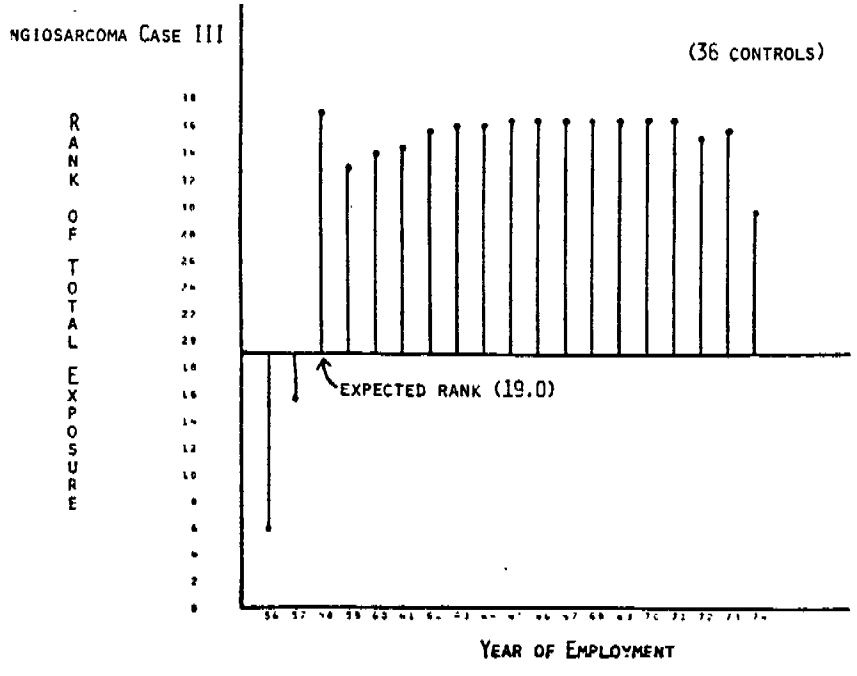

Fig 3. — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

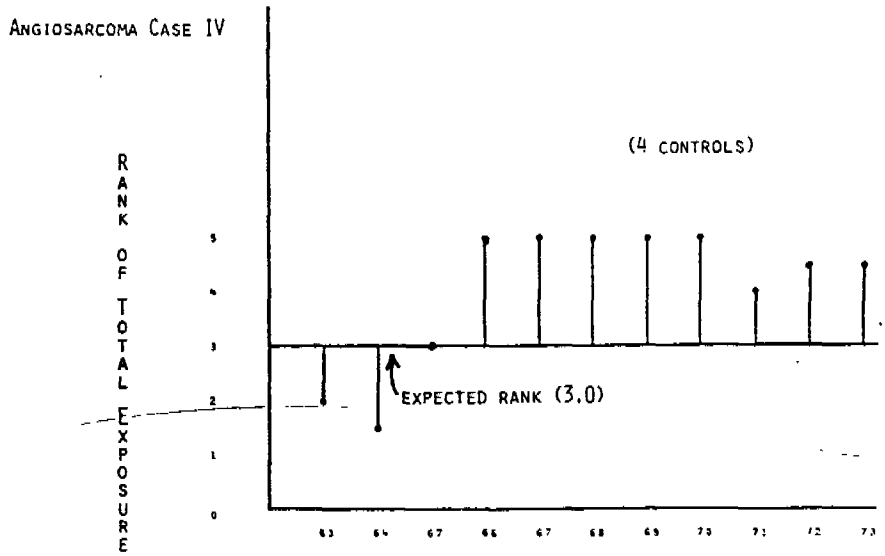

Fig 4. — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

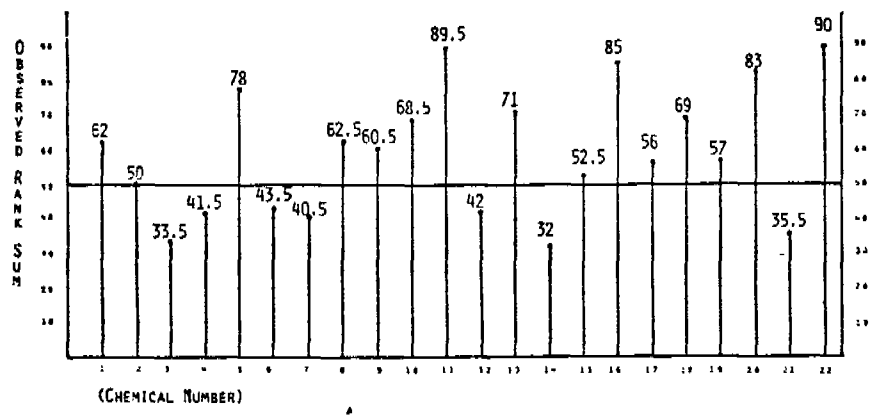

Fig 5. — Observed and expected cumulative exposure rank sums for four angiosarcoma cases compared with matched sets of controls. (Matched by age, sex, race, year of employment and survival as a B. F. Goodrich Chemical Company employee to January 1, 1974. The numbers of controls for the four angiosarcoma patients were 4, 23, 29 and 36. The maximum possible rank sum is 96 and the minimum is 4. Expected rank sum is 50. A rank sum of 80 or more would occur by chance 2.6% of the time. A rank sum of 20 or less would occur 2.6% of the time.)

sarcoma subjects also showed significantly high exposures to chemicals number 20 and 22. Chemical number 20 is a group of catalysts used only with vinyl chloride and chemical number 22 is hexane, used as a solvent for the group of vinyl chloride catalysts. In addition, the data also strongly suggest a high exposure to chemical number 11, diethyl maleate, also a specialized catalyst used only for a specialized process with vinyl chloride.

A clear pattern of exposure is apparent in Table 2. All four angiosarcoma subjects showed excess exposure to 5 of 20 chemicals (numbers 5, 11, 16, 20, 22). By chance, this would be expected to occur for only 1.25 chemicals. All four angiosarcoma subjects also had less than expected exposure to six additional chemicals (numbers 2, 3, 4, 7, 14, 21). The expectation again is only 1.25. When the binomial distribution is inspected (i.e., the distribution of the number of successes in four trials with the probability of success at each trial being one-half), the results are statistically significant ($\chi^2 = 36.7$: $p < 0.001$). These are summarized in Table 3. Once more the null hypothesis of random assignment of exposures is rejected. For chemicals number 6 and 8, the exposure was tied for all members of group 4 and they were not included in the analysis. Figs 1 to 4 show the observed to the expected rank exposure for each employee with angiosarcoma by each full year of exposure. The pattern is one of consistent high exposure as compared to the matched controls. It is evident that the system does reflect the autocorrelation in jobs over time as well as the exposure to vinyl chloride among the subjects with angiosarcoma.

To remove the assumption of independence from year to year (as would be required in new field studies), the CERM were summed over years for each angiosarcoma subject and the associated controls. These then provided a single ranking for each matched group. The observed independent ranks of the four angiosarcoma subjects were then summed and compared to the expected rank sums in 5. The exact distribution of the rank sums was obtained by direct enumeration. The angiosarcoma subjects again show significantly high exposure to chemicals number 16 (vinyl chloride), number 20 (catalysts), number 22 (hexane used as a catalyst solvent), and number 11 (diethyl maleate). Fig 6 displays the vinyl chloride rank of the angiosarcoma subject in each matched group; this is the chemical through which empirical validation of the procedure is achieved.

Prior knowledge of the etiology of angiosarcoma was used by the authors to validate these exposure indices. It is questionable what the situation would have been if such prior knowledge had not existed. This study would have shown that employees who subsequently developed angiosarcoma had had high exposure as compared to

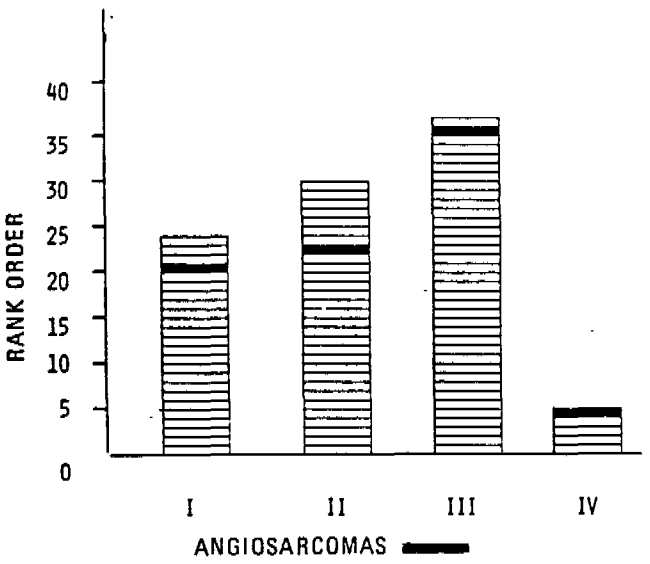

Fig 6. — Vinyl chloride exposure rank of matched individuals with angiosarcoma. (Matched by year of birth, sex, race, year of employment and survival as a B. F. Goodrich Chemical Company employee to January 1, 1974.)

matched controls for a set of four highly correlated chemicals selected from a larger set of 22 studied. These 22 had been selected because of potential toxicity or carcinogenicity by the following criteria: known hepatotoxin, suspected carcinogen, degree of toxicity, degree of contact, and location relative to vinyl monomer polymerization areas. The chemicals would certainly be suspect, but because of correlated exposures, a determination of an exact cause-effect relationship would not be possible. It is certain that further studies would be initiated to interpret the observed events.

The total cost incurred in setting up this system retrospectively (i.e., the cost of going back into records covering plant operation from the beginning up to the present), including the standardization of 321 job classifications ($450), the application of A-D codes to work histories for 1400 employees ($4,760), the assignment of exposure rating to each job classification for each of 35 years for each of 22 chemicals ($880), the extraction of medical history data ($6,000), and computerization ($7,920) was $20,010, or $16 to $17 per employee. The prospective cost, i.e., the cost of work that is recorded regularly forward in time (not including work and exposure history from past times) averaged $3,281 per year, or $2 to $3 per employee, with a breakdown as follows: job classification (1 to 3 new jobs per year), $60; work history (240 new employees per year), $136; exposure indices (20 new chemicals per year), $160; medical data $1,425; and computer costs $1,500. Costs were determined on the basis of actual man-hours worked using industrial hourly wages of the individuals who performed the work.

These data demonstrate empirically that a system of rank ordered individual exposure indices (CERM) for highly suspect chemicals can be implemented in an industrial environment and can identify a known causative relationship between exposure and the development of disease. This system can provide a means of monitoring industrial environments of any size at minimum costs. It can also allow for the introduction of sophisticated monitoring methods and prospective surveillance of an environment, taking into account co-factors which influence biological outcome.

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