CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE
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8EHQ - 1098 - 14286

October 2, 1998

Contains No CBI

MR 110665

TSCA 8(e) Coordinator
Mail Code 7407
Room E-G99 East Tower
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Sir:

The Vinyl Chloride Health Committee of the Chemical Manufacturers Association submits preliminary results from a case-control study of brain cancer occurrence in the workforce at a facility which manufactured vinyl chloride polymer and other products (the B.F. Goodrich Bells Lane Plant) in Louisville, Kentucky. These results are submitted pursuant to Section 8(e) of the Toxic Substances Control Act.

A preliminary draft report of the study, conducted by researchers at the University of Louisville, is enclosed. The study used data from the University of Louisville's Occupational Health Surveillance database, which contains estimates of exposure to vinyl chloride and 21 other chemicals. The primary analysis shows no association between brain cancer and exposure to vinyl chloride (CAS #75-01-4). A secondary analysis, however, seems to indicate a statistically significant association between total duration of employment at the plant and occurrence of brain cancer. It is difficult to draw a conclusion from the reported results, as they are incomplete and characterized as follows by the authors:

Interpretation

Based on the logistic regression model as provided by the SAS procedure LOGISTIC, there is no statistical evidence of any association between the occurrence of

brain cancer and exposure to vinyl chloride as measured by the average CERM exposure (CERM/DUR). The effect of the employ-ment duration (DUR) and the age at hire (STA_AGE) on the

occurrence of brain cancer, although statistically significant, is seen to be marginal. Additionally, the logistic regression analysis has confirmed the earlier findings of the rank-test method, of no statistical evidence against the hypothesis of no relation between the response variable (brain cancer occurrence) and workers' exposure to vinyl chloride.

The member companies of the Vinyl Chloride Health Committee, on whose behalf this submission is made, include:

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When we receive a final report, it will be submitted to you. In the meantime, if you have any questions regarding this letter, please contact Wendy Sherman of my staff at 703-741-5639.

Sincerely,

Courtney M. Price
Vice President, CHEMSTAR

Enclosure

cc: Vinyl Chloride Panel

BRAIN CANCER OCCURRENCE IN VINYL CHLORIDE- EXPOSED CHEMICAL WORKERS

ABSTRACT

Since the initial discovery in 1973 of hepatic angiosarcoma among vinyl chloride-exposed chemical workers by John L. Creech, Jr. (Creech JL and Johnson MN, 1974) at the B.F. Goodrich Bells Lane Plant in Louisville, Kentucky, there has been epidemiological speculation regarding the association of other cancers to vinyl chloride exposure. Initial epidemiological studies reported an increased association of brain cancers among their vinyl chloride-exposed cohorts. Tabershaw and Gaffey's (1974) mortality study of workers and manufacturers of vinyl chloride and polyvinyl chloride reported an increased association with vinyl chloride exposure. Subsequent epidemiological studies of other vinyl chloride worker populations have not confirmed this association. Follow-up studies by Tabershaw *et al.* (1975) and Wong *et al* (1991) of the same population again reported this increased association. The object of this study is to assess the relationship of vinyl chloride exposure and brain cancer occurrence through the prospective Occupational Health Surveillance Program at the B.F. Goodrich Bells Lane Plant in Louisville, Kentucky. This study utilized the University of Louisville's Occupational Health Surveillance database whose cohort is composed of over 4,000 workers at a single vinyl chloride polymer production facility. The database includes individual employee work history, medical illness and disease records including pathological specimens, laboratory and imaging studies. It also contains validated chemical exposure estimates to vinyl chloride and 21 other chemicals over a 54-year period. This study assessed each brain cancer occurrence in this work force using a retrospective/prospective case control analysis. Each brain cancer case was histologically confirmed when tissue was available. Exposure to vinyl chloride was estimated by use of cumulative exposure rank measure (CERM). The study analysis utilized the non-parametric rank-order method of Greenburg and

Tamburro (1981) modified by Rempala for each index case and its controls. The logistic-shift model described by Cusik (1985) was also used to determine the power statistic for the Greenburg and Tamburro non-parametric rank-order approach. In addition, a separate standardized mortality ratio (SMR) analysis was done using US and Kentucky as reference populations and a confirmatory logistic regression analysis was performed. The study analysis reevaluated the hypothesis that an association exists between vinyl chloride exposure and the development of brain cancer in chemically-exposed workers. Utilizing two different statistical methods, based on stratified analysis and (three) logistic regression models *(add third method)*, the obtained results were not statistically significant and therefore rejected the hypothesis of an association between brain cancer and vinyl chloride exposure. The final results of these analyses indicate no statistical association between accumulative exposure to vinyl chloride and brain cancer outcomes. These study analyses further support our initial observations in 1978 of the B.F. Goodrich Bells Lane worker population that strongly suggest no causal association between vinyl chloride and brain cancer.

BRAIN CANCER OCCURRENCE IN VINYL CHLORIDE- EXPOSED CHEMICAL WORKERS

Draft 1, 08/20/98

Introduction

Since the discovery of vinyl chloride-associated angiosarcoma of the liver, various traditional epidemiological studies of workers employed at vinyl chloride polymerization plants have reported an inconsistent statistical association between brain and central nervous system tumors and exposure to vinyl chloride. Of at least 10 independent epidemiological studies, six have shown no statistical association with vinyl chloride and four have reported a statistical association when compared to the United States' population. The largest cohort study initiated by Tabershaw-Cooper Associates in 1973 suggested there may be an excess of brain and central nervous system tumors; the follow-up study of the same population in 1980 by Cooper[1] studied an expanded population now reported a statistically-significant increase excess in brain tumors and the third follow-up by Wong and Thornton, published in 1991, also suggested a statistical increase in that cohort population. Approximately half (12) of the brain cancer cases came from plants #25 and #33, the same two plants that contributed the majority of angiosarcoma cases (one of which presumably is the B. F. Goodrich Bells Lane Plant, or our plant).

Many of the initial clinical epidemiological studies that found a higher association of central nervous system tumors in vinyl chloride workers than would be expected in comparison to the general U.S. population did have acknowledged weaknesses in their approach to exposure characterization where there was questionable validity in characterizing exposure of a given worker. In addition, as in most prior traditional epidemiological studies, the underlying cause of death was derived from death certificates without necessarily validating the reported

cause of death as to its anatomical and pathological accuracy. Those studies which did not find a higher association of brain cancer with vinyl chloride exposure were faulted because of the relatively small cohort size ranging from 1,000-2,000.

(insert table of all independent epidemiological studies related to vinyl chloride industrial workers in which brain cancer occurrence has been assessed)

The initial observations of Greenberg and Tamburro (1978; 1979) utilizing a non-parametric rank-order case-control assessment, revealed no association with rank-ordered exposure to vinyl chloride between index case and controls. This initial observation involved four brain cancer cases. Due to the highly unique characterization of each industrial worker to the relative degree of exposure to vinyl chloride, a follow-up study was instituted. This study's research objective was a retrospective analysis of a prospective occupational surveillance database testing the hypothesis that brain cancer occurrence is associated or causally related to vinyl chloride exposure utilizing the Greenberg rank-order case-control approach.

Vinyl chloride exposure has been confirmed as the causal agent for the development of angiosarcoma of the liver in chemically-exposed workers who have worked for more than

three years at exposures greater than 50-200 ppm time-weighted average (*REF:* Seminars in Liver Disease). Repeated epidemiological studies have confirmed the high association of vinyl chloride and the development of angiosarcoma of the liver in various cohorts on three continents (North America, Europe and Asia) (*REF:* Doll). Repeated epidemiological studies have not confirmed the initial observation that brain cancer occurrence is associated with vinyl chloride exposure (our NCI contract). The prospective assessment of the B. F. Goodrich Louisville cohort over the past 20 years provided a unique opportunity to address this question. This was especially so because of the cohort's detailed clinical characterization with regard to each individual worker's exposure, relative and absolute, health status and disease outcome.

Materials

The University of Louisville's prospective Occupational Surveillance database presently contains almost 4,000 documented industrial workers who were employed for one or more years at the Bells Lane plant in Louisville, Kentucky between its initial operation in 1942 until its first offspring companies, Zeon, Inc. (In 1990) and Geon, Inc. (In 1993) were created. This database contains:

1. Work history data consisting of standardized job classification codes from the initiation of plant operation in 1942 through the present.
2. individual employee work history records from the date of first employment through to the present, including their present employment status if retired or no longer actively employed (Appendix A).
3. Individual employee medical illness and disease records, including
   a. Annual medical history and physical examinations performed as a Federal regulatory requirement or by voluntary participation in the Occupational Health Surveillance Program. These history and physical examinations include detailed

neurological history and neurological physical examination data. Annual medical examination data is available in order 80% of employees employed on or after June 6, 1973.

b. Their present health status (whether the employee is alive or dead) and whether there has been any history of cancer.

c. Certification and documentation of the cause of death (available in approximately 490 of the 530 known deaths; 46 individuals have incomplete data and need further verification).

4. Chemical exposure estimates have been obtained by two independent methods. The first by a chemical exposure rating system established by Dr. R. A. Greenberg. This system consists of a 7-point (0 to 6) rank-order scale which estimates the exposure based on each job activity (classification).

The second system for assessing exposure consists of long and short term personal chemical monitoring data collected randomly on B. F. Goodrich employees. These constituted individual monitoring of various job classes utilizing personal charcoal pump monitors and the GC/MS analysis of these charcoal absorption units with regards to the specific chemical. There is available chemical monitoring data on three chemicals: chemical no. 16 (vinyl chloride), chemical no. 03, and chemical no. 07. A high correlation was found between the estimated rank order of exposures and individual job monitoring (Appendix F).

Method of Analysis

This report presents a statistical analysis of a prospective occupational surveillance study data of this industrial cohort consisting of 4,300 employees of the B. F. Goodrich Bells Lane

chemical plant in Louisville, Kentucky, employed for at least one year between its initial opening in 1942 and May 1998. The primary purpose of this study was to test the null hypothesis of no relation between the occurrence of brain cancer and vinyl chloride exposure as measured by Cumulative Exposure Rank Months (CERM). The hypothesis was tested by means of two rank statistics using a matched case-control design as described in the following section. The secondary purpose of the study was to identify any possible association between brain cancer occurrence and exposure to vinyl chloride. The statistical analysis for this part of the study was conducted by means of a binary logistic regression model, described below.

1. *Rank Method Analysis*

Data Description and Statistical Methodology

The data consists of the measurements of vinyl chloride exposure (in CERM) and the employment histories of a cohort of chemical workers identified as employees of B. F. Goodrich Bells Lane Plant in Louisville, Kentucky, employed in or after 1942 and no later than May 1998. Out of the initial cohort of 4,300 individuals satisfying this criterion, 12 were identified as deceased due to brain cancer and all remaining (deceased or not) as free of cancer at the time of the last contact. To each one of the 12 identified brain cancer cases, the individually-matched controls were selected out of the non-brain cancer members of the cohort. As the matching criterion, the time of employment (within 12 months) and the length of employment (within 12 months) were used. This process has resulted in the selection of the total of 94 individuals (including the cancer cases) out of the initial cohort and stratification of the selected group. The group was stratified into 12 separate strata with only one case per each stratum and the overall number of controls equal to 82. By design, no controls were shared by the cases. In cases when a control individual matched more than one case, he/she was assigned to the case with the longest employment history. Since CERM by

its design is only a relative measure of exposure and none of the identified 12 brain cancer victims was hired after May 1965, in order to avoid a possible misclassification of the individuals who joined the factory work force at a later date, CERM measurements of all employees with work histories past January 1, 1973, were truncated to that date.

The rank of exposure of each case within this stratum (consisting of individually-matched controls and self) was recorded and the sum of ranks as well as the weighed sum of ranks was calculated. In the case of the weighted rank-sum, the reciprocals of the number of controls per stratum plus two were used as the weights value. This particular choice of weights guarantees that the test, based on weighted rank sum statistic, is locally most powerful against location shifts and is standard in statistical analysis of this type. The p-values for the test statistics were calculated using normal approximation, which is appropriate under the null hypothesis that the stratum-specific distributions of the exposure levels for the cases and their matched controls were identical. The power of the tests was calculated under the shift model using the bootstrap algorithm described in Rempala *et al.* (1997) with the stratum-specific values of the shifts (measured in standardized CERM units) as presented in column two of Table 3 in the Results subsection which follows. The asymptotic test for the across-strata homogeneity of shifts was not performed due to a relatively small number of cases and thus possibly a very poor approximation of the test statistic. However, since the observed differences in the shift values from strata to strata were considerably large, no assumptions of the between-strata shift homogeneity were made.

Data Summary for Rank-Method Analysis

As described above, for the purpose of rank analysis, the group of 94 individuals consisting of 12 identified brain cancer victims and their individual controls was selected out of the initial cohort. Although the identified brain cancers were all white males, the exact race

and gender break-down of controls is not known since the data on gender and race of the individual cohort members employed between 1942 and 1973 was generally unavailable. However, based on the available data, it is estimated that the group of controls consisted of 93% white males, 1% minorities and 6% women. This approximate racial/gender classification for the group of 94 individuals is presented in Chart 1. The stratification structure , the employment dates and employment age for the cancer cases along with the age statistics for the matching controls are presented in Table 1. In the labeling of the table columns, *N* stands for the number of controls per stratum; *Start, Stop, Age* and *Dur* are, respectively, the employment start date, stop date (month and year only) and the employee's age and time of employment for the brain cancer cases. For the matching controls, the minimum and maximum age at time of employment (*Min Age, Max Age*), as well as average age (*Avg Age*) are also reported. From the data presented in Table 1, it is clear that among the cancer cases there are large differences in employment duration which range from 441 months to as little as slightly over 12 months. It is also apparent that the brain cancer occurred mostly among workers hired from the early 1940s to early 1950s (11 cases). Among the individuals hired after 1954, only one was identified as a brain cancer victim. At the time of employment, most of the brain cancer cases were in their 20s and 30s.

The measures of total exposure to vinyl chloride (as measured by CERM) for the cases along with the exposure statistics for matching controls are given in Table 2. The statistics presented for the controls are: minimum, maximum and average exposures in CERM (*Min CERM, Max CERM, Avg CERM*) and the exposure standard deviation (*CERM SD*). For the purpose of the across-strata comparison, the standardized measure of exposure (*Standardized CERM*) given by CERM/CERM SD was also calculated for both case and control CERM. The comparison of the case and average control exposure, based on standardized CERM for each stratum, is given in Chart 2. The visual analysis of the data in the chart seems to indicate no

Chart 1.

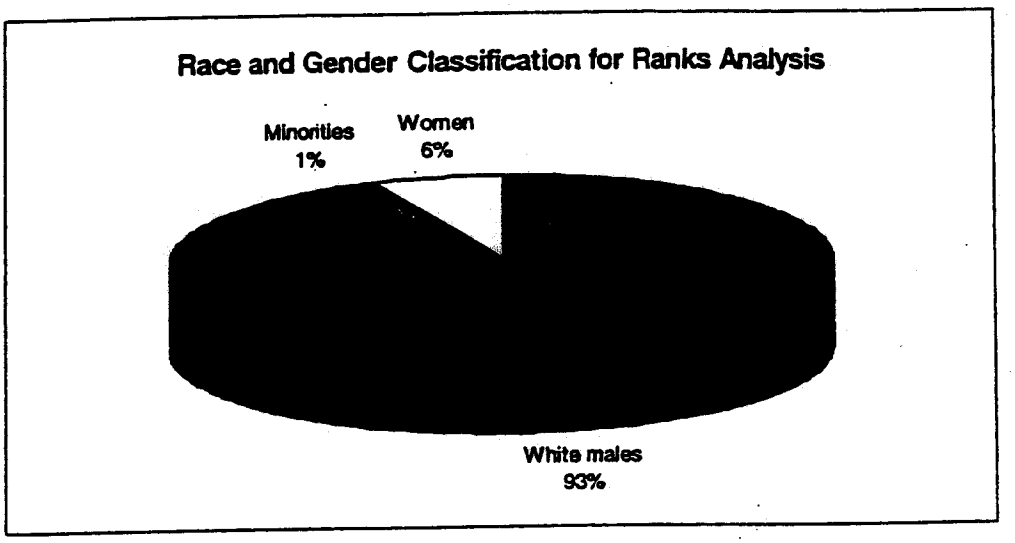


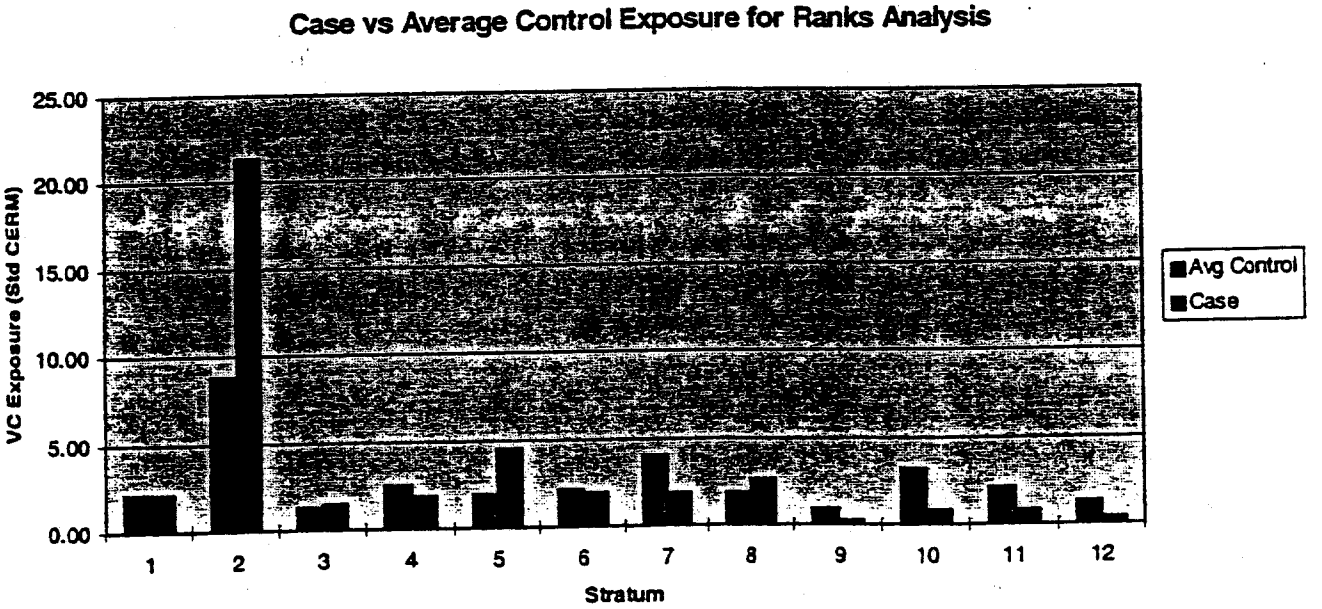
Table 1. Age and Employment Duration per Stratum

		CASE				CONTROLS		
Stratum	N	Start	Stop	Age	Months of Employment	Min Age	Max Age	Avg Age
1	3	Feb-42	May-73	22	375.68	21	24	23
2	3	Apr-65	Jul-78	34	158.93	33	35	34
3	2	Sep-49	Oct-81	22	385.58	21	22	22
4	13	Dec-45	Jun-63	27	209.79	26	28	27
5	4	Feb-43	Feb-44	18	12.26	18	19	18
6	7	Jan-54	Jun-87	21	401.26	19	23	21
7	10	Oct-44	May-65	36	247.27	35	38	36
8	4	Nov-49	Aug-71	36	261.67	36	38	37
9	15	Jan-50	Sep-52	23	32.28	22	25	24
10	6	Jan-47	Apr-70	33	279.52	33	35	34
11	5	Apr-47	Jan-84	23	441.17	23	24	24
12	10	Aug-49	Mar-51	23	18.18	21	24	22

Table 2. Comparison of Cases and Controls Exposures per Stratum

		CONTROLS					CASE	
Stratum	N	Min CERM	Max CERM	Avg CERM	CERM Standard Deviation	Standardized CERM	CERM	Standardized CERM
1	3	745.97	1763.98	1167.98	530.84	2.20	1135.56	2.14
2	3	260.18	324.07	287.73	32.84	8.76	700.51	21.33
3	2	436.01	1392.37	914.19	676.25	1.35	1027.07	1.52
4	13	208.97	1098.75	666.37	266.68	2.50	502.79	1.89
5	4	17.52	49.49	31.82	16.26	1.96	73.35	4.51
6	7	378.07	1618.18	875.39	411.16	2.13	804.20	1.96
7	10	632.44	1380.91	1091.13	268.85	4.06	513.90	1.91
8	4	339.93	1192.44	698.92	374.83	1.86	987.15	2.63
9	15	55.60	951.30	252.51	273.67	0.92	87.68	0.32
10	6	592.90	1469.11	1111.49	349.96	3.18	278.61	0.80
11	5	564.03	2091.05	1459.11	682.46	2.14	558.81	0.82
12	10	19.75	163.06	60.51	45.87	1.32	18.11	0.39

Chart 2.



obvious pattern of case over-exposure to vinyl chloride when compared with the average exposure of the matched control. In all strata but one (Stratum No 2), the differences between case and average control exposure levels seem to be relatively small.

Results

Based on the strata sizes obtained with our matching criterion, the values for rank-sum (Greenberg) and weighted rank sum (Cuzik) statistics were found to be 37 and about 4.96, respectively, with their corresponding approximately p-values for a two-sided test of 0.96 and 0.89, respectively. The power for the tests under a shift model was found to be 0.326 for Greenberg statistic and 0.092 for Cuzik statistic. These values are summarized in Table 2. The large discrepancy between the two tests seems to be caused by the considerable differences in the strata sizes (for all-equal strata, Greenberg and Cuzik tests coincide and thus must have the same power for the given values of stratum-specific shifts).

The values of the estimated stratum-specific shifts were obtained by taking the stratum-specific medians and averages of the differences in the cases and controls exposure values measured in standardized CERM units. The estimated values of the shift for each of the 12 strata, based on medians (*DIFF50*) and averages (*AVGDIFF*) are given in columns 2 and 3 of Table 3. Unfortunately, due to the fact that there was only one case per stratum and no assumptions of homogeneity were made, the standard errors of these estimates are quite large (about one standard unit).

Table 3. Number of controls per stratum and stratum-specific shift estimators

STRATUM	DIFF50 (SE =1)	AVGDIFF (SE =1)	N
1	0.2667	-0.0611	3
2	12.8380	12.5705	3
3	0.1669	0.1669	2
4	-0.4513	-0.6134	13
5	2.6576	2.5540	4
6	-0.2413	-0.1731	7
7	-2.5456	-2.1470	10
8	0.9484	0.7690	4
9	-0.0865	-0.6023	15
10	-2.4494	-2.3799	6
11	-1.7327	-1.3192	5
12	-0.5801	-0.9242	10

For the purpose of power calculations, the medians rather than averages were used for the shifts estimation, as they are less sensitive to outliers. However, it may be seen in Table 1 that the estimated values of the shifts (and thus the power calculations) would differ very little if the averages were used instead.

Interpretation

Based on the values of the test statistics and their corresponding p-values, the results obtained demonstrate no statistical evidence against the null hypothesis of no association between brain cancer occurrences and exposure to vinyl chloride, as measured in CERM.

Limitations

Since the number of brain cancers in the cohort was relatively small, the power of rank tests was also not very large. Additionally, the lack of across-strata shift homogeneity did not allow for the precise measurements of the shifts and possibly reduced the precision of the bootstrap power estimation algorithm. However, given the very large p-values obtained in the analysis, it seems reasonable to expect that the larger number of brain cancers in the study, while increasing the power, would most likely not result in the decrease of p-values to statistically-significant levels.

2. *Logistic Regression Analysis*

In addition to the rank test method described above, the binary logistic regression analysis was also performed. The purpose of this analysis was twofold: (a) to confirm the results of the rank tests' analysis concerning the hypothesis of a lack of association between the occurrence of brain cancer and vinyl chloride exposure and (b) to create a model of causal

relationship between brain cancer and vinyl chloride exposure (as measured by CERM) and test its statistical significance.

Data and Method Description

For the purpose of binary logistic regression analysis, individuals hired prior to January 1, 1972 with working histories of at least one year were selected from the initial cohort of 4,300 chemical workers of the Bells Lane chemical plant. The total number of individuals satisfying the above criterion was 1,338. As in the case of rank analysis, the same 12 cohort members were identified as the brain cancer victims and were assigned a response value of 1 (one). All remaining members of the selected sub-cohort were assigned a response value of 0 (zero), that is, free of cancer at the time of last contact. The following set of covariants was included in the logistic regression model:

- age at the time of initial employment (in years);
- duration of employment (in months);
- average monthly exposure to vinyl chloride (measured in CERM divided by the duration of employment in months).

As in rank method analysis, to avoid misclassification of latter-employed individuals, the CERM values and employment histories for all members of the selected sub-cohort were truncated at January 1, 1973. Since the data on race and gender of the cohort members hired prior to 1973 were largely unavailable, these variables were not included in the analysis.

To obtain the model of a causal relation between brain cancer occurrence (coded as a binary response variable) and the above set of explanatory variables, the standard maximum likelihood method of fitting the linear logistic regression model for a binary response variable as given in SAS procedure LOGISTIC (SAS Institute, 1992) was applied. This analysis was

conducted using data of the entire selected sub-cohort of 1,338 chemical workers.

Data Summary

The descriptive statistics calculated for all three covariants included in the logistic regression model are given in Tables 4-6, separately for two response groups. From this initial comparison of the descriptive statistics, it seems that on average, the employment duration was longer among brain cancer cases (average 235.36 months and median 254.47, as opposed to average of 74.73 months and median of 42.64 months for free-of-cancer workers). Moreover, the individuals identified as brain cancer victims were on average younger (average hiring age of 26.5) than their co-workers (average hiring age of 30). Most importantly, the exposure data given in Table 7 shows that the individuals who have developed brain cancer were, on average, slightly less exposed to vinyl chloride than the individuals who had not developed disease. The comparison done in this fashion is obviously compromised by the considerable difference in sizes among the two compared groups.

Table 4. Ranking statistics values, their corresponding p-values, and power under the shift model for shift values DIFF50 provided in Table 1.

STATISTIC	VALUE	APPROX. P-VALUE	POWER
Greenberg	37	0.9614949	0.326
Cuzik	4.9573996	0.8897312	0.092

Table 5.

	EMPLOYMENT DURATION (MONTHS)	
	Response =1 (Brain Cancer Occurrence)	Response=0 (No Brain Cancer Occurrence)
N	12	1326
Mean	235.36	74.73
Std Dev	153.61	78.72
Skewness	-0.32	1.74
Max	441.17	480.13
Q3	380.63	91.33
Median	254.47	42.64
Q1	95.6	21.83
Min	12.26	12

Table 6.

	AGE AT HIRE (YEARS)	
	Response =1 (Brain Cancer Occurrence)	Response=0 (No Brain Cancer Occurrence)
N	12	1326
Mean	26.57	29.85
Std Dev	6.58	9.06
Skewness	0.58	1.05
Max	36.44	66.72
Q3	33.51	35.40
Median	23.21	27.00
Q1	22.10	22.80
Min	17.73	11.33

Table 7.

	AVERAGE MONTHLY VC EXPOSURE (CERM/DUR)	
	Response =1 (Brain Cancer Occurrence)	Response=0 (No Brain Cancer Occurrence)
N	12	1326
Mean	2.69	2.95
Std Dev	1.47	2.95
Skewness	0.99	2.01
Max	5.98	25.18
Q3	3.40	4.15
Median	2.53	2.90
Q1	1.63	1.61
Min	1	0.01

Results

The maximum likelihood method, as used by the SAS system LOGISTIC procedure, indicated that the overall model fit for three considered initially-explanatory variable; duration of employment (*DUR*), age at hire (*STA_AGE*) and average monthly exposure to VC (*AVGCM16*) was found to be statistically signifcant (p-value < 0.001). However, as measured by Wald statistic criterion, the presence of the vinyl chloride exopsure variable in the model was not found to be statistically significant (p-value > 0.9). Thus, the model was adjusted with the help of the backward elimination procedure, and as a result, the exposure variable was removed from the model. The model with two covariants (*DUR* and *STA_AGE*) was found also to be statistically significant (p-value < 0.001) with the residual chi-square statistic value of approximately 0.126 with one d.f. (P-value > 0.9). The comparison of the overall model fit, as measured by both the score and log likelihood functions, for the logistic regression model with and without the vinyl chloride exposure variable is given in Table 8. The values of the negative log likelihood function when adjusted for the number of covariants (using Akaike Information Criterion, or AIC) and for the number of observations (using Schwartz Criterion, or SC), compared with their initial values for the model with three covariants have visibly decreased although the negative log likelihood function itself has in fact increased due to ther eduction of the number of covariants. The maximum likelihood estimators of the model coefficients for the variables *DUR* and *STA_AGE* are given in Table 9. Let us note that both values are very close to zero. These small values for the regression coefficients indicate that the model covariants seem to have only very small effect on the response variable. The detailed printout of the results of the LOGSTIC procedure for the initial model and then backward elimination steps can be found in the Appendix.

Table 8. The overall model fit after excluding the vinyl chloride exposure covariant as compared with the initial model

CRITERION	INITIAL VALUE (with 3 covariants)	FINAL VALUE (with 2 Covariants, after excluding VC exposure)
AIC	110.756	108.768
SC	131.551	124.365
-2LOG L	102.756	102.768
Score Stat.	60.463 (p<0.001)	60.202 (p<0.001)

Table 9. The final model maximum likelihood estimators

VARIABLE	DF	REGRESSION COEFFICIENT	WALD STATISTIC	P-VALUE	ODDS RATIO
Intercept	1	-3.83	9.28	0.0023	
DUR	1	0.000453	32.33	<0.001	1
STA AGE	1	-0.008	4.85	0.0277	0.992

Interpretation

Based on the logistic regression model as provided by the SAS procedure LOGISTIC, there is no statistical evidence of any association between the occurrence of brain cancer and exposure to vinyl chloride as measured by the average CERM exposure (*CERM/DUR*). The effect of the employment duration (*DUR*) and the age at hire (*STA_AGE*) on the occurrence of brain cancer, although statistically significant, is seen to be marginal. Additionally, the logistic regression analysis has confirmed the earlier findings of the rank-test method, of no statistical evidence against the hypothesis of no relation between the response variable (brain cancer occurrence) and workers' exposure to vinyl chloride.

Limitations

As in the case of the rank method, the major limitation of the study is a small number of brain cancers identified in the cohort. However, given the form of the logistic regression model obtained above, it is doubtful that even a relatively large increase in the number of identified brain cancers in the studied cohort would significantly change the model parameters.

Another limitation of the analysis is a lack of data on gender and race of the cohort workers employed at the B.F. Goodrich plant prior to January 1973. However, since only white males were identified as brain cancer victims, and given that the majority of the cohort is of the same race and gender, this limitation is of minor concern.

3. *Summary and Conclusions*

Two different statistical methods were applied to identify a possible association between vinyl chloride exposure as measured in CERM and the occurrence of brain cancer among an industrial cohort working at the B. F. Goodrich Bells Lane chemical plant between 1942 and May 1998. The total cohort consistent of 4,300 chemical workers out of which 12 white males were identified as deceased due to brain cancer.

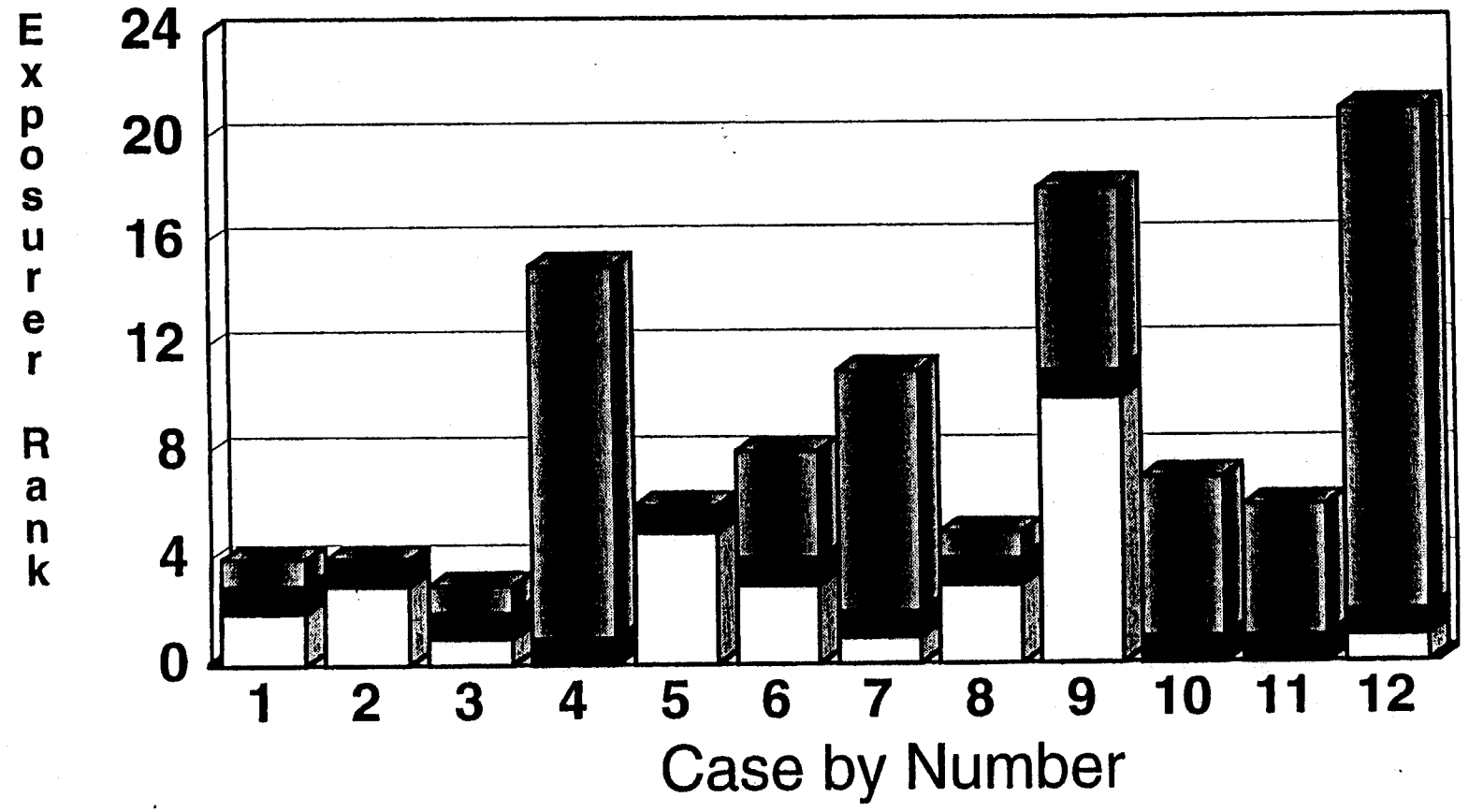
The first method based on stratified analysis looked for a possible causal relation between brain cancer and the total cumulative exposure to vinyl chloride while controlling for the exposure duration. For purposes of rank-test analysis, each of the 12 cancer cases was matched with a free-of-cancer co-worker on the basis of their common employment history. The number of cohort members who satisfied the control criterion was equal to 82, and only their CERM values were considered in the analysis. The rank statistics based on the case within-stratum CERM were then calculated and the null hypothesis of uniform distribution of the case CERM ranks within each stratum was tested. The details of the analysis were outlined in a previous section. The obtained p-values were not significant, and the hypothesis of no association between brain cancer development and vinyl chloride could not be rejected.

The second method employed the standard logistic regression model, using the duration of employment, age at employment and overall monthly average CERM exposure for each individual as the covariant. Since no brain cancers were found among workers from the initial cohort hired after May 1966, only workers with at least one year of work history, employed prior to January 1, 1973, were selected. The total number of such individuals was 1,338. The details of the analysis were outlined in a previous section.

The final results of the analysis indicated no statistically significant association between explanatory variables (including average CERM exposure to vinyl chloride) and the binary variable coding the cancer occurrence.

Vinyl Chloride and Brain Cancer

Case Control /Rank Exposure



□ Controls, Low ■ Index Case ■ Controls, High

Vinyl Chloride Angiosarcoma Cases

BFG Cases Ranked by Exposure