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Case-Control Study of Gliomas of the Brain among Workers Employed by a Texas City, Texas Chemical Plant

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Abstract. A Texas petrochemical plant had elevated standardized mortality ratios for neoplasms of the brain. A case-control study examined possible associations between gliomas of the brain and job title, departmental employment history, chemical exposure history, geographic location within plant, dates of employment, and residence. The greatest apparent risks were associated with exposure to carbon dioxide, diethyl sulfate, diethylene glycol, ethanol, ethylene, isopropanol, methane, tetraethylene glycol, and vinyl acetate; with first employment in the 1940s or early 1950s, and with residence in La Marque, Tex. No significant differences between cases and controls were apparent in duration of exposure to any of these chemicals.

Introduction

In February 1979, the National Institute for Occupational Safety and Health (NIOSH) and OSHA, with the aid of the company management, began an investigation of a cluster of primary brain tumors at a chemicals and plastics plant in Texas City, Tex. *Alexander* et al. [1] have described the characteristics of the brain tumor cases and the methods for case identification. Two retrospective cohort mortality studies of all male hourly workers employed at this plant from 1941 through 1977 have been reported [2,

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3]. Findings included an overall standardized mortality ratio [SMR = 100 (observed/expected)] for benign, malignant, and unspecified neoplasms of the brain of 206 ($p < 0.05$). For those who worked more than 20 years at the plant (i.e., who began work before 1957), the SMR was 377 ($p < 0.05$) [2]. No other cancers were found significantly in excess of expected, and the overall SMR was not elevated. We here describe a nested case-control study of primary brain tumor cases among the employees of that plant.

Austin and Schnatter [4] have recently published a parallel study which showed no association between exposures in the plant and brain gliomas. They used deceased employees whose deaths were known to the company as controls for the same cases, employed an unmatched design, and did not include analysis of residence. They were able, however, to use multiple comparison groups; one group excluded controls who had died of other malignancies while another permitted such decedents as controls. Subsets of these groups including only hourly employees permitted further refinement. These two studies are thus different enough to be complementary, not duplicative.

Methods and Materials

Case Identification

A total of 23 possible cases were identified: the company documented 12 cases from death certificates in their possession; lists of all adult males who were residents of surrounding counties and who died of malignant brain tumors between 1950 and 1977 were matched with company employment records, yielding 4 additional cases; another 3 cases became ill and died during the course of the study; and 4 additional deceased cases were found in the course of completing the cohort mortality study. We were able to obtain medical records for 20 of the possible cases and tissue specimens for 10.

The Armed Forces Institute of Pathology (AFIP) reviewed the tissue specimens. Where different diagnoses were recorded for the same patient, AFIP reviews were ranked first, autopsy reports second, surgical pathology reports third, diagnosis from the hospital chart fourth, and death certificate diagnosis last; the highest-ranked diagnosis was used for this study.

Since gliomas are carcinomas, arising from ectodermal tissue of the neural crest, while meningiomas arise from mesodermal embryonic tissue, we followed the recommendations of *Schoenberg* et al. [5], and limited consideration in this study to the 17 gliomas among the 23 former employees with death certificate diagnoses of brain tumor. This eliminated 1 case with a metastatic brain tumor from an unknown site, 1 who had been thought clinically to have a brain tumor but was found at autopsy to have a congenital malformation and no tumor, and 4 meningiomas. A summary of the cases excluded and included is given in table I.

Table I. Cases from cohort study included in and excluded from case-control study

Diagnosis	Included	Excluded
Gliomas	17	
Glioblastoma multiforme (includes diagnoses of astrocytoma grades III and IV)	14	
Thalamic glioblastoma suspected clinically; no tumor in biopsy of abnormal appearing area of brain cortex	1	
Pituitary adenocarcinoma suspected clinically; radiotherapy followed by proven glioblastoma 12 years later	1	
Astrocytoma grade II	1	
Metastatic tumor, unknown primary		1
Brain tumor suspected clinically, not found at autopsy		1
Meningioma, malignant		3
Meningioma, benign		1
Subtotal	17	6
Total	23	

Selection of Control Subjects

For each case, a pool of matched potential controls was drawn from the cohort of all people ever employed at the plant. Matching criteria were: race and sex matched the case; year of birth was within 3 years of the case's; date of first employment at the Texas City plant for the control was before that of the case, but year of first employment at the Texas City plant was not earlier than 3 years before the case's; the date the control was last employed was later than the case's last date of employment; the control, if dead, must not have died of a malignancy. For each case, 6 controls were then drawn by random number from the pool of employees meeting these criteria. No control was used for more than 1 case. Some cases and controls had prior experience in refineries or chemical plants, but the information available was, in our judgment, insufficient for analysis.

Data Collection

For each case and control, plant personnel completed coding sheets containing demographic data, date of each new job title or department code, job code, department code, date of each layoff, date of final termination (if no longer employed at the plant), and vital status (when known). NIOSH/OSHA researchers independently verified the accuracy of the coding.

Plant personnel provided translations for the job and department codes, indicated which department codes formed larger major department groups, and provided a list of chemicals used, produced, or redistributed in each department group. A 'department

group' is an operational unit of the plant manufacturing related products and within which employees often remained over fairly long periods. The departmental coding schemes used for accounting purposes within the plant have changed over the years, so a common list tracing the history of each department was prepared.

Plant engineers were able to characterize the chemical feedstocks, outputs, and intermediate products of each department through the years the plant has been in operation. Since industrial hygiene data were available only for recent years and for certain compounds, we equated the presence of a chemical in a department with potential worker exposure. This assumption was clearly not always accurate, nor were exposures necessarily equal in two departments using the same chemical.

Analysis

For each job, department, major department group, or chemical exposure common to at least 4 cases, an odds ratio was calculated and tested for possible statistical significance by *Mantel and Haenszel's* [6] procedure, using the matched data programs of *Rothman and Boice* [7]. Analyses were conducted for periods less than 15 years before the death of the case, 15 or more years before the death of the case, and any time before the death of the case (a case exposed for greater than 15 years and dying soon after last exposure would be counted in all three periods). Since this approach is a multiple-significance testing technique which should lead by chance to the finding of approximately one 'statistically significant' positive association, using a 90% (two-sided) confidence interval, for every 20 independent jobs, departments, or exposures considered, it is used here as an exploratory or hypothesis-generating mechanism; the probability values and confidence intervals cited throughout the paper are given only to show relative strength of associations.

Only those portions of the controls' work experiences which occurred during the time the corresponding case was employed were considered in this analysis, since the matching criteria selected controls with longer total work histories than the cases'.

Duration of exposure was examined for chemical exposures for which (a) the association with brain tumors reached statistical significance in the analyses described above or (b) previous reports suggested a possible relationship. For each chemical, cases' and controls' median months of potential exposure 15 years or more before death of the case were tabulated and a rank-sum test was performed [8]. Employees with no exposure were excluded.

Workers in a department nominally unexposed to a particular chemical could be exposed to toxic airborne vapors or dusts from an adjacent department. To assess this possibility, the years worked by each subject in each department group were tabulated, showing which department groups had about the expected 1:6 ratio of case to control-years, which groups had disproportionately more case-years, and which had fewer. This information was plotted on a map of the plant, which was inspected for clusters.

Non-Work Factors

We considered the possibility that the excess risk at the plant might be a reflection of an excess in the communities around the plant rather than a problem intrinsic to the plant. A case-location service was retained to determine past places of residence for the cases and controls and additional information was obtained through review of medical records retained at the plant. Analyses were conducted for communities in which at least 5 cases had lived, using a division of 'ever lived' versus 'never lived' in the community for periods

15 or more years before the death of the case, less than 15 years before the death of the case, and any time before the death of the case. The analysis of residence used all addresses up to the date of the case's death. A two-sided 90% confidence interval was calculated to display the strength of association. Addresses were also plotted on a map, which was inspected for further clues to the epidemiology of this occurrence.

Results

Demographics

Date of first employment of the control subjects at the Texas City plant averaged 18.0 months before that of the cases, and the control subjects were born, on average, 4 months before the respective case, with standard deviations 14.2 and 24 months, respectively. Only 5 controls meeting the matching criteria were available for one of the cases.

In-Plant Work History

'Operator' was the only job code represented by 4 or more cases: the Mantel-Haenszel odds ratio for operators was 0.54, with $\chi^2_{M\text{-}H} = 1.84$ (not statistically significant). There was no apparent commonality between the departments in which these operators had worked.

When analyzed by department codes, only the maintenance department had 4 or more cases; the Mantel-Haenszel odds ratio was 0.32 with $\chi^2_{M\text{-}H} = 1.37$ (not statistically significant). Grouping the department codes into major departments yielded no new groups of 4 or more cases.

When cases and controls were analyzed by potential chemical exposures, a new problem became evident: maintenance men moved throughout the plant and were exposed to many different agents in an irregular manner. Accordingly, we have examined the data in two ways: in the first, maintenance men were considered to have been exposed to every agent in the plant; in the second, they were excluded from analysis. The first method may be closer to reality; indeed, maintenance men may have received higher exposures to toxic chemicals than operators since, in maintenance work, they must open pipes, reaction vessels, and pumps. On the other hand, the assumption of exposure for all maintenance men, whether cases or controls, may tend to obscure an elevated odds ratio that might be present if exact data were available. Of the 505 chemicals reviewed, table II lists all chemicals to which at least 4 cases were exposed (excluding maintenance jobs).

Table II. Chemicals to which four or more cases were exposed

Acetaldehyde	Hydrochloric acid	Nonane(s)
Acetic acid	Hydroxypropyl acrylate	Potassium hydroxide
Acetone	Isopropanol	Sodium carbonate
Carbon dioxide	Isopropyl acetate	Sodium hydroxide
Diethanolamine	Isopropyl peroxydicarbonate	Styrene
Diethyl sulfate	Lubricating oil	Sulfuric acid
Diethylene glycol	Methylisobutyl ketone	Tetraethylene glycol
Ethanol	Methane	Toluene
Ethylene	Methanol	Triethylene glycol
Ethylene dichloride	Methyl ethyl ketone	Vinyl acetate
Ethylene glycol	Monoethanolamine	Vinyl chloride

Statistics for distribution of 'exposures' among cases and controls are presented in table III. The tables include the chemicals to which 4 or more cases were exposed and which showed the strongest positive association with brain tumors, plus vinyl chloride. Vinyl chloride monomer was included since it has previously been associated with brain tumor excess [9–11].

Results of analyses by duration of exposure are summarized in table IV. No statistically significant differences between cases and controls were apparent in duration of exposure to any chemical.

In the mapping analysis of work locations within the plant, no significant clustering of areas with proportionately more case-years than control-years was detected. Analysis of work locations of cases and controls within the plant offered no useful clues to the etiology of the tumors.

Residential Data

Addresses could be determined for 16 cases. The remaining case was known to have lived for 15 years in Texas City and in the nearby town of La Marque, but neither exact dates of residence in each community nor street addresses could be determined. Complete listings of at least the community of residence were available for 93 of the 101 controls; partial listings, often inexplicit as to the exact date of moving from one community to another, were available for another 7 controls. No information at all was available for the residence of 1 control. In most instances, streets or streets and numbers could be determined, but there were many instances where informants could no longer remember street addresses of 40 years ago.

Table III. Frequencies of exposure and odds ratios for potential chemical exposures

Chemical	Work period[2]	Maintenance men					
		excluded			counted as exposed[1]		
		E/UE	$R_{(M-H)}$	90% CI on $R_{(M-H)}$	E/UE	$R_{(M-H)}$	90% CI on $R_{(M-H)}$
Carbon dioxide	0–14	6/1	4.80	1.42–16.20	12/1	2.88	0.83–10.01
	15+	5/4	1.35	0.32–5.60	12/3	1.76	0.58–5.35
	ever	7/4	2.14	0.72–6.35	15/2	3.40	1.01–11.38
Diethyl sulfate	0–14	2/5	4.43	0.54–36.20	8/5	1.19	0.45–3.15
	15+	3/6	4.87	1.05–22.53	9/6	0.75	0.27–2.12
	ever	4/7	2.10	0.57–7.73	11/6	1.13	0.45–2.81
Diethylene glycol	0–14	2/5	(2)°	8.15–°	8/5	1.26	0.48–3.33
	15+	3/6	(3)°	95.55–°	9/6	1.05	0.36–3.06
	ever	4/7	(4)°	59.43–°	11/6	1.25	0.48–3.25
Ethanol	0–14	2/5	3.34	0.64–17.59	8/5	1.13	0.41–3.89
	15+	3/6	4.03	0.88–18.46	9/6	0.84	0.30–2.38
	ever	4/7	2.26	0.67–7.62	11/6	1.19	0.47–3.01
Ethylene	0–14	4/3	1.17	0.34–4.04	10/3	1.17	0.36–3.78
	15+	7/2	4.03	0.88–18.32	13/2	1.69	0.42–6.82
	ever	7/4	1.32	0.45–3.91	14/3	1.23	0.40–3.74
Isopropanol	0–14	5/2	4.91	0.94–25.57	11/2	2.75	0.80–9.46
	15+	4/5	0.87	0.20–3.95	10/5	0.76	0.25–2.31
	ever	6/5	1.78	0.45–6.98	13/4	1.73	0.59–5.07
Methane	0–14	3/4	1.46	0.39–5.56	9/4	1.38	0.44–4.39
	15+	6/3	3.08	0.79–12.02	13/2	2.12	0.66–5.32
	ever	6/5	1.80	0.60–5.43	14/3	2.01	0.66–6.19
Tetraethylene glycol	0–14	2/5	3.70	0.57–23.87	8/5	1.24	0.49–3.11
	15+	3/6	(3)°	20.24–°	9/6	1.19	0.38–3.72
	ever	4/7	(4)°	3.01–°	11/6	1.58	0.57–4.42
Vinyl acetate	0–14	5/2	3.10	0.80–12.05	11/2	2.67	0.85–8.38
	15+	5/4	2.74	0.57–13.20	11/4	1.89	0.62–5.75
	ever	6/5	3.30	0.84–12.88	13/4	2.47	0.88–6.94
Vinyl chloride	0–14	3/4	1.16	0.29–4.58	9/4	1.05	0.42–2.65
	15+	3/6	0.87	0.20–3.76	9/6	0.91	0.38–2.16
	ever	4/7	1.13	0.31–4.04	11/6	1.12	0.49–2.59

$R_{(M-H)}$ = Mantel-Haenszel odds ratio estimate; 90% CI = 90% confidence interval; °(N) = infinite odds ratio, based on N tables suitable for analysis; E = exposed; UE = unexposed.

[1] Maintenance employees who also worked in other departments without exposure counted as unexposed.

[2] 0–14 = work less than 15 years before death of case; 15+ = work 15 or more years before death of case. Cases with work experience in both the 0- to 14-year and 15+ year time periods are counted in each group.

Table IV. Median months of exposure to selected chemicals (15 years or more before death of case; employees with no exposure excluded)

	Time in maintenance department			
	excluded		counted as exposed	
	cases/controls	z[1]	cases/controls	z[1]
Carbon dioxide	44/36	0.30	45.5/39	1.14
Diethyl sulfate	7/58	−1.51	50/80	0.11
Diethylene glycol	50/61.5	−0.55	65.5/80.5	0.46
Ethanol	9/50	0.65	69/36	0.63
Ethylene	33/41	−0.62	87/59	0.36
Isopropanol	33/91	−1.47	55/57	0.29
Methane	19/38	−0.81	36/47	−1.10
Tetraethylene glycol	50/61.5	−0.36	81/84	0.77
Vinyl acetate	55/60.5	−0.42	63/84	0.35
Vinyl chloride	63/59	0.24	88/82	0.80

The expected value of the sum is $n_1(n_1+n_2+1)/2$ with variance = $n_1n_2(n_1+n_2+1)/12$.
[1][(observed rank-sum)−(predicted rank-sum)]/(predicted variance); $z > 1.96$ implies $p < 0.05$.

Table V. Distribution among cases and controls of community of residence

Community	Work period[1]	Cases lived ever/never	$R_{(M\text{-}H)}$	90% CI on $R_{(M\text{-}H)}$
La Marque	0–14	9/8	3.95	1.60–9.77
	15+	9/8	4.80	1.61–14.26
	ever	12/5	5.86	2.25–15.25
Texas City	0–14	5/12	0.48	0.16–1.41
	15+	4/13	0.28	0.09–0.86
	ever	6/11	0.49	0.19–1.29
Galveston	0–14	3/14	0.92	0.32–2.67
	15+	7/10	0.87	0.36–2.06
	ever	7/10	0.83	0.36–1.96

$R_{(M\text{-}H)}$ = Mantel-Haenszel odds ratio estimate; 90% CI = 90% confidence interval.
[1] 0–14 = work less than 15 years before death of case; 15+ = work 15 or more years before death of case.

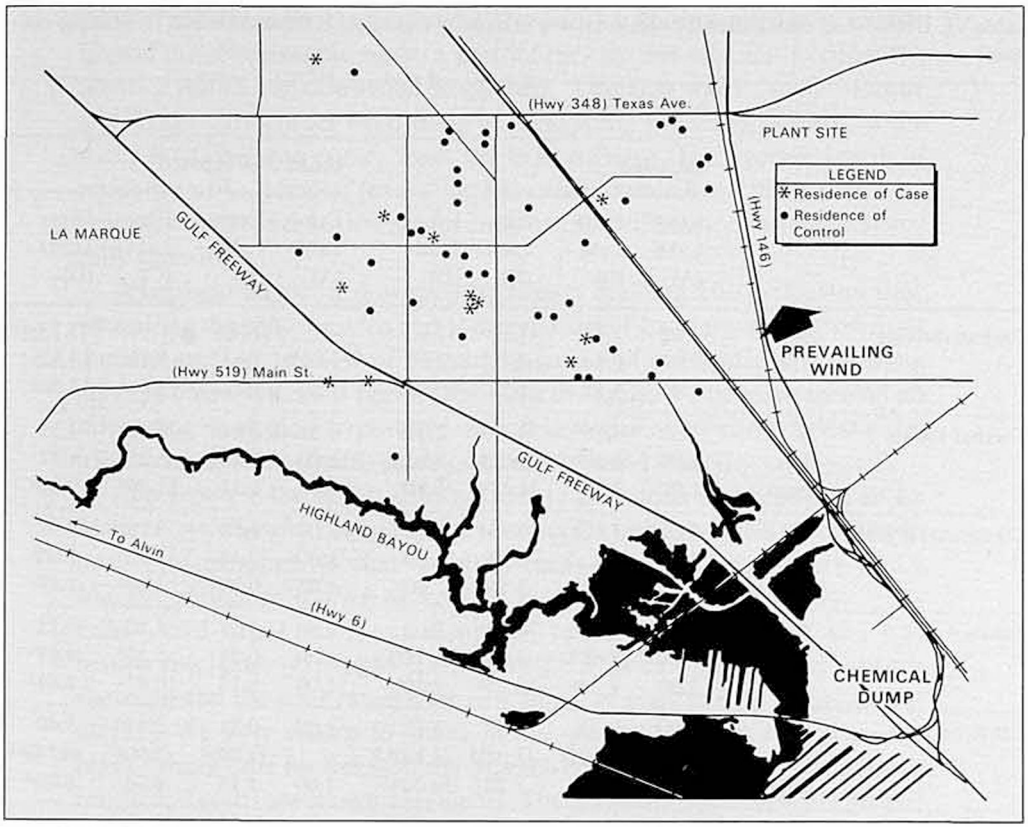

Fig. 1. Map of La Marque addresses ever held by cases and controls.

Table V shows the distribution of addresses among cases and controls (note: some subjects appear in both the 'less than 15 years' and 'greater than 15 years' columns). The odds ratio for Texas City differed markedly from 1, while that for Galveston is essentially equal to 1. La Marque had an apparent excess of cases over controls (maximum odds ratio = 5.86). It is a residential community, without heavy industry, and lies southwest of Texas City, west of the plant, and north of Galveston. A chemical dump, established in 1959 and listed by the Environmental Protection Agency as a high-priority site for emergency cleanup, is located at the southeast extremity of La Marque. Vinyl chloride levels as high as 161 parts per billion have been measured at the fence line of the dump [12]. Figure 1 shows that the

Table VI. Unmatched odds ratios for combinations of exposure to selected substances and La Marque residence

	Time	Maintenance men							
		excluded				counted as exposed			
		Exp– LaM– (A)	Exp+ LaM– (B)	Exp– LaM+ (C)	Exp+ LaM+ (D)	Exp– LaM– (A)	Exp+ LaM– (B)	Exp– LaM+ (C)	Exp+ LaM+ (D)
Carbon dioxide	0–14	1.00	7.11	3.20	32.00[a]	–	(1.00)[b]	(1.14)[b]	(3.73)[a, b]
	15+	1.00	2.54	4.71	22.00	1.00	1.43	5.43	13.82[a]
	ever	1.00	3.67	8.57	80.00[a]	1.00	1.78	2.33	17.50[a]
Diethyl sulfate	0–14	1.00	4.89[a]	4.40[a]	0.00	1.00	1.81	8.40	4.31
	15+	1.00	3.67[a]	5.50[a]	3.67[a]	1.00	0.36	6.25[a]	4.17
	ever	1.00	3.63	24.17[a]	5.80[a]	1.00	1.33	12.80[a]	7.00[a]
Diethylene glycol	0–14	1.00	7.67[a]	3.83[a]	0.00	1.00	1.69	5.79	4.91
	15+	1.00	inf.	3.43	16.00	1.00	0.48	3.75[a]	7.00[a]
	ever	1.00	3.78[a]	7.56[a]	17.00[a]	1.00	0.78	3.50[a]	8.49[a]
Ethanol	0–14	1.00	4.89[a]	4.40[a]	0.00	1.00	1.69	8.10	4.15
	15+	1.00	7.67[a]	4.60[a]	5.11[a]	1.00	0.38	5.20[a]	4.67[a]
	ever	1.00	4.29[a]	18.75[a]	7.50[a]	1.00	1.33	10.67[a]	8.62[a]
Ethylene	0–14	1.00	0.72	0.87	8.67	1.00	0.81	2.83	3.40
	15+	–	(1.00)[b]	(1.08)[b]	(4.88)[a, b]	–	(1.00)[b]	(5.90)[b]	(6.74)[a, b]
	ever	1.00	2.05	7.50	30.00[a]	1.00	1.15	6.00	8.44[a]
Isopropanol	0–14	1.00	6.00	7.50	7.50[a]	–	(1.00)[b]	(2.22)[b]	(2.78)[a, b]
	15+	1.00	0.56	3.33[a]	3.00	1.00	0.28	4.67[a]	3.73
	ever	1.00	1.64	11.50[a]	9.20[a]	1.00	1.02	5.40[a]	7.59[a]
Methane	0–14	1.00	0.53	0.71	inf.	1.00	0.59	1.22	3.67
	15+	–	(1.00)[b]	(1.22)[b]	(inf.)[a, b]	–	(1.00)[b]	(3.26)[b]	(8.29)[a, b]
	ever	1.00	3.17	9.50[a]	inf.[a]	1.00	1.78	5.25	14.54[a]
Tetraethylene glycol	0–14	1.00	7.67[a]	4.60[a]	0	1.00	1.69	6.75	4.50
	15+	1.00	7.67[a]	3.29[a]	15.33	1.00	0.45	3.63[a]	6.77[a]
	ever	1.00	2.75	8.80[a]	11.00[a]	1.00	0.74	3.78	7.56[a]
Vinyl acetate	0–14	1.00	7.11	6.40	16.00[a]	–	(1.00)[b]	(1.90)[b]	(3.03)[a, b]
	15+	1.00	0.67	0.89	10.67[a]	1.00	0.38	1.24	7.09[a]
	ever	1.00	2.36	7.80	17.33[a]	1.00	1.27	3.44[a]	11.63[a]
Vinyl chloride	0–14	1.00	2.67	6.00	0	1.00	2.20	9.00	6.00
	15+	1.00	0	1.60	4.00[a]	1.00	0.15[a]	2.25	4.50[a]
	ever	1.00	0.90	13.50[a]	2.25	1.00	1.20	8.57[a]	7.50[a]

known addresses for the cases who lived in La Marque appear to cluster toward the southern and western parts of the city, not adjacent to either the plant or dump nor downwind from them. Drinking water for La Marque and Texas City comes from deep wells, tapping the same stratum, while water for Galveston comes from the Brazos River. The average length of residence in La Marque (excluding those who never lived there) was 12.4 years for cases, and 16.3 years for controls; this difference was not statistically significant.

Highland Bayou, a slow-moving stream draining into Galveston Bay, runs along the southwestern and southern edge of La Marque, upwind from the community. In view of the large number of publications associating glioblastomas with viral agents [13–20], a mosquito-borne virus seemed an interesting etiological hypothesis, as did kerosene and various insecticides used to control mosquitos during and after World War II.

To separate the effects of exposures to chemicals and residence in La Marque, we classified subjects into 4 strata for each chemical according to history of exposure to that chemical (exp+ or exp–) and history of La Marque residence (LaM+ or LaM–). Each of 3 strata (exp+LaM+, exp–LaM+, and exp+LaM–) was compared to cases and controls who had neither risk factor (exp–LaM–); i.e., three 2×2 tables were analyzed for each chemical and the odds ratios were compared, as suggested by *Kleinbaum* et al. [21]. We were unable to maintain the matching in this step, since too many empty cells for use with the Mantel-Haenszel procedure would have resulted. Results are shown in table VI. The odds ratios generally are greater for La Marque residence without chemical exposure than for exposure to individual chemicals without La Marque residence and often are quite a bit greater for exposure to both risk factors than for either one alone. During the period longer than 15 years before the death of the case for analyses in

Explanation to table VI

Maintenance employees who also worked in other departments without exposure counted as unexposed. Except where otherwise indicated, all comparisons are to the unexposed/never lived in La Marque category. Column B may be interpreted as the effect of chemical exposure alone, column C as the effect of La Marque residence alone, and column D as the effect of both. Exp– = never exposed to the chemical; Exp+ = ever exposed to the chemical; LaM– = never lived in La Marque; LaM+ = ever lived in La Marque; inf. = no controls in the category results in infinite odds ratio. Figures in parentheses are odds ratios with reference to never lived in La Marque/exposed.

[a] Differs from column A; Fisher's exact test, $p < 0.05$.

[b] No cases in the never lived in La Marque/never exposed category result in infinite odds ratio.

which maintenance men were excluded, only ethanol and di- and tetraethylene glycol show a stronger association with disease than does La Marque residence.

In reviewing the death certificates obtained for case-finding, we found that 7 (9.9%) of 71 adult male residents of Galveston County whose death certificates were coded as 'malignant brain tumor' and who died between 1949 and 1977 had La Marque addresses on the death certificate. Estimates of La Marque's population over the same period were obtained [22]. Weighting the populations of the community and county for the calendar years under consideration yielded crude death rates of 2.00 adult male deaths per 100,000 total person-years at risk in La Marque and 1.63 for the remainder of Galveston County. The difference was not statistically significant ($p = 0.33$).

Discussion

The greatest apparent risks were associated with exposure to carbon dioxide, diethyl sulfate, diethylene glycol, ethanol, ethylene, isopropanol, methane, tetraethylene glycol, and vinyl acetate; with first employment in the 1940s or early 1950s; and with residence in La Marque [2]. The chemical associations found may need further study, but are not convincing evidence, particularly in view of *Austin and Schnatter's* [4] negative findings. The association with residence is somewhat stronger.

Among the in-plant exposures considered, the relationship between gliomas of the brain and carbon dioxide is statistically significant only when all work histories are included regardless of latency. We would expect a carcinogen to show stronger relationships when latency was considered; the absence of a latency effect, coupled with the fact that carbon dioxide exposures likely to be experienced by workers would have virtually no effect on normal physiologic levels, eliminates CO_2 from further consideration. Its appearance on the list serves to illustrate the pitfalls of multiple significance testing mentioned above and to inject a note of caution in forming conclusions based on other associations in this report. Methane, with 6 cases potentially exposed (excluding maintenance men), is similarly unlikely to be present in amounts capable of increasing exposure markedly over background levels produced by intestinal flora.

We were unable to find reports of carcinogenesis or mutagenesis testing on tetraethylene glycol. Diethylene glycol was found to cause bladder stones

and tumors in one test using rats [23], but has not been carcinogenic or mutagenic in other experiments [24, 25]. Excluding maintenance men, a total of 4 cases definitely worked in departments where di- or tetraethylene glycol was present. Even if the association were causative, the fraction of cases attributable would be insufficient to explain the observed excess; this positive finding may be the result of multiple significance testing.

Diethyl sulfate is considered a carcinogen and has caused brain tumors in experimental animals [26]. With regard to other chemicals, a statistically significant excess of brain tumors was observed in a British isopropanol plant, although the numbers were very small [27]. Several other cancers have been associated with isopropanol exposure, although pure isopropanol is not usually considered carcinogenic [28–30]. Ethylene, like vinyl acetate and vinyl chloride, has an unsaturated two-carbon moiety. Although both ethylene and vinyl chloride are metabolized through a highly reactive epoxide stage which may alkylate organic compounds [31, 32], ethylene is not mutagenic in Ames tests [NIOSH, unpubl. data] and was not found to have any effect in a 2-year exposure study using rats [33]. There is less information available on vinyl acetate; it is not mutagenic in bacterial assay [34, 35]. Information on association with length of exposure, latency, and number of cases who could be attributed to the chemical if it were a brain carcinogen does not point clearly toward any of these chemicals but observation of other clusters or cohorts might indicate that one of them is dangerous.

While some of the associations found could be considered weak evidence of carcinogenicity, none was conclusive. There are wide confidence intervals around all of the odds ratios given; therefore, differences between odds ratios should be interpreted cautiously.

It is possible that a critical exposure was more general than implied by the department group analysis used here, and that use of in-plant controls constituted over-matching which might have obscured a significant finding. We know of no satisfactory way to test this possibility within the confines of the present study.

Risk associated with La Marque residence seems greater than that associated with the chemicals studied. La Marque and Texas City share a common water source, but La Marque has a higher ratio of cases to controls than Texas City, therefore a water-borne environmental carcinogen [36] seems unlikely. Since there are no major chemical or other industries upwind from the community, airborne industrial carcinogens do not seem to be a likely explanation for the association observed. (The wind is domi-

nantly out of the south-southeast.) The cases' shorter average duration of residence in La Marque argues against a causal association with residence. From the comparison of crude death rates for La Marque and Galveston County, La Marque does not appear to be over-represented among brain tumor deaths, but this comparison does not assure that a cohort who lived there in the past, some of whom have moved away, is not at greater risk. A refinery adjoining this plant also appears to have an excess of brain tumors and is under study by NIOSH. Examination of the residence histories of the cases who worked at that refinery showed that only 3 of 8 had lived in La Marque.

The type of mosquito which constitutes the greatest problem in the La Marque area has a range of 25–50 miles, so control measures, which relied on DDT and γ-benzene hexachloride until the mid 1960s, have always been countywide and would not appear to explain localization to this area [37]. Italian farmers are reported to have higher brain tumor rates than urban workers, a finding which is statistically significant [38]. The clustering of cases near the periphery of the community may be meaningful, but further information is needed to understand it.

Greenwald et al. [39] have suggested that superior medical care may lead to more frequent diagnoses of brain tumors among employed workers with good medical insurance programs. They presented evidence of more sophisticated diagnostic methods in Eastman Kodak employees with brain tumors. Although it is reasonable to suppose such sophistication would lead to fewer missed diagnoses of brain tumors, their report has not achieved universal acceptance [40, 41] and does not directly assess the question of missed diagnoses in the comparison populations. *Schoenberg* et al. [42] found that differences between incidence rates in Rochester, Minn., where the Mayo Clinic provides virtually all medical care, and in Connecticut were mainly due to better diagnosis at autopsy; most of the excess cases in Rochester were due to meningiomas; and the differences in rates were most pronounced in the older age groups. About 70% of Rochester decedents had autopsies, compared to an estimated 38% in Connecticut; in Rochester, 60% of meningiomas were found at autopsy, compared to only 17% of glioblastomas. None of the cases in this series were first diagnosed at autopsy and gliomas predominated in this group (85 vs. 40.3% in Rochester). Our impression, from the medical records examined, is that the diagnoses in this case series did not hinge on either multiple or highly sophisticated tests, but we cannot determine the extent to which diagnostic sensitivity bias might be a factor in this cluster.

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