759 Neuroepidemiology

760 Case-Control Study of Gliomas of the Brain 761 among Workers Employed by a Texas City, 762 Texas Chemical Plant

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769 **Key Words.** Petrochemicals · Brain tumors · Occupation · Residence

771 **Abstract.** A Texas petrochemical plant had elevated standardized mortality ratios for
H 772 neoplasms of the brain. A case-control study examined possible associations between glio-
H 773 mas of the brain and job title, departmental employment history, chemical exposure his-
774 tory, geographic location within plant, dates of employment, and residence. The greatest
775 apparent risks were associated with exposure to carbon dioxide, diethyl sulfate, diethylene
776 glycol, ethanol, ethylene, isopropanol, methane, tetraethylene glycol, and vinyl acetate;
777 with first employment in the 1940s or early 1950s, and with residence in La Marque, Tex.
H 778 No significant differences between cases and controls were apparent in duration of expo-
779 sure to any of these chemicals.

782 Introduction

784 In February 1979, the National Institute for Occupational Safety and
785 Health (NIOSH) and OSHA, with the aid of the company management,
786 began an investigation of a cluster of primary brain tumors at a chemicals
787 and plastics plant in Texas City, Tex. *Alexander* et al. [1] have described the
H 88 characteristics of the brain tumor cases and the methods for case identifi-
H 89 cation. Two retrospective cohort mortality studies of all male hourly work-
790 ers employed at this plant from 1941 through 1977 have been reported [2,
791 3]. Findings included an overall standardized mortality ratio [SMR = 100
792 (observed/expected)] for benign, malignant, and unspecified neoplasms of
793 the brain of 206 ($p < 0.05$). For those who worked more than 20 years at
794 the plant (i.e., who began work before 1957), the SMR was 377 ($p < 0.05$)
795 [2]. No other cancers were found significantly in excess of expected, and the
796 overall SMR was not elevated. We here describe a nested case-control study
797 of primary brain tumor cases among the employees of that plant.

798 *Austin and Schnatter* [4] have recently published a parallel study which
799 showed no association between exposures in the plant and brain gliomas.
800 They used deceased employees whose deaths were known to the company
801 as controls for the same cases, employed an unmatched design, and did not
802 include analysis of residence. They were able, however, to use multiple
803 comparison groups; one group excluded controls who had died of other
804 malignancies while another permitted such decedents as controls. Subsets
H 05 of these groups including only hourly employees permitted further refine-
806 ment. These two studies are thus different enough to be complementary,
807 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 1.

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.

(3)

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). 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). 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).

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 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 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 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 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 ($p = 0.33$).

020 **Discussion**

022 The greatest apparent risks were associated with exposure to carbon
023 dioxide, diethyl sulfate, diethylene glycol, ethanol, ethylene, isopropanol,
024 methane, tetraethylene glycol, and vinyl acetate; with first employment in
H 25 the 1940s or early 1950s; and with residence in La Marque [2]. The chem-
H 26 ical associations found may need further study, but are not convincing evi-
027 dence, particularly in view of *Austin and Schnatter's* [4] negative findings.
028 The association with residence is somewhat stronger.

029 Among the in-plant exposures considered, the relationship between
N 30 gliomas of the brain and carbon dioxide is statistically significant only when
031 all work histories are included regardless of latency. We would expect a
032 carcinogen to show stronger relationships when latency was considered; the
H 33 absence of a latency effect, coupled with the fact that carbon dioxide expo-
034 sures likely to be experienced by workers would have virtually no effect on
035 normal physiologic levels, eliminates CO_2 from further consideration. Its
036 appearance on the list serves to illustrate the pitfalls of multiple significance
H 37 testing mentioned above and to inject a note of caution in forming conclu-
038 sions based on other associations in this report. Methane, with 6 cases
039 potentially exposed (excluding maintenance men), is similarly unlikely to
H 40 be present in amounts capable of increasing exposure markedly over back-
041 ground levels produced by intestinal flora.

042 We were unable to find reports of carcinogenesis or mutagenesis testing
043 on tetraethylene glycol. Diethylene glycol was found to cause bladder stones
044 and tumors in one test using rats [23], but has not been carcinogenic or
045 mutagenic in other experiments [24, 25]. Excluding maintenance men, a
046 total of 4 cases definitely worked in departments where di- or tetraethylene
047 glycol was present. Even if the association were causative, the fraction of
048 cases attributable would be insufficient to explain the observed excess; this
049 positive finding may be the result of multiple significance testing.

050 Diethyl sulfate is considered a carcinogen and has caused brain tumors
051 in experimental animals [26]. With regard to other chemicals, a statistically
052 significant excess of brain tumors was observed in a British isopropanol
053 plant, although the numbers were very small [27]. Several other cancers
054 have been associated with isopropanol exposure, although pure isopropanol
055 is not usually considered carcinogenic [28–30]. Ethylene, like vinyl acetate
056 and vinyl chloride, has an unsaturated two-carbon moiety. Although both
H 57 ethylene and vinyl chloride are metabolized through a highly reactive epox-
058 ide stage which may alkylate organic compounds [31, 32], ethylene is not
059 mutagenic in Ames tests [Niosh, unpubl. data] and was not found to have
H 60 any effect in a 2-year exposure study using rats [33]. There is less informa-
061 tion available on vinyl acetate; it is not mutagenic in bacterial assay [34,
H 62 35]. Information on association with length of exposure, latency, and num-
063 ber of cases who could be attributed to the chemical if it were a brain
H 64 carcinogen does not point clearly toward any of these chemicals but obser-
H 65 vation of other clusters or cohorts might indicate that one of them is danger-
066 ous.

H 67 While some of the associations found could be considered weak evi-
068 dence of carcinogenicity, none was conclusive. There are wide confidence
069 intervals around all of the odds ratios given; therefore, differences between
070 odds ratios should be interpreted cautiously.

071 It is possible that a critical exposure was more general than implied by
072 the department group analysis used here, and that use of in-plant controls
073 constituted over-matching which might have obscured a significant finding.
N 74 We know of no satisfactory way to test this possibility within the confines of
075 the present study.

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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 dominantly 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 a 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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References

1 Alexander, V.; Leffingwell, S.S.; Lloyd, J.W.; Waxweiler, R.J.; Miller, R.L.: Brain cancers in petrochemical workers – A case series report. Am. J. ind. Med. *1:* 115–123 (1980).

2 Waxweiler, R.J.; Alexander, V.; Leffingwell, S.S.; Haring, M.; Lloyd, J.W.: Mortality from brain tumor and other causes in a cohort of petrochemical workers. J. natn. Cancer Inst. *70:* 75–81 (1983).

3 Austin, S.G.; Schnatter, A.R.: A cohort mortality study of petrochemical workers. J. occup. Med. *25:* 304–312 (1983).

4 Austin, S.G.; Schnatter, A.R.: A case/control study of chemical exposures and brain tumors in petrochemical workers. J. occup. Med. *25:* 313–320 (1983).

5 Schoenberg, B.S.; Christine, B.W.; Whisnant, J.P.: The descriptive epidemiology of primary intracranial neoplasms: the Connecticut experience. Am. J. Epidem. *104:* 499–510 (1976).

6 Mantel, N.; Haenszel, W.: Statistical aspects of the analysis of data from retrospective studies of disease. J. natn. Cancer Inst. *22:* 719–748 (1959).

7 Rothman, K.J.; Boice, J.D.: Epidemiologic analysis with a programmable calculator (USDHEW:NIH, Washington 1979).

8 Hollander, M.; Wolfe, D.A.: Nonparametric statistical methods, pp. 68–75 (Wiley, New York 1973).

9 Maltoni, C.: Predictive value of carcinogenesis bioassays. Ann. N.Y. Acad. Sci. *271:* 431–437 (1976).

10 Byren, D.; Engholm, G.; Englund, A.; Westerholm, P.: Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. Environ. Health Perspect. *17:* 167–170 (1976).

11 Waxweiler, R.J.; Stringer, W.; Wagoner, J.K.; Jones, J.; Falk, H.; Carter, C.: Neoplastic risk among workers exposed to vinyl chloride. Ann. N.Y. Acad. Sci. *271:* 40–48 (1976).

12 Texas Air Control Board: Vinyl chloride monomer air sampling at Texas City 'Wye' waste pits, La Marque, Tex., August 5–6, 1980 (Austin 1980).

13 Becker, L.E.; Narayan, O.; Johnson, R.T.: Studies of human papovavirus tumor antigen in experimental and human cerebral neoplasms. J. can. Sci. neurol. *3:* 105–109 (1976).

14 Birkmeyer, G.D.; Miller, F.; Marguth, F.: Oncorna-viral information in human glioblastomas. J. neurae Transm. *35:* 241–254 (1974).

15 Bendheim, P.E.; Dinowitz, M.: Particles resembling oncornaviruses: spontaneous release from cultured meningioma cells. Archs Neurol. *34:* 105–108 (1977).

16 Cuatico, W.; Cho, J.-R.; Spiegelman, S.: Molecular evidence for a viral etiology of human CNS tumors. Acta neurochir. *35:* 149–160 (1976).

17 London, W.T.; Houff, S.; Madden, D.L.; Fuccillo, D.A.; Gravell, M.; Wallen, W.C.; Palmer, A.E.; Sever, J.L.: Brain tumors in owl monkeys inoculated with a human polyoma virus (JC virus). Science *201:* 1246–1249 (1978).

18 Ida, N.; Ikama, Y.; Ogawa, K.; Takada, M.; Sugano, H.: Cell culture from a rat brain tumor induced by intracerebral inoculation with murine sarcoma virus. J. natl Cancer Inst. *53:* 431–447 (1974).

19 Tanaka, R.; Koprowski, H.; Iwasaki, Y.: Malignant transformation of hamster brain cells in vitro by human papovavirus BK. J. natn. Cancer Inst. *56:* 671–673 (1976).

20 Yung, W.K.; Blank, N.K.; Vick, N.A.: 'Glioblastoma' – Induction of a reproducible autochtonous tumor in rats with murine sarcoma virus. Neurology *26:* 76–83 (1976).

21 Kleinbaum, D.G.; Kupper, L.L.; Morgenstern, H.: Epidemiologic research: Principles and quantitative methods, p. 407 (Lifetime Learning Publications, Belmont 1982).

22 City of La Marque, Tex., Comprehensive Planning Program: Economic development, capital improvements, environmental assessment (Wise, Dallas 1981).

23 Fitzhugh, O.G.; Nelson, A.A.: Comparison of the chronic toxicity of triethylene glycol with that of tetraethylene glycol. J. ind. Hyg. Toxicol. *28:* 40–43 (1946).

24 Weil, C.S.; Carpenter, C.P.; Smyth, H.F.: Urinary bladder calculus and tumor response following either repeated feeding of diethylene glycol or calcium stone implantation. Ind. Med. Surg. *36:* 55–57 (1967).

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25 Pfeiffer, E.H.; Dunkelberg, H.: Mutagenicity of ethylene oxide and propylene oxide and of the glycols and halohydrins formed from them during the fumigation of foods. Food Cosmet. Toxicol. *18:* 115–118 (1980).
26 Druckrey, H.; Kruse, H.; Preussman, R.; Ivankovic, S.; Landschutz, C.: Cancerogene alkylierende Substanzen. III. Alkylhalogenide, Sulfate, Sulfonate, und ringgespannte Heterocyclen. Z. Krebsforsch. *74:* 241 (1970).
27 Alderson, M.R.; Rattan, N.S.: Mortality of workers on an isopropyl alcohol plant and two MEK dewaxing plants. Br. J. ind. Med. *37:* 85–89 (1980).
28 Enterline, P.E.; Lilis, R.; Alexander, V.; Maltoni, C.: Importance of sequential exposure in the production of epichlorohydrin and isopropanol. Ann. N.Y. Acad. Sci. *381:* 344–349 (1982).
29 Weil, C.S.; Smyth, H.F.; Nale, T.W.: Quest for a suspected industrial carcinogen. Archs ind. Hyg. occup. Hlth *5:* 535–547 (1952).
30 Hueper, W.C.: Occupational and environmental cancers of the respiratory system. Specific occupational cancers and their environmental counterparts (Springer, New York 1966).
31 Ehrenberg, L.; Osterman-Golkar, S.; Segerback, D.; Svensson, K.; Calleman, C.J.: Alkylation of haemoglobin after metabolic conversion of ethene to ethene oxide in vivo. Mutat. Res. *45:* 175–184 (1977).
32 Green, T.; Hathaway, D.E.: The biological fate of vinyl chloride in relation to its oncogenicity. Chem.-biol. Interactions *11:* 545–562 (1975).
33 Gralla, E.J.: A twenty-four month inhalation toxicology study in Fischer-344 rats exposed to atmospheric ethylene (Chemical Industry Institute of Toxicology, Research Triangle Park 1980).
34 Bartsch, H.; Montesano, R.: Prescreening of environmental and industrial chemicals in a series of short-term tests for the detection of potential carcinogens. Comm. Eur. Communities (Rep.) EUR; ISS EUR 6388, Environ. Res. Programme, pp. 269–373 (1980).
35 Lijinsky, W.; Andrews, A.W.: Mutagenicity of vinyl compounds in *Salmonella typhimurium*. Teratog. Carcinog. Mutagen. *1:* 259–267 (1980).
36 Cantor, K.P.; Hoover, R.; Mason, J.T.; McCabe, L.J.: Associations of Cancer mortality with halomethanes in drinking water. J. natn. Cancer Inst. *61:* 979–985 (1978).
37 Mix, D.: Personal communication.
38 Musicco, M.; Filippini, G.; Bordo, B.M.; Melotto, A.; Morello, G.; Berrino, F.: Gliomas and occupational exposure to carcinogens: case-control study. Am. J. Epidem. *116:* 782–789 (1982).
39 Greenwald, P.; Friedlander, B.R.; Lawrence, C.E.; Hearne, T.; Earle, K.: Diagnostic sensitivity bias – an epidemiologic explanation for an apparent brain tumor excess. J. occup. Med. *23:* 690–694 (1981).
40 Gann, P.; Rosenman, K.D.: Conclusions questioned in brain tumor excess study. J. occup. Med. *24:* 428 (1982).
41 Greenwald, P.; Friedlander, B.R.; Lawrence, C.E.; Hearne, T.; Earle, K.: Author's response. J. occup. Med. *24:* 428–432 (1982).
42 Schoenberg, B.S.; Christine, B.W.; Whisnant, J.P.: The resolution of discrepancies in the reported incidence of primary brain tumors. Neurology *28:* 817–823 (1978).

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L 001 **Table I. Cases from cohort study included in and excluded from case-control study**

002	Diagnosis	Included	Excluded
005	Gliomas	17	
007	Glioblastoma multiforme (includes diagnoses of astrocytoma		
008	grades III and IV)	14	
010	Thalamic glioblastoma suspected clinically; no tumor		
011	in biopsy of abnormal appearing area of brain cortex	1	
013	Pituitary adenocarcinoma suspected clinically; radio-		
014	therapy followed by proven glioblastoma 12 years later	1	
016	Astrocytoma grade II	1	
018	Metastatic tumor, unknown primary		1
020	Brain tumor suspected clinically, not found at autopsy		1
022	Meningioma, malignant		3
024	Meningioma, benign		1
026	Subtotal	17	6
029	Total	23	

L 034 **Table II. Chemicals to which four or more cases were exposed**

035	Acetaldehyde	Hydrochloric acid	Nonane(s)
036	Acetic acid	Hydroxypropyl acrylate	Potassium hydrox-
037	Acetone	Isopropanol	ide
038	Carbon dioxide	Isopropyl acetate	Sodium carbonate
039	Diethanolamine	Isopropyl peroxydicarbonate	Sodium hydroxide
040	Diethyl sulfate	Lubricating oil	Styrene
041	Diethylene glycol	Methylisobutyl ketone	Sulfuric acid
042	Ethanol	Methane	Tetraethylene glycol
043	Ethylene	Methanol	Toluene
044	Ethylene dichloride	Methyl ethyl ketone	Triethylene glycol
045	Ethylene glycol	Monoethanolamine	Vinyl acetate
068			Vinyl chloride

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L 072 **Table III. Frequencies of exposure and odds ratios for potential chemical exposures**

073 Chemical	Work period	Maintenance men					
075		excluded			counted as exposed[1]		
077							
078 V 081		E/UE	$R_{(M-H)}$	90% CI on $R_{(M-H)}$	E/UE	$R_{(M-H)}$	90% CI on $R_{(M-H)}$
087 Carbon dioxide	0–14	6/1	4.80	1.42–16.20	12/1	2.88	0.83–10.01
089	15+	5/4	1.35	0.32–5.60	12/3	1.76	0.58–5.35
090	ever	7/4	2.14	0.72–6.35	15/2	3.40	1.01–11.38
109 Diethyl sulfate	0–14	2/5	4.43	0.54–36.20	8/5	1.19	0.45–3.15
111	15+	3/6	4.87	1.05–22.53	9/6	0.75	0.27–2.12
112	ever	4/7	2.10	0.57–7.73	11/6	1.13	0.45–2.81
131 Diethylene glycol	0–14	2/5	(2)*	8.15–*	8/5	1.26	0.48–3.33
133	15+	3/6	(3)*	95.55–*	9/6	1.05	0.36–3.06
134	ever	4/7	(4)*	59.43–*	11/6	1.25	0.48–3.25
153 Ethanol	0–14	2/5	3.34	0.64–17.59	8/5	1.13	0.41–3.89
155	15+	3/6	4.03	0.88–18.46	9/6	0.84	0.30–2.38
156	ever	4/7	2.26	0.67–7.62	11/6	1.19	0.47–3.01
175 Ethylene	0–14	4/3	1.17	0.34–4.04	10/3	1.17	0.36–3.78
177	15+	7/2	4.03	0.88–18.32	13/2	1.69	0.42–6.82
178	ever	7/4	1.32	0.45–3.91	14/3	1.23	0.40–3.74
197 *Isopropanol*	0–14	5/2	4.91	0.94–25.57	11/2	2.75	0.80–9.46
199	15+	4/5	0.87	0.20–3.95	10/5	0.76	0.25–2.31
200	ever	6/5	1.78	0.45–6.98	13/4	1.73	0.59–5.07
219 Methane	0–14	3/4	1.46	0.39–5.56	9/4	1.38	0.44–4.39
221	15+	6/3	3.08	0.79–12.02	13/2	2.12	0.66–5.32
222	ever	6/5	1.80	0.60–5.43	14/3	2.01	0.66–6.19
241 Tetraethylene glycol	0–14	2/5	3.70	0.57–23.87	8/5	1.24	0.49–3.11
243	15+	3/6	(3)*	20.24–*	9/6	1.19	0.38–3.72
244	ever	4/7	(4)*	3.01–*	11/6	1.58	0.57–4.42
263 Vinyl acetate	0–14	5/2	3.10	0.80–12.05	11/2	2.67	0.85–8.38
265	15+	5/4	2.74	0.57–13.20	11/4	1.89	0.62–5.75
266	ever	6/5	3.30	0.84–12.88	13/4	2.47	0.88–6.94
285 Vinyl chloride	0–14	3/4	1.16	0.29–4.58	9/4	1.05	0.42–2.65
287	15+	3/6	0.87	0.20–3.76	9/6	0.91	0.38–2.16
288	ever	4/7	1.13	0.31–4.04	11/6	1.12	0.49–2.59

N 307 $R_{(M-H)}$ = 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.
V 308
309 [1] Maintenance employees who also worked in other departments without exposure counted as unexposed.
310 [2] 0–14 = work less than 15 years before death of case; 15+ = work 15 or more years before death of case. Cases
311 with work experience in both the 0- to 14-year and 15+ year time periods are counted in each group.

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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	$R_{(M-H)}$	90% CI on $R_{(M-H)}$
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

$R_{(M-H)}$ = 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.

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		1.43	5.43	13.82[a]
	ever	1.00	3.67	8.57	80.00[a]	1.00	1.78	2.33	17.50[a]
						1.00			
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]

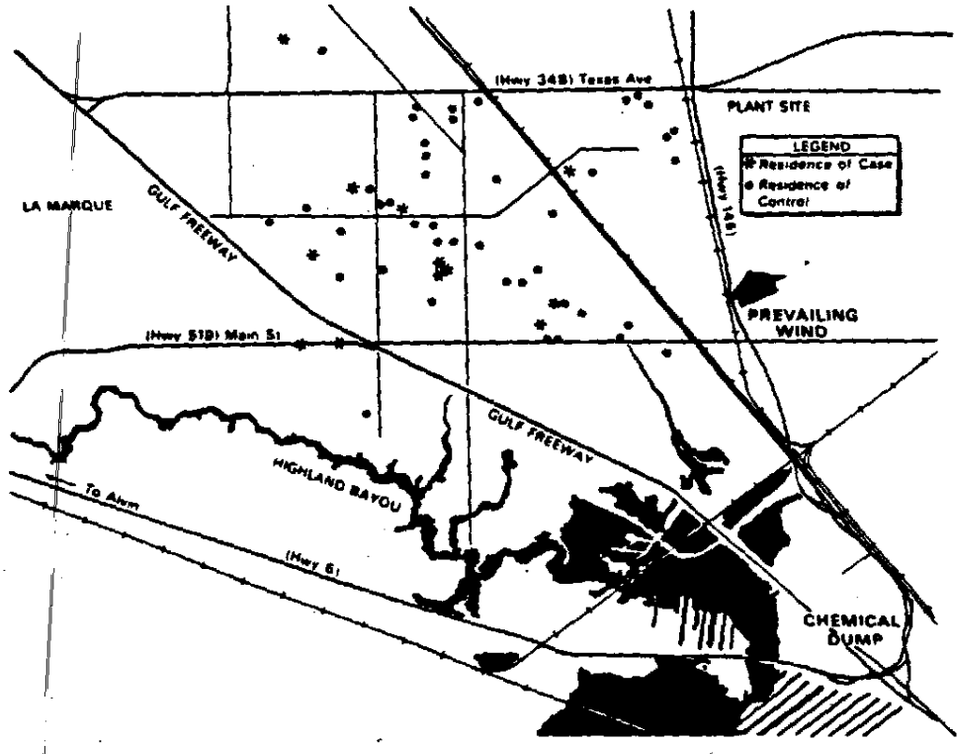
Maintenance employees who also worked in other departments without exposure counted as unexposed. Except where otherwise indicated, all comparisons are to the unexposed/never lived in La Marque category. Column B may be interpreted as the effect of chemical exposure alone, column C as the effect of La 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.

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

(19)



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August 27, 1984

CERTIFIED MAIL

Mr. F. Walter Conrad
Baker & Botts
3000 One Shell Plaza
Houston, Texas 77002

Re: No. G-83-48 (Consolidated); Dorothy Bell, Individually and as Executrix of the Estate of Dewey Bell, Deceased and Thelma O. Kingsbury, Individually and as Representative of the Estate of Thomas Page Kingsbury, Deceased vs. Stauffer Chemical Company, et al.; In the United States District Court for the Southern District of Texas, Galveston Division

Dear Walter:

This letter is to confirm our conversation of August 24th, in which I agreed to suspend your need to answer our discovery until such a time as we would later request, and in which you agreed to supply us, as soon as possible, with all information with regard to the purchase of any vinyl chloride. As you know, it is our hope that we will be able to show that Stauffer Chemical Company did not supply any vinyl chloride to the plant in question. Since we have a November discovery cut off, we shall need this information by at least October 1, 1984. Any help in this regard would be appreciated.

Yours truly,

Andrew S. Hanen

169/lap

UCC 071861