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A Case-Control Study of Brain Tumor Mortality at a Texas Chemical Plant

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A plant-based case-control study was undertaken to investigate a possible excess of brain tumor mortality identified at a Texas Chemical plant from a sample-based cohort study. Work histories and presumptive exposures of 28 former employees who had died of primary intracranial neoplasms were contrasted with those of two matched comparison groups in an effort to identify a possible etiologic agent. Because the sample-based cohort study suggested they might be at increased risk, those employees hired prior to 1945, those employed from one to four years and those employed for 20 or more years were studied separately. No statistically significant associations were found, although an elevated risk was suggested for employment in the machine shop prior to 1945 based on three exposed cases.

Results from a recent retrospective mortality study of current and former employees of the Dow Chemical U.S.A., Texas Division have indicated that, while an excess risk for brain tumor probably does not exist for the overall population, an apparent excess risk may exist for those first employed prior to 1945.[1] Among all hires, a possible excess appeared confined to those employed from one to four years and to those employed greater than 20 years. A plant-based case-control study was undertaken in an attempt to localize the risk to a particular process area, chemical or physical exposure agent, or job classification. The present investigation differs somewhat from a case-control study reported earlier,[2] due to more extensive case ascertainment and a more refined case definition. In addition, the present study considers separately the various subsets of cases identified from the retrospective mortality study as possibly at higher risk.

There are few known risk factors for brain neoplasms in humans. A review of the epidemiology of brain tumors has been recently published[3] and is recommended for a more thorough discussion. Incidence and mortality rates rise steeply after age 30 to a peak between 55 and 64 years, and are relatively higher among whites and males.[4,5] Within the past few years, several toxicologic and epidemiologic reports have focused on the possible etiologic role of chemicals and, to a lesser extent, viruses. Experimental systems for inducing gliomas, a common histological type of brain tumor, by direct injection of chemical carcinogens and viruses have been summarized.[6] Animal studies have suggested that acrylonitrile can induce CNS tumors,[7] and controlled exposures to extremely high levels of vinyl chloride (2,500 to 10,000 parts per million) have produced brain tumors in rats.[8] Other experimental brain carcinogens, such as some of the nitrosoureas, are recognized and have been summarized elsewhere.[9]

The epidemiologic reports have been less definitive. A study of records maintained by the Oil, Chemical and Atomic Workers Union noted a proportionate excess of brain tumors among union members, but was unable to link the observations to specific exposures.[10] Excess mortality due to brain neoplasms has been reported among other petroleum refinery and petrochemical employees[11,12] and among a cohort of Swedish chemists.[13] Other mortality studies of employees in these industries have failed to demonstrate an excess risk for brain neoplasms.[14-17] Thus, it is not clear whether the elevated brain tumor risks observed in some petrochemical plants, if real, are isolated incidents or indicative of the effects of a widely disseminated brain carcinogen.

It was the purpose of this investigation to determine whether or not a risk for brain tumor mortality could be associated with a specific job assignment, with employment in a particular process area, or with presumptive exposure to a chemical or physical agent. Because no a priori hypothesis existed regarding a specific exposure agent, this

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was considered a hypothesis-generating investigation, i.e., it was intended to suggest areas for more rigorous study in other similar populations.

Materials and Methods

Case Ascertainment and Definition — The sources used for ascertainment of cases of primary intracranial neoplasms among former employees have been described in detail elsewhere.[1] Briefly, there were four such sources: company records, deaths recorded for a four-county area proximate to the plant, follow-up of a 5% random sample of the ever-employed population, and unsolicited reports of cases to the National Institute for Occupational Safety and Health (NIOSH).[18]

All available death certificates maintained by the company medical department were reviewed for a diagnosis suggestive of a primary brain neoplasm. This identified brain tumor deaths among employees who died while active with the company or otherwise eligible for a company death benefit as well as any among "left" employees who had been followed in previous chemical-specific cohort studies.[19]

Deaths from primary intracranial neoplasms among former employees who were residents of Brazoria County, Texas, and contiguous counties (Harris, Galveston and Matagorda) were identified in two stages. The Texas Bureau of Vital Statistics Mortality Tape (all Texas deaths, 1964-1979) and an ancillary data file (Texas cancer deaths only, 1949-1963) were searched by NIOSH for all deaths from primary intracranial neoplasms or brain-stem lesions among residents of the four-county area of interest. These deaths represented all deaths with the underlying cause coded as brain cancer from 1949-1963, coded as brain tumor from 1964-1979, or coded as brain-stem lesions from 1964-1979 among residents for the four counties. These deaths were then manually matched against Dow employment records to determine a prior history of employment.

The follow-up of the 5% random sample of present and former employees identified two additional cases of brain tumor among short-term employees. Another brain tumor case came to attention as a result of a telephone call from a spouse who was aware of these investigations from the attendent media coverage.

Histopathology was sought under the auspices of NIOSH on each suspected case of primary intracranial neoplasm. The case definition for analysis was then made based on the best available medical evidence, including information from medical records, surgical-pathology specimens and autopsy findings. Thus, the case population for this case-control study differs somewhat from the case population that constituted the observed deaths in the sample-based cohort study.[1] Specifically, four individuals considered among the observed brain tumor deaths did not meet the criteria for inclusion as cases in the case-control study. Two of these individuals had metastatic lesions, a third had a neurogenic sarcoma, and the fourth had a cyst on the brain. Seven cases, not included among the observed, did meet the criteria and were included in the case-control study. The death certificate for one indicated a cerebral hemorrhage and for another a lesion of the brain stem. Available medical records for both revealed primary intracranial neoplasms. The remaining five cases were excluded from the sample-based cohort study solely because they did not meet the requirements for residency in one of the four counties or for having died within the time frame for case ascertainment. Neither of these requirements was viewed as necessary for admission to the case-control study.

In addition to considering all primary intracranial neoplasms together in the analysis, an attempt was made to examine separately malignant neoplasms and the histologically distinct category of glioblastoma (which includes astrocytomas, grades III and IV).

Selection of Control Groups — Two control groups were selected using a multiple-match-per-case design. The first, control group A, was selected from among all deaths, excluding those due to cancer, known to the company. Deaths from malignant neoplasms were excluded in the event the putative "brain carcinogen" was a multiple-site carcinogen; their inclusion then might have masked an association. The controls were restricted to white males to reflect the race and sex distribution of the cases. Four controls were matched to each case based on age at death ± 5 years and year of death. When more than four potential matches were available for any given case, four were selected randomly using a computer program. For one case there were only three available controls who satisfied the matching criteria. In addition, four other cases could not be matched directly on year of death so that controls for these cases were matched on year of death ± 5 years. One control was later dropped when a discrepancy in his year of birth was discovered. According to information from his work history, this individual was older than indicated on his death certificate and then did not satisfy the matching criteria.

The second control population, control group B, was selected from the 5% sample already described.[1] The pool of potential controls was again restricted to white males, and four controls were matched to each case on year of birth ± 2 years, and category of duration of employment (calculated as the time difference between first date of employment and the last date of employment while ignoring breaks in service) (≤ 1 year, 1 through 4 years, 5 through 9 years, 10 through 14 years, 15 through 19 years, and ≥ 20 years). For one case the year of birth criterion was expanded to ± 5 years and only three suitable controls could be found. Again, when more than four potential controls were available, four were selected at random.

Exposure Characterization — Complete company work histories, as available from Personnel Department records, were coded and computerized for both cases and controls. This coding retained the specificity of the original hard-copy work history, including basic demographic information as well as detailed job classifications, departments, dates of job changes and dates of and reason for terminations. For analytical purposes, however, it was necessary to consolidate the specific job classification and department titles into manageable, yet meaningful groupings. Departments were grouped according to related process or function by on-site company industrial hygienist.

A total of 237 department titles were, thus, reduced to 46 department groupings. Often a single process area had been referred to historically by a number of similar names, so the 237 titles did not represent 237 different work areas.

To further investigate a consistent, although not statisti-

cally significant, elevated risk found earlier for having been a salaried employee at termination of employment,[2] job classification titles were grouped into six socioeconomic categories following those developed by the Bureau of the Census. A total of 269 job titles were reduced to six categories ranked from presumed highest to lowest socioeconomic group: managers and administrators (high-level management); professional, technical and kindred (chemists, research personnel, and engineers); craftsmen, foremen and kindred (skilled trades and first-line supervision); operative (inorganic and organic chemical production personnel); clerical and kindred (clerks); and laborers and kindred (unskilled). Cases and controls were compared for highest job category achieved and for ever having been assigned to any of the job categories.

Classification of subjects by work area, or by job title can be a somewhat crude method for comparing exposure histories and may obscure an association with a chemical or physical agent exposure that may be common to several work areas or jobs.[20] Thus, subjects in this study were also classified by presumptive exposure to specific chemical or physical agents. In the previous study,[2] the focus had been mainly on comparisons of presumptive exposures to process chemicals. This was expanded in the present investigation to compare cases and controls with respect to presumptive exposure to the main agents, including those materials not directly related to chemical production.

On-site industrial hygienists established chemical and physical agent-specific exposure profiles for each subject based on the work history and job function. The presumptive exposures for the job function were developed through interviews with employees knowledgeable of the process and the job, and knowledgeable of process changes and the use of available survey data. This was done with the industrial hygienist being "blind" to whether the subject was a case or a control, although the identity of the subject was known to the industrial hygienist.

Identity of the subject permitted the industrial hygienist to question former co-workers concerning job duties, whenever there were ambiguities in the work history. In some instances, the department and/or the job titles were too broad to establish an individual's work experience; interviews with former co-workers offered the only identifiable source of information to determine the subject's department assignment. While it is quite possible the co-workers were aware of the case-control status of the subject when provided his identity, it is not believed a systematic bias in misclassification of exposure resulted. No attempt was made to reveal to the interviewee the reason for the inquiry, and the size of the plant and number of individuals questioned would make a systematic bias unlikely.

Analytical Strategy — Both department assignment and presumptive chemical exposures were regarded as dichotomous variables (ever or never assigned, ever or never exposed) for analytical purposes. Since for both control groups A and B a full complement of four controls could not be matched to each case, an analysis for a data set with a variable matching ratio was performed.[21] Point estimates of the odds ratio were calculated,[22] and confidence limits for the odds ratio were taken as test-based limits,[23] based on the point estimates and the χ from hypothesis testing. In some instances, the matching was dissolved and the data were stratified by variables into 2 x R tables to assess interaction and to control confounding.[24] Pooled point estimates and χ values were calculated and an asymptotic likelihood ratio test[25] was employed to test the hypothesis that the odds ratio was uniform across the strata (test for homogeneity). All analyses were done on a programmable calculator with a packaged set of programs.[26]

Results

Twenty-eight decedents met the criteria for having a primary intracranial neoplasm and constituted the case population. Selected demographic and employment information is presented for each of the cases in Table 1. The median age at death was 57 years, with a range from 27 to 69 years. The deaths occurred over a 32-year period, 1945-1977, and no additional brain tumor deaths were observed among former employees through 1979, even though case ascertainment has been updated through this period. The distribution of cases by tumor type reveals the majority (71%) of the neoplasms to be of glial origin. Nearly 58% of all the intracranial neoplasms were indicated to be glioblastomas (this includes the astrocytomas grades III and IV) and 29% were of an unspecified nature.

The matching technique employed resulted in 110 decedents in control group A and 111 individuals in control group B successfully matched to the 28 cases. Table 2 presents some descriptive data by case-control status. The cases and controls were quite similar with respect to all factors on which they were matched. The only possible exception is that the cases were employed on the average 13.4 man-months longer than control group B. This difference would have likely been smaller if the matching had been more stringent among those with more than 20 years of employment and had consideration been given to incorporating service breaks in the matching process.

There was an even larger difference in the mean duration of employment between the cases and control group A; (41 man-months) the greater duration observed among the latter reflects the proportionately large share of vested employees among the deaths known to the company. The mean year of hire among the cases and the two control groups was similar, although the controls not matched on length of employment (control group A) began employment, on the average, later than did the cases.

Matched odds ratios for department assignment are presented for the comparisons with control groups A and B in Tables 3 and 4, respectively. None of the odds ratios are significantly elevated, and there is a lack of consistency in direction between the odds ratios for the comparisons with the two control groups. For instance, there is nearly a two-fold risk of brain tumor and having been assigned to a magnesium department in the comparison with control group A. It would appear, however, that perhaps length of employment is a confounding variable, because the odds ratio is close to unity in the comparison with control group B which was matched to the cases on length of employment.

The distribution of cases and both control groups by highest job classification achieved may be found in Table 5. The distributions by ever having been assigned to a job classification were similar. Generally, the cases and controls from group B were distributed across job classification categories nearly identically.

Table 1 — Characteristics of Brain Tumor Cases

Case No.	Year of Hire	Year of Death	Age at Death	Usual Job at Dow	Duration of Employment*	Time Interval Since Entry†	Tumor Type (Source)‡
01	1940	1975	61	Machinist	13;3	34;5	Astrocytoma, grade IV (SPR)
02	1941	1958	39	Machinist	3;3	17;10	Glioblastoma multiforme (SPR)
03	1943	1951	48	Operator	8;11	8;11	Brain tumor (MR)
04	1943	1960	56	Laborer	1;1	17;4	Glioblastoma multiforme (DC)
05	1950	1974	48	Mechanic	1;6	23;6	Oligodendroglioma (SPR)
06	1941	1952	36	Operator	4;5	10;10	Carcinoma of brain (DC)
07	1941	1965	49	Chemical engineer	4;2	23;10	Astrocytoma, grade III (Aut)
08	1942	1973	68	Metal dipper	1;2	30;10	Astrocytoma, grade IV (MR)
09	1941	1962	53	Painter	0;1	21;1	Glioblastoma multiforme (MR)
10	1943	1966	62	Roustabout	17;8	23;5	Brain tumor (DC)
11	1942	1969	58	Clerk	0;3	26;11	Glioblastoma multiforme (DC)
12	1971	1977	69	Research scientist	0;11	5;6	Glioblastoma of frontal lobe (MR)
13	1941	1977	57	Manager	35;3	35;4	Medulloblatoma (MR)
14	1943	1961	67	Paint shop foreman	14;9	17;9	Astrocytoma, grade III (Aut)
15	1941	1971	59	Production foreman	30;4	30;6	Malignant glioma (MR)
16	1941	1961	49	Operator	19;4	19;4	Glioblastoma,Rt temporal lobe (MR)
17	1943	1964	60	Pipefitter	21;8	21;8	Brain tumor malignant (DC)
18	1950	1977	61	Material handling technician	27;0	27;0	Malignant brain tumor (MR)
19	1941	1968	55	Boilermaker-welder	27;11	27;11	Astrocytoma, grade IV (MR)
20	1943	1977	51	Boilermaker	31;2	34;4	Carcinoma of brain (MR)
21	1968	1976	38	Operator	8;2	8;2	Glioblastoma multiforme (MR)
22	1943	1965	62	Oiler	0;5	21;4	Glioblastoma multiforme (SPR)
23	1946	1970	46	Operator	23;11	23;11	Glioblastoma multiforme (MR)
24	1940	1945	27	Pipefitter	2;7	4;1	Cancer of brain (DC)
25	1944	1970	64	Metal dipper	1;5	25;10	Astrocytoma (MR)
26	1942	1976	65	Machine shop foreman§	34;2	34;6	Glioblastoma multiforme (MR)
27	1953	1963	36	Rigger§	10;2	10;5	Malignant brain tumor (MR)
28	1945	1973	67	Laborer	0;1	27;8	Glioblastoma (DC)

* Years; months

† Time interval between date of hire end date of death

‡ MR indicates medical records; DC, death certificate; SPR, surgical pathology report; AUT, autopsy

§ Death certificate did not indicate presence of intracranial neoplasm

Control group A and the cases were distributed quite differently, and this no doubt reflects the weighting of these controls toward employees with longer company service. There is a larger percentage of persons who attained the craftsmen and foremen category in this control group, and a smaller percentage represented at the higher (manager and administrator, professional and technical) and lower (clerical and laborers) ends of the job classification scale.

A total of 79 specific chemical and physical agents were listed as presumptive exposures for cases or controls by the industrial hygienists. Tables 6 and 7 present the distribution of cases and control groups A and B, respectively, by presumptive exposure to specific agents. None of the matched odds ratios for exposure to any of the agents was significantly elevated. Those agents to which cases and controls had the most frequent potential for exposure were chlorine, hydrogen chloride, and sulfur dioxide. Exposure to these agents was common among employees who were assigned to magnesium production and the frequency of exposure among cases and controls reflects the relatively large proportion of these employees who had been assigned to the Magnesium Department. Exposure to solvents, such as carbon tetrachloride (no longer used for such a purpose), mineral spirits and toluene was common among employees who were engaged in a specific craft, e.g., machinists. Exposure to the majority of the remaining chemical agents was less frequent. This is not surprising given the large number of individuals employed and the diversity of chemical operations over the years.

As mentioned earlier, a retrospective mortality study of a 5% random sample of the ever employed population suggested that any brain tumor mortality excess, if present, was confined to two subgroups of the population those employed from 1 to 4 years and those employed 20 or more years. There was also a suggestion that the risk was further confined to those individuals first employed prior to 1945, although there were too few observed and expected deaths among those hired later to state this unequivocally. Each of the subgroups suggested to be at increased risk was further explored by the case-control method in an attempt to identify a specific etiologic agent in the work environment that may have been responsible.

Table 2 – Descriptive Demographic Data by Case-Control Status

Demographic Variables	Mean ± SD		
	Cases (N=28)	Control Group A (N=110)	Control Group B (N=111)
Year of birth	1912.6 ± 9.6	1912.0* ± 9.5	1913.0* ± 9.4
Year of death	1967 ± 8.6	1967* ± 8.5	1958† ± 8.3
No. of man-months employed	143.0 ± 141.5	184.0 ± 121.3	129.6* ± 126.2
Year of hire	1945.1 ± 7.6	1947.2 ± 8.1	1945.5 ± 5.7

* Controls were matched to cases on these variables
† Only 40 of 111 controls were known deceased as of Dec. 31, 1977

First, since it was apparent there might be an increased risk for having been employed for more than 20 years we examined the department assignments, job classification distribution and presumptive exposure to chemical and physical agents among this subset of cases and their controls from group B. Comparisons with control group A were considered less valid due to the weighting of this group toward employees with longer service and have been ignored. Of the nine observed deaths noted among this subcohort in the sample-based cohort study, two were determined to not have been primary intracranial neoplasms on review of available medical records and histopathology and have been excluded from the case-control study. An additional case whose death certificate indicated a lesion of the brain stem and who had been employed greater than 20 years was included when medical records revealed a primary intracranial neoplasm.

Table 8 presents the comparisons of cases employed greater than 20 years and control group B with respect to several exposure variables. There were elevated risk estimates associated with having been employed in the Pipe or Boiler Shop, in a Maintenance area, or in Administrative Services. The small number of subjects with a common exposure history makes interpretation of these data difficult. There was an elevated risk for having been potentially exposed to carbon tetrachloride; however, only two of the

Table 3 – Matched Odds Ratios for Department Assignment (Ever): Comparison With Control Group A*

Department	No. of Exposed Cases	No. of Exposed Controls	Odds Ratio	90% Confidence Limits
Maintenance	6	45	0.39	0.18-0.87
Magnesium	11	27	1.93	0.95-3.93
Pipe and Boiler Shop	5	27	0.66	0.27-1.61
Administrative Service	5	20	0.97	0.75-1.25
Paint Shop	2	14	NC†	NC
Power	1	15	NC	NC
Styrene	3	11	NC	NC
Chlorine	2	12	NC	NC
Chlorinated Methanes	0	12	NC	NC
Material Handling	2	9	NC	NC
Yard and Utility	2	9	NC	NC
Machine Shop	3	7	NC	NC

* There were 25 other departments in which at least one case or control had worked; however, the total number of cases and controls assigned to each was fewer than 10 and no more than two cases had one of these departments in common
† NC indicates not calculated because fewer than five cases had exposure

Table 4 – Matched Odds Ratios for Department Assignment (Ever): Comparison With Control Group B*

Department	No. of Exposed Cases	No. of Exposed Controls	Odds Ratio	90% Confidence Limits
Magnesium	11	40	1.15	0.56-2.36
Administrative Services	5	27	0.68	0.28-1.66
Maintenance	6	25	0.92	0.41-2.06
Pipe and Boiler Shop	5	15	1.45	0.55-3.82
Paint Shop	2	16	NC†	NC
Machine Shop	3	11	NC	NC
Chlorine	2	12	NC	NC
Caustic	2	10	NC	NC
Yard and Utility	2	10	NC	NC
Styrene	3	8	NC	NC
Material Handling	2	7	NC	NC

* There were 24 other departments in which at least one case or control had worked; however, the total number of cases and controls assigned to each was fewer than nine and no more than two cases had one of these departments in common
† NC indicates not calculated because fewer than 5 cases had exposure

Table 5 – Distribution of Highest Job Classification Achieved by Case-Control Status

Job Classification	Cases	Control A	Control B
Managers and administrators	2 (7.1)*	4 (3.6)	5 (4.5)
Professional and technical	2 (7.1)	3 (2.7)	8 (7.2)
Craftsman and foremen	13 (46.4)	66 (60.0)	49 (44.1)
Operatives	8 (28.6)	30 (27.3)	33 (29.7)
Clerical	1 (3.6)	2 (1.8)	4 (3.6)
Laborers and other unskilled	2 (7.1)	5 (4.5)	12 (10.8)
Total	28 (100.0)	110 (100.0)	111 (100.0)

* Numbers in parentheses are percent of total

Table 6 – Matched Odds Ratios for Presumptive Exposure (Ever) to Specific Chemical and Physical Agents: Comparison With Control Group A*

Chemical or Physical Agent	No. of Exposed Cases	No. of Exposed Controls	Odds Ratio	90% Confidence Limits
Chlorine	14	48	1.33	0.65-2.71
Hydrogen chloride	13	42	1.40	0.70-2.80
Sulfur dioxide	11	26	2.02	0.99-4.11
Carbon tetrachloride	5	20	1.00	...†
Noise	5	40	0.26	0.10-0.67
Mineral spirits	4	9	NC‡	NC
Welding fumes	4	24	NC	NC
Cutting oils	4	9	NC	NC
Sodium hydroxide	3	12	NC	NC
Crystalline silica	3	9	NC	NC
Toluene	3	11	NC	NC

* There were 68 other chemical or physical agents to which cases or controls had presumptive exposure; however, the total number of cases and controls with presumptive exposure to each was less than 20 and no more than two cases had presumptive exposure to any of these agents

† Test based confidence intervals will not compute when $x_{MH} = 0$

‡ NC indicates not calculated because there were fewer than five exposed cases

Table 7 – Matched Odds Ratios for Presumptive Exposure (Ever) to Specific Chemical and Physical Agents: Comparison With Control Group B*

Chemical or Physical Agent	No. of Exposed Cases	No. of Exposed Controls	Odds Ratio	90% Confidence Limits
Chlorine	14	55	1.03	0.81-1.31
Hydrogen chloride	13	51	1.02	0.81-1.29
Sulfur dioxide	11	39	1.19	0.58-2.43
Noise	5	22	0.92	0.35-2.45
Carbon tetrachloride	5	14	1.50	0.60-3.74
Welding fumes	4	14	NC†	NC
Cutting oils	4	10	NC	NC
Toluene	3	16	NC	NC
Sodium hydroxide	3	15	NC	NC
Crystalline silica	3	10	NC	NC

* There were 68 other chemical or physical agents to which cases or controls had presumptive exposure; however, the total number of cases and controls with presumptive exposure to each was less than 20 and no more than two cases had presumptive exposure to any of these agents

† NC indicates not calculated because there were fewer than five exposed cases

cases had a work history that was suggestive of this exposure.

Another subcohort suggested to be at an increased risk for brain tumor was that group of employees employed from 1 to 4 years. There were seven cases who were employed for from 1 to 4 years, so again the relatively small sample size precludes many meaningful comparisons. Table 9 presents the exposure variable comparisons between these cases and their matched controls from group B. Only the odds ratio (OR) for having been assigned to a Magnesium Department is elevated for this group (OR = 2.67, 90% confidence limits = 0.74 – 9.62); however, this was not statistically significant.

As mentioned earlier, the greatest risk for mortality from brain tumor appeared confined to the subcohort hired prior to 1945. This association with employment in the early years of the Texas Division was explored further by restricting the case-control analysis to department assignments held prior to 1945, and by dissolving the matching among the cases and controls. There were only four departments in which at least three cases had held an assignment prior to 1945: Magnesium, Administrative Services, Machine Shop and Pipe or Boiler Shop. Odds ratios were sightly elevated, but not significant, for having been assigned to Magnesium (COR = 1.20, Fisher[27] exact upper p value = 0.46) or to the Pipe or Boiler Shop (COR = 1.38, Fisher exact upper p value = 0.46) prior to 1945. The association with having been assigned to the Machine Shop prior to 1945 was even stronger (COR = 5.3, Fisher exact upper p value = 0.09); however, there were only three cases with such a history. According to available records, all

Table 8 – Exposure Variable Comparisons of Cases Employed > 20 Years With Matched Controls From Group B

Exposure Variable	No. of Exposed Cases	No. of Exposed Controls
Department assignment (ever)*	(N=8)	(N=31)
Maintenance	4	13
Magnesium	2	10
Pipe and Boiler Shop	3	7
Administrative Services	2	13
Caustic	2	4
Chlorine	2	2
Presumptive exposure to chemical or physical agent (ever)		
Chlorine	5	19 (1.13; 0.3-4.1)†
Hydrogen chloride	4	17
Sulfur dioxide	2	12
Noise	3	11
Welding fumes	3	5
Carbon tetrachloride	2	3
Cutting oils	2	2
Job classification (highest achieved)		
Managers and administrators	1	4
Professional, technical and kindred	1	2
Craftsmen, foremen and kindred	4	18
Operatives	2	7
Clerical	0	0
Laborers	0	0

* There were 25 other departments in which at least one case or control had worked; however, the total number of cases and controls assigned to each was fewer than five and no more than one case had one of these departments in common

† Numbers in parentheses are odds ratio; 90% confidence intervals computed only when there were five or more cases with a history of exposure

Table 9 – Exposure Variable Comparisons of Cases Employed One to Four Years With Matched Controls From Group B

Exposure Variable	No. of Exposed Cases	No. of Exposed Controls
Department assignment (ever)*	(N=8)	(N=32)
Magnesium	5	12 (2.67; 0.7-9.6)†
Paint Shop	1	6
Administrative Services	1	4
Chlorine	0	5
Machine Shop	1	3
Maintenance	1	3
Presumptive exposure to chemical or physical agent (ever)		
Chlorine	4	19
Hydrogen chloride	5	15 (2.02; 0.5-8.1)
Sulfur dioxide	5	12 (2.67; 0.7-9.6)
Carbon tetrachloride	2	6
Noise	1	3
Job classification (highest achieved)		
Managers and administrators	1	0
Professional, technical and kindred	0	0
Craftsmen and foreman	3	13
Operatives	3	13
Clerical	0	2
Laborers	1	4

* There were 10 other departments in which at least one case or control had worked; however, the total number of cases and controls assigned to each was fewer than four and no more than one case had one of these departments in common

† Numbers in parentheses are odds ratio; 90% confidence interval, computed only when there were five or more cases with a history of exposure

three of these individuals had malignant intracranial tumors and these were indicated to have been glioblastomas.

Restricting the case-control analysis to the 25 malignant intracranial neoplasms had no material effect on the results. Further restricting the analysis to cases indicated to have been glioblastomas (including the astrocytomas, grades III and IV) yielded the findings in Table 10. Elevated, but not significant, odds ratios were noted for having been assigned to a Magnesium Department (OR = 1.40) or the Machine Shop (OR = 4.16). There were elevated odds ratios for having been potentially exposed to chemicals closely associated with these departments; chlorine, hydrogen chloride, and sulfur dioxide and carbon tetrachloride, respectively.

Discussion

This case-control study of 28 cases of primary intracranial neoplasm failed to identify a significantly elevated risk with a job assignment in any particular department, or with presumptive exposure to any specific chemical or physical agent. Furthermore, the distribution of the cases and controls by job classification category did not differ materially. This lack of association is not surprising, given that the estimation of expected deaths derived from the sample-based cohort study suggests that overall there is, at most, only a slight excess of brain tumor deaths among the Dow, Texas Division work force. Without an overall excess, one would expect the job and department assignments and exposures of the cases to be distributed much the same as that of the entire work force.

Table 10 – Exposure Variable Comparisons of Glioblastoma Cases With Matched Controls From Group B

Exposure Variable	No. of Exposed Cases (N=16)	No. of Exposed Controls (N=63)
Department assignment (ever)*		
Magnesium	7	22 (140; 0.6-3.4)†
Administrative Services	4	14
Maintenance	3	12
Pipe or Boiler Shop	1	7
Machine Shop	3	4
Presumptive exposure to chemical or physical agent (ever)		
Chlorine	8	28 (1.26; 0.5-3.1)
Hydrogen chloride	7	28 (0.97; 0.4-2.4)
Sulfur dioxide	7	22 (1.40; 0.6-3.4)
Noise	2	12
Carbon tetrachloride	3	6
Job classification (highest achieved)		
Managers and administrators	1	4
Professional, technical and kindred	2	5
Craftsmen, foremen and kindred	5	21 (0.91; 0.3-2.5)
Operatives	6	21 (1.17; 0.5-2.9)
Clerical	1	2
Laborers	1	10

* There were 25 other departments in which at least one case or control had worked; however, the total number of cases and controls assigned to each was fewer than seven and no more than one case had one of these departments in common

† Numbers in parentheses are odds ratio; 90% confidence interval, computed only when there were five or more cases with a history of exposure

The apparent elevated risk for an assignment in a Magnesium Department seen in the comparison of cases with control group A was noticeably absent in the comparison with control group B. This appears to have been due to the difference between the cases and control group A with respect to length of service with the company. The Magnesium Department is often an entry level area for unskilled labor. During the war years, and in the immediate postwar period there appears to have been a great turnover in personnel in this production area. Thus, there were many employees with relatively short duration of service to the company, most or all of it in the magnesium production areas. Because control group A was somewhat biased toward employees with longer service, it was overrepresented by skilled employees (e.g., craftsmen) and underrepresented by the unskilled. This bias apparently led to a positive association with having been employed in a magnesium department.

Restricting the case-control analysis to subgroups of cases identified from the sample-based cohort study as being at increased risk appeared warranted. There were several of these subgroups, such as those employees with from one to four years of service, those with more than 20 years of service and those employees first employed prior to 1945. Analyses of these subgroups failed to identify a significant risk for assignment to any particular department, or presumptive exposure to a chemical or physical agent; although in some subsets the number of cases was small.

The apparent increased risk for having been employed in the Machine Shop prior to 1945 is interesting and may be indicative of an exposure or other factor which was unique to having been employed in this area during the period. Since only three cases had a history of employment in this area, it is difficult to evaluate this association. Decoufle[28] noted a slight excess mortality from CNS neoplasms (five observed *v* 3.3 expected) among a cohort of machinists employed five or more years in oil mist-exposed jobs; although none of these deaths were among those considered to have been heavily exposed. Jarvholm et al[29] examined cancer incidence and mortality among 792 Swedish men employed at sometime between 1950 and 1966 and who had worked at least five years in jobs with oil mist exposures. There were no brain tumor cases observed among the 43 incident cancers noted over the follow-up period 1958-1976. While excess cancer of other sites has been reported among machinists by others,[30,31] CNS neoplasms were not noted to have been observed in excess of expected.

It is generally assumable that industrial hygiene conditions in the chemical industry in the early 1940s were quite different than they are presently. Other than the three cases noted to have been employed in the Machine Shop, the lack of a common documented work experience among the subgroup of cases employed during this period does not allow one to focus the risk on any particular department, job classification or presumptive exposure. The effects of a general exposure that pervaded all operations might not be discriminated with the use of the case-control methodology, however.

The early 1940s also represented an unusual period in terms of hiring practices in American industry. As World War II progressed and young men were drafted into military service, industry began hiring those not eligible to serve, including females and males who were selected out of the military. The effect of this selection process on the mortality experience of industrial cohorts is not clear, but could be playing some role. As further studies are done on other industrial cohorts, it will be interesting to note whether or not this relationship, with first employment in the early 1940s, also emerges.

Due to extensive benefits programs offered by many large employers, industrial cohorts usually have access to more sophisticated medical care than does the general population. Differences between the mortality experience of these cohorts and the general population have typically

been ascribed to occupational exposures, and the influence of this diagnostic access bias has been largely ignored. Recent evidence indicates that industrial populations with such benefit programs may receive a more sophisticated diagnostic workup when brain tumor is suspected than does the general population.[32] One would expect this diagnostic access bias would have the effect of overstating the risk of brain tumor mortality among industrial cohorts relative to the general population.

Case-control studies are particularly prone to a number of potential biases, which can inadvertently lead to incorrect results. The biases of most concern are selection bias, information bias and confounding bias.[25] Selection bias refers to a distortion of the estimate of effect (odds ratio) resulting from the manner in which cases and controls are selected into the study. A selection bias may have occurred in this study, although considerable effort was expended to minimize its effect.

Since the cases studied are, in all probability, a sample of the brain tumor deaths among former employees (due to incomplete case ascertainment), it was important that the ways in which the sample was unrepresentative of the larger group be known, so that controls could be selected in the same manner. The cases studied were strongly suspected to have been employed for a longer duration with the company than were unascertained cases. To compensate for this, one of the control groups, group B, was matched to the cases on length of employment. Control group A, like the cases, was somewhat biased toward employees with longer service anyway, since it was selected from among deaths known to the company.

Information bias refers to the distortion of the estimate of effect resulting from misclassification of subjects on either the disease or exposure variables. If the case definition was somewhat loose and individuals who did not truly have primary intracranial neoplasms were included as cases, then differences in exposure history between cases and controls could be diluted and obscured. The case definition employed in this study attempted to incorporate the best available medical information, although, for some cases this consisted of only the death certificate.

The employees' company work history record served as the primary source of exposure information in this study. While it is believed to be the best available documented source of information for such a purpose, there may be inadequacies in the record. Both job classification title and department name and the relevant calendar dates are detailed in the record. In most instances, these were quite descriptive and subjects could be grouped by similar exposure history quite easily for analytical purposes. In some instances, job title and department were rather nonspecific and the industrial hygienist had to infer exposure history from interviews with employees with historical knowledge, or from other records available. Industrial hygiene survey data were not available for the early years of operations and since there was no chemical or physical agent suspected as an etiologic agent a priori, no attempt was made to rank exposure levels. Some misclassification of exposure was, thus, possible; however, every effort was made to classify individuals correctly and since the industrial hygienist was unaware of the case or control status of the subjects, it is unlikely a systematic misclassification occurred.

Probably of more concern, the relatively small number of cases available for study and the relatively low background worker population exposure rate to each of a wide variety of agents combine to limit the statistical power of this case-control study. For example, assuming an α-level of 0.05, the study would have had a 90% chance of detecting, as significant, a 3½-fold risk for having been employed in a magnesium department. The study would have had less power to detect associations of similar strength with other exposure variables to which the background worker population exposure rate was less.

Finally, bias due to confounding variables may also distort the estimate of effect. Confounding variables in this study would be those factors associated with the risk for brain tumor and independently associated with any of the exposure variables. Matching in the design of the study and stratification in the analysis were employed to control all factors thought to have been potential confounders. There is always the possibility that some variables not measured could have confounded the results.

In conclusion, this plant-based case-control study of brain tumor mortality failed to identify any significant associations with workplace exposures, although an elevated risk was suggested for employment in the Machine Shop prior to 1945 based on three exposed cases.

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Searching for Self

Childhood is a time for play, for experimentation, for fantasy, for exploration. Everything is new. Everything is curious. Few of us have been able to escape the fascination (and frustration) of watching a child explore. No place is too perilous, no object too valuable, no obstacle too insurmountable. They braille their way fearlessly over the world seeing, listening, responding. *The mystery the child is searching for, is itself.* The key to the mystery lies in the child's receptiveness. If its search is impeded or blocked, the child will scream in frustration. A child's nature requires experience, organization, verification, and validation. All the material which is so essential for children to emerge as the fully functioning, unique individuals they are is already present in them. But in childhood, there is yet no personhood. Children are total potential. Even when basic expression is mastered, children are still mainly a copy of the others in their lives. Yet already in the specialness of their receptivity and environment, their unique selves are being formed.

– From *Personhood* by Leo F. Buscaglia, Ph.D., Fawcett Columbine, New York, 1982.