A PROGRESS REPORT: THE INVESTIGATION OF BRAIN TUMORS AT THE TEXAS DIVISION OF DOW CHEMICAL

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INTRODUCTION

Three recent epidemiologic studies have linked brain cancer with employment in the petroleum industry. In 1979, a brain cancer excess was identified among Canadian refinery workers.[1] In 1980, an increased risk of brain cancer was reported among union members who had worked at oil refineries or petrochemical plants in Texas.[2] Also in 1980, preliminary findings indicated that a brain cancer cluster had occurred among workers in a petrochemical plant in Texas City, Texas.[3,4]

To further evaluate the apparent association between employment in the petroleum industry and brain cancer, the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) undertook a review of death certificates of brain cancer cases among adult male residents of a three-county area along the Texas Gulf coast which contains numerous refineries and petrochemical plants. In one of the counties, Brazoria County, Dow Chemical was listed on the death certificate as "usual employer" for one-third of the malignant brain tumor deaths. Although Dow Chemical has been the largest single employer in Brazoria County for the past 40 years, this observation was sufficiently striking to warrant further investigation.

The investigation at Dow Chemical was planned to proceed through three stages: (1) preliminary estimates of risk; (2) additional case ascertainment; and (3) more definitive estimates of risk with attempted identification of specific risk factors.

Preliminary estimates of risk were obtained through two iterations of a case–control study based on Brazoria County death certificates (county-based case–control study); the death certificates were first examined by themselves, then employment history at Dow verified using company personnel records was incorporated in the second iteration. In the next stage, additional cases were ascertained by linking Texas vital records of four adjacent counties with company personnel records and through pursuit of unsolicited leads. Fourteen additional brain tumor cases among former Dow employees were discovered, which, when added to the 11 Dow cases ascertained through the county-based case–control study, brought the case total to 25. On the basis of these results, more definitive risk estimation has been initiated by means of a cohort mortality study based on a sample of the 44,000 workers who have been employed by Dow Chemical since 1940 (sample-based

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cohort study). Protocols have also been developed for studies which will be used to attempt to identify specific risk factors.

This report presents the results of the county-based case–control study and of additional case ascertainment efforts. It also describes the progress of the sample-based cohort mortality study and outlines plans for future attempts to identify specific risk factors.

Preliminary Estimates of Risk

County-Based Case–Control Study

To determine whether or not former Dow employees were over-represented among the brain tumor deaths in Brazoria County and to arrive at preliminary estimates of the relative risk of Dow employees dying from brain tumors, a case–control study based on Brazoria County death certificates was conducted.

The cases included in this county-based case–control study represent the complete set of reported brain tumor deaths among adult male residents of Brazoria County from 1964 to 1979. The cases were initially identified by searching computer tape copies of the Texas Bureau of Vital Statistics file of all deaths for those years. All deaths satisfying the following criteria were selected as potential cases:

1. Place of residence was Brazoria County.
2. Sex was male.
3. Age at death was 20 years or greater.
4. Underlying cause of death was coded by state nosologists as a primary intracranial neoplasm (see Table 1 for designated ICD codes).

The death certificates of the potential cases were then reviewed by a qualified nosologist to verify the accuracy of the state-assigned ICD codes. Two potential cases, an intracranial tumor due to skin cancer and a metastatic cancer of the brain, were excluded from the study on the basis of this review. The death certificates of the remaining cases were reviewed to identify those cases that had been properly coded as primary intracranial neoplasms according to the ICD rubrics in effect at the time of death, but would not now be coded as primary intracranial neoplasms. Two such cases, a "metastatic CNS malignant melanoma" (code 191, 8th Revision) and an "internal hydrocephalus due to a paraphyseal cyst" (223, 7th Revision) were identified and subsequently excluded from the study.

Ultimately 25 cases were included in the study. All of the cases were among whites.

Controls were selected from the same Texas Bureau of Vital Statistics data file used to identify the cases. Each case was assigned four matched controls according to the following selection criteria.

1. Place of residence, sex, race, and year of death was the same as the case.
2. Age at death was within 1 year of the case except for two cases who were assigned controls within 2 years of their respective ages at death. This modification was necessary due to a limited number of deaths within the particular age/race strata of the two cases.
3. Cause of death was not a primary intracranial neoplasm; i.e., the state-assigned ICD code for underlying or contributing cause of death did not equal any of the codes defining a case.

In order to determine past employment at Dow Chemical, the death certificates of all 125 cases and controls were examined to determine if Dow Chemical was

listed as the "usual employer." On the basis of this review, 32% of the cases were found to be former Dow employees, as were 18% of the controls.

To determine whether employment at Dow was associated with an increased risk of death due to brain tumor, the maximum likelihood estimate of the odds ratio[5] was calculated; 90% confidence intervals were also calculated.

The maximum likelihood estimate of the odds ratio indicated an elevated relative risk of death due to brain tumor among those decedents with Dow Chemical listed as "usual employer" on the death certificate. The odds ratio was 2.11, with a lower limit of the 90% confidence interval of 0.94 and the upper limit of 4.71 (see AUTHORS' NOTE).

Refinement of the County-Based Case–Control Study

Although the county-based case–control study suggested an increased relative risk of brain tumor among Dow employees, this finding was based primarily on occupational information appearing on death certificates, which is frequently scanty or unrepresentative of a decedent's complete occupational history. Therefore, to minimize bias that may be associated with the inaccuracies of occupational information contained on death certificates, the county-based case–control study was reanalyzed after company personnel records were examined to determine whether any of the cases and controls had ever been employed by Dow.

Upon matching the death certificates of the cases and controls with the company personnel records, the initial percentage of former Dow employees among the brain tumor cases was increased from 32% to 44%. An increase from 18% to 25% occurred among the controls. All of the cases and controls initially identified as former Dow employees by death certificate information were subsequently verified by personnel record matching.

Analysis of the data of the county-based case–control study with Dow employment determined by review of company personnel records again indicated an increased relative risk of death due to brain tumor given Dow employment. When Dow employment was defined as ever having worked at the plant, the maximum likelihood estimate of the odds ratio was 2.54. The lower limit of the 90% confidence interval was 1.23 and the upper limit 6.80 (see AUTHORS' NOTE).

ADDITIONAL CASE ASCERTAINMENT

With the county-based case–control study indicating an elevated risk of brain tumors at Dow Chemical, additional studies to further delineate risk and to attempt to identify specific risk factors were appropriate. However, because the 11 brain tumor deaths documented via the county-based case–control study were restricted to individuals who were Brazoria County residents at the time of death, it was decided to expand the geographic coverage of case ascertainment.

The primary thrust of these case ascertainment activities involved the manual matching of personnel records with two additional computer-selected lists of deaths due to brain tumor. The first list was produced by searching a data base maintained by the M.D. Anderson Hospital and Tumor Institute of all Texas cancer deaths from 1949 to 1963 for malignant brain cancer deaths among residents of Brazoria and three adjacent counties, Harris, Galveston, and Matagorda. The second list was produced by searching the Texas Bureau of Vital Statistics data base of all Texas deaths from 1964 to 1979 for all brain tumor deaths among residents of the three adjacent counties. The cases identified by these searches and by the case–control study represented all deaths with the underlying cause coded as brain cancer from 1949 to 1963 (ICD codes 193, 6th Revision or 193.0, 193.9, 7th Revision) or coded as

TABLE 1

INTERNATIONAL CLASSIFICATION OF DISEASE CODES FOR BRAIN TUMOR BY REVISION

Description of Codes	Effective Dates for Texas Death Data		
	Revision 7 1964–1968	Revision 8 1969–1978	Revision 9 1979–
Malignant neoplasm of brain	193.0	191	191.0–8
Malignant neoplasms of CNS	193.9	192.9	191.9
Benign neoplasm of brain	223	225.0	225.0
Neoplasm of brain (nature unspecified)	237	238.1	239.6

brain tumor from 1964 to 1979 (see TABLE 1 for designated ICD codes) among male residents of the 4-county region. These deaths were then matched against the estimated 37,000 personnel records of all former Dow employees.

The preliminary matches were scrutinized by a two-part review process. First, demographic information obtained through the state data base and information contained in the company's personnel files for the matches were compared to confirm the correctness of each of these initial matches. Second, the death certificates of matches were obtained and reviewed to verify that the cause of death was a primary intracranial neoplasm. Eight matches passed both reviews and were subsequently designated as cases.

Six additional cases were identified by one of the following methods:

1. Review of death certificates on file in the company medical department;
2. Manual search of city and county death certificate files; and
3. Follow-up of unsolicated leads.

The death certificate of each potential case identified by one of these activities was matched with the respective personnel record and reviewed as previously described before being considered a case. One female who had died of a brain tumor was identified through company medical record files, but was excluded from further consideration because she had only worked at an offsite company hospital.

When the additional brain tumor cases ascertained by the various methods just described were added to the 11 Dow cases ascertained as part of the county-based case–control study, the number of Dow cases totaled 25. Detailed case descriptions appear in TABLE 2. All of the cases were white males. The ages at death ranged from 37 to 69 years, and as seen in FIGURE 1, 40% of the cases died between the ages of 60–69. The distribution of deaths as depicted in FIGURE 2 spanned a 27-year calendar period beginning in 1951 and ending in 1977.

Distributions of the cases by date of hire and calendar period of employment demonstrated two noteworthy characteristics. As seen in FIGURE 3, the majority of the cases were hired prior to 1950. More specifically, 84% of the cases were initially hired from 1940 to 1946. Equally as striking is the observation that 68% of the cases were concurrently employed for the calendar period from 1943 to 1944, and 56% for the calendar period from 1950 to 1952. The full span of this distribution is presented in FIGURE 4.

TABLE 2

DOW BRAIN TUMOR CASE DESCRIPTIONS

Case Number	Year of Death	Age at Death	Cause of Death (ICD Rev. No.)	Duration of Employment*	Latency*	Best Diagnosis (Source)†
1	1951	48	237 (6)	8, 11	8, 11	Brain tumor (MR)
2	1952	36	193 (6)	4, 5	10, 10	Carcinoma of brain (DC)
3	1958	39	193.0 (7)	3, 3	17, 10	Glioblastoma multiforme (SPR)
4	1960	56	193.0 (7)	1, 1	17, 4	Glioblastoma multiforme (DC)
5	1961	67	193.0 (7)	14, 9	17, 9	Astrocytoma, gr. III (AUT)
6	1961	49	193.9 (7)	19, 4	19, 4	Glioblastoma, rt. temporal lobe (MR)
7	1962	53	193.0 (7)	0, 1	21, 1	Glioblastoma multiforme (MR)
8	1964	60	193.0 (7)	21, 8	21, 8	Brain tumor malignant (DC)
9	1965	49	193.0 (7)	4, 2	23, 10	Astrocytoma, gr. III (AUT)
10	1965	62	193.0 (7)	0, 5	21, 4	Glioblastoma multiforme (SPR)
11	1966	62	237 (7)	17, 8	23, 5	Brain tumor (DC)
12	1968	55	191 (8)	27, 11	27, 11	Astrocytoma, gr. IV. (MR)
13	1969	58	192.9 (8)	0, 3	26, 11	Glioblastoma multiforme (DC)
14	1970	46	192.9 (8)	23, 11	23, 11	Glioblastoma multiforme (MR)
15	1970	64	191 (8)	1, 5	25, 10	Astrocytoma (MR)
16	1971	59	191 (8)	30, 4	30, 6	Malignant glioma (MR)
17	1973	68	191 (8)	1, 2	30, 10	Astrocytoma, gr. IV. (MR)
18	1974	48	192.9 (8)	1, 6	23, 6	Oligodendroglioma of brain (SPR)
19	1975	61	191 (8)	10, 9	34, 5	Astrocytoma, gr. IV (SPR)
20	1976	65	191 (8)	34, 0	34, 2	Glioblastoma multiforme (MR)
21	1976	38	192.9 (8)	8, 2	8, 2	Glioblastoma multiforme (MR)
22	1977	61	191 (8)	27, 0	27, 0	Malignant brain tumor (MR)
23	1977	69	191 (8)	0, 11	5, 6	Glioblastoma of frontal lobe (MR)
24	1977	51	191 (8)	31, 2	34, 4	Carcinoma of brain (MR)
25	1977	57	191 (8)	35, 3	35, 4	Medulloblastoma (MR)

* Years, months, i.e., 4, 5 equals 4 years and 5 months.

† MR: medical records; DC: death certificate; SPR: surgical path report; AUT: autopsy.

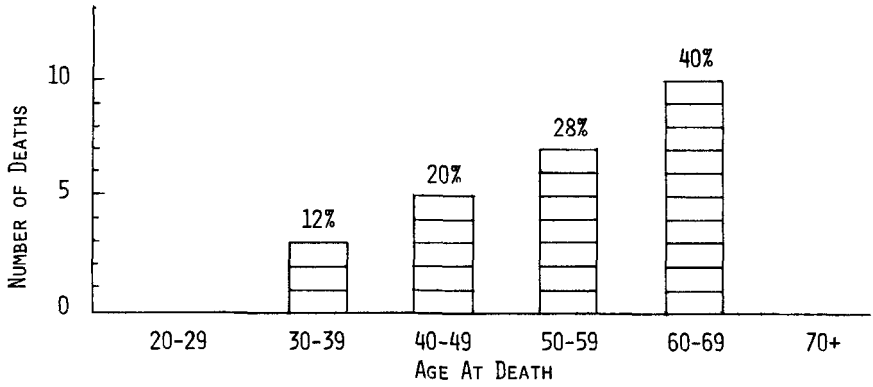

FIGURE 1. Distribution of cases by age at death. Cases among former employees.

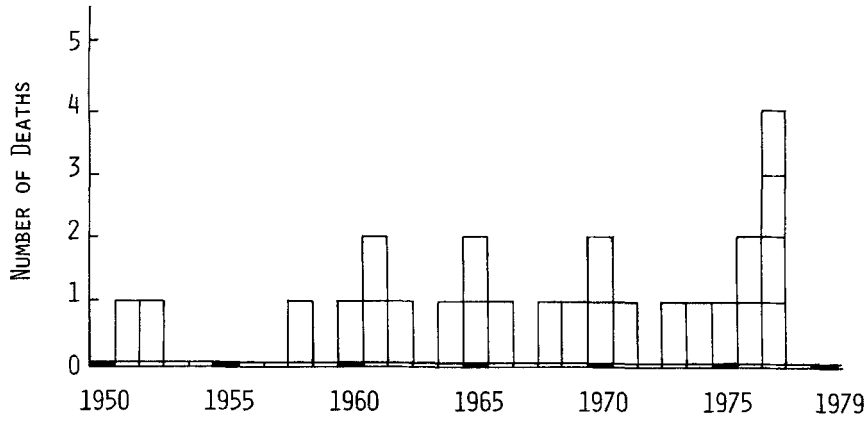

FIGURE 2. Distribution of cases by year of death. Cases among former employees.

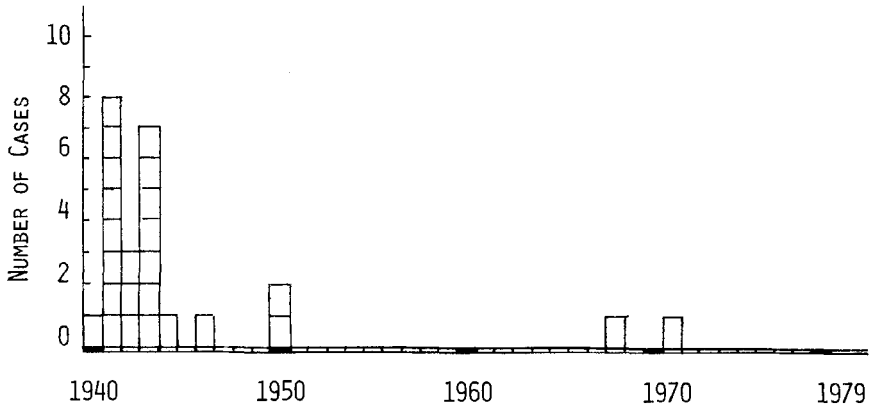

FIGURE 3. Distribution of cases by date of hire. Cases among former employees.

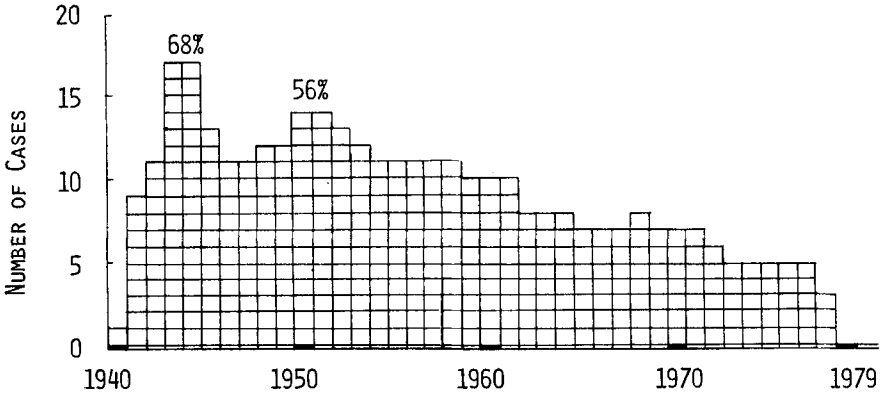

FIGURE 4. Distribution of cases by concurrent period of employment. Cases among former employees.

The cause of death listed on the death certificate has been supplemented by the acquisition of diagnostic information contained in medical records and pathology and autopsy reports. Each diagnosis listed in TABLE 2 is based on the best information currently available for each case. Of the 25 cases, 16 are glioblastomas or astrocytomas (Grade III or IV). Of the 9 remaining cases, 4 can only be characterized as malignant brain tumor, and 2 as brain tumors of unspecified nature. The remaining cases include 1 astrocytoma (grade unspecified), 1 medulloblastoma, and 1 oligodendroglioma. These diagnostic characterizations may change as the pathology follow-up is completed.

MORE DEFINITIVE ESTIMATES OF RISK WITH IDENTIFICATION OF RISK FACTORS

Study Design Considerations

With the base of the investigation broadened from 11 to 25 brain tumor cases at Dow Chemical, additional studies could now be initiated to refine the preliminary estimates of risk from the county-based case–control study and to attempt to identify risk factors that may present avenues for elimination of the suspected, but as yet unknown, hazards.

In the course of these additional studies, numerous relationships will be investigated. These will include investigation of exposure to various chemical and physical agents, the duration of such exposures, and the latency from date of first exposure to date of diagnosis or death. Given the distribution of the cases by calendar period of employment, associations involving date of hire and calendar periods of concurrent employment should also be examined.

In most situations, this set of investigations could be accomplished using standard cohort study methods; however, in this instance, a cohort study of the entire plant population is not feasible. In order to conduct such a study, demographic and work history summaries of the estimated 37,000 former employees would need to be abstracted from microfiche documents and entered into a computer data base; i.e., automated. Work histories of the more than 7,000 current employees would also have to be abstracted and then combined with selected demographic

variables routinely automated by the company's personnel department. Furthermore, subcohorts of the plant population defined in terms of year of hire, calendar period of employment or job assignment that might serve as the basis of a smaller scale cohort study cannot be easily identified from the alphabetically ordered personnel files.

The usefulness of an alternate type of study, a case-control study, also is restricted by the storage mode of the records. Ideally, when selecting controls, one would want to match several controls with each case by parameters such as age, race, sex, and date of hire. Because it is not possible to easily select employees from the files by any of the before-mentioned matching parameters, selection of matched controls would require some sort of sampling scheme.

The study design developed circumvents the apparent data management problems associated with such a large, unwieldy data set by using a 5% sample of the employee population on which to base a cohort study and a series of case–control studies. The 5% sample that has been selected can be characterized as a random-start, systematic sample. The sample was taken first by using a random process to determine which of the first 20 records contained in the company's alphabetically ordered personnel files would serve as a starting point and then by selecting every 20th record thereafter.

Sample-Based Cohort Study

The cohort study based on the 5% sample will be used to refine the preliminary estimates of risk of death due to brain tumor for the entire plant population and selected subcohorts defined by date of hire, duration of employment and calendar periods of employment.

The sample-based cohort study represents a modest departure from standard cohort study methods. For a standard cohort study, the analytical result, a Standardized Mortality Ratio (SMR), is obtained by dividing the number of observed deaths by the number of expected deaths for a particular cause of death. The observed deaths are normally ascertained by follow-up of the entire study population at risk of disease. The expected deaths are estimated by a life-table technique in which the U.S. general population death rates are applied to the total person-years-at-risk of the entire study population.

In the sample-based cohort study, neither the expected nor the observed deaths used to calculate the sample-based SMRs will include the experience of the entire population at risk. Using the previously mentioned life-table technique, one can estimate the expected number of deaths for the 5% sample after completing vital status follow-up of the sample. The expected deaths of the 5% sample will then be adjusted to reflect the expected mortality experience of 100% of the cohort by multiplying the expected brain tumor deaths of the 5% sample by 20. The observed brain tumor deaths will consist of the 25 cases listed in TABLE 2 ascertained by the methods previously described. If, however, new cases are discovered serendipitously or in the course of ascertaining the vital status of the 5% sample, they will be added to the observed cases. Any cases discovered among the 5% sample will be added without amplification or adjustment for the fact that they were derived from the follow-up of a 5% sample. A schematic representation of the calculation of the sample-based SMR for brain tumors appears in FIGURE 5.

It is anticipated that the sample-based SMRs should provide minimal estimates of risk due to differences in the coverage of the sampling methods for observed and expected brain tumor deaths. Although based on a 5% sample, the denominator of any of the sample-based SMRs will represent the number of expected deaths for the

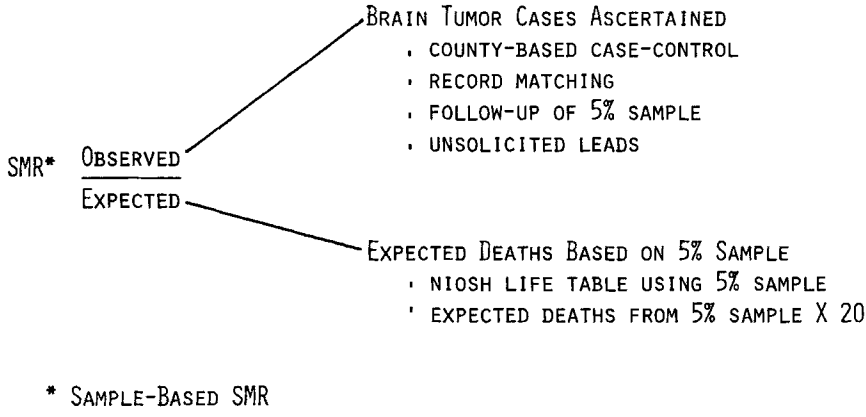

FIGURE 5. Calculation of sample-based Standard Mortality Ratio (SMR).

entire plant population regardless of geographical distribution. Because of the limitations of the case ascertainment methods, the numerator of the sample-based SMRs will primarily be restricted to deaths among former employees who at the times of their deaths were residents of a 4-county area proximate to the plant. Certainly, over the past 40 years, a large proportion of the estimated 37,000 former employees left the area and a number of them have since died of brain tumors outside the 4-county catchment area. Because the vast majority of brain tumor deaths which occurred outside the catchment area will not be included in the observed deaths but will be represented in the expected deaths, the sample-based SMRs should be smaller than the actual or true SMRs for this industrial population.

The sample-based cohort study is nearing completion. Basic demographic data and dates of Dow employment for each of the 5% sample cohort have been abstracted and automated. Vital status follow-up has been initiated through record linkages with the Social Security Administration and the Internal Revenue Service. With the completion of these follow-up activities, the analysis phase of the sample-based cohort study will begin.

In-Plant Case–Control Studies

A series of case–control studies are planned in order to investigate risk associations involving exposure to particular chemical agents. If such associations were to be investigated using the sample-based cohort, over 2,000 work histories would need to be reconstructed. With a case–control approach, only 125 to 250 work histories would be required, depending upon the number of matched controls per case.

The cases for these in-plant case–control studies would consist of those brain tumor deaths already ascertained and any new cases discovered prior to the completion of the study. The sets of matched controls would be selected from the 5% sample of all current and former employees used in the sample cohort study. Because detailed demographic variables and work history summaries for the 5% sample have been automated, it should be possible to select closely matched con-

trols by key parameters such as date of hire, age at hire, and duration of employment.

The in-plant case–control studies are anticipated to begin when the sample-based cohort study has been completed.

Summary

During the six-month period since this investigation was initiated, an increased risk of death due to brain tumor was linked with employment at the Texas Division of Dow Chemical by the results of a case–control study based on county death certificates. Specifically, the county-based case–control study yielded an odds ratio of 2.54 with a 90% confidence interval of the odds ratio extending from 1.23 to 6.80. Additional investigations were initiated which resulted in the ascertainment of 25 brain tumor deaths among former Dow employees. Of these cases, 84% were initially employed between 1940 and 1946 and 64% can be described as glioblastomas or astrocytomas grade III and IV. Detailed protocols have been developed for a sample-based cohort study and a series of in-plant case–control studies. The sample-based cohort study is nearing completion and the in-plant case–control studies are anticipated to begin in the near future.

The study design serving as the framework of this investigation represents a modest departure from the traditional epidemiologic study designs. This sample-based approach was designed to circumvent or minimize the usual problems associated with the use of massive collections of data that have been partially automated, if at all. The anticipated benefits will be conservation of limited staff resources and a reduction of the time necessary to complete a large-scale epidemiologic investigation.

Acknowledgments

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Authors' Note: The odds ratios presented at the conference have been replaced with two summary odds ratios for greater clarity in presentation and to incorporate new information that became available soon after the conference. The authors' conclusions drawn from the summary odds ratios are identical to those presented at the conference.

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