An Investigation of Brain Tumors Among Chemical Plant Employees Using a Sample-Based Cohort Method

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Using a modification of the traditional cohort mortality methodology, risk estimates of death due to brain tumors were calculated for production and nonproduction employees of Dow Chemical U.S.A., Texas Division. A total of 25 malignant, benign and unspecified brain tumors were identified using a geographically limited record-linkage process. Expected deaths were extrapolated from 1,666 white males in a 5% sample of the 1940 through 1977 total workforce. The resulting sample-based standardized mortality ratios (which were not evaluated for statistical significance) suggest, at most, only a slight increased risk of mortality from brain tumors for the overall time period. There was, however, a probable elevated risk associated with first employment prior to 1945. To date, diminished risk has been noted for those hired during subsequent years.

Causes of brain neoplasms in humans are largely unknown.[1] Within the past few years, some epidemiologic reports have suggested that populations employed in the petroleum refining and chemical industries may be at increased risk[2-6]; however, the findings have not been consistent.[7-11] Thus, it is not clear whether the elevated brain tumor risks observed in some of these industries are due to specific workplace exposures, or to other nonoccupational factors.

In the course of a previous investigation,[4] epidemiologists from the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) reviewed death certificates of brain tumor cases among adult male residents of an area along the Texas Gulf Coast. For the brain tumor decedents of one of the counties included in the review, Brazoria County, Dow Chemical was listed on one third of the death certificates as "usual employer." Although Dow Chemical has been the largest single employer in the county since the plant was opened in 1940, this observation prompted a series of additional investigations.

Initially, by means of a case-control study based on death certificates of decedents who were Brazoria County residents at the time of their death, analyses were conducted to determine whether employment at Dow Chemical U.S.A., Texas Division was a risk factor for death due to brain tumor.[12] The risk estimates from this preliminary county-based case-control study triggered two more extensive in-plant research projects: one, a cohort mortality study; and the other, a case-control study. The first is reported in this article; the second, in a companion article.[13]

The objectives of this cohort mortality study were to refine the overall preliminary brain tumor risk estimates from the county-based case-control study and, for the purpose of focusing supplementary studies,[13] to present the risk estimates in terms of duration of employment, date of hire and interval since hire. These objectives could have been accomplished via a standard retrospective cohort mortality design;[14] however, the size of the work force ever employed (approximately 40,000) would have made the collection of the necessary demographic and work history information difficult. Therefore, alternate methods that did not require data collection and follow-up of the entire employee population were used to approximate the observed and expected deaths and to develop the associated standardized mortality ratios (SMRs). To distinguish this study from the traditional cohort mortality approach it will be referred to as a "sample-based cohort mortality study."

Methods and Materials

Ascertainment of the Observed Deaths — The observed deaths were ascertained using a geographically limited

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record-linkage process.[4] Two computerized data bases containing Texas vital statistics data were searched to identify malignant, benign, and unspecified brain tumor deaths (see Table 1 for appropriate International Classification of Diseases [ICD] codes) among white male residents of a contiguous four-county area surrounding the plant: Brazoria, Harris, Galveston and Matagorda counties. One of these data bases, maintained by the Texas Bureau of Vital Statistics (TBVS), included data on all Texas deaths from 1964 through 1979. Data for the entire period were obtained; but, to be consistent with the study period used to estimate expected deaths, only those deaths that occurred through Dec. 31, 1977 were used in the calculations. The other data base, maintained by the M. D. Anderson Hospital and Tumor Institute, Houston, was identical to that of TBVS but also contained data on all Texas cancer deaths from 1949 through 1963. This data base was used to identify malignant brain tumor deaths that occurred prior to 1964. The names and selected demographic information of the decedents identified by the data base searches were manually matched against the personnel files of all white males formerly employed by the Dow Texas Division. The resulting matches became the observed deaths of the study.

Death certificates were requested for the observed deaths. The certificates and their respective ICD codes assigned by TBVS nosologists were reviewed by NIOSH-contracted and company nosologists and these codes were converted to the *ICD 8th Revision* for analysis. While clinical and pathological information was requested from either the hospital identified on the death certificate or the attending physician, such information was not used to influence the coding of the death certificates but, rather, to aid in the interpretation of the final result and to define the cases for the subsequent case-control study.

Estimation of Expected Deaths — Calculation of the number of expected deaths in the study was based on a 5% systematic sample of all employees (production and non-production) of the Dow Texas Division hired from 1940 through 1977.

Following a random start, every 20th record was selected from the alphabetically ordered personnel files. From each, the following information was extracted when available: full employee name, social security number, sex, race, date of birth, first date of employment and last date of employment. Comparisons of hiring distributions of the overall sample with historical plant c[e]nsus figures were made to assess the representativeness of the sample.

Follow-up and analyses were confined to white males due to the small numbers of females and nonwhite males. The primary source of vital status follow-up information was the Social Security Administration, current through Dec. 31, 1977. Other follow-up sources included those of the Internal Revenue Service, the Texas Department of Public Safety (drivers licenses) and the TBVS. A private locator service was contracted to find sample members who could not be located by other means.

Most recent address was sought for those located as alive. For those located as deceased prior to Dec. 31, 1977, the residence at the time of death was abstracted from the death certificate.

Since the observed deaths due to brain tumor were confined to those who died as residents of the four-county area, but the follow-up of the 5% sample had no such geographic restriction, three separate estimates of expected deaths among Dow Texas Division employees were calculated.

The first of these estimates assumed that none of the 5% sample cohort members migrated from and that all brain tumor deaths among former employees occurred in the four-county area in which the observed deaths were ascertained. Therefore, each sample member was considered to be at risk of death due to brain tumor through the end of the study period or his date of death, which ever occurred first. The resulting person-years of observation accumulated by the sample from 1949 through 1977 were multiplied by the age- and calendar-specific malignant brain tumor death rates of U.S. white males to estimate the expected malignant brain tumor deaths of the sample. Similarly, the person-years of observation from 1964 through 1977 were multiplied by the appropriate death rates to obtain the expected number of benign and unspecified brain tumors. Person-years of observation prior to 1949 and 1964 were not incorporated in calculations of expected malignant or benign and unspecified brain tumor deaths, respectively, because case ascertainment was not possible given the record-linkage procedures used. The expected brain tumor deaths (malignant, benign and unspecified) of the sample were then combined and multiplied by 20 (the reciprocal of the sampling fraction) to obtain the expected brain tumor deaths for all white male Dow Texas Division employees. This estimate will be referred to as estimate A of the expected.

Recognizing that some migration out of the four-county area took place among former employees, adjustment methods were used to develop two additional estimates of expected brain tumor deaths.

A method developed by NIOSH used last known address found during follow-up procedure. It assumed that each sample member whose last known address was outside the four-county area had migrated on his last date of employment. The same assumption was made for those lost to follow-up. Examples of the periods of observation defined for situations encountered in the study are illustrated in Fig. 1. Calculations based on the person-years of observation obtained by this method paralleled those outlined for

Table 1 — ICD Codes for Brain Tumor by Revision

Effective Dates for Texas Data Files	Revision		
	6th and 7th: 1950-1968	8th: 1969-1978	9th: 1979-Present
Malignant neoplasm of brain and CNS	193	191 192	191 192
Benign neoplasm of brain and CNS	223	225	225
Neoplasm of brain and CNS (nature unspecified)	237	238	239

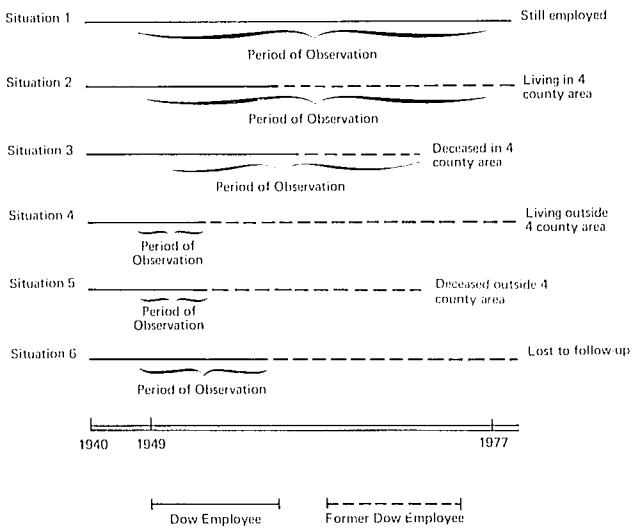

Fig. 1 – Periods of observation for six situations encountered in study.

estimate A. The person-years of observation were multiplied by the appropriate rates to give expected brain tumor deaths for the sample. These numbers were, in turn, multiplied by 20 to give estimate B of the expected deaths.

A second independent migration adjustment procedure, developed by Dow epidemiologists, was also done. Since addresses obtained from Internal Revenue Service records were not available to the company, this procedure made an adjustment to the expected number of deaths of estimate A based on the residence distribution of those sample members who died of any malignant neoplasm. (Address information could have been obtained from other sources, such as the state drivers license bureau.) The fraction of total malignant neoplasm deaths (1949-1977) in the 5% sample, who were residents of the four-county area at the time of death, was calculated for each of four length of employment strata. These fractions were then multiplied by estimate A, strata by strata, to yield estimate C. This method assumed that the residence distribution of brain tumor deaths in and out of the four-county area paralleled that of all malignant neoplasm deaths in the sample.

Calculation of Sample-Based SMRs – As with a traditional cohort mortality study, the observed deaths were divided by estimates of expected deaths and multiplied by 100 to yield SMRs, in this case three sets of sample-based SMRs. Significance testing seemed inappropriate given the developmental nature of the study design, the various assumptions concerning migration, and the errors inherent to the sampling procedures. To place the point estimates of the sample-based SMRs in perspective, the number of observed deaths corresponding to each is presented in the figures.

Results

Descriptive Statistics of the 5% Sample – The overall 5% sample (all sexes and races) that was selected consisted of 2,096 current and former employees. Hiring distributions estimated from the overall 5% sample were compared with estimates obtained from company personnel department reports (Fig. 2). There were four notable discrepancies between the distributions. The numbers of hirees estimated by the 5% sample were lower than the estimates of the company from 1944 through 1946, from 1955 through 1956, and from 1960 through 1963, but were higher than the company estimates for 1952 and 1953.

After excluding all females and nonwhite males, the remaining sample included 1,666 white males employed between Jan. 1, 1940 and Dec. 31, 1977. Distributions of hiring by race and sex, however, were not available from company records to compare with the equivalent distributions of the white males in the sample.

Table 2 presents the vital and employment status distribution of the white males in the sample by length of employment. The large turnover in the work force is readily apparent: less than 20% were still employed with the company, nearly 50% were employed for less than one year, and nearly 65% for less than five years.

Vital status follow-up activities located all but 31 (1.9%) white male members of the 5% sample. Of those lost to follow-up, 26 worked less than five years and only one worked longer than 10 years, the length of time currently required to become completely vested in the company pension plan. Of those located, 1,329 (79.8%) were alive as of Dec. 31, 1977 and 306 (18.4%) were dead. Death certificates were obtained for all but three (0.9%) of the known deaths.

Observed Deaths of the Sample-Based Cohort – The list of county deaths that contained information on 957 brain tumor deaths among white male adult residents of Brazoria, Harris, Galveston and Matagorda counties was matched against company personnel records. Twenty-five brain tumor deaths among former employees were observed through Dec. 31, 1977; 19 from Brazoria County and six from Harris County. No deaths of the former employees were ascertained in either Galveston or Matagorda counties. With the exception of two deaths in the early 1950s, the deaths were fairly evenly distributed from the late 1950s through 1977. Although searched for, no deaths among the former employees were ascertained in 1978 or 1979. Seventeen of the 25 brain tumor deaths were among employees hired from 1940 through 1943.

The average age-at-hire of the brain tumor decedents (26.1) compares closely with that of the study cohort (27.9). Both of these are lower than their respective values for those hired from 1940 through 1944, which were 30.5 and 31.3.

According to the cause of death appearing on the death certificate, 20 (80%) of the 25 brain tumor deaths were due to malignant brain tumor. Three were due to benign brain tumors, one was due to a neurogenic sarcoma and one was described as a "metastatic CNS malignant melanoma."

For 19 of the 25 deaths, clinical and/or pathological information was available. With two exceptions, the additional information confirmed the cause of death coding based on the death certificate. One exception was a death coded as a benign brain tumor according to ICD rules, but characterized in the medical record as due to hydrocephalus caused by an hypophyseal cyst of the third ventricle. The other was characterized in the medical record as a metastatic brain tumor with the primary site assumed to be the lung.

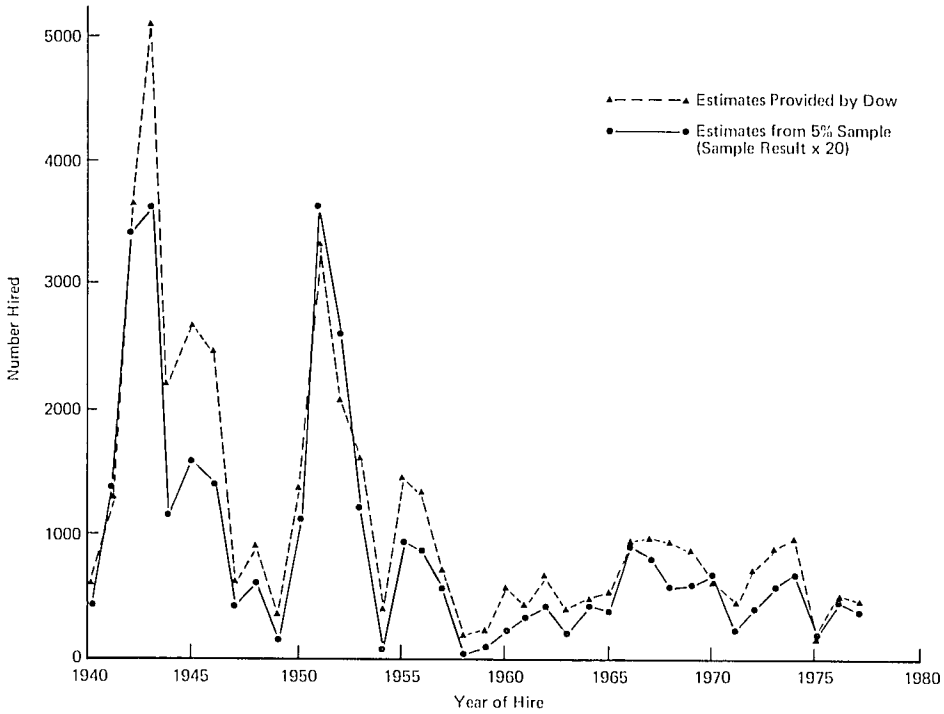

Fig. 2 – Distributions of Dow Chemical U.S.A. Texas Division Employees by Year of Hire, Personnel Department estimates *v* 5% sample estimates all sexes and races, 1940-1977.

On the basis of best diagnosis available, 12 of the 25 deaths were glioblastomas (either stated to be glioblastomas or astrocytomas grade III or IV). Of the remaining 13 deaths, three could only be characterized as malignant brain tumors and three as benign brain tumors. The other deaths included one malignant glioma, one medulloblastoma, one oligodendroglioma, neurogenic sarcoma, metastatic CNS malignant melanoma, hydrocephalus, and metastatic tumor from the lung.

Although not clinically attributable to brain tumors, the latter four deaths by nosologic convention fell in the ICD categories evaluated in this study. To maintain consistency with the U.S. general population death rates used to calculate expected deaths, these four were included among the observed deaths. Detailed demographic, work history and cause of death information for each of the observed deaths is contained in Table 3.

Expected Deaths and Sample-Based SMRs – Based on follow-up of the 5% sample, there were 43.9 malignant, benign and unspecified brain tumor deaths expected by method A among all present and former employees. Compared with the 25 observed brain tumor deaths, this yielded a sample-based SMR of 57. This sample-based SMR is unadjusted for migration of former employees outside the four-county area in which the observed deaths were ascertained and, consequently, underestimates the brain tumor mortality experience among former and current employees. It, and other SMRs based on method A, are presented for perspective and to convey the uncertainty in the accuracy of the adjusted estimates.

Observed and expected deaths from brain tumors by year of hire, interval from first hire and duration of employment are shown in Table 4.

Figures 3 and 4 present the spectrum of sample-based SMRs (methods A, B and C) by duration of employment, for all periods of hire and for 1940 through 1944, respectively. In most instances, the two migration-adjusted SMRs, (estimates B and C) appear closer to one another than to

Table 2 – Vital and Employment Status (as of 12/31/77) by Duration of Employment – White Males

Status	Duration of Employment, yr				
	<1	1-4	5-19	20+	Total (%)
Employed	16	56	115	127	**314** (18.8)
Left Employment					
Known alive	566	171	219	59	**1,015** (60.9)
Deceased	153	71	55	27	**306** (18.4)
Unknown	24	2	5	0	**31** (1.9)
Total (%)	**759** (45.5)	**300** (18.0)	**394** (23.6)	**213** (12.8)	**1,666** ...

Table 3 – Detailed Case Descriptions of Observed Brain Tumor Deaths

	Year of Hire	Year of Death	Age at Death	Interval Since Hire, yr; mo	Duration of Employment, yr; mo	Cause of Death From Certificate (ICD Revision No.)	Best Diagnosis (Source)*
1	1940	1975	62	34; 5	13; 3	191 (8)	Astrocytoma, grade IV (SPR)
2	1941	1952	37	10; 10	4; 5	193.0 (7)	Carcinoma of the brain (DC)
3	1941	1962	53	21; 1	0; 1	193.0 (7)	Glioblastoma multiforme (DC)
4	1941	1971	59	30; 6	30; 4	191 (8)	Malignant glioma (MR)
5	1941	1977	58	35; 4	35; 3	191 (9)	Medulla blastoma (MR)
6	1941	1961	50	19; 4	19; 4	193.9 (7)	Glioblastoma, R temporal lobe (MR)
7	1941	1958	39	17; 10	3; 3	193.0 (7)	Glioblastoma multiforme (SPR)
8	1941	1965	50	23; 10	4; 2	193.0 (7)	Astrocytoma, grade III (AUT)
9	1941	1968	55	27; 11	27; 11	191 (8)	Astrocytoma, grade IV (MR)
10	1942	1973	69	30; 10	1; 2	191 (8)	Astrocytoma, grade IV (MR)
11	1942	1969	58	26; 11	0; 3	192.9 (8)	Glioblastoma multiforme (DC)
12	1943	1977	51	34; 4	33; 9	191 (9)	Carcinoma of brain (MR)
13	1943	1964	60	21; 8	21; 8	193.0 (7)	Brain tumor malignant (MR)
14	1943	1966	62	23; 5	17; 8	237x (7)	Brain tumor (DC)
15	1943	1960	56	17; 4	1; 1	193.0 (7)	Glioblastoma multiforme (DC)
16	1943	1951	48	8; 11	8; 11	237x (7)	Brain tumor (MR)
17	1943	1975	66	32; 00	27; 0	192.4 (8)	Neurogenic sarcoma (DC)
18	1946	1970	46	23; 11	23; 11	192.9 (8)	Glioblastoma multiforme (MR)
19	1950	1974	49	23; 6	1; 6	192.9 (8)	Oligodendroglioma of brain (SPR)
20	1950	1977	61	27; 0	27; 0	191 (9)	Parietal lobe brain tumor (MR)
21	1951	1963	54	12; 8	10; 2	193.0 (7)	Metastatic brain tumor (AUT)
22	1953	1975	57	21; 6	21; 6	191x (8)	Metastatic CNS malignant melanoma (DC)
23	1963	1965	23	1; 3	1; 3	223 (7)	Internal hydrocephalus (DC)
24	1968	1976	38	8; 2	8; 2	192.9 (8)	Glioblastoma multiforme (DC)
25	1971	1977	70	5; 6	0; 11	191 (9)	Glioblastoma of frontal lobe (MR)

* MR indicates medical records; DC, death certificates; SPR, surgical pathology report; AUT, autopsy

the unadjusted SMRs (estimate A). However, the migration-adjusted and unadjusted estimates converged among the subgroups employed for the longest duration.

Adjustment method B, (Fig. 3) which assumed former employees located outside the four-county area migrated on their last date of employment, yielded an overall sample-based SMR of 126 (19.8 expected deaths). There was a slight deficit of observed deaths noted among those employed less than one year and from five to 19 years (SMRs= 65 and 86, respectively) and an excess mortality noted among those employed one to four years and 20 or more years (SMRs=175 and 214, respectively). When the risk of mortality due to brain tumors was examined after 20 years since date of hire, 16 deaths were observed and 9.4 estimated (SMR=170).

When considering those hired before 1945 separately (Fig. 4), it would appear that this group is probably at excess risk of mortality from brain neoplasms. The observed exceed what is expected for each length of employment category, with an overall sample-based SMR of 185. By contrast, the overall SMR for the subset hired after 1945 is estimated to be 75 and the observed exceed expected only among those employed for 20 or more years (three observed ν 1.3 expected). One of these three deaths was the metastatic CNS malignant melanoma.

Results generated from adjustment method C, which relied on the residence distribution of the malignant neoplasm deaths in the 5% sample, were generally quite comparable with those generated from adjustment method B. The overall sample-based SMR was estimated to be 118 (21.1 expected deaths). Elevated mortality risks were again suggested for the subsets employed from one to four years and for greater than 20 years (SMRs=149 and 191, respectively). Mortality was less than or equal to expected for those employed less than one year and for those employed five to 19 years (SMRs=52 and 102, respectively). When the data were examined for 20 or more years since first employment, irrespective of length of employment, the sample-based SMR was 148.

Again, it appeared that those first employed prior to 1945 were at increased risk (SMR=184), and this was independent of length of employment beyond one year (less than one year, SMR=111; one to four years, SMR= 217; five to 19 years, SMR=200; 20+ years, SMR=176). The overall SMR for those first employed after 1945 was quite low (SMR=59) and, again, observed exceeded expected for only one length of employment category, 20+ years.

Discussion

This investigation involved a novel study design that has some obvious strengths and weaknesses. By using a sample-

Table 4 — Observed and Expected Deaths due to Brain Tumors by Year of Hire, Interval From Date of Hire and Duration of Employment

Duration of Employment, yr	Interval From Date of Hire, yr*											
	<20				≥20				Total			
	Obs	Exp_A	Exp_B	Exp_C	Obs	Exp_A	Exp_B	Exp_C	Obs	Exp_A	Exp_B	Exp_C
Employees Hired From 1940 Through 1944												
<1	0	3.2	0.6	0.6	2	5.6	1.2	1.0	2	8.8	1.8	1.6
1-4	3	2.0	0.6	0.8	2	4.0	1.0	1.5	5	6.0	1.6	2.3
≥5	2	2.1	1.8	1.1	8	4.9	3.8	4.3	10	7.0	5.6	5.4
Total	**5**	**7.3**	**3.0**	**2.5**	**12**	**14.5**	**6.0**	**6.8**	**17**	**21.8**	**9.0**	**9.3**
Employees Hired From 1944 Through 1977												
<1	1	6.0	1.7	3.0	0	4.2	1.1	2.1	1	10.2	2.8	5.1
1-4	1	3.5	1.8	2.1	1	1.2	0.4	0.7	2	4.7	2.2	2.8
≥5	2	4.5	3.8	3.4	3	2.7	1.9	2.3	5	7.2	5.7	5.7
Total	**4**	**14.0**	**7.3**	**8.5**	**4**	**8.1**	**3.4**	**5.1**	**8**	**22.1**	**10.7**	**13.6**

* Obs indicates observed deaths; Exp_A, expecteds estimate A; Exp_B, expecteds estimate B; Exp_C, expecteds estimate C

based cohort method to estimate the expected number of deaths and a regional record-linkage process to identify the observed, resources were used more efficiently. This efficiency was gained at some expense of confidence in validity of the results; however, it is believed that this compromise was acceptable, given the objectives of the study.

Underlying the whole approach is the assumption that brain tumor mortality among present and former employees in the four-county ascertainment area properly reflects the experience of the total plant population. This assumption, though reasonable, remains untested and the direction of any associated bias has not been determined.

In addition, the 5% sample may not provide a truly representative estimate of person-years at risk, either in total number or in the various age or calendar-year subcategories. If the distribution of company census figures (Fig. 2) is correct, the underrepresentation by the sample of

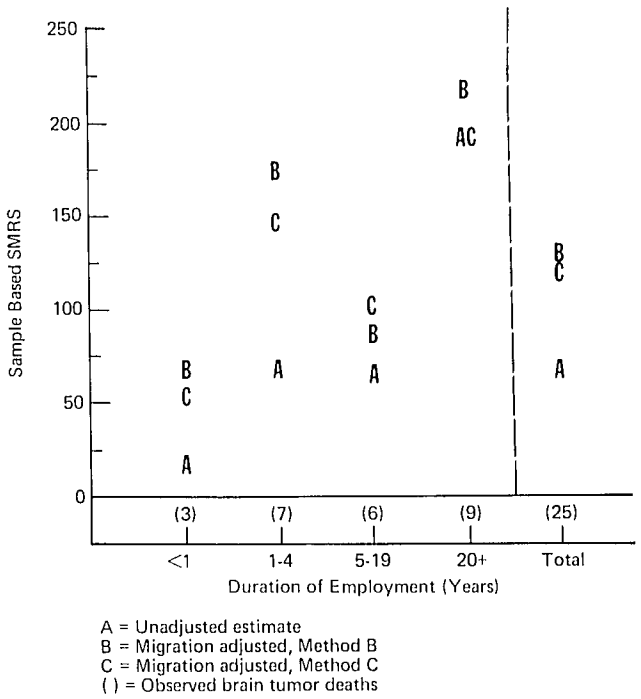

Fig. 3 — Sample-based SMRs derived by methods A, B, and C by duration of employment, Dow Chemical U.S.A. Texas Division, all hires, 1940-1977.

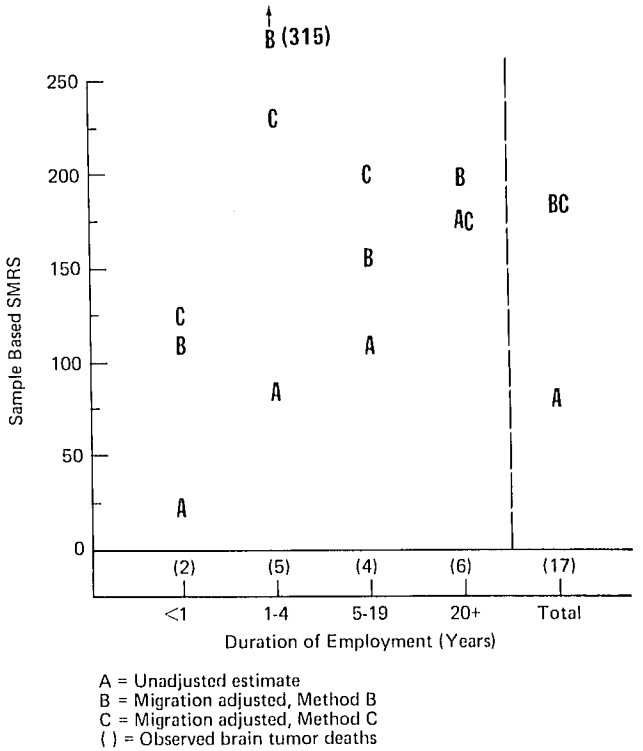

Fig. 4 — Sample-based SMRs derived by methods A, B, and C by duration of employment, Dow Chemical U.S.A. Texas Division hired 1940-1944.

employees hired during specific periods, especially from 1944 through 1946, could have artificially reduced the number of expected deaths and caused the sample-based SMRs to be slightly inflated. Subsequent data collected by the company for all employees with one or more years of employment would suggest that the 5% sample is more representative than indicated in Fig. 2.

Conversely, the inclusion of nonproduction employees with low potential for occupational exposures to chemicals could have diluted any risks associated with specific putative agents. Therefore, the sample-based SMRs may underestimate the actual risk among selected categories of production workers.

With regard to the sample-based SMRs calculated from expected brain tumor deaths derived from each of the three methods, those obtained from method A generally understate the brain tumor mortality risks. Even though the record-linkage procedure used to identify observed brain neoplasm deaths was geographically restricted to a four-county area, and would have missed brain tumor deaths among former employees who had migrated, this method assumed no migration in the calculation of person-years at risk and expected deaths. Sample-based SMRs based on method B overstate the risks to some degree, since the method for deriving them assumed migration from the area on the last day of employment and, thereby, ignored a certain number of person-years at risk. Underlying method C was the assumption that the residence distribution of brain tumor deaths in and out of the four-county area paralleled that of all malignant neoplasms in the sample.

Although the two adjustment procedures were developed independently by NIOSH and Dow and were based on different assumptions, they yielded fairly close results. This strengthened the confidence in the joint findings. Unfortunately, no acceptable procedures were available to test the statistical significance of the findings and therefore, chance variation was not considered in evaluating these results.

In summary, the sample-based SMR for the total cohort was 57. When migration adjustment was applied, this value increased to 118 or 126 depending on the method used. With due consideration for the problems inherent in the design, this study, at most, would suggest only a slight increased risk of death due to brain tumors for the total Texas Division employee population. Among those hired before 1945, the magnitude of the overall sample-based SMRs varied between 78 (unadjusted) to 184 (both migration adjustments), suggesting a probable increased risk among this early hired group. The available data indicate that the group hired after 1944 has not, at least to the present time, experienced comparable risks (SMR A=36, SMR B=75, SMR C=59).

Efforts to identify a specific process or chemical as an etiological agent for brain tumor mortality were beyond the scope of this investigation. A case-control study of brain tumor mortality, which evaluated the exposure-disease associations at this plant in a more analytical fashion, has been completed and is the subject of the companion article.[13]

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Erratum

In the original article "Measurement of IgG Antibody and Airborne Antigen to Control an Industrial Outbreak of Hypersensitivity Pneumonitis" by C. E. Reed, M.D.; M. C. Swanson, B.A.; M. Lopez, M.D., et al, which appeared in Vol. 25, No. 3 (March), 1983 issue, pp. 207-210, the unit of measure was inadvertently omitted from Table 1. The tabular information refers to grams of antigen per grams of dry slime.