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Brain Cancer in Petrochemical Workers: A Case Series Report

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Eighteen primary brain cancer deaths among male workers at one Texas petrochemical plant from 1965-1980 are reported. Federal officials from OSHA and NIOSH are performing with company cooperation an historical prospective cohort mortality study, a case-control study, and neuropathological case confirmation. Average age at death was 53 (range 30-66). Median employment was 21 years and median latency was 24 years. 15/18 tumors were glioblastoma multiforme, an unusual histologic distribution. A preliminary estimate reveals a plant-wide excess brain cancer risk twice expected among 6,800 white males at the plant since 1941. Brain cancer mortality rates in surrounding counties are in the median range for US counties from 1950-1969. Ten recognized or suspected carcinogens are present in quantities $> 10^6$ lbs/yr. To date no common chemical exposures or work assignments have been identified among the cases. Data on 26 experimental brain carcinogens and relevant epidemiological studies are provided.

Key words: occupational brain cancer, chemically induced brain cancer, petrochemical workers and brain cancer, brain cancer in Texas, brain cancer - environmental etiology, OSHA/NIOSH joint brain cancer study, case series report - brain cancer, epidemiology of occupational brain cancer

Eighteen primary brain cancer deaths have occurred among workers at one US petrochemical plant. We believe this is the largest single series of presumably occupationally related brain cancers reported to date in the medical literature.

In November 1978 the Occupational Safety and Health Administration (OSHA), the Federal occupational health enforcement agency of the US Department of Labor, received an employee complaint that work-related chemical exposures might have caused brain tumors in fellow workers as well as his own recently diagnosed brain cancer.

OSHA's Office in Clear Lake City, Texas, began an investigation of brain cancer mortality at the employee's work site, a moderate-sized petrochemical production facility in Texas City, located in Galveston County south of Houston. Workers, surviving family

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members, union officials, local physicians and hospital staff, Texas state health officials, and company personnel were interviewed. Four primary brain tumor deaths were discovered among former employees in this way. It is ironic that the worker who filed the original complaint with OSHA was found to have a metastatic carcinoma to the brain and is not counted among the cases. The plant physician subsequently reviewed death information maintained by the company medical department, primarily covering workers who died while employed and also those who, by virtue of 15 years of company service, were eligible for death benefits. Ten deaths from primary brain cancer were thus identified, including the four previously found. OSHA then requested technical assistance from the National Institute for Occupational Safety and Health (NIOSH), its companion research agency in the US Department of Health and Human Services.

In February 1979 OSHA, NIOSH, and the company established a collaborative study plan to investigate the apparent excess of brain cancer among workers at the plant. An historical prospective cohort mortality study was begun to determine more exactly the risk for brain cancer, and whether there exists any other unusual mortality pattern among plant employees. Also included is a case-control study of all primary brain cancer cases to ascertain whether a particular job or chemical exposure at the plant is associated with an excess risk of brain cancer. Finally, a reference neuropathology laboratory has agreed to examine autopsy and surgical pathology specimens to provide histologic confirmation of the cause of death in each case. Each of these studies is well under way, and results are expected within a few months.

An experimental case-finding technique was added to the study design to provide an early estimate of the total number of brain tumors. A computer-assisted search was conducted using Texas Bureau of Vital Statistics data maintained by the M. D. Anderson Tumor Institute Department of Epidemiology. Since company records showed that 99% of plant employees reside in Galveston, Harris and Brazoria counties, a list of all primary brain cancer deaths among males more than 20 years of age from 1950 through 1977 was obtained for these three counties. This list of 732 primary brain cancer deaths was matched against company personnel files. Three additional confirmed cases resulted. Further investigation of company records revealed two more cases, and three other employees with brain tumors became ill during the preliminary period of the study. All those affected were deceased as of March 1980. The current total of 18 deaths is the subject of this case series report.

Work history data for the 18 cases are provided in Table I. The average age at death for the cases was 53; the youngest died at age 30, and there were four deaths after age 60. Half of the deaths occurred between ages 50 and 59. The pattern of age at death observed in this brain tumor series does not differ substantially from those reported for adults of employment age in other series [1-3].

Total length of employment at the plant ranged from one month to slightly more than 35 years, with a median value of 21 years. Two cases had short periods of employment, 38 and 29 days, respectively. Median length of employment excluding these two cases was 23 years. The interval from first employment to death, which provides an estimate of latency, varied from as few as 3½ years to nearly 36 years, with a median of 24 years.

No particular trend or clustering by hire date among the cases has been identified as compared to the general plant population. One case was hired in late 1940 as part of a small plant start-up crew. Three others were hired in 1941 during the first year of plant operation, and the rest at fairly regular intervals, until the last group of four started work during 1953. The first death occurred in 1956, followed by five others during the 1960s. Twelve of the deaths occurred after 1970, three of them during the past year. No

TABLE I. Work History Data for 18 Primary Brain Cancer Cases in a Texas Petrochemical Plant

Case	Date of hire	Date of death	Age at death	Length of employment (years-months)	Job title	Department
1	12/16/40	05/15/64	51	3-6	Operator	Production
2	05/18/41	02/19/66	56	24-8	Operator	Production
3	07/29/41	05/18/76	66	31-8	Foreman	Maintenance
4	11/30/41	12/13/65	55	20-4	Operator	Production
5	07/09/44	10/28/79	59	35-0	Boilermaker	Structural Shop
6	09/18/44	05/21/74	55	0-1	Operator	Production
7	09/18/46	03/07/79	55	32-3	Laborer/Oiler	Maintenance
8	09/26/46	03/22/73	63	26-6	Operator	Production
9	09/21/48	07/02/75	49	2-1	Pipefitter	Maintenance
10	03/02/49	06/05/71	61	22-3	Operator	Production
11	01/25/50	01/13/68	66	16-7	Equip. Operator	Maintenance
12	10/19/50	05/14/74	59	17-1	Operator	Energy Systems
13	10/23/50	02/18/80	57	28-10	Operator	Production
14	09/19/51	01/08/74	52	22-3	Machinist	Machine Shop
15	04/27/53	10/03/56	33	0-1	Machinist	Maintenance
16	08/17/53	04/05/62	30	8-7	Weighmaster	Shipping
17	08/21/53	05/05/71	44	17-3	Operator	Production
18	10/30/53	12/21/78	49	24-8	Weighmaster	Shipping

TABLE II. Current Plant Work Force by County of Residence

County of residence	Type of employee		Total	Percent
	Hourly	Salaried		
Galveston	1,389	609	1,998	90.0
Harris	44	110	154	6.9
Brazoria	41	15	56	2.5
Other	7	4	11	0.5
Total	1,481	738	2,219	100.0

Source: Data provided by company.

established pattern is evident from this distribution of the years of death, but there is no evidence that the rate of appearance of cases is declining.

The plant has a current work force of slightly more than 2,200, including nearly 1,500 hourly employees. The average age is 44, and approximately 1,050 current employees have 25 or more years of company service. Since the plant began operation in 1941, there have been a total of 8,850 employees. These include 6,802 white males, 884 black males, 1,083 white females, and 81 black females through April 1979. The distribution by county of residence for current workers is provided in Table II. The plant also engages a temporary independent contractor work force of 100-250 daily, mostly for construction jobs. Unfortunately, no employment records are available for this latter group.

Demographic and cause of death data from the death certificates are provided in Table III. All cases occurred among male employees, 17 whites and one black. The mortality rate for primary brain cancer in Texas among black males is about one-half that for

TABLE III. Death Certificate and Medical Records Data for 18 Primary Brain Cancer Cases in a Texas Petrochemical Plant

Case	Race/sex	Residence	Place of birth	Cause of death	
				Death certificate	Medical records
1	WM	Galveston	Texas	Carcinoma of brain	Glioblastoma (MR) ^a
2	WM	Galveston	Missouri	Malignant brain tumor	Meningioma (A)
3	WM	Harris	Texas	Brain tumor	Glioblastoma (A)
4	WM	Galveston	Texas	Brain tumor - meningioma	Meningioma (MR)
5	WM	Galveston	Louisiana	Glioblastoma	Glioblastoma (SP)
6	WM	Galveston	Texas	Brain tumor - glial IV ^b	No records available
7	BM	Galveston	Texas	Glioblastoma	Glioblastoma (MR)
8	WM	Galveston	Texas	Glioblastoma	Glioblastoma (SP)
9	WM	Harris	Texas	Astrocytoma	Astrocytoma - grade I (SP)
10	WM	Galveston	Texas	Malignant glioma	Glioblastoma (MR)
11	WM	Galveston	New Mexico	Glioblastoma	Glioblastoma (A)
12	WM	Galveston	Norway	Glioblastoma	Glioblastoma (SP)
13 ^c	WM	Galveston	Texas	Glioma - grade III	Astrocytoma - grade IV ^b (MR)
14	WM	Galveston	Texas	Glioblastoma	Glioblastoma (A)
15	WM	Harris	Texas	Glioblastoma	No records available
16	WM	Galveston	Louisiana	Brain tumor	Glioblastoma (A)
17	WM	Galveston	Texas	Malignant glioma	Glioblastoma (SP)
18	WM	Galveston	Texas	Brain tumor	Glioblastoma (A)

^aSource: MR - medical records; A - autopsy; SP - surgical pathology.^bAstrocytoma grade IV and glial IV are equivalent terms for glioblastoma multiforme.^cData from company records, death certificate not available.

white males [4]. However, very little can be said regarding the racial distribution of cases, since it appears that a relatively small number of blacks were employed at the plant until recent years.

All but one of the cases were native-born Americans; the lone exception was a Norwegian. The great majority of the cases were born in Texas, two were from Louisiana, and one each were from New Mexico and Missouri. None of the US states of origin have a particularly high risk for brain cancer compared to the US national average.

Fifteen of the cases were Galveston County residents at the time of death; the other three were from Harris County. The possibility of an environmental etiology related to Galveston County was considered. Data from the National Cancer Institute for brain cancer mortality rates for Harris, Galveston, and Brazoria counties from 1950-1969 are in the mid-range for Texas and US national values, as shown in Table IV. Surveys made by the Texas State Department of Health for the years 1975 through 1978 showed that the Galveston County annual brain cancer crude mortality rates were respectively 4.4, 4.2, 3.6, and 4.5 per 100,000. There is no evidence from these data that local environmental factors outside the plant are responsible for the apparent excess of brain cancer.

To obtain an initial estimate of the brain cancer risk, deaths among adult white males in Galveston County were analyzed using the list described previously. A total of 47 primary brain cancer deaths occurred in the county from 1956 through 1977 among white males aged 20 through 64. The white male population of employment age at risk in the plant from 1956 through 1977 is estimated as 3,700.* To permit a rough comparison between the plant and the overall county populations, information from the US Census and the Health Services Administration was used [5, 6]. In 1970 the Galveston County white male population aged 20 through 64 numbered 35,988. This number represents a conservative estimate of the white male county population during the period 1956 through 1977, since no allowance has been made for migration or for population growth after 1970. Thus, the plant population at risk represented somewhat less than 10.3% of the county-wide white male population during the period 1956 through 1977. Yet during this period, ten of 47 brain tumor deaths among adult white male county residents aged 20 through 64 occurred in plant employees, slightly more than 21% of the total. This suggests an approximate plant-wide risk about twice that of the county as a whole.

TABLE IV. Brain and Other CNS Cancer Mortality, 1950-1969: Average Annual Age Adjusted Rates per 100,000*

Location	White male	White female	Black male	Black female
United States	4.4	2.9	2.3	1.5
Texas	4.3	2.9	1.9	1.5
Galveston County	4.5	2.9	2.5	2.1
Harris County	4.5	3.6	2.0	1.9
Brazoria County	3.1	3.9	1.2 ^a	1.5

*The range of US rates for white males for states with >10 deaths from 1950-1969 was 3.1-5.4. The range of Texas rates for white males for counties with >10 deaths from 1950-1969 was 2.3-10.8.

^aBased on one case.

Source. US Cancer Mortality by County, 1950-1969, National Cancer Institute, DHEW Pub. No. (NIH) 74-615, Bethesda, Maryland, 1974.

*This estimate is based on the following assumptions: 77% of the plant population have been white males, 90% lived in Galveston County; and except for 1,050 long-term employees (>25 years) turnover from 1941 through 1979 was roughly constant at 158 white males per year.

The underlying causes of death as recorded on the death certificates are listed in Table III. Nine cases of glioblastoma multiforme were recorded directly on the certificate. Further investigation of hospital and physicians' records provided evidence that there were six additional cases of glioblastoma multiforme among the total of 18. Preliminary medical evidence thus suggests that 83% (15/18) of the tumors were glioblastomas. Because this type of tumor usually accounts for 25–50% of deaths in reported brain cancer series, this would indicate an excess of glioblastoma multiforme among these cases [1–3, 7, 8]. The difficulty of precise neuropathological diagnosis for brain cancer is recognized, and the pathology review is expected to define this observation more completely.

The plant is a diversified petrochemical manufacturing facility with a large number of major product lines, which over the years have included ethylene, butadiene, naphtha, ethylene dichloride, diethyl sulfate, glycols, aldehydes, acetates, alcohols, amines, organic acids, and plastics and resins (polyethylene, vinyl chloride–vinyl acetate co-polymers, phenol-formaldehyde resin). Review of the plant's chemical inventory reveals the presence of at least ten recognized or suspected carcinogens in significant quantities as raw materials, reaction by-products, or manufactured compounds. These are shown in Table V.

Careful preliminary examination of the work histories of affected employees does not yet establish any common job title, department code, or chemical exposure. Eight of the men were chemical operators in production departments, but they were spread throughout the plant and worked on different chemical processes. Five others were maintenance workers who may have had the opportunity for plant-wide exposures over the years. Two worked in the chemical shipping department as weighmasters with likely multiple exposures, and three worked in various construction trades. Detailed work histories for the cases are limited to employment by the company with two exceptions.

Case 1 was a salaried employee at a nearby petrochemical plant from 1948 to 1964, and Case 6 worked as a pipefitter from 1952 to 1974 in the same nearby plant. The extensive examination of work histories in the case-control study offers the best opportunity to establish a connection between a particular chemical exposure or type of work and an excess risk of brain cancer.

A detailed literature search for compounds inducing brain cancer has identified 26 different chemicals from experimental animal studies, as shown in Table VI. Review of available epidemiological studies provided in Table VII offers several intriguing clues, but little solid documentation for occupationally related brain tumors, except in the case of vinyl chloride [9, 10]. Recent mortality studies of oil refinery workers in Canada [11] and petrochemical workers in Texas [12] suggest the possibility of an excess brain cancer risk among these groups, although no specific causative agent has yet been identified.

TABLE V. Recognized and Suspected Carcinogens in a Texas Petrochemical Plant*

Benzene	Isopropyl oils
Diethyl sulfate	Trichloroethane
Dioxane	Trichloroethylene
Ethylene dichloride	Vinyl chloride
Hydrazine	Vinylidene chloride

*Quantities > 10⁶ lbs/yr.

Source: Data provided by company.

TABLE VI. Experimental Brain Carcinogens

2-Acetylaminofluorene [13]	Elaiomycin [21]
Acrylonitrile [14]	Ethyl methanesulphonate [22]
1-Aryl-3,3-dialkyltriazenes [15]	Ethyl nitrosobiuret ^a [16]
Azoethane ^a [16]	Ethyl nitrosoarea ^a [23]
Azoxyethane ^a [16]	1-Methyl-2-benzyl-hydrazine ^a [15]
Azoxymethane [15]	Methyl methanesulphonate [24]
Butylnitrosoarea [17]	Methylnitrosoarea ^a [25]
Cycasin [18]	Methylnitrosoarethane (intraplacental) [26]
1,2-Diethylhydrazine [15]	Procarbazine ^a [23]
Diethylnitrosamine ^a [15]	Propane sulfone [27]
Diethyl sulfate ^a [19]	Propylene imine [27]
Dimethylbenzanthracene ^a [20]	Pyrolizidine alkaloids [28]
Dimethyl sulfate ^a [19]	Vinyl chloride [29]

^aTransplacental carcinogenesis.

Numbers in brackets indicate reference sources.

TABLE VII. Epidemiological Studies: Clues to Human Brain Cancer Etiology

Aluminum workers [30]	Machinists [39]
Anticonvulsant use [31, 32, 33]	Oil refinery workers [11]
Farm/rural residents [3]	Petrochemical workers [12]
Geographic clustering	Rubber workers [40, 41, 42]
Kentucky [34,35], Rhone Valley [36]	Toxoplasmosis [43]
Halomethanes in drinking water [37]	Vinyl chloride workers [9, 10, 44, 45]
Lead smelter workers [38]	

Numbers in brackets indicate reference sources.

A comparison of experimental studies, epidemiological data, and the plant chemical inventory shows that vinyl chloride and diethyl sulfate are possible suspect agents for inducing brain cancer in these workers. On the basis of prior knowledge from human and animal studies, and its presence in the work environment under poorly controlled circumstances in the past, vinyl chloride must be the first compound considered. However, to date, examination of the work histories of the 18 cases does not support a significant positive association with vinyl chloride exposure, and other agents must therefore be carefully evaluated.

The information available indicates that this number of brain tumors is excessive in a population of this size, and that the tumors are likely to be occupationally related. There is no good evidence so far to implicate non-plant, general environmental factors. A very careful and thorough investigation of this situation must be completed, since a previously unsuspected chemical exposure may be responsible for this striking appearance of brain cancers among workers in a single petrochemical plant.

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