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DRAFT VI

Brain Cancer in Petrochemical Workers - A Case Series Report

Nineteen primary brain cancer deaths have been found among workers at one United States petrochemical plant. We believe this is the largest single series of presumably occupationally-related brain cancers reported in the medical literature.

In November, 1978, the Occupational Safety and Health Administration (OSHA), the Federal occupational health enforcement agency of the U.S. 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 Houston, Texas began an investigation of brain cancer mortality at the employee's worksite, a moderate-sized petrochemical production facility in Texas City, located in Galveston County south of Houston. Workers, family members and surviving relatives, 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 medical department, primarily covering workers who died while employed and who by virtue of 15 years of company service were eligible for death benefits. Ten deaths from primary brain cancer were identified. These ten

included 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 U.S. Department of Health, Education, and Welfare.

In February, 1979 OSHA, NIOSH, and the company established a collaborative study plan to investigate the apparent excess of brain cancers. An historical prospective cohort mortality study was begun to determine the Standardized Mortality Ratio (SMR) for brain cancer, and whether there exists any other unusual mortality pattern. Also included within the cohort study is a case-control study of all primary brain cancer cases to establish whether a particular job or chemical exposure at the plant is associated with an excess risk of brain cancer. A reference neuropathology laboratory has agreed to examine autopsy and surgical pathology specimens to provide histologic confirmation of the cause of death. Each of these studies is well underway, 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 extent of the problem. A computer-assisted search was conducted of 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 twenty 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. Four additional confirmed cases resulted. Further investigation of company records revealed two more cases. Three other employees became ill during the preliminary period of the study. All cases were deceased as of March, 1980. The current total of 19 cases is the subject of this case series report.

Work history data for the 19 cases are provided in Table 1. The average age at death for the cases was 52; the youngest died at age 30, and there were four deaths after age 60. Over half the deaths occurred between ages 50 and 59. The age distribution observed in this series does not differ significantly from that reported in other series.[1,2,3]

Total length of employment at the plant ranged from 1 month to slightly more than 35 years, with a median value of 20 years. Two cases had short exposure periods of 38 and 29 days respectively. Median length of employment excluding these two cases was 22 years. The interval from first employment to death, which provides an estimate of latency, varied from as few as 3 1/2 years to nearly 36 years, with a median of 24 years. The median values for exposure and latency period in this series are typical of those found for other tumor types in occupational cancer investigations and are consistent with a hypothesis of occupational etiology resulting from chemical exposures.

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 more were hired in 1941 during the first year of plant operation, and the others 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 1960's. Twelve of the deaths occurred after 1970, three of them during the past year. No established pattern is evident from the observed years of death, but there is no evidence that the rate of appearance of cases is declining.

The plant has a current workforce of slightly more than 2,200, including nearly 1,500 hourly and production 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 December, 1979. The distribution by county of residence for current workers is provided in Table 2. The plant also engages a temporary independent contractor workforce of 100-250 daily, mostly for construction jobs. Unfortunately, no employment records are available for this group.

Demographic and cause of death data from the death certificates are provided in Table 3. All cases occurred among male employees, 18 whites and 1 black. The mortality rate for primary brain cancer in Texas among black males is about one-half that for white males.(4) However, very little can be said regarding the racial distribution of cases, since it appears

that increased numbers of black employees have been employed at the plant only in recent years.

All but one of the cases were native-born Americans; the lone exception was Norwegian. The great majority of the cases were born in Texas, two were from Louisiana, and one each was from Massachusetts, New Mexico, and Oklahoma. None of the U.S. states of origin have a particularly high risk for brain cancer, compared to the U.S. national average. There is presently no information available about the age of the cases when they moved to Texas, or where else they may have lived.

Sixteen 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. County-wide data from the National Cancer Institute on the brain cancer mortality rates for Harris, Galveston, and Brazoria Counties from 1950-1969 are in the mid-range for Texas and U.S. national values as shown in Table 4. A survey made by the Texas State Department of Health for 1977 showed that the Galveston County brain cancer crude mortality rate was 3.6/100,000. 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, brain cancer deaths among adult white males in Galveston County were analyzed using the list described previously. A total of 54 primary brain cancer deaths occurred in the county from 1962 through 1977. To establish a rough

comparison, information from the Health Services Administration on county population characteristics was used.(5) In 1970 Galveston County was 68% white, and 62% of the population were between the ages of 14 and 64. A 1970 county population estimate was 170,000 of whom 49% were males.(6) Thus, the white male population of employment age at risk during 1962-1977 was somewhat less than 38,000; the plant white male population was about 1,800 or about 5% of the county total. Yet during this period, 11 of 54 brain tumor deaths among county residents occurred in plant employees, nearly 20% of the total. This suggests an approximate plant-wide risk of about four-fold.

The underlying causes of death as recorded on the death certificates are listed in Table 2. 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 19. According to these records one case also was reported to be a metastatic lesion to the cerebellum. Preliminary medical evidence thus suggests that 81% (15/19) of the tumors were glioblastomas. Because this type of tumor usually accounts for 40-55% of deaths in reported brain cancer series, this would indicate an excess of glioblastoma multiforme among these cases.(1,2,3,7,8) The difficulty of precise neuropathological diagnosis for brain cancer is recognized, and the pathology review is expected to better define this observation.

The plant is a diversified petrochemical manufacturing facility with a large number of major product lines, including ethylene, butadiene, naphtha,

ethylene dichloride, diethyl sulfate, glycols, aldehydes, acetates, alcohols, amines, organic acids, and plastics and resins (polyethylene, vinyl chloride-vinyl acetate copolymers, phenol-formaldehyde resin). Review of the plant's chemical inventory reveals the presence of at least 11 recognized or suspect carcinogens in significant quantities as raw materials, reaction by-products, or manufactured compounds. These are shown in Table 5. 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. Six 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. Five worked in various construction trades. Work histories on the cases are limited to employment by the company with two exceptions. Case 1 was a salaried employee at a nearby petrochemical plant from 1948-1964, and Case 6 worked as a pipefitter from 1952-1974 in the same plant. No information about other potential chemical exposures is presently available. The detailed 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 6. Review of available epidemiological studies provided in Table 7

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 as yet no specific causative agent has been identified.

A comparison of experimental studies, epidemiological data, and the plant chemical inventory shows that vinyl chloride, acrylonitrile, 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 19 cases does not support a significant positive association with vinyl chloride exposure, and other agents must 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 to implicate non-plant, general environmental factors. A very careful and thorough investigation of this situation must be made, since a previously unsuspected chemical exposure may be responsible for this striking appearance of brain cancers in a single petrochemical plant.

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Table 1. WORK HISTORY DATA FOR 19 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	09/19/46	03/07/79	55	32-3	Laborer/Oiler	Maintenance
8	09/26/46	03/22/73	63	26-6	Operator	Production
9	01/12/48	01/26/71	53	1-2	Painter	Maintenance
10	09/21/48	07/02/75	49	2-1	Pipefitter	Maintenance
11	03/02/49	06/05/71	61	22-3	Operator	Production
12	01/25/50	01/13/68	66	16-7	Equip. Operator	Maintenance
13	10/19/50	05/14/74	59	17-1	Operator	Energy Systems
14	10/23/50	02/18/80	57	28-10	Operator	Production
15	09/19/51	01/08/74	52	22-3	Machinist	Machine Shop
16	04/27/53	10/03/56	33	0-1	Machinist	Maintenance
17	03/17/53	04/05/62	30	8-7	Weighmaster	Shipping
18	08/21/53	05/05/71	44	17-3	Operator	Production
19	10/30/53	12/21/78	49	24-8	Weighmaster	Shipping

Table 2. CURRENT PLANT WORKFORCE BY COUNTY OF RESIDENCE

County of Residence	Type of Employee Hourly	Salaried	Total	Percent
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

Table 3. DEATH CERTIFICATE DATA FOR 19 PRIMARY BRAIN CANCER CASES IN A TEXAS PETROCHEMICAL PLANT

Case	Race/ Sex	Residence	Place of Birth	Cause of Death: Death Certificate	Cause of Death: Medical Records
1	WM	Galveston	Texas	Carcinoma of Brain	Glioblastoma (MR)*
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	No Records Available
7	BM	Galveston	Texas	Glioblastoma	Glioblastoma (MR)
8	WM	Galveston	Texas	Glioblastoma	Glioblastoma (SP)
9	WM	Galveston	Massachusetts	Cerebellar Tumor	Metastatic Cerebellar Tumor (SP)
10	WM	Harris	Texas	Astrocytoma	Astrocytoma-Grade I (SP)
11	WM	Galveston	Texas	Malignant Glioma	Glioblastoma (MR)
12	WM	Galveston	New Mexico	Glioblastoma	Glioblastoma (A)
13	WM	Galveston	Norway	Glioblastoma	Glioblastoma (SP)
14+	WM	Galveston	Texas	Glioma-Grade III	Astrocytoma-Grade IV (MR)
15	WM	Galveston	Texas	Glioblastoma	Glioblastoma (A)
16	WM	Harris	Texas	Glioblastoma	No Records Available
17	WM	Galveston	Louisiana	Brain Tumor	Glioblastoma (A)
18	WM	Galveston	Texas	Malignant Glioma	Glioblastoma (SP)
19	WM	Galveston	Texas	Brain Tumor	Glioblastoma (A)

+Data from company records, death certificate not available
*Source: MR-Medical Records; A-Autopsy; SP-Surgical Pathology

Table 4. 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*	1.5

*Based on one case

The range of U.S. rates for males for counties with >10 deaths from 1950-1969 were 3.1-5.4 (white) and 1.3-3.9 (black). The range of Texas rates for white males for counties with >deaths from 1950-1969 was 2.3-10.8.

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

Table 5. RECOGNIZED AND SUSPECT CARCINOGENS IN A TEXAS PETROCHEMICAL PLANT

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

Table 6. EXPERIMENTAL BRAIN CARCINOGENS

2- Acetylaminofluorene (13)
Acrylonitrile (14)
1-Aryl-3,3-Dialkyltriazenes (15)
Azoethane* (16)
Azoxyethane* (16)
Azoxymethane (15)
Butylnitrosourea (17)
Cycasin (18)
1,2-Diethylhydrazine (15)
Diethylnitrosamine* (15)
Diethyl Sulfate* (19)
Dimethylbenzanthracene* (20)
Dimethyl Sulfate* (19)
Elaiomycin (21)
Ethyl methanesulphonate (22)
Ethylnitrosobiuret* (16)
Ethylnitrosourea* (23)
1-Methyl-2-Benzyl-Hydrazine* (15)
Methyl methanesulphonate (24)
Methylnitrosourea* (25)
Methylnitrosourethane (intraplacental) (26)
Procarbazine* (23)
Propane Sultone (27)
Propylene Imine (27)
Pyrrolizidine Alkaloids (28)
Vinyl Chloride (29)

*Transplacental carcinogenesis

Table 7. EPIDEMIOLOGICAL STUDIES:
CLUES TO HUMAN BRAIN CANCER ETIOLOGY

Aluminum Workers (30)

Anti-Convulsant Use (31,32,33)

Farm/Rural Residents (3)

Geographic Clustering
Kentucky (34,35), Rhone Valley (36)

Halomethanes in Drinking Water (37)

Lead Smelter Workers (38)

Machinists (39)

Oil Refinery Workers (11)

Petrochemical Workers (12)

Rubber Workers (40,41,42)

Toxoplasmosis (43)

Vinyl Chloride Workers (9,10,44,45)

Brain Cancer Cluster Investigation in a Texas City, Texas Chemical Plant

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Introduction:

In February of 1979, The National Institute for Occupational Safety and Health (NIOSH) of the Department of Health and Human Services, th Occupational Safety and Health Administration (OSHA), of the Department of Labor, and the Union Carbide Corporation began an investigation of a cluster of brain tumors at the company's Texas City, Texas plant. The initial events and the characteristics of the cases have been described by Dr. Victor Alexander. We here describe the conduct and present status of a case-control study of occupational histories of employees of that plant who developed primary brain tumors.

Methods and Materials:

The method of case identification has been described by Dr. Alexander; the company was able to identify 12 cases, matching company records with lists of all adult males who were residents of surrounding counties and who died of malignant brain tumors yielded four more cases, three additional cases became ill and died during the course of the study, and three cases have been found so far in the course of determining the vital status of all workers ever employed in the plant. Medical records and tissue specimens were obtained, where possible, and a best diagnosis was chosen from the available evidence.

Following the advice of Schoenberg et al., we included all deaths due to primary intracranial neoplasms except those of the pituitary. This excluded one case with a metastatic lesion and one with a congenital anomaly but with no tumor found at autopsy. Two of the most recently discovered cases have not been included, pending confirmation of the diagnosis. Analyses of the residual 18 cases will be done both for the group as a whole and for the 15 proven gliomas.

For each employee, the company completed coding sheets containing identifying personal data, date of each new job title or department code, job code, department accounting code, and date of each layoff or date of termination. Vital status was coded, when known. Every 50th record was copied and sent to NIOSH for independent verification of coding. A random sample of the original records will be drawn by NIOSH and used for verification of completeness of cohort identification.

Six controls were drawn for each case from the pool of all people ever employed at the plant. Cases were matched to potential controls by race and sex; date of birth was matched to within three years; date of first hire for the control was before that of the case, but not more than three years before; the date the control was last employed was later than the case's last date of employment. The control could be living but, if dead, must not have died of a malignancy. Pools of controls meeting the criteria outlined above were formed and the actual controls used were drawn by random number from the pool.

The company provided translations for the job and department codes and provided a list of chemicals encountered in each major department group. The departmental coding schemes used for accounting purposes within the plant have changed over the years, so a common list tracing the history of each department was prepared and all codes were transformed to conform to a single coding scheme. Although catalysts have changed often, there appears to be no problem in characterizing the feedstocks, intermediate products, and output of each department through the years the plant has been in operation.

Each job, department, major department group, or chemical exposure represented by at least three cases was tested for possible significance by X^2 or Fisher's Exact Test. Since this approach is a multiple sampling technique which should lead to about one "significant" association for every twenty jobs, departments, or exposures considered, it is used here as an hypothesis generating mechanism, not as a means of properly testing the hypotheses. For example, since at least one case was exposed to each of nearly 200 chemicals, chance alone should lead to identification of about 10 chemicals whose proportion is significantly different between cases and controls. About half of the ten would be positive and half would be negative associations.

Results:

Only one job code, "Operator" was represented by more than three cases. Table I shows the distribution of operators among the cases and controls. There is no significant difference in proportions.

When analyzed by department accounting code, only the maintenance department, with eight cases, was represented by more than three cases. Table II shows the distribution of maintenance department workers among the cases and controls. Grouping the accounting codes into major departments did not yield any new concentrations of three or more cases. There were no significant differences in proportions.

When cases and controls were analyzed by chemical exposures, a new problem was encountered: the exact exposure of a maintenanceman is difficult to characterize accurately, due to their mobility throughout the plant. Accordingly, as a first step, we have examined the data in three ways: in the first, maintenancemen are excluded from analysis; in the second, they are considered to have been exposed to everything in the plant; in the third, they are considered to have been exposed to nothing in the plant. The data are presented in Tables III, IV, and V; only those chemicals to which more than three cases were exposed and which showed a relative risk greater than 1.0 are tabulated.

Discussion:

So far in the course of this investigation, no convincing association has been found between any historical exposure and the development of brain tumors at this plant. The incomplete characterization of the maintenance employees' exposures is a significant weakness in the analysis done so far, but fortunately can be corrected, at least in part, by further review of existing records. Some of the maintenance department employees had reasonably well defined exposures; for example, one case was an instrument repairman whose work rarely took him out of the instrument shop. We plan to define exposures of cases and controls who worked for the maintenance department as completely as possible and study the full data set. At that time, there should also be enough information at hand to study the exposures by latency.

It is possible that the tumors seen are the result of a more general effect or exposure. We plan to examine the geographic location within the plant of cases and controls, to see if any pattern emerges, and will atempt to determine the residence at time of first hire, to see if there appears to be any unusual clustering outside the plant.

Finally, we must ask whether we are really seeing an effect which requires explanation. The excess of observed over expected reported earlier[2], combined with an apparent excess when compared to local rates[3], could be the result of chance. The reported correlations

with duration of employment and latency since first employment argue against this hypothesis but do not refute it. Inquiry into exposures present in other populations with apparent excesses of brain tumors may provide needed additional clues.

Table I: Distribution of Operators Among Cases and Controls

IA. All Cases	Cases	Controls	Total
Operators	9	49	58
Non-operators	9	59	68
Total	18	108	126

Odds ratio = 1.2; $X^2 = 0.045$; p greater than 0.75

IB. Proven Gliomas	Cases	Controls	Total
Operators	7	40	47
Non-operators	8	50	58
Total	15	90	105

Odds ratio = 1.1; $X^2 = 0.024$; p greater than 0.75

Table II: Distribution of Maintenance Workers Among Cases and Controls

IIA. All Cases	Cases	Controls	Total
Maintenance workers	7	46	53
Non-maintenance workers	11	62	73
Total	18	108	126

Odds ratio = 0.86; $X^2 = 0.087$; p greater than 0.75

IIB. Proven Gliomas	Cases	Controls	Total
Maintenance workers	7	37	44
Non-maintenance workers	8	53	61
Total	15	90	105

Odds ratio = 1.3; $X^2 = 0.163$; p greater than 0.75

Table III: Distribution Among Cases and Controls of Workers Exposed to Selected Chemicals (Maintenancemen Excluded)

IIIA. All Cases		Cases	Cont.	Total	Odds	p*
Exposed	1. Diethyl ether	3	2	5		
	2. Ethanol	3	2	5	7.87	0.07
	3. Sodium phosphate salts	3	2	5		
	4. Lubricating oil	6	15	21	3.20	0.30
	5. Monoethanolamine	4	10	14	1.73	0.42
	6. Ethylene glycol	3	8	11	1.41	0.80
	7. Naphtha	3	8	11		
	8. Potassium hydroxide	2	5	7	1.44	0.81
Unexposed	1. Diethyl ether	4	21	25		
	2. Ethanol	4	21	25		
	3. Sodium phosphate salts	4	21	25		
	4. Lubricating oil	1	8	9		
	5. Monoethanolamine	3	13	16		
	6. Ethylene glycol	4	15	19		
	7. Naphtha	4	15	19		
	8. Potassium hydroxide	5	18	23		
Total		7	23	30		

* Fisher's exact test

Table III (Con't): Distribution Among Cases and Controls of Workers Exposed to Selected Chemicals (Maintenancemen Excluded)

IIIB. Proven Gliomas		Cases	Cont.	Total	Odds	p*
Exposed	1. Diethyl ether	2	1	3		
	2. Ethanol	2	1	3	13.0	0.11
	3. Sodium phosphate salts	2	1	3		
	4. Lubricating oil	4	9	13	inf.	0.23
	5. Monoethanolamine	3	6	9	4.00	0.29
	6. Ethylene glycol	2	5	7	1.80	0.86
	7. Naphtha	2	5	7		
	8. Potassium hydroxide	2	2	4	6.00	0.98
Unexposed	1. Diethyl ether	2	13	15		
	2. Ethanol	2	13	15		
	3. Sodium phosphate salts	2	13	15		
	4. Lubricating oil	0	5	5		
	5. Monoethanolamine	1	8	9		
	6. Ethylene glycol	2	9	11		
	7. Naphtha	2	9	11		
	8. Potassium hydroxide	2	12	14		
Total		4	14	18		

* Fisher's exact test

Table IV: Distribution Among Cases and Controls
of Workers Exposed to Selected Chemicals
(Maintenancemen Counted as Exposed)