

Risk of astrocytic brain tumors associated with occupational chemical exposures

A case-referent study

by Terry L Thomas, PhD,^{1,6} Patricia A Stewart, MS,¹ Annette Stemhagen, DrPH,² Pelayo Correa, MD,³ Sandra A Norman, PhD,⁴ Margit L Bleecker, MD, PhD,^{5,6} Robert N Hoover, MD, ScD¹

THOMAS TL, STEWART PA, STEMHAGEN A, CORREA P, NORMAN SA, BLEECKER ML, HOOVER RN. Risk of astrocytic brain tumors associated with occupational chemical exposures: A case-referent study. *Scand J Work Environ Health* 13 (1987) 417-423. A case-referent study was conducted on the risk of brain tumors among workers exposed to organic chemicals in petroleum refining and chemical manufacturing. Brain tumor cases in northern New Jersey, Philadelphia, and the Gulf Coast of Louisiana were identified from death certificates of a recent three-year period. The cases (N = 300) were white men aged ≥ 30 years with a confirmed diagnosis of glioblastoma multiforme, astrocytoma, or a mixed glioma with astrocytic cells. The referents (N = 386) were white men who died from causes other than brain tumor, epilepsy, cerebrovascular disease, suicide, or homicide and were frequency-matched with the cases on age at death, year of death, and study area. Next-of-kin were interviewed for complete occupational histories. No statistically significantly elevated odds ratios (OR) were associated with employment in the chemical industry. The risk of astrocytic tumors was elevated among the subjects with production or maintenance jobs in petroleum refining (OR 1.7, 95 % confidence interval 0.7-4.2); however, it decreased with duration employed. There were nonsignificant excess risks of astrocytic tumors among the men exposed to cutting fluids (OR 1.6) or organic solvents (OR 1.3), and also among the subjects exposed to lubricating oils (OR 1.4), organic solvents (OR 1.5), or cutting fluids (OR 1.8) for ≥ 20 years.

Key terms: acrylonitrile, astrocytic brain tumors, chemical manufacturing, formaldehyde, lubricating oils, organic solvents, petroleum refining, phenolic compounds, polycyclic aromatic hydrocarbons, vinyl chloride.

Reports of clusters of brain tumors among workers in oil refineries and chemical plants located in the Gulf Coast area of Texas (1, 15, 18, 24, 26) prompted an epidemiologic investigation of brain tumor risk in other areas of the United States that had a heavy concentration of petroleum and chemical industries. A recent literature review (25) noted that some common exposures among occupational groups with a high risk of brain tumors were organic solvents, lubricating oils, polycyclic aromatic hydrocarbons, formaldehyde, vinyl chloride, acrylonitrile, and phenolic compounds. Al-

though expected numbers could not be calculated for specific cell types, many of the earlier studies had suggested that the elevated risks were cell-type specific and were limited to glioblastoma multiforme and astrocytoma (25).

A case-referent study was conducted in northern New Jersey, Philadelphia (Pennsylvania), and the Gulf Coast of Louisiana to investigate findings of hypothesis-generating studies and to evaluate other risk factors for brain tumors. The present analyses focused on risks for astrocytic tumors (glioblastoma multiforme, astrocytoma, and mixed glioma with astrocytic cells) among men employed in the petroleum refining and chemical manufacturing industries and evaluated risks for particular organic chemical exposures thought to be associated with excess brain tumor risk.

Subjects and methods

Because this investigation was planned to test hypotheses regarding the association between brain tumor mortality risk and employment in the petroleum and chemical industries, study areas were chosen on the basis of employment patterns by industry. Three geographic areas with consistently high proportions of the workforce employed in the petroleum refining and

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chemical manufacturing industries combined were northern New Jersey, the Philadelphia, Pennsylvania, standard metropolitan statistical area, and the Gulf Coast area of Louisiana. Each study area included at least one standard metropolitan statistical area and surrounding counties in which a substantial proportion (5 to 19 %) of the workforce was likely to have been employed in the industries of interest.

Permission was obtained from state vital records offices to review causes of death among usual residents of the selected study areas and to utilize information from death certificates of cases and referents to contact their next-of-kin. Cases were white men, aged 30 years or older, who died of brain or other central nervous system tumors [International Classification of Disease 9th Revision (ICD-9) (29) codes 191, 192, 225, 239.7] during a three-year period and who were usual residents of counties in the selected study areas. The study period for Louisiana was 1 January 1978 through 30 June 1980, and for the other two study areas it was 1 January 1979 through 31 December 1981. The total number of cases ascertained from computer listings was 741.

With the use of a matching ratio of 1 : 1, referents were randomly selected from white male residents who had died of causes other than brain tumor, cerebrovascular disease (ICD-9 codes 430–438), epilepsy (ICD-9 code 345), suicide, and homicide. Cerebrovascular disease and epilepsy were excluded to decrease the likelihood of including undiagnosed brain tumor cases in the reference series. Suicide and homicide were excluded due to the sensitive nature of cause of death and the potential difficulties in obtaining responses from next-of-kin. The referents were frequency-matched to the cases by age and year of death. The resultant age and year of death distributions for the cases and referents were nearly identical.

Death certificates were not obtained for one case and four referents who died in states outside the study areas; therefore a total of 1 478 subjects were left whose next-of-kin could be contacted for interview. Informants listed on the death certificates were contacted first by letter and next by telephone to ascertain the identity and address of the next-of-kin. The next-of-kin was chosen according to the following hierarchy: (i) spouse (65 %), (ii) adult child or parent (22 %), (iii) sibling (8 %), (iv) other (5 %). Next-of-kin of 212 study subjects (86 cases, 126 referents) either could not be traced or could not be identified from information available on the death certificates. About 70 % [N = 869, 483 cases (74 %), 386 referents (63 %)] of the 1 266 next-of-kin who were located agreed to be interviewed. The final study group was a sufficient size to detect an excess brain tumor risk of 2.0 or greater among men employed in the suspect "high risk" industries with a statistical power of 70 %.

In order to assess potential response bias, we compared the demographic characteristics on the death certificates of subjects with completed interviews (com-

pletes) with those whose next-of-kin could not be located (untraced) and those whose next-of-kin refused to be interviewed (refusals). There were slightly lower proportions of white-collar workers and married men among the untraced than among the refusals and completes. Because their next-of-kin were difficult to locate, the untraced had a slightly higher proportion of subjects who died in the earliest years of the study period. There was little variation between refusals and completes with respect to age, marital status, and job status (ie, blue collar versus white collar). Since there were also no differences in the proportions of cases and referents by these variables, it could be assumed that there was little or no response bias affecting these factors. The response rate varied substantially by study area, being highest in Louisiana (81 %), and might have been affected more by regional social attitudes than by other variables.

Because earlier studies suggested that an excess risk of brain tumors in the petroleum and chemical industries was limited to specific cell types (25), the present analyses included study subjects as cases only if the best diagnostic information available indicated the presence of an astrocytic brain tumor (astrocytoma, glioblastoma multiforme, mixed glioma with astrocytic cells). Hospital records were sought for the 483 cases with completed interviews. Forty-eight of the cases did not have primary brain tumors and were excluded from further consideration. The remaining cases consisted of 300 men with astrocytic tumors and 135 with other (N = 90) or undetermined (N = 45) cell types. Two hundred and twenty-nine (76 %) of the astrocytic tumors were pathologically confirmed, and the remaining 71 were diagnosed by physicians on the basis of appearance in computerized tomography. The final data set considered in this report consisted of the 300 cases with astrocytic tumors and 386 referents.

The lifetime occupational history data collected in the interview included the following information on each job held by the study subject since the age of 15 years: job title, brief job description, kind of company or organization, company name, job location (city, state), employment dates, and hours worked per week. Information on ethnic background, education, and other possible risk factors for brain tumors, including history of head injuries, seizures, drug usage, family history of cancer, and other environmental factors was also collected. Interviewers were blinded regarding the case-referent status of the subject until the end of the interview.

Each job entry in a study subject's work history was assigned a Standard Industrial Classification (SIC) code for industry (16) and a census code for occupation (3). The "high risk" industries considered in these analyses were petroleum refining (SIC 291–299) and the manufacture of chemicals and allied products (SIC 281–289).

An industrial hygienist (PAS) classified each job according to whether it had potential exposure to

organic solvents, lubricating oils, polycyclic aromatic hydrocarbons, formaldehyde, acrylonitrile, vinyl chloride, or phenolic compounds. All coding was done blindly, ie, without knowledge of whether the subject was a case or referent. Jobs considered to have potential exposure to acrylonitrile in these data included those in the production of plastics or rubber, but they were primarily in farming where acrylonitrile may be used as a pesticide. Jobs with exposure to vinyl chloride were production jobs in the plastics industry. Formaldehyde-exposed jobs were those that involved oil drilling, cloth dyeing, carpentry, certain laboratory work (eg, biological science and histology laboratories), and the manufacture and sale of furniture and clothing. Mechanics, precision metal workers, refinery workers, and truck and bus drivers were assigned lubricating oil exposure, and cutting fluid exposure was assigned primarily to jobs that involved precision metal work. The category of lubricating oils included all oils and hydraulic fluids used to lubricate motors, engines, and equipment, while cutting fluids, a specialized subset of lubricating oils, included only those used to lubricate and cool cutting surfaces in precision metal work. Jobs in laboratories, carpentry, painting, pipefitting, cloth dyeing, construction, and printing were considered to have potential exposure to phenolic compounds (ie, phenol, cresol, creosote, hydroquinone, phenolic resins, quinone, and resorcinol). Polycyclic aromatic hydrocarbon exposure was assigned to mechanics, gas station attendants, plumbers, roofers, oil workers, precision metal workers, foundry and steel workers, boiler room operators, and truck and bus drivers.

Nearly all of the jobs that were considered exposed to the aforementioned substances also might have involved contact with organic solvents, and there was considerable overlap between the various exposure categories. Because so many subjects were considered exposed to solvents, the industrial hygienist classified exposure by presumed frequency of solvent use. A job was assumed to have "low" exposure if it was likely to involve the use of solvents less than once per workday. "Moderate" exposure was assigned to a job if solvent use was likely to have been one to several times per day, while jobs requiring more constant solvent contact were considered to have "high" exposure.

The unexposed subjects for the analyses by industry included those never employed in the petroleum refining or chemical manufacturing industries. In the analyses by organic chemical substance, a study subject was considered to have been "exposed" to a substance if he ever had a job that might have involved contact with the substance, the unexposed being men who never had a job involving the particular organic chemical substance being considered. Excluding those ever exposed to any of the other substances would have resulted in a reference group that was largely white collar and that might differ from the exposed group in many characteristics. Duration of exposure was estimated from the calculation of the total number of years spent in "exposed" jobs. If dates worked were unknown for a particular job, the job was excluded from the analyses by duration employed.

To estimate the relative risk of brain tumors, we calculated the maximum likelihood estimates of the odds ratio (OR) for brain tumors and the 95 % confidence intervals (95 % CI) (8) for each industry and organic chemical substance of interest. Since the cases and referents were frequency-matched on study area, age, and year of death only to obtain a reference series that was similar to the cases with respect to these factors, an unmatched analysis was conducted and was stratified by potential confounders. Variables assessed for possible confounding were age at death, history of cigarette smoking, history of alcoholism, ethnic background, and highest level of education. Level of education was the only variable which appeared to be related both to brain cancer and the exposures of interest; thus, all analyses were stratified by it. The analyses by organic chemical substance were also stratified by a variable which indicated ever or never exposure to the other chemicals. An odds ratio was considered statistically significant if the 95 % confidence interval did not include 1.0. A chi-square test for linear trend was used to determine whether trends by duration employed were significant (19).

Results

Table 1 shows the odds ratios for astrocytic brain tumors among the study subjects who were ever em-

Table 1. Odds ratios for astrocytic tumors among study subjects ever employed in petroleum refining or chemical manufacturing. (SIC = Standard Industrial Classification, 95 % CI = 95 % confidence interval)

| Industry | Production & maintenance | | | | White collar only | | | | All workers | | | |
|---|--------------------------|-----------|-----------------|---------|-------------------|-----------|-----------------|---------|-------------|-----------|-----------------|---------|
| | Case | Referents | OR ^a | 95 % CI | Cases | Referents | OR ^a | 95 % CI | Cases | Referents | OR ^a | 95 % CI |
| Petroleum refining (SIC 291—299) | 15 | 12 | 1.7 | 0.7—4.2 | 3 | 4 | 0.8 | 0.1—4.6 | 18 | 16 | 1.5 | 0.7—3.2 |
| Chemical manufacturing (SIC 281—289) | 26 | 31 | 1.2 | 0.7—2.2 | 16 | 13 | 1.2 | 0.5—2.7 | 42 | 44 | 1.2 | 0.7—2.0 |

^a Maximum likelihood estimate of the odds ratio stratified by educational class. Note: Unexposed subjects in each of these analyses were men who had never worked in either industry.

ployed in petroleum refining or chemical manufacturing. The risk was slightly elevated among all the men ever employed in either of the "high risk" industries, but neither result was statistically significant. Men employed in production and maintenance jobs in petroleum refining had elevated astrocytic tumor risk, and those only employed in white-collar jobs did not. However, the confidence intervals for the two OR estimates overlapped. In chemical manufacturing, the odds ratios for those employed in production and maintenance jobs were the same as those for men employed in white-collar jobs. Analyses of astrocytic tumor risk in petroleum refining by duration employed indicated that risk was highest among those employed in the industry for less than five years (table 2), and the odds ratios decreased with increasing duration employed. This finding was true for all workers combined and for those employed in production and maintenance.

Table 2. Odds ratios for astrocytic tumors among study subjects ever employed in the petroleum refining industry by duration employed. (C = number of cases, R = number of referents)

| | Ever employed in petroleum refining | | | Production or maintenance job in petroleum refining | | |
|---|-------------------------------------|-----|-----------------|---|-----|-----------------|
| | C | R | OR ^a | C | R | OR ^a |
| Not employed in petroleum refining (ie, unexposed) ^b | 242 | 327 | 1.0 | 242 | 327 | 1.0 |
| Duration employed in petroleum refining (years) | | | | | | |
| < 5 | 6 | 2 | 3.9 | 5 | 1 | 6.7 |
| 5-9 | 4 | 4 | 1.3 | 2 | 2 | 1.3 |
| ≥ 20 | 4 | 8 | 0.7 | 4 | 7 | 0.8 |

^a Maximum likelihood estimate of the odds ratio stratified by educational class.

^b The unexposed subjects in each of these analyses were men who had never worked in any of the "high risk" industries.

Table 3. Odds ratios for astrocytic brain tumors among subjects whose jobs ever might have involved exposure to selected organic chemical substances. (95% CI = 95% confidence interval)

| Substance | Exposed astrocytic tumor cases | Exposed referents | OR ^a | 95% CI |
|----------------------------------|--------------------------------|-------------------|-----------------|---------|
| Acrylonitrile | 27 | 43 | 0.9 | 0.5-1.6 |
| Formaldehyde | 38 | 50 | 1.0 | 0.6-1.7 |
| Lubricating oils | 116 | 140 | 1.1 | 0.8-1.6 |
| Organic solvents | 195 | 246 | 1.3 | 0.8-1.9 |
| Cutting fluids | 49 | 42 | 1.6 | 1.0-2.6 |
| Polycyclic aromatic hydrocarbons | 134 | 174 | 0.9 | 0.7-1.4 |
| Phenolic compounds | 67 | 100 | 0.8 | 0.5-1.2 |

^a Maximum likelihood estimate of the odds ratio stratified by educational class and other exposures.

Note: The unexposed subjects for each calculation were those whose jobs had never involved exposure to the substance of interest.

Table 3 shows results for the selected organic chemical substances. The OR estimates were slightly elevated for organic solvents (OR 1.3) and cutting fluids (OR 1.6), but neither was statistically significant. The odds ratio for vinyl chloride was 1.3 [omitted from table due to small numbers (3 cases, 6 referents, 95% CI 0.8-2.0)]. No excess risk of astrocytic tumor mortality was seen among the men who had jobs that might have involved exposure to acrylonitrile, formaldehyde, lubricating oils, polycyclic aromatic hydrocarbons, or phenolic compounds.

The odds ratios for astrocytic tumors by duration of "exposed" jobs are shown in table 4 by organic chemical substance. Astrocytic tumor mortality risk was the highest in the 20 or more years category for lubricating oils (OR 1.4), organic solvents (OR 1.5), and cutting fluids (OR 1.8), but for none of these exposures was there any consistent or significant trend by duration.

Table 5 shows results for total duration of solvent exposure by the highest level of solvents to which subjects were classified as exposed. The odds ratio was elevated among the subjects whose highest exposure was low (OR 1.4) or moderate (OR 1.6) and who were exposed to organic solvents for 20 or more years. No excess risk was seen among the men classified as having high solvent exposure. However, the number of workers exposed in each duration category was small.

The findings for cutting fluids were examined further with calculations of OR estimates for specific precision metal work jobs which would involve the exposure (table 6). Overall, the odds ratio for precision metal work was 1.6 (95% CI 1.0-2.6). The odds ratios increased with duration employed for all the precision metal workers combined. The highest risk was seen for tool and die makers. However, none of the men had this job for 20 or more years. Machinists had an odds ratio of 1.8 after 20 years of employment, but the number of men classified in individual duration categories was small.

Discussion

Analyses for two "high-risk" industries suggested that there might be an elevated risk of astrocytic brain tumor mortality associated with ever having a job that involved chemical exposure in oil refining, but not with chemical manufacturing. These results would be consistent with reports suggesting elevated brain tumor risk among production and maintenance workers in oil refining (21, 23, 26) and contrary to other studies of refinery workers which failed to find excess risk of brain tumors (6, 10, 14, 20, 27). However, none of the odds ratios in the current study were statistically significant, and the decreasing risk by duration employed casts doubt on the causality of the association. The highest risk occurred among the men who worked less than five years (OR 3.9), were hired before the age of

Table 4. Odds ratios for astrocytic tumors among subjects whose jobs ever might have involved exposure to selected organic chemical substances by duration of "exposed" jobs. (C = number of cases, R = number of referents)

| | Type of exposure | | | | | | | | | | | | | | | | | | | | |
|---|------------------|-----|-----------------|--------------|-----|-----------------|------------------|-----|-----------------|------------------|-----|-----------------|----------------|-----|-----------------|----------------------------------|-----|-----------------|--------------------|-----|-----------------|
| | Acrylonitrile | | | Formaldehyde | | | Lubricating oils | | | Organic solvents | | | Cutting fluids | | | Polycyclic aromatic hydrocarbons | | | Phenolic compounds | | |
| | C | R | OR ^a | C | R | OR ^a | C | R | OR ^a | C | R | OR ^a | C | R | OR ^a | C | R | OR ^a | C | R | OR ^a |
| Unexposed ^b | 273 | 343 | 1.0 | 262 | 336 | 1.0 | 184 | 246 | 1.0 | 105 | 140 | 1.0 | 251 | 344 | 1.0 | 166 | 212 | 1.0 | 233 | 286 | 1.0 |
| Duration of exposed jobs ^c (years) | | | | | | | | | | | | | | | | | | | | | |
| < 5 | 9 | 8 | 1.5 | 16 | 16 | 1.1 | 32 | 29 | 1.3 | 31 | 46 | 0.7 | 15 | 11 | 1.6 | 37 | 37 | 1.1 | 20 | 27 | 0.8 |
| 5-9 | 9 | 11 | 1.2 | 11 | 10 | 1.5 | 26 | 51 | 0.7 | 49 | 68 | 1.0 | 10 | 14 | 1.0 | 27 | 46 | 0.7 | 15 | 23 | 0.7 |
| ≥ 20 | 8 | 10 | 1.3 | 7 | 18 | 0.6 | 43 | 44 | 1.4 | 98 | 105 | 1.5 | 18 | 13 | 1.8 | 53 | 70 | 1.0 | 22 | 35 | 0.8 |

^a Maximum likelihood estimate of the odds ratio stratified by educational class and other exposures.

^b The unexposed subjects in each of these analyses were those whose jobs never involved exposure to the substance of interest.

^c The specific durations of exposure exclude the subjects whose duration was unknown.

Table 5. Odds ratios for astrocytic tumors among subjects whose jobs might have involved exposure to organic solvents by highest exposure level and total duration of solvent-exposed jobs.

| | Highest exposure | | | | | | | | |
|---|------------------|-----------|-----------------|----------|-----------|-----------------|-------|-----------|-----------------|
| | Low | | | Moderate | | | High | | |
| | Cases | Referents | OR ^a | Cases | Referents | OR ^a | Cases | Referents | OR ^a |
| Unexposed ^b | 105 | 140 | 1.0 | 105 | 140 | 1.0 | 105 | 140 | 1.0 |
| Duration of solvent exposure ^c (years) | | | | | | | | | |
| < 5 | 12 | 16 | 0.6 | 10 | 22 | 0.5 | 9 | 8 | 0.9 |
| 5-19 | 18 | 24 | 0.9 | 22 | 29 | 1.1 | 9 | 15 | 0.6 |
| ≥ 20 | 27 | 32 | 1.4 | 57 | 51 | 1.6 | 14 | 22 | 1.1 |
| Total | 65 | 86 | 1.1 | 92 | 111 | 1.2 | 38 | 49 | 1.0 |

^a Maximum likelihood estimate of the odds ratio stratified by educational class and other exposures.

^b The unexposed subjects in each of these analyses were those whose jobs had never involved exposure to organic solvents.

^c The specific durations of exposure exclude the subjects whose duration was unknown, but these subjects are included in the "Total."

Table 6. Odds ratios for astrocytic tumors among precision metal workers.

| | Tool & die maker (census codes 634, 635) | | | Machinist (census codes 637, 639) | | | Sheet metal worker (census codes 653, 654) | | | Other precision metal workers | | | All precision metal workers (census codes 634-655, 702-709) | | |
|--|--|-----------|-----------------|-----------------------------------|-----------|-----------------|--|-----------|-----------------|-------------------------------|-----------|-----------------|---|-----------|-----------------|
| | Cases | Referents | OR ^a | Cases | Referents | OR ^a | Cases | Referents | OR ^a | Cases | Referents | OR ^a | Cases | Referents | OR ^a |
| | Unexposed ^b | 257 | 347 | 1.0 | 257 | 347 | 1.0 | 257 | 347 | 1.0 | 257 | 347 | 1.0 | 257 | 347 |
| Duration employed in precision metal work ^c (years) | | | | | | | | | | | | | | | |
| < 5 | 2 | 1 | 2.5 | 4 | 5 | 0.9 | 2 | 2 | 1.3 | 6 | 4 | 2.4 | 12 | 11 | 1.4 |
| 5-19 | 5 | 1 | 8.3 | 5 | 8 | 0.8 | 2 | 2 | 1.8 | 7 | 7 | 1.6 | 15 | 14 | 1.5 |
| ≥ 20 | — | — | — | 5 | 4 | 1.8 | — | — | — | 2 | 3 | 0.8 | 14 | 12 | 1.8 |
| Total | 9 | 4 | 3.1 | 15 | 19 | 1.1 | 5 | 5 | 1.4 | 16 | 14 | 1.8 | 43 | 39 | 1.6 |

^a Maximum likelihood estimate of the odds ratio stratified by educational class.

^b The unexposed subjects in each of these analyses were those who never had a job as a precision metal worker.

^c The specific durations exposed exclude the subjects whose duration was unknown, but these subjects are included in the "Total."

40 years (OR 3.9), and died more than 10 years after they first worked in the industry (OR 3.9). Earlier clusters of brain tumors seen in particular refinery populations could represent an excess risk due to the presence of a particular exposure or could represent geo-

graphic variation in disease. Those findings were based on hypothesis-generating methodologies (24, 26) or very small numbers of deaths (21, 23). The only large cohort study which suggested a brain tumor excess among refinery workers had a short follow-up period

(21). Other cohort studies did not find brain tumor excesses, but included white-collar workers (6, 14, 20) or had short follow-up periods (10). As noted, our analytic study also generated little evidence to suggest that excess brain tumor risk is associated with long-term employment in the petroleum refining industry. Thus, in the aggregate, as stronger epidemiologic methodologies have been used to study brain tumor risk among refinery workers, the association has weakened. Intensive studies of refinery populations are unlikely to yield any further insight regarding the etiology of brain tumors if the number of workers exposed to a putative causative agent is small.

Contrary to the results of some earlier studies (1, 18), no excess astrocytic tumor mortality risk was associated in our study with employment in the chemical manufacturing industry. However, in the present study, the numbers of study subjects ever employed in specific types of chemical plants were too small to evaluate subsets of this complex industry.

There was an elevated risk of mortality from astrocytic tumors that was almost twofold among subjects who worked in jobs with probable exposure to cutting fluids for more than 20 years. Precision metal workers also had elevated astrocytic tumor risk. Although not statistically significant, these findings would be consistent with those of previous studies that suggested an elevated brain tumor risk among machinists (4, 5, 9, 22, 28).

Astrocytic tumor mortality risk among men exposed to organic solvents was highest among those exposed for 20 or more years and whose highest exposure was classified as low or moderate. Although there was no excess risk for men who were classified as ever having high solvent exposure, there were relatively few subjects in the heavy use category. These findings could be consistent with numerous other epidemiologic studies that have detected elevated risk of brain tumors among workers exposed to organic solvents (25). Many organic solvents are highly lipid-soluble, pass readily through the blood-brain barrier, are known to be neurotoxic (7), and could be human carcinogens (7, 11).

A number of potential methodologic concerns is raised by a study based on data from death certificates. First is the concern about completeness of case ascertainment. This was not considered a major limitation because the tumors of particular interest were the astrocytic cell types, which are rapidly fatal (2). It has been estimated that in the United States 97 % of the incident cases of all malignant brain tumors would eventually be identified from death certificates (17). Thus it is unlikely that a significant proportion of incident cases of astrocytic tumors was missing from the present series.

A second limitation of this investigation was the use of death certificates to select the reference series. Although the referents were representative of the population of white men who died at the ages selected, they

might not have been representative of the population in general with respect to characteristics that lead to early death. A comparison of two reference series selected for a study in Minnesota indicated that deceased referents were heavier smokers and heavier consumers of alcohol and drugs than the living reference series. However, there were no substantial differences between those two reference series in usual occupation (12, 13).

Finally, the analyses for organic chemical substances should be interpreted with caution because of the crudity of the method used to estimate exposures. The intent of this exposure classification was merely to refine hypotheses regarding specific exposures that may be implicated in excess brain tumor risk. Exposures were assigned to jobs based on job title, industry, and description of duties provided by next-of-kin; therefore, some misclassification is likely. A problem in identifying exposures based on job title is the uncertainty of whether the exposure actually occurred. For some substances, the problem is likely to be minimal. For example, cutting fluid exposure was assigned primarily to jobs that involve precision metal work, and it is highly likely that most of the men who worked in these jobs would have had some contact with cutting fluids. On the other hand, acrylonitrile exposure was assigned to any job where exposure was possible but not necessarily likely (eg, farmers who might have exposure to acrylonitrile, which is often used in pesticides). Therefore, some of our classifications included men who might never have been exposed to the substance. Because coding was done without knowledge of the cause of death of the study subjects, any misclassification is likely to have been random, thus tending to underestimate any true differences between the cases and referents.

In summary, these analyses failed to provide persuasive evidence of a causal association between astrocytic tumor mortality risk and employment in the industries considered to be "high risk." This result may have been due to the small number of study subjects employed in these industries, even though the study areas were chosen to maximize the proportion of the general population employed in the petroleum and chemical industries. If a particular chemical substance present in these industries is responsible for excess brain tumor risk, the number of persons actually exposed may be too small to detect an elevated risk when these industries are studied as a whole, without attention to particular exposures. Alternatively, the previous observations of clusters in particular plants may be due to chance. This study did indicate that some exposures common to these industries were associated with elevated risk of astrocytic tumor mortality, and future investigations could focus on solvents, cutting oils, and other exposures that may be common to the high-risk groups.

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