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Brain tumors and occupational risk factors

A review

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THOMAS TL, WAXWEILER RJ. Brain tumors and occupational risk factors: A review. *Scand J Work Environ Health* 12 (1986) 1—15. Little is known about the etiology of tumors of the brain and central nervous system (CNS); however, epidemiologic studies have indicated recently that excess brain and CNS tumor risk may be associated with employment in certain occupations or industries. Some studies have shown that certain white-collar professional groups (eg, artists, laboratory professionals, veterinarians, embalmers) appear to have an elevated risk of brain tumors, and they raise the issue of a diagnostic sensitivity bias. Some blue-collar occupational groups, including rubber workers, oil refinery workers, chemical plant workers, polyvinyl chloride workers, machinists, and others, have been reported to have an elevated risk of brain tumors. Most of these workers are potentially exposed to multiple chemicals; nevertheless they have some exposures in common, for example, exposure to organic solvents, lubricating oil, acrylonitrile and vinyl chloride, formaldehyde, polycyclic aromatic hydrocarbons, and phenolic compounds.

Key terms: organic solvents, lubricating oils, acrylonitrile, vinyl chloride, formaldehyde, polycyclic aromatic hydrocarbons, phenolic compounds.

The age-adjusted average annual incidence rate for malignancies of the brain and central nervous system (CNS) among white men in the United States (US) during 1973—1977 was 6.7 per 100 000, and the corresponding mortality rate was 4.9 per 100 000 (104). Mortality rates for malignant brain and CNS tumors among all age groups over 55 years have been steadily increasing since the 1940s (95). Mortality and incidence rates for CNS malignancies in the United States are higher among white men than among women and blacks (45, 104). About half of the brain tumors (benign and malignant) diagnosed among white men of all ages are glioblastoma multiforme, but this cell type accounts for a much lower percentage of the brain tumors diagnosed among women and blacks (5). There is a dramatic peak in mortality due to brain and CNS malignancies among white men between 45 and 65 years of age (45); the peak corresponds with that in the incidence rate for glioblastoma multiforme between the same ages (74). These patterns imply that some genetic and/or environmental risk factor(s) may be responsible for the elevated rates among white men compared with women and blacks. The age peak and increasing rates over calendar time suggest an environmental risk factor, possibly occupational.

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One of the difficulties in comparing epidemiologic studies of brain and CNS tumors is disease definition and terminology. The term "CNS tumors" includes tumors of the brain, cranial nerves, and cranial meninges; however, because more than 90 % of CNS tumors are brain tumors (104), we have used the terms brain cancer (malignancies only) and brain tumor to refer to all CNS tumors throughout our review, regardless of the original author's definition or terminology. More confusing is the fact that brain tumors can be coded as malignant [International Classification of Diseases, Eighth Revision (ICDA-8) code 191, 192], benign (ICDA-8 code 225), or unspecified as to malignant or benign (ICDA-8 code 238). Unfortunately, if a physician records just the words "brain tumor" on a death certificate, as is often the case, the unspecified code (ICDA-8 238) will be assigned as the underlying cause of death. Upon later pathological review, many of these cases may be shown to be primary malignant tumors. In addition, there may be some misclassification on the death certificates between primary brain tumors and those that are metastatic from other cancer sites (62). Thus, if brain tumor risk is to be thoroughly evaluated, it is important to report all ICD codes for primary brain tumors (ICD 191, 192, 225, and 238) separately and combined. In most instances investigators have reported mortality or incidence only for tumors of the brain specified as malignant; however, in the accompanying tables, we have indicated which results also include tumors coded as benign or unspecified.

Very little is known about the etiology of brain tumors; however several associations with occupational and other environmental and genetic factors have appeared in the epidemiologic literature (23). Although

Table 1. Brain tumors among white-collar and professional occupations in surveys of mortality by occupation.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Professional & technical, US	1950	SMR	169	1.34*	Guralnick (25)
Professional & technical, Canada	1965—1973	SMR	10	1.95	Howe & Lindsay (33)
Accountants & auditors, US	1950	SMR	27	1.93*	Guralnick (25)
Financial workers, MA	1971—1973	sMOR	13	2.29*	Dubrow & Wegman (17)
Treasurers, financial managers, bank officers, MA	1971—1973	sMOR	5	3.47*	Dubrow & Wegman (17)
Managers, officials, proprietors, manufacturing, US	1950	SMR	43	1.30	Guralnick (25)
Managers, officials, proprietors, WA	1950—1979	PMR	64	1.50*	Milham (48)
Purchasing agents, buyers, sales managers, WA	1950—1979	PMR	12	1.78	Milham (48)
Sales managers (age 65—74 years), UK	1970—1972	PMR	..	2.47	Registrar General (65)
Purchasing agents & buyers, sales managers, CA	1959—1961	PMR	5	2.89	Peterson & Milham (63)
Credit men, WA	1950—1979	PMR	6	2.97*	Milham (48)
Insurance agents, brokers, underwriters, & appraisers, WA	1950—1979	PMR	21	1.58	Milham (48)
Engineers, nec, WA	1950—1979	PMR	26	1.47	Milham (48)
Engineers, nec, CA	1959—1961	PMR	10	2.16*	Peterson & Milham (63)
Mechanical engineers, WA	1950—1979	PMR	8	4.22*	Milham (48)
Aeronautical engineers, CA	1959—1961	PMR	4	2.17	Peterson & Milham (63)
Electrical engineers, CA	1959—1961	PMR	5	1.55	Peterson & Milham (63)
Electrical engineers (age 65—74 years), UK	1970—1972	PMR	..	2.75	Registrar General (65)
Inspectors, nec, WA	1950—1979	PMR	7	2.48	Milham (48)
Inspectors, nec, CA	1959—1961	PMR	10	2.55*	Peterson & Milham (63)
Checkers, examiners, inspectors, MA	1971—1973	sMOR	4	5.57*	Dubrow & Wegman (17)
Public utility supervisors & officials, WA	1950—1979	PMR	10	1.99	Milham (48)
Clergymen, WA	1950—1979	PMR	14	1.99*	Milham (48)
Dentists, CA	1959—1961	PMR	2	1.52	Peterson & Milham (63)
Teachers, US	1950	SMR	21	1.75*	Guralnick (25)
Artists & art teachers, CA	1950—1979	PMR	4	2.98	Peterson & Milham (63)
Teachers, except music & art, CA	1959—1961	PMR	8	2.41*	Peterson & Milham (63)
Teachers, elementary & secondary, MA	1971—1973	sMOR	7	3.71*	Dubrow & Wegman (17)
Professors & instructors, CA	1959—1961	PMR	6	2.92*	Peterson & Milham (63)
School professions, MA	1971—1973	sMOR	10	2.54*	Dubrow & Wegman (17)
Lawyers & judges, CA	1959—1961	PMR	5	1.91	Peterson & Milham (63)
Lawyers & judges, WA	1950—1979	PMR	13	1.88*	Milham (48)
Lawyers & judges, MA	1971—1973	sMOR	7	5.56*	Dubrow & Wegman (17)
Postal clerks, CA	1959—1961	PMR	6	2.76*	Peterson & Milham (63)
Postal clerks, MA	1971—1973	sMOR	5	2.86	Dubrow & Wegman (17)
Officers, enlisted men, armed forces, nec, CA	1959—1961	PMR	27	1.56*	Peterson & Milham (63)
Armed forces (British & foreign), UK	1970—1972	SMR	..	1.83	Registrar General (65)
Armed forces (British & foreign), UK	1961	SMR	..	1.67	Logan (39)

[a] US = United States, MA = Massachusetts, WA = Washington, UK = United Kingdom, and nec = not elsewhere classified.
[b] PMR = proportionate mortality ratio, SMR = standardized mortality ratio, PIR = proportionate incidence ratio, SIR = standardized incidence ratio, SRR = standardized rate ratio, sMOR = standardized mortality odds ratio, and OR = odds ratio.
[c] Ratio = observed:expected ratio or odds ratio.
* Statistically significant (Poisson) at the 0.05 level.

no causal industrial exposures have been identified, brain tumors seem to cluster in certain occupational groups. Historically, the first occupational association with brain tumors was reported among workers in the rubber industry (42). Since 1968, clusters of brain tumors have been seen among workers involved in polyvinyl chloride production, oil refining, petrochemical production, pharmaceutical production, use or production of formaldehyde, and other occupations. This review summarizes the scientific literature on occupational risk factors for brain tumors and examines some of the exposures that may be implicated.

The measures of association shown in the tables are not directly comparable; thus we have used a test of statistical significance to evaluate the relative importance of the results shown. Because the authors of the numerous studies discussed in this review used a variety of statistical tests to judge the significance of their results, we have ignored the original significance tests. Instead, we applied a common test statistic to each result for which the authors supplied an observed number of brain tumor events and an expected number of events or an observed:expected (O:E) ratio. If the O:E ratio was not provided by the original author, we calculated it from the data published. This calculation includes results presented in the form of the proportionate mortality ratio (PMR), the standardized mortality ratio (SMR), the standardized incidence ratio (SIR), the proportionate incidence ratio (PIR), the standardized mortality odds ratio (sMOR), and the standardized rate ratio (SRR). The statistical significance of each of these results was determined from a table of significance factors for the ratio of a Poisson variable to its expectation (6). Since brain cancer

accounts for only 2.5 % of all cancer deaths (45), the underlying Poisson assumption of a rare event is satisfied in this case. Because our test is inappropriate for case-referent analyses, the statistical significance of the odds ratios from the case-referent analyses presented in the tables was determined with the 95 % confidence intervals provided by the authors.

Surveys of mortality by occupation

Information from death certificates, registries, or record linkage systems has been used in many surveys to examine disease risks by occupation. Surveys of mortality by industry were not included in tables 1 and 2 because of a lack of specificity with regard to occupation; however results from some of these surveys are discussed in relationship with specific hypotheses presented later in this review. Because an exhaustive list of occupations reported in these surveys would be too lengthy to show in a single table, we decided to limit the results shown; thus, standardized mortality ratios, standardized incidence ratios, and standardized mortality odds ratios of less than 1.3 are not shown and proportionate mortality ratios of less than 1.5 are not shown. Results from the Washington state mortality data (48) were obtained from a table of statistically significant results for brain cancer.

The data indicated that certain white-collar and professional groups may have an elevated brain cancer risk (table 1). These groups include financial managers and accountants, sales agents, engineers, teachers, lawyers and judges, postal clerks, and persons in the armed forces. These occupational groups presumably have minimal exposure to chemicals and other potentially carcinogenic agents in their jobs. White-collar and professional groups may receive better than average medical and diagnostic services because of their socioeconomic status and, thus, may be more likely than the population in general to have a brain tumor diagnosed (24). Mortality was elevated among California residents in the armed forces (63) and among British members of the armed forces (39, 65), who typically receive regular medical surveillance.

Table 2 shows blue-collar worker groups with elevated brain cancer mortality in occupational surveys. The most interesting are the elevated brain cancer mortality ratios for electricians and power servicemen in four of the surveys (25, 48, 63, 64). Several of the occupations listed in table 2 involve exposure to solvents and organic chemicals, but no prominent patterns of common exposures are evident for particular occupations.

Several of these surveys obtained the information on occupation from death certificates. Because the "usual occupation" listed on the death certificate may be more representative of last occupation, many of the persons classified in white-collar management occupations could have begun their employment in blue-collar jobs. Occupations were not cross-classified by industry; thus it is not possible to evaluate whether elevated risk occurred among white-collar managers in particular industries. Furthermore, relatives of a deceased individual may tend to "upgrade" the deceased's occupation socioeconomically.

Table 2. Brain tumors among blue-collar occupations in surveys of mortality by occupation.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Operatives & kindred workers, MA	1971—1973	sMOR	4	3.26	Dubrow & Wegman (17)
Painters, paperhangers, glaziers, US	1950	SMR	32	1.39	Guralnick (25)
Carpenters (age 20—54 years), MA	1971—1973	sMOR	7	2.74*	Dubrow & Wegman (17)
Brickmasons, stonemasons, tile setters, MA	1971—1973	sMOR	4	3.14	Dubrow & Wegman (17)
Electricians, US	1950	SMR	31	2.21*	Guralnick (25)
Electricians, WA	1950—1979	PMR	43	1.60*	Milham (48)
Electricians, Los Angeles County, CA	1972—1977	PIR	11	1.42	Preston-Martin et al (64)
Linemen & servicemen, telegraph, telephone, power, CA	1959—1961	PMR	5	2.07	Peterson & Milham (63)
Welders, metal, Sweden	1961—1973	SRR	44	1.44*	Englund et al (18)
Boilermakers, CA	1959—1961	PMR	3	2.18	Peterson & Milham (63)
Machinists & job setters, US	1950	SMR	37	1.42	Guralnick (25)
Machinists (age 20—54 years), MA	1971—1973	sMOR	5	3.12*	Dubrow & Wegman (17)
Airplane mechanics & repairmen, WA	1950—1979	PMR	14	2.01*	Milham (48)
Firemen & fire protection workers, WA	1950—1979	PMR	14	1.77	Milham (48)
Crane derrickmen & hoistmen, CA	1959—1961	PMR	3	2.23	Peterson & Milham (63)
Deliverymen & routemen, CA	1959—1961	PMR	6	2.03	Peterson & Milham (63)
Glass & ceramic makers, UK	1970—1972	SMR	..	1.31	Registrar General (65)
Glass workers, Sweden	1961—1973	SRR	10	2.39*	Englund et al (18)
Farmers & farm workers, Canada	1965—1973	SMR	4	1.77	Howe & Lindsay (33)
Railroad clerks, WA	1950—1979	PMR	13	3.48*	Milham (48)

[a] See table 1 (footnote a) for a definition of the abbreviations.
[b] See table 1 (footnote b) for a definition of the abbreviations.
[c] Ratio = observed:expected ratio or odds ratio.
* Statistically significant (Poisson) at the 0.05 level.

Production of synthetic rubber

Table 3 shows results from studies of workers in the production of synthetic rubber. In 1949, an unusual cluster of deaths from CNS tumors was observed among residents of Summit County, Ohio, and a possible link with the rubber industry was suggested (42). Subsequently, a cohort mortality study of workers in a rubber plant in the same county indicated an elevated brain cancer risk among employees in the curing and tire-building department (43). Later studies of the same plant population also implied that men employed in tire assembly and tire building had an elevated brain cancer risk, but brain cancer mortality was less than expected in the entire plant population (51, 52). The elevated risk occurred primarily among men whose attained age was less than 65 years (O:E = 8:1.3), those who had worked less than 15 years (O:E = 7:1.4), and those who started working in the industry after 1925 (O:E = 8:1.8). The findings suggested that the elevated risk may be associated with exposures introduced into the work environment in more recent time periods (51). Exposures in the tire curing, building, and assembly areas included hexamethylenetetramine and drum resins containing coal tar, carbon tetrachloride, and other solvents (51, 52). A slightly elevated brain cancer risk was seen among workers in the rubber industry in Sweden (18), but brain cancer mortality was not elevated among US rubber workers in a 1950 survey by industry (26) nor in other cohort studies of US rubber plants (46, 83) nor among workers in the rubber and cablemaking industries in England (19).

Polyvinyl chloride production

A cohort was assembled from 34 plants to examine the relationship between polyvinyl chloride (PVC) exposure and risk of cancer (11, 85). Among persons who had worked for at least one year in a job involving exposure to vinyl chloride, the total number of brain cancers observed was significantly greater than expected (table 4). The twelve brain cancers observed during the study period included four glioblastoma, two astrocytoma, one ependymoma, and five unspecified.

A proportionate mortality ratio study of deceased workers in two plants using vinyl chloride monomer indicated an increased relative frequency of brain cancer (53). Five deaths were observed, and only 1.2 were expected (table 4). Three of the five brain cancers were

Table 3. Brain tumors among workers in the production of synthetic rubber.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Tire building & curing, Ohio	1940—1964	SRR	4	5.63*	Mancuso et al (43)
One rubber plant, US	1940—1974	SMR	20	0.80	Monson & Nakano (52)
Tire building	1940—1974	SMR	7	1.90	Monson & Nakano (52)
Tire assembly (≥ 5 years)	1940—1976	SRR	7	4.1*	Monson & Fine (51)
Rubber industry, Sweden	1961—1973	SRR	30	1.23	Englund et al (18)
Rubber products industry, US	1950	SMR	13	..	Guralnick (26)
Four US rubber plants — Men	1940—1973	SMR	14	0.78	McMichael et al (46)
Tire building, US	1951—1971	OR	5	1.10	Symons et al (83)
Tire assembly, US	1951—1971	OR	1	0.43	Symons et al (83)
Rubber & cablemaking industry, UK	1968—1974	SMR	20	0.84	Fox & Collier (19)
Tire sector	1968—1974	SMR	10	1.08	Fox & Collier (19)

[a] See table 1 (footnote a) for a definition of the abbreviations.
[b] See table 1 (footnote b) for a definition of the abbreviations.
[c] Ratio = observed:expected ratio or odds ratio.
* Statistically significant (Poisson) at the 0.05 level.

Table 4. Brain tumors among workers in the production of polyvinyl chloride (PVC).

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
PVC workers exposed ≥ 1 years, US	1930—1972	SMR	12	2.03*	Cooper (11)
PVC workers ever exposed, US	1947—1973	PMR	5	4.17*	Monson et al (53)
PVC workers exposed ≥ 5 years, > 15 years latency, US	1942—1973	SMR	3	4.98*	Waxweiler et al (97)
Vinyl chloride monomer & PVC production workers, Sweden	1940—1974	SMR	2	6.12	Byren et al (9)
PVC workers, Germany	< 1959—1974	SMR	2	1.62	Weber et al (98)
PVC workers ever exposed, UK	1940—1974	SMR	2	0.55	Fox & Collier (20)

[a] US = United States, Germany = Federal Republic of Germany, UK = United Kingdom.
[b] See table 1 (footnote b) for a definition of the abbreviations.
[c] Ratio = observed:expected ratio or odds ratio.
* Statistically significant (Poisson) at the 0.05 level.

glioblastoma multiforme, and the cell types of the other two were not specified.

Elevated brain cancer risk associated with polyvinyl chloride production was observed in a cohort study which combined data from four plants (table 4) (97). One major plant was common to this study and those done by Tabershaw (85), Cooper (11), and Monson (53). Among workers with at least five years' exposure to polyvinyl chloride and surviving 15 years since first exposure, three brain cancers occurred and less than one was expected. Four additional brain tumors occurred among employees who had less than five years' exposure to vinyl chloride. Three persons who worked at the plants under study but never in the vinyl chloride-exposed areas also died from brain tumors. No expected numbers were shown for these categories of workers. Nine of the ten brain tumors were histologically confirmed as glioblastoma multiforme. Age at death for these decedents ranged between 33 and 65 years. Other exposures that workers might have encountered included acrylates, acrylonitrile, and chlorinated solvents (96).

Studies of polyvinyl chloride workers in Germany and Sweden suggested an excess brain cancer risk (table 4), but the observed numbers of brain cancer deaths were very small (9, 98). Analyses of mortality among 7 000 men potentially exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain indicated no excess brain cancer risk (20).

Petroleum refining and petrochemical production

The first report of elevated brain tumor risk among oil refinery workers appeared in 1979 (table 5). In a cohort study of 1 205 men employed in a Canadian oil refinery for more than five years, three deaths from brain cancer were observed and only 0.77 was expected (87). This excess was confined to workers for whom less than 20 years had elapsed since first employment (O:E = 3:0.46). The work histories of the three brain cancer cases were vague with regard to occupational exposures. Two died at 41 years of age and one at age 43.

A proportionate mortality ratio study of deceased active and retired members of the Oil, Chemical, and Atomic Workers International Union (OCAW) in Texas indicated an elevated frequency of deaths from brain cancer among white male hourly workers employed in petroleum refining and petrochemical plants (90, 92). The increased relative frequency of brain tumors occurred primarily among active employees in

Table 5. Brain tumors among workers in petroleum refineries and petrochemical production.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Refinery workers (≥ 5 years), Canada	1928—1976	SMR	3	3.90	Theriault & Goulet (87)
All OCAW members in refineries A, B, C, TX	1943—1978	PMR	33[d]	2.10*	Thomas et al (92)
Active OCAW members in refineries A, B, C	1943—1978	PMR	25[d]	2.29*	Thomas et al (92)
OCAW members — refinery A	1943—1978	PMR	16[d]	2.14*	Thomas et al (92)
OCAW members — refinery B	1943—1978	PMR	10[d]	1.90	Thomas et al (92)
OCAW members — refinery C	1943—1978	PMR	7[d]	2.35	Thomas et al (92)
OCAW members in refineries A, B, C					
Lube oil refining	1943—1978	OR	5	1.6	Thomas et al (91)
Pumping of products	1943—1978	OR	7	2.8	Thomas et al (91)
Texaco (A) — salaried & hourly	1947—1977	SMR	31	1.08	Divine et al (15)
Texaco (A) — research & quality control labs	1947—1977	OR	8	3.9**	Divine et al (15)
Texaco (A) — lube oil refining	1947—1977	OR	3	4.1**	Divine et al (15)
Gulf (B) — all hourly workers	1935—1978	SMR	20[d]	0.90	Wen et al (99)
Gulf (B) — hourly workers (≥ 20 years)	1935—1978	SMR	15	1.40	Wen et al (99)
Mobil (C) — salaried & hourly	1945—1979	SMR	9	1.09	Morgan & Wong (54)
Ninteen refineries, US	1977—1979	SMR	8	1.63	Schottenfeld et al (75)
Ninteen refineries, US	1977—1979	SIR	9	1.29	Schottenfeld et al (75)
Petroleum & coal products, US	1950	SMR	13	..	Guralnick (26)
Eight oil refineries, UK	1950—1975	SMR	36	0.80	Rushton & Alderson (70)
Oil distribution centers, UK	1950—1975	SMR	39	1.07	Rushton & Anderson (71)
Exxon — operator, mechanic, laborer	1970—1977	SMR	4	1.11	Hanis et al (28)
Union Carbide (NIOSH), TX	1941—1979	SMR	22[d]	2.06*	Waxweiler et al (95)
Union Carbide (company) — > 6 months	1941—1977	SMR	10	2.00	Austin & Schnatter (3)
Petrochemical operators, LA and TX	1970—1980	PMR	12[d]	3.40*	Nicholson et al (56)
Dow Chemical, TX	1949—1977	Sample-based SMR	25[d]	1.26	Reeve et al (66)

[a] OCAW = Oil, Chemical, and Atomic Workers International Union; TX = Texas, US = United States; UK = United Kingdom, NIOSH = National Institute for Occupational Safety and Health; LA = Louisana.
[b] See table 1 (footnote b) for a definition of the abbreviations.
[c] Ratio = observed:expected ratio or odds ratio.
[d] Observed includes benign and unspecified brain tumors.
* Statistically significant (Poisson) at the 0.05 level.
** Statistically significant at the 0.05 level using the author's significance test.

three oil refineries (A, B, and C) in the Beaumont-Port Arthur area of the Texas gulf coast (table 5). A nested case-referent study comparing work histories of the brain tumor cases with those of persons who died from other causes indicated an elevated brain tumor risk among OCAW members whose jobs involved the intra-plant pumping and transporting of bulk liquids (crude oil and products) and the manufacture of lubricating oil, but the odds ratios were not statistically significant (91).

Industry-sponsored studies of refineries A, B, and C indicated slightly different results (table 5); however, the study groups differed substantially in terms of hourly/salaried status, average duration employed, and induction-latency period. A cohort mortality study of white male Texaco (refinery A in references 90, 91, 92) salaried (white-collar) and hourly (blue-collar) employees combined indicated no excess mortality from brain cancer (15). A nested case-referent analysis indicated significantly elevated odds ratios for brain cancer among persons whose longest job was in research and quality control laboratories or in lubricating oil refining (15). All male hourly employees of the Gulf refinery (refinery B in references 90, 91, 92) did not have a significantly elevated standardized mortality ratio for brain cancer; however, mortality was slightly elevated among those who had worked at the plant for more than 20 years (99). The number of brain cancer deaths observed among white male salaried and hourly employees of the Mobil refinery (refinery C in references 90, 91, 92) was almost the same as that expected (54). Among white men employed 10 or more years at the Mobil refinery there were slightly elevated standardized mortality ratios for brain cancer (10—29 years, SMR 142.4; $\geq$ 30 years, SMR 133.5).

In a mortality study of oil refinery workers employed by 19 US companies (table 5), eight deaths from brain cancer were observed, and 4.9 were expected (SMR 1.63) (75). The investigators suggested that there may have been underreporting of deaths because of the short study period (two years) and the lag time between the date of death and receipt of a death certificate. Cancer incidence among actively employed refinery workers during the study period was compared with that for the United States from cancer registry incidence data. Nine incident cases of brain cancer were reported, and about seven were expected. No analyses by duration of employment or occupation were shown.

Brain cancer mortality was not excessive among 35 000 employees of eight British oil refineries between January 1950 and December 1975 (table 5) (70); however, about 20 % of the study subjects had scientific, technical, administrative, clerical, or engineering jobs, most of which are presumably low-exposure occupations. The same difficulty occurred in a cohort of workers at oil distribution centers in England (71), in which supervisors, managers, administrators, and clerical workers were included in the analyses. Analyses were not shown separately for blue-collar (hourly) employees. In one study of refinery workers, investigators found no association between brain cancer risk and oil refinery employment (28), and two other groups of investigators did not report the observed and expected values for brain cancer (29, 84). The follow-up period for several studies (28, 29, 75, 84) was very short (less than 10 years), and risks of fatal disease with long latency periods may have been underestimated.

A cluster of primary brain cancer deaths among workers at a Union Carbide petrochemical plant in Texas City, Texas, was reported in 1980 (2). All of the decedents were less than 66 years of age at death, and the best medical information available indicated that 15 of 18 tumors were glioblastoma multiforme. A cohort mortality study of workers at this plant showed a significantly elevated standardized mortality ratio for brain tumors among white male hourly workers (table 5) (95). A similar analysis of the same data by the company also indicated a significantly elevated brain cancer risk among workers who ever held hourly positions (3), but nested case-referent analyses indicated no significantly elevated odds ratios associated with exposure to any specific chemicals (4, 35).

Operating engineers employed in the petrochemical industry in Texas and Louisiana had an elevated frequency of brain tumors (observed 18, PMR 1.73) (56). This excess was primarily due to a significantly elevated proportionate mortality ratio for brain tumors among persons employed as operators in oil refineries and petrochemical plants (table 5).

A sample-based cohort mortality study of workers at a Dow Chemical petrochemical plant in Freeport, Texas, suggested a slightly increased risk from brain tumors (table 5) (66). Clinical or pathological information was obtained for 19 of 25 brain tumors. Based on the best medical information available, 12 were glioblastoma multiforme, and two others were gliomas. A nested case-referent study failed to identify a significantly elevated risk associated with employment in any particular department or with exposure to any specific chemical or other agent (8).

Other chemical production

Studies of chemical plant workers exposed to formaldehyde showed inconsistent results regarding brain tumor risk. A cohort mortality study of 2 026 workers at a large formaldehyde-producing plant suggested that workers hired before 1961 had an elevated brain cancer risk (table 6) (103). Two of the three persons with brain cancer died after a latency period of 10 years. A proportionate mortality ratio study of workers at another plant involved in the production of formaldehyde and its use in the production of resins did not show an elevated frequency of brain cancer (44); however only 136 decedents had been exposed to formaldehyde. Both of these studies included small numbers of exposed workers. No data for observed and ex-

pected numbers of brain cancer deaths were presented in a report of the mortality experience of 7 680 workers exposed to formaldehyde in the British chemical industry (1).

An elevated relative frequency of brain cancer was seen among plant employees but not among sales representatives of a large pharmaceutical firm (89). Brain cancer mortality was elevated among white male production workers (O:E = 8:1.6) and administrative and clerical workers (O:E = 4:1.0) (table 6). Production workers in this industry are exposed to multiple chemical and biological agents.

Acrylonitrile has been reported to cause brain tumors in animals (41); however only one epidemiologic study of acrylonitrile-exposed workers has shown an excess of brain cancer (table 6). Two brain cancer deaths were observed among acrylonitrile polymerization workers in the United Kingdom, and only 0.7 was expected (100). In other studies, brain tumor risk was not elevated (57) or not shown (14, 88).

Nuclear industry

A study of workers at a nuclear fuels fabrication plant indicated elevated brain cancer mortality and incidence among male plant employees (table 7) (27). It was assumed that all employees had exposure to low levels of gamma radiation; however other exposures in the plant were similar to those in metal working and fabricating plants and included metal fumes, metal dusts, and oil mists. Seven of the eight incident brain tumors were gliomas, and one was not specified. All except one of the men with a brain tumor were between the ages of 40 and 56 years at death.

White men employed at the Rocky Flats nuclear weapons fabrication facility for at least two years between 1952 and 1979 (102) had a slight excess mortality from malignant brain tumors (table 7), and there was a significant excess of benign and unspecified tumors of the brain (O:E = 6: $\leq$ 1.48). Exposures in the work environment included plutonium, uranium, beryllium, other metal dusts, oil mists, and other exposures typical of machining operations. Increasing mortality trends by latency were seen for brain tumors; however most of the tumors occurred among persons employed less than 15 years. A hospital record review of 16 cases in persons who had ever worked at the plant indicated that 14 were gliomas. Age at death ranged from 31 to 77 years, with a median age of 50.5. A nested case-referent study failed to identify any particular jobs or exposures associated with unusually high brain tumor risk (67).

A cohort mortality study of white men employed at a Union Carbide nuclear weapons facility showed an excess of brain cancer deaths among workers in departments that did not have exposure to mercury (table 7) (12). The operations in these departments included

Table 6. Brain tumors among workers in other chemical plants.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Formaldehyde producers, US (hired < 1960)	1940—1977	SMR	3	2.13	Wong (103)
Pharmaceutical production, US	1954—1976	PMR	8	5.00*	Thomas & Decoufle (89)
Pharmaceutical office workers, US	1954—1976	PMR	4	4.00*	Thomas & Decoufle (89)
Acrylonitrile polymerization, UK	1950—1978	SMR	2	2.90	Werner & Carter (100)
Acrylonitrile polymerization, US	1950—1976	SIR	1	..	O'Berg (57)
Chemicals & allied products, US	1950	SMR	22	1.00	Guralnick (26)
Chemical workers, Italy	1979—1980	OR	4	1.9	Musicco et al (55)

[a] US = United States, UK = United Kingdom.
[b] See table 1 (footnote b) for a definition of the abbreviations.
[c] Ratio = observed:expected ratio or odds ratio.
* Statistically significant (Poisson) at the 0.05 level.

Table 7. Brain tumors among workers in the nuclear fuels and weapons fabrication industry.

Occupation or type of work	Study period	Measure of association[a]	Observed brain tumor events	Ratio[b]	Reference
Nuclear fuels fabrication	1956—1978	SMR	4	2.40	Hadjimichael et al (27)
Rocky flats — employed ≥ 2 years					
Malignant brain tumors	1951—1977	SMR	6	1.49	Wilkinson et al (102)
Benign & unspecified	1951—1977	SMR	6	4.05*	Wilkinson et al (102)
Union Carbide — nonmercury	1953—1978	SMR	13	2.30*	Cragle et al (12)
Hanford plant employees	1955—1974	SMR	28	0.99	Gilbert & Marks (22)

[a] SMR = standardized mortality ratio.
[b] Ratio = observed:expected ratio or odds ratio.
* Statistically significant (Poisson) at the 0.05 level.