VISTA

Interoffice Communication

To: T. Grumbles and Dr. Hamm

From: D. Penney

Date: November 2, 1993

Subject: **Brain tumors and occupational risk factors**

Dr. Mundt has provided what he considers the best review he has found on the epidemiology of brain cancer in general. I think it would be useful for you to look at this review this paper prior to our meeting on November 11. A general conclusion that can be drawn from this review is that not very much is known about the causes of brain cancer. A summary of some of the key points of this review is provided below.

- The brain and other CNS cancer incidence rate amongst white males in the U.S. is 6.7 per 100,000. The mortality rate is 4.9 per 100,000. These figures are based on 1973-1977 data.

- A high percentage of brain tumors reported on death certificates are gliomas, particularly glioblastoma multiforme. Other types of brain tumors reported include astrocytomas and ependymomas. Many death certificates list unspecified brain tumor as the cause of death.

- Mortality rates from brain cancers amongst individual over 55 years of age have been steadily increasing since the 1940s.

- Diagnostic bias does not seem to explain all of this increase. This suggests that some genetic and/or environmental risk factor(s) may be involved.

- Brain tumor clusters have been observed in certain occupational groups, including polyvinyl chloride production, oil refining, petrochemical production, pharmaceutical production, use or production of formaldehyde.

- Most epidiemilogical studies of brain tumors do not specify the cell type. It is possible that risk factors vary by cell type.

- This article reports that gliomas have been induced in animals by inhalation of vinyl chloride.

REVIEWS

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Brain tumors and occupational risk factors

A review

by Terry L Thomas, MS,[1] Richard J Waxweiler, PhD[2]

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	2.07*	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	2.65*	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	8	2.76*	Peterson & Milham (63)
Postal clerks, MA	1971—1973	sMOR	6	2.86	Dubrow & Wegman (17)
Officers, enlisted men, armed forces, nec, CA	1959—1961	PMR	27	1.58*	Peterson & Milham (63)
Armed forces (British & foreign), UK	1970—1972	SMR	..	1.83	Registrar General (65)
Armed forces (British & foreign), UK	1961	SMR	..	1.57	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)
Fireman & 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)
Delivarymen & 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—1978	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—1976	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	6	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)
Nineteen refineries, US	1977—1979	SMR	8	1.63	Schottenfeld et al (75)
Nineteen 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 (68)

[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 intraplant 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; ≥ 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: ≤ 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—1976	SMR	2	2.90	Werner & Carter (100)
Acrylonitrile polymerization, US	1950—1976	SIR	1	..	O'Berg (57)
Chemicals & allied products, US	1960	SMR	22	1.00	Gurainick (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.

separation of a uranium isotope through an electromagnetic process and other engineering and manufacturing processes in the fabrication of nuclear weapons.

Workers employed in the manufacture, chemical separation, and purification of plutonium at the Hanford plant in Washington state did not have an elevated brain cancer risk (22) overall (table 7) or in any cumulative radiation dose category. Data for men in metalworking and machining occupations were not shown separately.

None of the studies at nuclear weapons fabrication facilities showed an association of elevated brain cancer risk in relation to any particular radiation level. One factor common to all of the facilities was the presence of machining operations in which there was an opportunity for exposure to metal dusts and fumes and lubricating oil mists. Beryllium was machined at one of the facilities (102).

Other industrial workers

Numerous chemicals, some of which contain formaldehyde, are used in photographic processing operations, and high levels of formaldehyde have been measured in print laboratories (21). After preliminary studies indicated a possible brain cancer excess among employees of an Eastman Kodak plant, a nested case-referent study of brain cancer by exposure category indicated an elevated risk among photographic processing workers exposed to color developers (24). Risks were slightly elevated among workers exposed to solvents, animal tissue, and film developers (table 8). None of the results were statistically significant. No deaths from brain cancer were observed among 208 deceased white male press photographers who often developed their own film (49).

A study of 47 glioma cases diagnosed in 1979 and 1980 in Milan, Italy, indicated a twofold excess risk of glioma among textile workers (55). The odds ratio of 2.1 was not statistically significant (table 8). About 20 % of the cases had worked in the textile industry, where formaldehyde and other chemicals were used in processing fabrics. In a 1950 survey, US men employed in yarn, thread, and fabric mills had an elevated standardized mortality ratio for brain cancer (26).

White male members of the Pattern Makers League of North America who died between 1972 and 1978 had an increased relative frequency of brain tumor deaths (68). The proportionate mortality ratios were elevated among pattern makers who worked predominantly with wood and among those who worked predominantly with metal (table 8). A cohort analysis of cancer morbidity among automobile pattern makers who worked with wood found no significant excess of brain cancer (79).

Machinists employed at an automobile manufacturing plant for five years or more in jobs with exposure to cutting oil mists did not have a significantly elevated risk of death due to brain cancer (O:E = 5:3.3) (13). Among men who entered the study group after 1948,

Table 8. Brain tumors among other industrial workers.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Kodak workers (age 55—59 years), NY	1964—1975	SIR	14	2.81*	Greenwald et al (24)
Kodak workers — solvents	1956—1975	OR	32	1.40	Greenwald et al (24)
Kodak workers — color developers	1956—1975	OR	6	2.16	Greenwald et al (24)
Kodak workers — animal tissue	1956—1975	OR	13	1.32	Greenwald et al (24)
Kodak workers — black & white developers	1956—1975	OR	7	1.31	Greenwald et al (24)
Textile workers, Italy	1979—1980	OR	10	2.1	Musicco et al (55)
Yarn, thread, fabric mills, US	1950	SMR	32	1.45	Gurainick et al (26)
Pattern makers — wood, US	1972—1978	PMR	7[d]	1.75	Robinson et al (68)
Pattern makers — metal, US	1972—1978	PMR	5[d]	2.94	Robinson et al (68)
Automobile wood pattern makers, MI	1970—1978	SIR	1	1.63	Swanson & Belle (79)
Automobile machinists (1948+), US	1937—1967	SMR	3	3.75	Decoufle (13)
Aviation electronics workers, US	1950—1980	PMR	9	3.01*	Sweeney & Ahrenholz (80)
Aluminum reduction workers, US	1948—1976	SMR	8[d]	2.25	Milham (47)
Bus mechanics, UK	1967—1975	SMR	4	3.20	Rushton et al (72)
Railroad carmen, Canada	1965—1977	SMR	7	2.78*	Howe et al (32)
Railroad — welding fumes, Canada	1965—1977	SMR	10	3.18*	Howe et al (32)
Railroad workers, US	1967—1979	SMR	5	1.32	Schenker et al (73)
Asbestos insulation workers, US	1967—1976	SMR	21[d]	1.59	Seidman et al (76)
Electricians, linemen, servicemen, engineers, MD					
Glial tumors	1969—1982	OR	27	2.15*	Lin et al (38)
Unspecified brain	1969—1982	OR	15[d]	1.54	Lin et al (38)

[a] NY = New York, US = United States, MI = Michigan, UK = United Kingdom, MD = Maryland.
[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.

however, there was a notable excess of brain cancer deaths (table 8).

A proportionate mortality ratio analysis indicated that white male hourly and salaried employees of an aviation electronics plant had an elevated frequency of deaths from brain cancer (table 8) (80). Six of the nine brain cancers were glioblastoma multiforme, one was neurilemmoma, and two were unspecified. Potential workplace exposures included trichlorethylene, beryllium, and a halogenated aromatic hydrocarbon balancing fluid. All five hourly employees with brain cancer had worked as machinists.

A mortality study of aluminum reduction plant workers (table 8) indicated an elevated risk of benign brain tumors (observed 5, SMR 9.09) but not malignant tumors (observed 3, SMR 0.99) (47). All five persons with benign brain tumors had worked in "exposed" jobs in the carbon plant, rodding, potlining, potrooms, or quality control. Exposures included fluorides, particulate alumina, polycyclic aromatic hydrocarbons, and sulfur dioxide. An excess of benign neoplasms was found in another study of workers employed in 14 aluminum reduction plants (69); however no details were given regarding the primary site of these tumors.

Maintenance workers exposed to hydrocarbons in the form of diesel exhaust in London bus garages had a slightly elevated standardized mortality ratio for brain cancer (SMR 1.21) (72). This excess was primarily due to the elevated standardized mortality ratio for brain cancer among bus mechanics, who were also exposed to oils, greases, and solvents (table 8).

A study of Canadian railroad workers exposed to diesel fumes and coal dust showed an elevated brain cancer risk among carmen (table 8) (32). Railroad workers exposed to welding fumes had a threefold excess of brain cancer mortality. A survey of mortality by occupation in Sweden also showed excess brain cancer among welders (table 2) (18). US railroad workers had a slightly elevated standardized mortality ratio for brain cancer (table 8), but no data were shown for those with high levels of exposure to diesel or welding fumes (73).

A slightly elevated brain tumor risk was reported in a cohort study of asbestos insulation workers (table 8) (76). These workers were employed primarily in the building construction trades, but they also could have worked in shipyards, chemical plants, and oil refineries, where there are exposures to numerous substances.

A case-referent study using the occupation listed on death certificates suggested an elevated risk of glioma and unspecified brain tumors among a category of workers which included electric and telephone company servicemen, linemen, foremen, and engineers; railroad and telecommunication engineers; electricians; and electric and electronic engineers (table 8) (38). These findings are consistent with those seen in four surveys of mortality by occupation (table 2) that found elevated brain cancer mortality among electricians and power servicemen. Electrical engineers (table 1) also had elevated brain cancer mortality. These occupations have potential exposure to electromagnetic fields, polychlorinated biphenyls, solder fluxes, and solvents.

Professional and other nonindustrial groups

The National Institute for Occupational Safety and Health (NIOSH) evaluated the mortality experience of white men employed as motor vehicle examiners in New Jersey for at least six months between 1944 and 1973 (77). The examiners were exposed daily to motor vehicle exhaust consisting of aldehydes, carbon dioxide, carbon monoxide, hydrocarbons, lead compounds, nitrogen, oxides of nitrogen, oxygen, and sulfur dioxide. Four deaths from brain cancer were observed, and only 1.7 were expected (table 9). All four brain cancers were malignant gliomas.

A proportionate mortality ratio study of professional artists indicated a significant threefold excess frequency of brain cancer deaths among white male artists (table 9) (50). The excess deaths were not linked to any particular art specialty. Artists may be exposed to numerous potentially carcinogenic substances including components of pigments, dyes, solvents, metal fumes, and dust.

Professional chemists are exposed to numerous chemical agents in the laboratory setting. An elevated standardized mortality ratio for brain cancer was seen among 526 chemists who had been educated at one school in Sweden (58) between 1930 and 1949. No brain cancer deaths occurred among 331 men educated at a second Swedish school (58). Further follow-up of the first cohort indicated a significantly elevated mortality from brain cancer (table 9) (59). Other studies of chemists have not reported elevated brain cancer mortality (31, 37).

Members of the Royal College of Pathologists in 1973 were followed for vital status in 1981 (30). Among 2 300 men, six deaths from brain cancer occurred and less than two were expected (table 9). Hematology was a common subspecialty among the decedents with brain cancer. Pathologists are exposed to formaldehyde and other laboratory chemicals. Anatomists, who are exposed to similar chemicals, had a significantly elevated brain cancer risk (78) compared with the US general population (table 9). When another professional group was used for a comparison, the standardized mortality ratio was 6.00. Risk appeared to increase by duration of employment, but was also elevated among those employed less than 20 years. Risk was elevated regardless of presumed level of exposure to formaldehyde. Four of the 10 brain cancers were listed as "astrocytoma" on the death certificate, while the remaining six were listed as "glioblastoma."

Proportionate mortality ratio analyses of deaths among embalmers and funeral directors in New York

Table 9. Brain tumors among professional and other nonindustrial workers.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Moto vehicle examiners, NJ	1944—1973	SMR	4	2.35	Stern et al (77)
Professional artists, US	1940—1969	PMR	8	2.90*	Miller et al (50)
Chemists — one school, Swedan	1930—1977	SMR	5	4.17*	Olin & Ahlbom (59)
DuPont chemists, US	1964—1977	SIR	2	0.67	Hoar & Pell (31)
Pathologists, UK	1974—1981	SMR	6	> 3.00*	Harrington & Oakes (30)
Anatomists, US	1924—1979	SMR	10	2.71*	Stroup et al (78)
Embalmers, NY	1925—1980	PMR	6	2.34	Walrath & Fraumeni (93)
Embalmers, CA	1925—1980	PMR	9	1.94	Walrath & Fraumeni (94)
Embalmers, Ontario	1950—1977	SMR	3	1.15	Levine et al (36)
Female cosmetologists, CT	1935—1978	SIR	16	1.68	Tola et al (86)
Registered female nurses, WI	1963—1977	PMR	21	1.61	Katz (34)
Veterinarians, US	1947—1977	PMR	28	1.63*	Blair & Hayes (7)
Farmers after 1960, Italy	1979—1980	OR	13	3.6*	Musicco et al (55)
Agricultural industry, Canada	1965—1973	SMR	4	2.68	Howe & Lindsay (33)
Agricultural workers, Sweden	1961—1973	SMR	744	1.08*	Wiklund (101)

[a] NJ = New Jersey, US = United States, UK = United Kingdom, NY = New York, CA = California, CT = Connecticut, WI = Wisconsin.
[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.

(93) and California (94) indicated elevated frequencies of brain cancer deaths (table 9). Among white men in New York licensed only as embalmers, there was a 2.5-fold excess (93). A cohort mortality study of Ontario embalmers did not show an excess brain cancer risk, but the study group was small, and no data were shown by latency or duration of exposure (36). Embalming fluids consist primarily of formaldehyde, but also contain phenol and methanol.

Professional cosmetologists are occupationally exposed to numerous chemical substances, including formaldehyde solutions, hair dyes, permanent wave solutions, and other cosmetic preparations. Female cosmetologists in Connecticut had an elevated incidence of brain cancer (table 9) (86). This excess was more prominent among those who began hairdressing school between 1925 and 1934 (observed 6, SIR 2.02). Ten of the 16 cases observed were histologically confirmed glioblastoma multiforme.

A significantly elevated frequency of nervous system cancers was seen among registered nurses in Wisconsin in a comparison with other gainfully employed women (table 9) (34). The observed number of deaths was also greater than the number expected on the basis of mortality among other female professional workers (PMR 1.47).

An analysis of mortality among veterinarians indicated an excess frequency of deaths from brain cancer (table 9) (7). The increased relative frequency was not confined to any particular veterinary specialty group.

Four studies have shown an elevated brain cancer risk among farmers (table 9). Odds ratios for gliomas were statistically significant among Italian farmers who had been farming for more than 10 years and among those who had been engaged in farming since 1960, when the use of phosphoric acid and organochlorine compounds became very common as pesticides in Italy (55). A study of primary CNS neoplasms in Minnesota indicated a slightly higher than expected proportion of farm residents among the brain tumor cases (10). The authors speculated that there may be an association with toxoplasmosis gondii infection. Elevated brain cancer risk was also found in a study of Swedish agricultural workers (101) and among agricultural workers in Canada (33).

Discussion

There were several limitations in the presented epidemiologic studies. First, there is a paucity of case-referent studies of brain tumors; thus most of the information was obtained from mortality studies that lacked sufficient statistical power to evaluate specific occupational risk factors adequately for brain tumors. The observed and expected numbers of brain tumor cases in most of the studies were very small. Exposure information was ascertained from work histories in some of the studies and from interview data in some, but, in others, no specific information on workplace exposures was available. In the nested case-referent studies the numbers were very small, and there were difficulties in relating exposures to specific jobs. In most instances workers had multiple exposures, and risks due to any single exposure could not be adequately evaluated.

Brain tumor diagnosis was ascertained from death certificates in most of the studies; therefore the accuracy of the diagnoses may be questionable. The diagnosis "brain tumor" listed on a death certificate would be nosologically coded as a primary tumor of the brain, unspecified as to whether malignant or benign. Many

of these tumors may actually have been primary malignancies of the brain. Alternatively, since the brain is a common site for metastases of other primary cancers, some death certificate diagnoses may not reflect the actual primary site. A study of deceased persons in the Third National Cancer Survey areas indicated that about 97 % of deaths from malignant brain tumors would be ascertained from death certificates (62), whereas only 89 % of all primary brain cancer diagnoses on death certificates were confirmed by hospital records. This finding indicates that about 10 % of the brain cancer cases ascertained from death certificates may be misdiagnosed. The issue of misdiagnosis is not considered a major problem, particularly if the general population is used to calculate expected numbers of death in studies that ascertain cause of death from death certificates.

In 1981 Greenwald et al (24) concluded that an excess of brain tumors noted among Kodak employees may have resulted from a "diagnostic sensitivity bias." This conclusion was drawn because none of the results of the nested case-referent study were statistically significant and because Kodak employees had brain tumor diagnoses that were histologically confirmed more often than did other brain tumor patients in New York. This explanation might appear plausible in light of the excess risk noted in several professional and white-collar groups; however, all of the workers reported to have elevated brain tumor risk in this review were probably not enrolled in comprehensive medical surveillance programs. Furthermore excess brain tumors were seen only among certain subgroups of some plant populations (eg, workers in the tire building sector of rubber production, refinery workers in lubricating oil manufacture). In addition other groups with medical surveillance programs, for example, Du Pont employees, do not show an elevated brain tumor risk (61).

Despite limitations in study methodology, some similarities are seen between the findings of these studies with respect to age and cell type diagnoses. Ages at death for most of the brain tumor cases ranged between 40 and 65 years. It is not clear whether this pattern reflects the age distribution of the populations studied or a biological phenomenon related to the origin of brain tumors. Age-specific mortality rates for US white males indicate a peak between the ages of 45 and 65 years (45).

Very few studies included diagnostic information from sources other than death certificates. Since death certificates do not often indicate the cell type of these tumors, most studies grouped all brain tumors without distinction by cell type. It is possible that risk factors vary by cell type. In the studies that had diagnostic information from medical records, a high percentage of the diagnoses were gliomas, particularly glioblastoma multiforme; however, no expected numbers could be calculated for this type.

Table 10 shows selected categories of exposures common to the work environments of the occupational groups that appear to have an elevated brain tumor risk. This list is by no means all-inclusive, and one must keep in mind that most of the occupational groups listed are exposed to multiple agents. Numerous groups with elevated brain tumor risk are likely to be exposed

Table 10. Common occupational exposures among groups with elevated brain tumor risk.

Occupational group potentially exposed	Exposure					
	Organic solvents	Lubricating oils	Acrylonitrile or vinyl chloride	Formaldehyde	Polycyclic aromatic hydrocarbons	Phenols and phenolic compounds
Acrylonitrile polymerization workers	×		×			
Airplane mechanics and repairmen	×	×			×	
Aluminum reduction plant workers	×				×	
Anatomists				×		×
Artists	×					
Bus mechanics	×	×			×	
Chemists	×					×
Cosmetologists				×		×
Electricians	×					
Embalmers				×		×
Farmers and agricultural workers	×	×				×
Formaldehyde production workers				×		
Machinists	×	×			×	
Motor vehicle examiners					×	
Nuclear fuels & weapons fabrication	×	×			×	
Nurses						×
Oil refinery workers	×	×			×	×
Pathologists				×		×
Pattern makers — metal	×	×				
Petrochemical plant workers	×					×
Pharmaceutical workers	×			×		×
Photographic process workers	×			×		×
Polyvinyl chloride production workers	×		×			
Rubber workers	×		×		×	×
Textile workers	×			×		×
Veterinarians				×		×

to organic solvents. This broad category of compounds includes aliphatic hydrocarbons and aliphatic halognated hydrocarbons like methylene chloride, carbon tetrachloride, tetrachloroethylene, and others. It also includes aromatic hydrocarbon solvents like benzene and toluene. One of the common acute effects of exposure to many of these compounds is CNS depression (16); however solvents are not known to cause brain tumors experimentally. Oil refinery workers, chemical plant workers, rubber workers, and many other occupational groups are exposed to organic solvents.

Exposure to polycyclic aromatic hydrocarbons occurs in the rubber manufacturing, petroleum refining, and aluminum reduction industries. Motor vehicle examiners and bus mechanics may also be exposed to these hydrocarbons in motor vehicle exhaust. Certain polycyclic aromatic hydrocarbons have induced brain tumors in animals by direct implantation and transplacentally, but not by inhalation exposure (81).

Lubricating oils produced by oil refineries are used for maintaining mechanical equipment and machines and for lubricating cutting edges. Thus several of the groups with elevated brain cancer mortality are exposed to various types of lubricating oils.

Gliomas have been experimentally induced in animals by inhalation exposure to acrylonitrile and vinyl chloride (40, 41). These compounds are similar in chemical structure and are found in plastics departments in the rubber industry, in polyvinyl chloride production, and in acrylonitrile polymerization.

Formaldehyde has recently been shown to induce nasal cancer in rats (82), a finding implying that it may also be carcinogenic in humans. Several of the groups with elevated mortality from brain cancer were occupationally exposed to formaldehyde. These groups include blue-collar workers involved in formaldehyde production, photographic processing and textile production, professionals who use formaldehyde in the laboratory setting, and embalmers.

Phenols and phenolic compounds are used widely in manufacturing industries, and many of the compounds have commercial uses. These include phenol, chlorophenols, cresol, resorcinol, hydroquinone, and quinone. Phenolic compounds are used in the production of explosives, fertilizers, textiles, paints and paint removers, rubber, wood preservatives, synthetic resins, pharmaceuticals, photographic chemicals, rubber, and organic chemicals. Commercial uses include fungicides and herbicides, disinfectants, laboratory reagants, and photographic processing (60). Acute intoxication of these compounds causes severe CNS effects, including tremors, convulsions, vertigo, and mental disturbances. None of these compounds have induced brain tumors experimentally; however some phenols are known to be tumor promoters and cocarcinogens in certain tissues (16).

Of the broad categories of aforementioned substances, only a few have been shown to cause brain tumors in laboratory animals. These include certain polycyclic aromatic hydrocarbons, vinyl chloride, and acrylonitrile. However, several of the substances, specifically, formaldehyde, certain solvents, and some phenolic compounds, are known to cause neurotoxic effects after acute high-level exposure. Thus, the brain is obviously a target organ for the toxic effects of these materials.

Clearly, further epidemiologic studies are necessary to evaluate the relationship between brain tumors and occupational exposures. These studies should include large numbers of cases and diagnostic confirmations so that data may be analyzed by cell type. Sufficient care should be used in selecting referents so that the diagnostic sensitivity problem, if it exists, is minimized. Finally, and most importantly, an attempt should be made to develop detailed occupational exposure indices.

NOTE: Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the United States Department of Health and Human Services.

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KETCHUM PUBLIC RELATIONS
M E M O

TO: Thomas Barfkecht, James G. Bryant, Craig H. Farr, John L. Festa, Marcia Hardy, Stewart E. Holm, Robert G. Kaley, III, Florence Kinoshita, Robert Ku, David McAllister, Willie Owens, David Penney, Kerry Peters, Robert Smerko, Don Townsend, Phil Watanabe, John Wilkinson

FROM: Liz Tait
Ketchum Public Relations

DATE: November 23, 1993

PAGES: 2 (two)

SUBJECT: Answers About "Sources" for the IGCCA Dioxin Q&A Document

cc: Brad Lienhart
Ann Mason
Elizabeth Brooks .

As most of you know from the last Dioxin Work Group meeting, Bob Ku and I have been working in tandem on a first draft of the IGCCA dioxin Q&A document. We've met in person and by telephone in the last couple of weeks, and Bob is completing a draft which I am editing for lay comprehensibility and suitable tone, content and structure. I will distribute it to each of you on December 1, 1993, as planned.

Bob's answer to the question "What are the sources of dioxin in the environment to which I may be exposed?" is general, which may be enough for a document as modest in scope as this one. In any case, he is reluctant to answer in greater detail on behalf of your respective industries, and suggested that some of you draft a one- to one-and-one-half page (double-spaced) response to the issue of source emissions based on your knowledge and experience. He suggested the following assignments:

Pulp and paper mills –	Stewart Holm and John Festa
Vinyl manufacturing –	Dave Penney
Incineration –	Phil Watanabe
Manufacture of chlorinated pesticides –	Phil Watanabe and Bob Kaley
Manufacture of chlorine and chlorinated compounds –	Bob Smerko

Natural Sources – ?

cc: J. Ledvina - Horton
T. Grumbles - Horton

A

CHEMICAL MANUFACTURERS ASSOCIATION
CHLORINE CHEMISTRY COUNCIL
SCIENCE TASK GROUP

DIOXIN WORK GROUP

MINUTES OF MEETING

NOVEMBER 9, 1993

M Street Conference Room — CMA, Washington, D.C.

PARTICIPANTS	AFFILIATION
R. G. Kaley, Chair	Monsanto Company
S. E. Holm	Georgia Pacific
F. Kinoshita	Hercules, Inc.
D. Penny	Vista Chemical
R. Smerko	Chlorine Institute
P. Watanabe	Dow Chemical
J. Wilkinson	Vulcan Chemicals
CMA Staff	
A. M. Mason, Staff Executive	CMA
D. B. Fischer	CMA
M. Gallant*	CMA
R. B. Lienhart*	CMA
By Invitation	
E. Tait*	Ketchum

* Indicates Part-Time Attendance

The following business items were discussed. Action items are underlined.

1.0 Administration

1.1 Minutes:

The minutes of the October 1, 1993, meeting were approved without changes.

1.2 Meeting Expectations:

The work group identified the following meeting expectations:

a. Agree on Mission Statement
b. Concur with direction of sub-group
c. Identify new challenges

1.3 Meeting/Conference Call Schedule:

- Conference Call: Thursday, Dec. 16,1993 1:00-3:00 p.m.

Topic: Discuss dioxin Q/A document

- Next Meeting: Tuesday, Jan. 11, 1994 9:00a.m.-3:30p.m.

1.4 Work Group Mission Statement

The work group discussed and revised the draft mission and goal statements. A. Mason will make the changes.

2.0 International Joint Commission

B. Lienhart presented a summary of the IJC Meeting. He discussed the groups on which additional industry representatives could serve, including the IJC Science Advisory Board.

During his presentation, he discussed several issues including the:

- Virtual Elimination Task Force's final report and the recommendations that call for a thorough evaluation of chlorine chemistry - specifically recommendation 22.
- Weight-of-evidence workshop which was a series of case studies but not a process for determining the weight-of-evidence.
- Formation of an IJC ad-hoc group to address weight-of-evidence. The group discussed the IJC weight-of-evidence group, identified the key players, and discussed alternatives.

J. Wilkinson reminded the group that an understanding of the IJC process will be important for U.S. legislative efforts. The work group suggested a joint meeting with the Federal Advocacy Task Group to discussion scope and direction of the dioxin issues and to agree on a joint strategy. A. Mason and M. Gallant will work on setting up this joint meeting.

3.0 American Public Health Association (APHA)

During a discussion on the APHA resolution, B. Lienhart discussed the process and indicated that CCC will be sending a follow up letter to APHA.

R. Kaley will send A. Mason a copy of Dr. Frank's speech for distribution to the work group.

4.0 Sub-group Reports:

4.1 Dioxin Q/A Subgroup

E. Tait, Ketchum Associates, presented the status of the Q/A document and passed out two documents: one prepared by Ketchum and the other by R. Ku.

She lead a discussion about the scope and audience for the document. The Work Group agreed that the primary audience is the public and the answers would be two-tiered: the first part of the answer should be targeted to the general public and then followed by more detailed fact-based answers.

The Work Group was asked to send third party quotes to A. Mason and E. Tait on key issues.

The Work Group agreed that the primer will have references.

The work group discussed and agreed to the following schedule. E. Tait will send out a revised draft by 12/1/93. Each member will send comments back to E. Tait for receipt by 12/9/93. E.Tait, R. Ku, and CMA staff will meet on 12/9/93 to revise the document. The Work Group will have a conference call on 12/16/93 to look at the revised document. E. Tait will send another draft out by 12/15/93 for a second conference call on 1/3/94 that will approve the document.

The work group reminded the group that these drafts should not be distributed publicly. Each member was asked to work with their own attorney during their internal review process.

The work group emphatically stated that NO document should go to the European partners for broad distribution until after the revised draft is prepared from the 12/16/93 conference call.

4.2 Dioxin Science Subgroup:

P. Watanabe presented a summary of the conference calls and discussed the key scientific issue areas.

P. Watanabe outlined the plans for a group meeting at L. Birnbaum's EPA laboratory in January and a co-sponsored ILSI workshop to discuss immunotoxicologic tests and their interpretation.

The outcome of the ILSI conference is a published paper outlining the issues/controversy around the different models and interpretation around toxicology and immunotoxicology.

F. Kinoshita presented an overview of the current EPA work on host resistant model.

The group discussed the importance of getting NOEL's.

The sub group urged a joint meeting with the endocrine sub group of the Science and Health Work Group. P. Watanabe and A. Mason will work out these details.

The work group approved the concept of the ILSI workshop and recommended $20K for its funding. P. Watanabe and A. Mason will take this recommendation to the Science Task Group.

R. Ku is asked to coordinate with R. Kaley on the Toxicity Equivalence Factors to ensure consistency with previous CMA comments to EPA (re: PCB panel).

The group discussed meeting with Linda Birnbaum in Washington but the work group recommended waiting until after the Dioxin Science Subgroup visit in January.

4.3 Dioxin Reassessment Subgroup

D. Penney presented the subgroup's work plan and identified the key tasks for the subgroup.

The work group discussed the pros and cons of advocating for an EPA stakeholder meeting to discuss the Risk Characterization chapter. The subgroup scheduled a conference call Friday, Nov. 12, 1993, 9:00am to noon eastern time to set the agenda for the meeting with Bill Farland.

D. Penney identified the opportunities and constraints about jointly funding work to evaluate the science issues in the Risk Characterization chapter. The subgroup recommended jointly funding the scientific panel and/or review of the Risk Characterization chapter. The subgroup agreed that CMA/CCC will develop and submit separate interpretative analysis and comments.

D. Penney and J. Festa will explore how best to fund a joint scientific evaluation of the Risk Characterization chapter.

D. Penney and A. Mason will prepare the 1st draft requesting additional funds for the subgroup review.

D. Penney and A. Mason will communicate with M. Ferris and L. Smith about the need for additional funds and will transmit the request for additional funding to the Science Task Group and Operating Committee.

The work group endorsed having a joint meeting with AFPA to review the tasks of covering all aspects of the dioxin reassessment process. A. Mason will work with J. Festa to coordinate a joint meeting.

4.4 NRDC Petition:

J. Wilkinson briefed the group about a meeting with outside counsel discussing a long term strategy around the NRDC petition, the pulp and paper cluster rule, and the dioxin reassessment process.

These lawyers indicated that the industry may want to begin building factual basis to challenge EPA if it becomes necessary or to file an amicus to support EPA vs. other litigants. J. Wilkinson identified a timeline for future conversations with outside legal advisors and D. Fischer discussed some of the key aspects underlying future basis for discussion.

EPA will take no action on the NRDC petition until the dioxin reassessment is completed.

5.0 Pulp and Paper Cluster Rule:

S. Holm identified the AFPA actions on the pulp and paper cluster rule. He indicated that there was a reg-neg on the land part of the rule.

S. Holm discussed some of the proposed tests that AFPA is considering; including a chemical characterization of dioxin and chlorinated phenol compounds.

6.0 NIOSH:

R. Kaley presented an overview of a conversation with E. Delzell on the examination of the NIOSH dioxin study. She indicated that there was one plant driving the conclusions.

J. Collings, G. Bond, R. Kaley plan to meet on Dec. 20, 1993. R Kaley will summarize these discussions at the next Work Group meeting.

7.0 CanTox Incineration:

B. Lienhart said that CanTox is about to release the chapter to the work group for review. A. Mason will send the document to the Work Group and to the RCRA Combustion Work Group for its quick review.

8.0 Adjourn

The meeting adjourned at 3:30 p.m. Eastern.

Ann M. Mason
Associate Director
Regulatory Affairs

MINUTES SUBJECT TO APPROVAL
November 10, 1993

AMM/DF

The Vinyl Institute

A Division of The Society of The Plastics Industry, Inc.

The Campaign Against Vinyl — The Facts

In recent years, certain environmental groups have pushed for the elimination of various chlorine-containing products, claiming that their manufacture represents a threat to human health and the environment. But the evidence these groups present to support their campaign against chlorine rely either on bad science or emotional rhetoric.

One product singled out for attack is PVC (polyvinyl chloride, or vinyl), the world's second largest selling plastic material. What's vinyl's crime? Apparently, nothing more that its use of chlorine as a feedstock. In fact, Greenpeace has admitted in public meetings that vinyl is merely a piece in its "chess game" against the entire petrochemical industry.

One result of this chess game campaign can be seen in the April 1992 report issued by the International Joint Commission of the United States and Canada. That report, the IJC's sixth biennial report on Great Lakes water quality, deals with those lake contaminants known as persistent toxic substances. However, one of the specific recommendations in the report (Recommendation Seven) suggests that the IJC develop timetables to sunset the use of chlorine and chlorine-containing compounds used as industrial feedstocks. Vinyl is the largest such use for chlorine and is *not* a persistent toxic substance.

Why the vinyl industry vigorously objects to the IJC's recommendations, especially Recommendation Seven:

- The report treats all chemicals within a class the same, regardless of the safe performance history of individual products within the class. Vinyl is one of those products with a demonstrated record of safe production and use.
- The report acknowledges, but deliberately chooses to ignore, that harmful effects *have not* been established for many of the substances it examines. Vinyl is one of those substances for which the IJC does not establish, with any scientific validity, harmful effects.
- The report erroneously concludes that chlorine-based manufacturing is an uncontrollable process and that the environmental impact of that process is unknown and unpredictable. To the contrary, the manufacture of vinyl chloride and polyvinyl chloride is a sophisticated and well-understood process that is entirely predictable and controllable. All of the by-products are known and quantifiable.

In fact, one independent consultant, ICF Incorporated, characterized Recommendation Seven as "overly broad and not supported by analysis of risk and costs, including net environmental costs."

In essence, through business and payroll taxes, the vinyl industry is being forced to underwrite an effort that will put it out of business — without justification!

More facts about vinyl's environmental performance:

- The overall vinyl production process has a 99+ percent conversion rate. By-products are either contained, neutralized, recycled or incinerated, or disposed of in an environmentally approved manner.

-more-

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- Vinyl is a highly efficient user of energy and feedstocks. For instance, it takes about half the energy to make PVC sewer pipe as it does to make other plastic pipe, and about a third the amount it takes to make cast iron pipe. In its 1992 lifecycle comparison of various packaging materials, Chem Systems found vinyl to be the material with "the lowest production energy and carbon dioxide emissions, and the lowest fossil fuel and raw material requirements of the plastics studied."
- Vinyl chloride, the raw material used to make vinyl plastics, is one of the most studied and carefully regulated chemical substances in use today. There are strict controls in place to measure and limit all environmental emissions. Those controls, along with voluntary efforts undertaken by industry, have virtually eliminated any health hazards to workers and plant-site communities.
- Since the 1970s, the industry has reduced its VCM emissions in the U.S. more than 95%.

What are the consequences of eliminating the production and use of vinyl?

In April 1993, the consulting firm of Charles River Associates, Boston, looked at the cost to replace vinyl with alternative materials in fourteen major applications and markets. The study calculated the amount of material needed to maintain the same market share currently held by vinyl in each application. It also estimated, where appropriate, the capital cost to build new capacity or convert existing capacity to produce that material or fabricate end-products from it, and considered any incremental or additional costs to install the material compared to the current cost to install the vinyl product.

*The study found that the cost to replace vinyl in these markets would require an additional investment of **$974 million** in new equipment and cost consumers **$6.7 billion** more per year to purchase substitute materials.*

The vinyl industry contributes $4 billion to the U.S. economy each year and operates 1,008 plants in the Great Lakes states alone, where approximately 60% of its employment is concentrated. Eliminating vinyl would shut down this business, and have serious implications for customers in hundreds of markets, including health care, communications, aerospace, automotive, retailing, textiles, construction, durable goods and agriculture.

Even more important are the societal benefits at risk by eliminating the use of vinyl. A few examples:

- Pipe made from it economically delivers pure water to places that have never had this basic necessity; PVC irrigation pipe helps increase crop yields, and studies have shown that PVC pipe is less expensive to install and maintain than competitive materials.
- Medical goods and pharmaceutical packaging made from vinyl help provide a higher, safer standard of health care.
- Wiring made from it makes electrical service safer and more dependable.
- Construction products made from it make housing more affordable.
- Packaging made from it reduces food spoilage and waste, and helps package designers create innovative "downsized" packaging that reduces landfill waste.

The industry's position

The vinyl industry is proud of its environmental performance and welcomes an examination of its record. Any such review, however, should be based on sound science and conducted in the public interest. The current campaign against vinyl does neither and does society a misservice by potentially restricting the use of products that have demonstrated their value for years.