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Sirs:

You may wish to bring the attached paper to the attention of your various committees interested in vinyl chloride health effects. It describes VC as the only recognized central nervous system carcinogen.

Very truly yours,

John T. Barr, Manager
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JTB:pbr
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OCCUPATIONAL EXPOSURE AND BRAIN TUMORS

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Epidemiological evidence of an occupational risk of brain cancer has been reported in four industries where chemical exposures are likely, most recently in a series of prospective studies in the petrochemical industry. However, only in the case of vinyl chloride exposure has an occupational central nervous system carcinogen been identified. This report reviews the convergence of epidemiological and laboratory evidence that established the occupational carcinogenicity of vinyl chloride, and discusses in detail the current evidence for an occupational risk of brain tumors in the petrochemical industry.

INTRODUCTION

Primary brain tumors of the glioma series, which make up about half of all brain tumors, show a male-to-female ratio of about 1.5 to 1. Brain tumors in general appear to be increasing in incidence among older cohorts (Waxweiler et al., 1983). Thus brain tumors in general, and glioma series tumors in particular, are sometimes considered as a priori likely suspects in the search for occupationally related tumors. Furthermore, gliomas can be produced experimentally in rats by at least four groups of experimental chemicals: aromatic hydrocarbons, *N*-nitroso compounds, triazenes,and hydrazines. More recently, brain tumors including gliomas have been shown to be produced by inhalation in rats by three industrial chemicals, bis(chloromethyl) ether, vinyl chloride, and acrylonitrile (Maltoni et al., 1982). These experimental results, together with the established history of brain-tumor carcinogenesis in vinyl chloride workers, have led many researchers to lend at least preliminary credence to reports of brain tumors occurring in other industries where there are chemical exposures. Most recently, a series of studies have suggested excess risk of brain tumors in the petrochemical industry.

Evidence suggesting an excess of brain tumors has now been reported for at least four occupational groups: rubber workers (beginning with Mancuso's investigations in the 1950s), chemists, vinyl chlo-

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ride workers, and petrochemical workers. However, the convergence of epidemiological and laboratory investigations that is usually accepted as the informal criterion of proof in such situations has been hard to demonstrate (see, e.g., Cole and Merletti, 1980; Doll and Peto, 1981). Thus, Mancuso's original observations in the rubber industry were not followed by the identification of any specific carcinogen, and the existence of an occupational risk of brain tumors in rubber workers is currently open to doubt (Mancuso, 1982; Symons et al., 1982). Brain-tumor risk in chemists has been shown only in a series of Swedish studies, and as yet no likely carcinogen has been identified (Olin and Ahlbom, 1982). The convergence of an epidemiologically identified risk and a suspected carcinogen has been demonstrated only among vinyl chloride workers. Thus Cole, in his surveys of occupational carcinogenesis, recognizes only vinyl chloride as an established industrial brain carcinogen (Cole and Merletti, 1980). Doll and Peto, more conservatively, admit the brain only as a "possible" site of occupational carcinogenesis (Doll and Peto, 1981). The history of vinyl chloride as a central nervous system (CNS) carcinogen is discussed in the next section.

Historically, the establishing of occupational or environmental risks has often been a complex and drawn-out process, sometimes requiring decades for the development of a consensus on a particular exposure. Thus although the issue of excess risks of brain tumors in rubber workers is currently in debate, the persistence of reports of brain tumor excesses in this and other industries has, as it were, promoted brain tumors to the top of the list of tumors that may be associated with important occupational risk (along with lung cancer, leukemias and lymphomas, primary liver cancer, and, more recently, melanoma). This was the situation in 1978 when a cluster of brain tumors was reported in petrochemical workers in Texas, initiating a major wave of research into the subject. The petrochemical research is also reviewed in this article.

VINYL CHLORIDE AS A BRAIN CARCINOGEN

Cole observes that occupational carcinogens are usually recognized because they generate an unusually high rate among a small exposed population, and because they produce tumors that are otherwise unusual (Cole and Goldman, 1975). Vinyl chloride (VC) is the classic case of a carcinogen that has such an effect, producing in workers exposed to high levels of the gas the very rare angiosarcoma of the liver (ASL). The first reported case of ASL in a vinyl chloride worker was diagnosed at the B. F. Goodrich company in Louisville, Kentucky, in May, 1970; the second in March, 1973; and the third, at autopsy, in December, 1973 (Heath et al., 1976). Since the incidence of ASL in the United States

was then 20–25 cases/yr, the appearance of 3 cases among a small group of workers prompted considerable concern. Furthermore, concurrent studies by Viola (1971) had shown skin, lung, and bone tumors in rats exposed to VC by inhalation. [Viola's carcinogenesis studies were reportedly an outgrowth of his work on acroosteolytis in VC-exposed workers. Hepatitis-like liver changes had been reported as early as 1949 (Nicholson, 1977).].

Following Viola, Maltoni demonstrated angiosarcomas in rats exposed to VC in 1972 (Maltoni et al., 1982). This result was communicated to the Manufacturing Chemists Association, which following the discovery of the third case at B. F. Goodrich, made public the finding of three cases of angiosarcoma in VC-exposed workers in the *Wall Street Journal*. With this announcement, a major effort began to study vinyl chloride workers, including a National Institute of Occupational Safety and Health (NIOSH) follow-up study of 1294 workers with extensive VC exposure in four plants. A concurrent histopathology study reviewed tumors reported on death certificates of *all* workers in the four plants.

The NIOSH study, published in 1976, showed very high relative risks in the category "biliary and liver cancer." The relative risk was 11 for workers with 10 or more years of exposure and 16 for workers with 15 or more years of exposure. Furthermore in the concurrent histopathology study, 11 of 14 reported liver and biliary cancer cases on death certificates were ASL (Waxweiler et al., 1976). These observations have remained the primary epidemiological basis for the assertion of the carcinogenicity of vinyl chloride.

However the study also observed a significantly increased relative risk for brain tumors, with 3 observed and 0.6 expected among workers exposed more than 15 years. At the same time Maltoni (1976a) reported that brain tumors as well as ASL could be produced in rats exposed to VC by inhalation. Furthermore the NIOSH histological study showed that 9 of 10 brain-cancer deaths in the VC worker cohort were glioblastoma multiformes (the most commonly occurring tumor in the glioma series). This proportion was thought to be unusually high. [However, it has been shown that the expected proportion of glioma-series tumors in such a series depends heavily on the number diagnosed at autopsy (Schoenberg et al., 1978)]. These results were sufficient for the development of a reasonable consensus that brain tumors as well as ASL were associated with VC exposure. The primary evidence in the development of the consensus was the correspondence between the human data and the laboratory inhalation studies, in which the exposure levels were thought to be close to human occupational exposures. (see, e.g., Wagoner and Infante, 1977). Vinyl chloride is the only occupational chemical carcinogen for which a correspondence exists.

Waxweiler et al. (1983) also note that in the 9 glioblastoma multiforme cases identified in the VC workers histology study, the average

time since first exposure to vinyl chloride was 21 yr. Thus the epidemiological observation of risk may have followed the oncogenic exposure by a generation, and the circumstance of exposure could well have changed by the time the risk was recognized. This long latency period is characteristic of occupational carcinogenesis. The excess risk of mesothelioma in asbestos workers, for example is not generally observable until 20 yr after exposure (Selikoff, 1977). The long latency period has important consequences in the case of brain tumors, which are not rare tumors.

The identification of VC-produced brain tumors, currently the only accepted example of occupational CNS carcinogenesis, offers some important lessons for studies of other industries. First, vinyl chloride was identified as a CNS carcinogen because it produces, as its primary effect, the extremely rare ASL. The excess risk of brain tumors would probably not have been recognized if it had not "piggybacked" on the rarer tumor. Second, the brain was only recognized as an additional site of carcinogenesis because comparable ranges of tumors were seen in human and animal inhalation studies. There is no other occupational carcinogen for which such a correspondence is currently known. Third, the number of tumors reported in the primary study was very small: there were 3 cases in the high-exposure cohort, and 10 in the concurrent histopathology study. Fourth, the period between initial exposure and observation was so long that observed effects may in fact have been archaeology rather than epidemiology—the carcinogenic situation may well have no longer existed when the excess risk was observed.

BRAIN TUMORS AND PETROCHEMICAL EXPOSURE

The intensive study of brain tumors in the petrochemical industry began in 1978 when as employee at the Union Carbide plant in Texas City, Texas, reported a newly diagnosed brain tumor to the local office of the Occupational Safety and Health Administration (OSHA). A joint study with the Oil, Chemical and Atomic Workers union (OCAW) and company representatives identified a total of 10 brain-tumor deaths and cases among workers at the plant (not including the original complainant, whose tumor proved to be metastatic). This number was sufficient for the OSHA office to request a formal study by NIOSH. A joint study, with Union Carbide researchers, was initiated. A proportional mortality study of OCAW members in South Texas was already in progress, and additional studies in other refineries and chemical plants were initiated over the next year.

However, in 1979 both the Three Mile Island incident and the Federal declaration of emergency status for the Love Canal area took place,

and in the ensuing controversies over environmental carcinogenesis the atmosphere became polarized between industry and governmental–union forces. As a result, competing industry and government–union studies were set up in several of the exposed petrochemical cohorts in Texas and Louisiana. When a meeting was convened at the New York Academy of Sciences in 1980 to review the studies, a total of eight were presented, four from each group. The four governmental–union studies uniformly indicated a twofold risk of brain cancer among petrochemical workers; the four industry studies uniformly failed to detect any excess risk. "To the innocent observer," *Science* reported, "the crisp pattern of falling chips appeared at first sight to display blatant gerrymandering" (Lewin, 1980). It was also true, however, that the range of methods and cohorts involved was considerable and that there was extensive methodological disagreement. Reeve et al. (1985) reviewed the issues. The primary methodological questions were (1) the tendency of proportional mortality studies, as carried out by NIOSH, to inflate cancer risk, and (2) the tendency of industry-wide cohort studies, as carried out by the industry groups, to bury small groups of at-risk workers in very large cohorts. These issues were not resolved as, with the new Federal administration in 1981, NIOSH capacity to continue the epidemiology studies was lost. With no pressure from the regulatory side, the industry studies appear to have slowed down also.

However, most of the proportional mortality studies were eventually converted to standardized mortality form, and a review of these studies is now possible. Savitz and Moure (1984) have recently reviewed the six prospective studies of refinery workers that were initiated by labor–governmental and industry groups in 1979–1980. Table 1 is adapted from Savitz and Moure, with the addition of results from two studies of petrochemical plant workers, those of Waxweiler et al. (1983) and Reeve et al. (1983). [One study, that of Thomas et al. (1982); remains a proportional mortality rate study (PMR): the others use standardized mortality ratios.]

All cohorts of petrochemical workers had low overall mortality, as is generally the case in studies of "healthy workers," and six of the seven for which all-site cancer mortality or incidence were reported showed lowered total cancer rates. [The exception was the PMR study of Thomas et al. (1982).] However, brain-tumor rates were elevated in all but two of the studies, the exceptions being the refinery-wide study of Wen et al. (1983), which included salaried workers, and the industry-wide study of the British petrochemical industry by Rushton and Alderson (1981). There was additional evidence of an association in more detailed substudies. Thus Savitz and Moure (1984) note that while Hanis et al. (1982) report an overall relative risk of 1.02 for brain tumors in their study of the Baton Rouge Exxon refineries, a more highly exposed

TABLE 1. Relative Risk for Brain Cancer and Melanoma in Prospective Epidemiological Studies of Refinery and Petrochemical Workers[a,b]

	All cancers		Brain		Melanoma	
Study	RR	*N*	RR	*N*	RR	*N*
Theriault and Goulet, (1979)	0.89	25	3.90	3	—	—
Rushton and Alderson, (1981)	0.89	1147	0.80	36	2.16	14
Schottenfeld et al. (1981) (mortality)	0.76	127	1.63	8	—	—
Schottenfeld et al. (1981) (incidence)	0.86	240	1.29	9	1.32	13
Thomas et al. (1982) (PMR)	1.19	474	2.28	27	1.61	11
Hanis et al. (1982)	0.92	249	1.02	5	—	—
Wen et al. (1983)	0.96	839	0.99	30	1.22	16
Waxweiler et al. (1983)	0.81	131	1.81	13	—	—
Reeve et al. (1983)	N/A	N/A	1.09	25	—	—

[a] Adapted from Savitz and Moure (1984).
[b] RR, relative risk, *N*, number.

subgroup had a higher risk. In the Reeve et al. study of Dow chemical workers, while the overall relative risk was 1.09, the risk among workers hired before 1945 was 1.83 (Reeve et al., 1983).

On the basis of the first six studies, Savitz and Moore comment that there was reasonably consistent evidence of a potential association between petrochemical exposure and brain cancer. The two chemical-plant studies appear to strengthen the association.

In an independent review of all NIOSH investigations in eight individual refineries and chemical plants in Texas, Reeve et al. (1983) note that inconsistencies remain in the plant-by-plant results, and that case-control studies within the studied cohorts show no consistent patterns of exposure. However the consistently elevated brain-tumor risk in the prospective studies appears sufficient at least for this line of research to continue.

Savitz and Moure note that melanoma risk is rather consistently elevated in the studies of petrochemical cohorts, as well as brain-tumor risk. This result is of interest because of an emerging pattern in recent studies of nuclear fabrication workers. Hadjimichael et al. (1983), in their study of the United Nuclear facility in Connecticut, observed relative risks of 2.40 for brain tumors and 2.12 for melanoma, against an

all-sites relative risk of 0.88. Furthermore, Wilkinson et al. (1983) observed a tripled risk of brain tumors at the Rocky Flats nuclear plant, and Austin (1981) observed a tripled risk of melanoma at the Lawrence Livermore laboratory. Attempts to explain these risks by radiation exposures have proved generally unsuccessful; the similarity with the pattern of risk among petrochemical workers suggests that perhaps the cause is in some other aspect of the fabrication process.

CONCLUSION

Although this review suggests that the issue of brain tumors in petrochemical workers is at least worth further study, most of the prospective studies appear to have been dropped. However, a second wave of large case-control studies of occupational exposure in brain tumors has now been set in motion (see Table 2). In these studies, all brain-tumor cases or deaths in a specific case-finding area over a specific period are interviewed, either in person or by proxy. These large studies may eventually resolve the issue of whether there is a genuine

TABLE 2. Case-Control Studies Currently in Progress of Occupational Exposure in Glioma Patients

Investigator	Site	Number of cases	Number of controls	Source of cases	Location
Thomas, T. L., NCI Environmental Epidemiology Branch	CNS	600	600	Death certificate	New Jersey/ Louisiana
Preston-Martin, S., University of Southern California	CNS	300	300	Incidence	Los Angeles County
Moss, A. R., University of California, San Francisco	Glioma	500	500	UCSF clinical cases and death certificates	Northern California
Buffler, P., University of Texas	Glioma	650	870	Incidence	Coastal Texas and Louisiana
Ahlbom, A., Hudinge University Hospital, Sweden	Brain	150	300	Clinical cases in 2 hospitals	Hudinge
Musicco, M., Neurological Institute C. Besta, Milan	Meningioma/ glioma	800	1,600	Hospital cases	Milan

[a] From Muir and Wagner (1982) and P. Buffler, personal communication

excess risk in petrochemical workers. [However, Cole notes that such large case-control studies are only effective when the exposed group makes up at least 2–3% of the population studied (Cole and Goldman, 1975).] It should also be noted that while large case-control studies of brain tumors may identify industry-wide risk, they cannot, by their nature, identify the pattern of tumor sites associated with a specific exposure. This latter information is generally accepted as important in establishing risk.

In conclusion, the prospective studies of petrochemical worker cohorts reviewed here suggest that there is an increased risk of brain tumors associated with petrochemical exposure, possibly accompanied by an increased risk of melanoma. No evidence of a specific carcinogen has been established, and while the current generation of large case-control studies will probably identify any overall risk in the industry, these studies will not identify the pattern of sites at risk. In the light of the consistency between the petrochemical worker studies and the recent nuclear-fabrication worker studies, there is an argument for a coherent program of prospective research in these cohorts. Other studies that could usefully be coordinated with such a program include a review of the specific-exposure inquiries in the petrochemical worker cohorts, an examination of the change in the incidence of glioma series tumors among all brain tumors, and an exploration of other associations between brain tumors and melanoma.

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