CHEMICAL MANUFACTURERS ASSOCIATION

March 17, 1986

Dear Vinyl Chloride Panel and Research Coordinator Member:

Dr. Brian Benett of ICI sent me the enclosed "Register of Cases of Angiosarcoma of the Liver Due to Exposure to Vinyl Chloride." Please note that the rigister is marked confidential, and therefore should be used for your internal purpose only. Also enclosed is an artile I received from Mr. John Barr on "Occupational Exposure and Brain Tumors."

Sincerely,

Has Shah

Has Shah, Ph.D.
Manager
Vinyl Chloride Panel

Enclosures

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AIR PRODUCTS

R&S 002509

27 February 1986

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Dr. Roy Gottesman
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Wayne, NJ 07470

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
Regulatory Response

JTB:pbr
0608c

Enclosure: Moss, J. Toxicol. Environ. H. 16 703-711 (1985)

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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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

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

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

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