

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

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 an 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.

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

Study	All cancers		Brain		Melanoma	
	RR	N	RR	N	RR	N
Therault 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

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.

REFERENCES

- Austin, D. F. 1981. Population-based tumor registries in the identification of occupational carcinogens. Proceedings of the 1980 International Symposium on Cancer, Sept. 14–18, 1980. In *Cancer: Achievements, Challenges and Prospects for the 1980s*, eds. J. H. Burchenal and H. F. Oettgen, vol. 1, pp. 291–298. New York: Grune and Stratton.
- Cole, P., and Goldman, M. B. 1975. Occupation. In *Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control*, ed. I. F. Fraumeni, pp. 167–184. New York: Academic.
- Cole, P., and Merletti, F. 1980. Chemical agents and occupational cancer. In *Cancer and the Environment*, eds. H. B. Demapoules and M. A. Mehlman, pp. 399–417. Park Forest South, IL: Pathotox.
- Doll, R., and Peto, R. 1981. *The Causes of Cancer*, p. 1243. Oxford: Oxford University Press.
- Hadjimichael, O. C., Ostfeld, A. M., D'Atri, D. A., and Brubaker, R. E. 1983. Mortality and cancer incidence experience of employees in a nuclear fuels fabrication plant. *J. Occup. Med.* 25:48–61.
- Hanis, N. M., Holmes, T. M., Shallenberger, L. G., and Jones, K. E. 1982. Epidemiologic study of refinery and chemical plants workers. *J. Occup. Med.* 24:203–212.
- Heath, C. N., and Falk, H. 1976. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. *Ann. N.Y. Acad. Sci.* 267:231–236.
- Lewin, R. 1980. Research News: Government/industry dispute brain tumor risk. *Science* 210:996–997.
- Maltoni, C. 1976a. Predictive value of carcinogenesis bioassays. *Ann. N.Y. Acad. Sci.* 271:431–443.
- Maltoni, C. 1976b. Precursor lesions in exposed populations as indicators of occupational cancer risk. *Ann. N.Y. Acad. Sci.* 271:444–447.
- Maltoni, C., Ciliberti, A., and Caretti, D. 1982. Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. *Ann. N.Y. Acad. Sci.* 381:216–249.