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CHEMICAL MANUFACTURERS ASSOCIATION

December 7, 1992

Dear Vinyl Chloride Research Coordinators:

Dr. Otto Wong's response to our letter to the editor of the American Journal of Industrial Medicine is enclosed. Please review the letter and call me if you have any comments.

In response to my last mailing regarding the ATSDR Vinyl Chloride Data Needs, Dr. James Knaak of OxyChem has requested a conference call to discuss a course of action. Please complete the enclosed availability survey for the conference call and return it to me by fax a (202) 887-1237.

If you have any questions, please call me at (202) 887-1192.

Sincerely,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Enclosures

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November 30, 1992

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Re: Revised response to Dr. Shah's Letter to the Editor

Dear Ms. Burger:

Thank you for your review of our response to Dr. Shah's letter. We have revised our response according to your comments, and have shortened it considerably. Enclosed please find two copies of our revised response. If you have further questions or comments, please let us know.

Sincerely yours,

Applied Health Sciences, Inc.
by:

Otto Wong, Sc.D., F.A.C.E.
Chief Epidemiologist

Encl.
cc: M. Donald Whorton, MD
bcc: Hasmukh C. Shah, Ph.D.

Dr. Shah's Letter (1993) raised several issues of potential diagnostic bias on the brain cancer and emphysema findings in our recent paper of vinyl chloride workers (Wong et al., 1991). These are important and pertinent questions not only in our study of vinyl chloride exposed workers, but also in occupational epidemiologic studies in general.

Brain Cancer

The first issue was the potential diagnostic bias of brain cancer in occupational studies. As Dr. Shah correctly pointed out in his letter, there are reports in the literature documenting the potential bias resulting from the more complete reporting and/or diagnoses of brain tumors in employees of large corporations than in the general population. Greenwald et al. (1981) reported a significantly higher frequency of brain scans (61.1% v. 30.0%) and pneumoencephalograms (35.2% v. 17.1%) than in other brain tumor patients in the same state. They concluded that the "diagnostic sensitivity bias" would appear to pertain to conditions that are difficult to diagnose, such as brain tumors, and to industries where workers have such employee benefits as health insurance and high-quality employee medical services with referral and follow-up. Thus, the apparent excess of brain tumors may have resulted from this "diagnostic sensitivity bias" arising from the more complete medical evaluation of employees of large corporations. "Diagnostic sensitivity bias" in brain cancer has also been discussed by other investigators (Wong et al., 1986; Wong and Raabe, 1989).

The participants in our vinyl chloride study were employees of major corporations in the chemical industry, and were covered by comprehensive medical care programs. Therefore, our finding of a brain cancer excess could very well have been subjected to the "diagnostic sensitivity bias."

In our 1991 paper, although we reported a statistical significant increase of brain cancer, we did not discuss our finding in relation to findings reported by other investigators; nor did we conclude that the observed brain cancer excess was related to vinyl chloride exposure. Although Dr. Shah did not raise the question explicitly in his letter, it seems to us that the most

only 15% of the excess, the increase would no longer be statistically significant. By way of comparison, the SMR for cancer of the liver, which has been demonstrated to be associated with vinyl chloride exposure, in our study was 6.41 (lower 95% confidence limit of 4.50).

With respect to length of exposure, there was no clear upward trend for brain cancer in our study, especially when compared to the striking upward trend observed for cancer of the liver. Perhaps the most remarkable difference between brain cancer and liver cancer (the latter was clearly related to vinyl chloride) is the analysis based on time of first exposure. For liver cancer, the excess was most evident among employees first exposed before 1950, when the exposures were higher than those in later years. For brain cancer, the reverse was true: significant excess was reported only among those first exposed after 1960. This observation argues against a causal role of vinyl chloride.

As we stated in our 1991 paper, the brain cancer excess in the CMA cohort occurred at primarily two plants. Wu et al. (1988) conducted a detailed analysis of both brain cancer and liver cancer at these two plants, and found that the increased brain cancer mortality was not associated with vinyl chloride exposure. On the other hand, these authors demonstrated a significant association between liver cancer and vinyl chloride exposure. Thus, no causal link between brain cancer and vinyl chloride exposure was found in the CMA cohort.

This conclusion is supported by other studies. Recently, collaborators from four European countries (Italy, Norway, Sweden and U.K.) in a cohort of 12,706 vinyl chloride workers reported a brain cancer SMR of 1.07 based on 14 observed deaths (Simonato et al., 1991). This collaborative study included the two previous small Swedish studies (Byren et al., 1976; Hagmar et al.,1990), which reported an increase of brain cancer. In addition, this study also included updates of studies which had not reported an excess of brain cancer previously (Jones et al., 1988; Pirastu et al., 1990; Storetvedt Heldaas et al., 1984). Furthermore, a small Canadian study also reported no excess of brain cancer (Theriault and Allard, 1981). Therefore, studies from both Europe and Canada support our interpretation of the CMA study in this country that the observed brain cancer excess was not related to vinyl chloride exposure.

condition in a review or comparison of world literature on vinyl chloride.

The Seventh Revision of the International Classification of Diseases (ICD7), which was used in the original as well as the subsequent updates of the CMA study, does not recognize that these different diagnostic terms for chronic obstructive airway disease describe the same generic condition. In ICD7, the code for chronic bronchitis is 502, whereas the codes for emphysema and COPD are found within 527 ("other diseases of the lung and pleural cavity"). Emphysema is coded 527.1, and COPD is coded 527.2. On the other hand, chronic bronchitis with emphysema is coded 502.0. In an historical mortality study, the codes for various subgroups of nonmalignant respiratory disease are further complicated by the changes in nomenclature over time.

In our study we found an overall mortality deficit of nonmalignant respiratory disease (SMR = 0.79), consistent with other studies reviewed by Doll (1988) and the most recent IARC collaborative study (Simonato, et al., 1991). However, in our study, we found a significant mortality excess of emphysema/COPD, accompanied by a significant mortality deficit of other nonmalignant respiratory disease:

Disease category	Observed	Expected	SMR
Nonmalignant respiratory disease	70	87.61	0.79
Emphysema/COPD	41	22.83	1.79 s
Other nonmalignant respiratory disease	29	64.78	0.45 s

s = significant at the 0.05 level

As Doll (1988) pointed out in his comments on the above result in our study, the potential for diagnostic misclassification between emphysema/COPD and other nonmalignant respiratory disease in some patients was certainly possible. This diagnostic problem of COPD based on death certificates in epidemiologic studies has also been discussed in detail recently by Selikoff (1992).

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