CHEMICAL MANUFACTURERS ASSOCIATION

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August 11, 1993

Dear Vinyl Chloride Panel Research Coordinators:

Copies of the Panel letter to the editor of the *American Journal of Industrial Medicine* and the response from Dr. Otto Wong are enclosed for your information. If you have any questions, please call me at (202) 887-1192.

Sincerely,

Hasmukh Shah

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Enclosures

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LETTER TO THE EDITOR

Diagnostic Bias in Occupational Epidemiologic Studies

Key words: vinyl chloride exposures, mortality study, emphysema, brain cancer

The study of vinyl chloride workers by Wong et al. [1991] is an important contribution to our knowledge of the health of people occupationally exposed to this substance. However, the discussion of findings with respect to two causes of death does not include some results that affect their evaluation.

One is the apparent excess of brain cancer. There is a good deal of data in the literature showing that diagnostic bias is important when one tries to attribute death to brain cancer [Greenwald et al., 1981; Helseth et al., 1988; Kurland et al., 1982]. In particular, Greenwald et al. [1981] have shown that an excess of brain cancer in Kodak employees was associated with more thorough diagnostic studies and access to comprehensive medical care, rather than with chemical exposure history. The study by Wong et al. [1991] does not discuss diagnostic bias as a possible explanation of special importance, all the more so since there is no firm confirmation of this finding in other studies [Doll, 1988].

The second finding, the significance of which is affected by other factors, is the excess in emphysema mortality. This is a finding with an inverse dose-response relationship based on duration of employment and an ambiguous relationship with latency, accompanied by a complementary deficit of an almost equal magnitude for deaths due to other nonmalignant respiratory diseases (which can be confused with emphysema). In 1988, Sir Richard Doll dismissed this excess emphysema mortality as not being an effect of vinyl chloride exposure because of such inconsistencies.

Readers who do not know the literature would not be able to put those findings from the Wong et al. [1991] study in perspective without this kind of information.

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LETTER TO THE EDITOR

Diagnostic Bias in Occupational Epidemiologic Studies: An Example Based on the Vinyl Chloride Literature

Key words: vinyl chloride, brain cancer, emphysema, chronic obstructive pulmonary disease, diagnostic bias

INTRODUCTION

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% vs. 30.0%) and pneumoencephalograms (35.2% vs. 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 the 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

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TABLE I. Cohort Studies of Workers Exposed to Vinyl Chloride*

Authors and location	Cohort size	Brain cancer SMR
Byren et al. [1976], Sweden	771	2/0.33 = 6.12 s
Hagmar et al. [1990], Sweden	2,031	6/2.60 = 2.29 ns
Smulevich et al. [1988], USSR	3,232	4/2.61 = 1.53 ns
Cooper [1981], USA	10,173	12/5.90 = 2.03 s
Waxweiller et al. [1976], USA	1,294	3/0.90 = 3.29 ns
Wu et al. [1989], USA	4,835	15/9.20 = 1.62 ns

*s = significant at the 0.05 level; ns = nonsignificant at the 0.05 level.

programs. Therefore, our finding of a brain cancer excess could very well have been subjected to this 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 important question is "does exposure to vinyl chloride increase the risk of brain cancer?" The answer to this question should be based not only on our study but also on all other pertinent studies in the literature.

Prior to the publication of our 1991 paper, there were a number of cohort studies of workers exposed to vinyl chloride reporting an increased risk of brain cancer (Table I).

Based on a cursory reading of the literature (as Table I suggests), one may be led to believe that there are consistent reports of an increased risk of brain cancer among vinyl chloride workers in this country. In reality, all the American cohort studies were based on the same population. The Tabershaw and Gaffey [1974], the Cooper [1981], and the Wong et al. [1991] reports were all based on the same cohort study sponsored by the Chemical Manufacturers Association (CMA). The workers studied by Waxweiller et al. [1976] and Wu et al. [1989] were employees at plants which also participated in the CMA study. Thus, those who are not familiar with the history of the CMA study can easily be confused and led to assume that there had been more than one American study reporting a brain cancer excess. Essentially the same excess might be counted more than once.

To evaluate the relationship between vinyl chloride and brain cancer in the CMA cohort, we must examine, among other criteria, the strength of association [Hill, 1965]. The overall brain cancer standardized mortality ratio (SMR) reported by Wong et al. [1991] was 1.80 (23/12.76), only a modest increase [e.g., see Monson, 1990]. Furthermore, the excess was only marginally significant at the 0.05 level (lower 95% confidence limit of 1.14). Even if the diagnostic sensitivity bias accounted for 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. [1989] 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 the United Kingdom) 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 [Thériault 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.

Sir Richard Doll [1988] in a recent review combined the data from four major studies from the United States, United Kingdom, Canada, and Italy, and reported a small nonsignificant increased risk of brain cancer (29 observed vs. 19.54 expected; summary SMR = 1.48). With the updated International Agency for Research on Cancer (IARC) collaborative study, which includes both the United Kingdom and the Italian studies that Doll relied on, the summary brain cancer SMR will be even lower. In Doll's combined data, our study was the only one reporting a statistically significant brain cancer excess. We conclude that our finding of an excess of brain cancer among U.S. vinyl chloride workers reported earlier was not likely related to the chemical. The most likely explanation is that the excess was due either to chance [Doll, 1988] or to the diagnostic sensitivity bias discussed above [Greenwald et al., 1981].

EMPHYSEMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Dr. Shah's second concern about the excess of emphysema/chronic obstructive pulmonary disease (COPD) brings out important issues in evaluating chronic airway obstructive disorders. In our 1991 paper, we were concerned that the term "emphysema" was too narrow a diagnostic term. The diagnostic term more frequently used in the United States is "chronic obstructive pulmonary disease." Emphysema and COPD are two diagnostic terms for chronic airway obstructive disorders and do not represent different conditions.

In his review Doll [1988] noted:

TABLE II. Significant Mortality Excess of Emphysema/COPD Accompanied by 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.

> International comparisons of chronic nonmalignant respiratory diseases are complicated by the usage of different terms to describe what is now agreed is best called chronic obstructive lung (or pulmonary) disease, but which in the past tended to be called emphysema in the U.S. and chronic bronchitis in the United Kingdom. It must, therefore, be presumed that the two categories of "emphysema" and "chronic bronchitis" used respectively in the two large national studies were meant to describe the same thing.

Thus, in accordance with Doll's comments, one must include COPD with either chronic bronchitis or emphysema if one is to include all of the diagnostic terms for apparently the same 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 (see Table II).

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].

In addition to this potential diagnostic misclassification, we did not observe any upward trend in emphysema/COPD mortality by length of exposure to vinyl chloride; in fact, we observed an inverse relationship. Thus, this lack of a positive dose-response relationship argues against the interpretation that the excess was solely occupational in origin.

In our 1991 paper, we stated that we could not explain the emphysema/COPD excess, due to the limited exposure data and, more importantly, the lack of smoking data. Our primary objective in reporting the emphysema/COPD result was to alert other investigators. Clearly, one must include all of the diagnoses used in that particular country to make certain that the comparisons are similar. For example, if Jones et al. [1988] had included ICD 527 with ICD 502 in their U.K. study, they might have found a different result. The same is true for the von Greiser et al. [1982] study in Germany cited by Doll [1988].

In summary, although we agree that the excess of emphysema/COPD reported in our study could have been due in part to diagnostic misclassification, we do not believe that the issue of chronic obstructive airway disease in relation to vinyl chloride exposure has been examined in sufficient detail. This issue can be assessed best by a comprehensive review of the world literature of epidemiologic studies of vinyl chloride workers, a review that includes the gamut of terminology for chronic airway disorders.

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