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American Journal of Industrial Medicine 24:249–250 (1993)

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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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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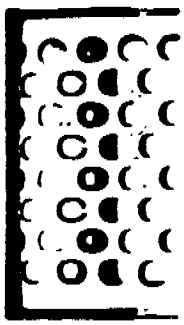


An Industry-Wide Epidemiologic Study Of Vinyl Chloride Workers, 1942–1982

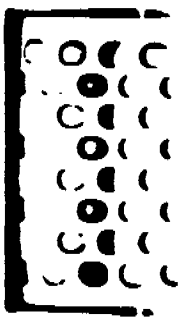
Otto Wong, ScD, M. Donald Whorton, MD, Donna E. Follart, MD, and David Ragland, PhD

The cohort consisted of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride prior to 1 January 1973. These men were employed at 37 plants in the U.S., belonging to 17 companies. Observation of the mortality experience of the cohort was updated from 31 December 1972 to 31 December 1982 (the study now covering 1942–1982). A total of 1,536 cohort members were identified as having died. The observed mortality, by cause, was compared with the expected based on U.S. mortality rates, standardized for age, race, and calendar time. Analyses by length of exposure, latency, age at first exposure, calendar year of first exposure, and type of products were performed. The study confirmed that the vinyl chloride workers experience a significant mortality excesses in angiosarcoma (15 deaths), cancer of the liver and biliary tract (SMR = 641), and cancer of the brain and other central nervous system (SMR = 180). In addition, the study also found a significant mortality excess in emphysema/chronic obstructive pulmonary disease (COPD) (SMR = 179). On the other hand, the study did not find any excess in either respiratory cancer or lymphatic and hematopoietic cancer. This study also found an increase in biliary tract cancers, independent from liver cancer.

Key words: angiosarcoma, liver cancer, brain cancer, chronic obstructive pulmonary disease

BACKGROUND

In 1974, three cases of angiosarcoma of the liver were reported among workers employed at a vinyl chloride (VC) polymerization plant in the U.S. [Creech and Johnson, 1974]. About the same time, similar cancerous hepatic effects were reported in laboratory animals exposed to vinyl chloride [Maltoni et al., 1981]. Since then, a number of epidemiologic studies have confirmed the association between angiosarcoma of the liver and occupational exposure to vinyl chloride [Tabershaw and Gaffey, 1974; Cooper, 1981; Fox and Collier, 1977; Waxweiler et al., 1976; Jones et al., 1988]. In addition to angiosarcoma of the liver a number of other cancer sites have also been implicated, including the overall digestive system [Thériault and Allard, 1981; Chiazze et al., 1977; Smulevich et al., 1988], the respiratory system [Monson



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Scand J Work Environ Health 14 (1988) 61—78

Effects of exposure to vinyl chloride

An assessment of the evidence

by Sir Richard Doll, FRS[1]

DOLL R. Effects of exposure to vinyl chloride: An assessment of the evidence. *Scand J Work Environ Health* 14 (1988) 61—78. This paper reviews the possible effects of vinyl chloride on the mortality of occupationally exposed men and the carcinogenic effects that might be observed in the general population as a result of environmental pollution with vinyl chloride. The results of four studies fulfilling the criteria of providing substantial numbers of observations more than 25 years after first exposure and covering a period long enough for more than 10 % of the workers to have been expected to die constitute the basis for the assessment of the occupational hazards. Other studies provide only supplementary information. The data permit two conclusions. First, men occupationally exposed to vinyl chloride have experienced a specific hazard of angiosarcoma of the liver. Second, any other occupational hazards that may have existed have been small. No positive evidence of a hazard of any nonmalignant disease or any type of cancer other than angiosarcoma of the liver has been found except possibly for a small hazard of lung cancer when exposure was heavy. More definite conclusions might be reached if those who have studied exposed employees could present their results in appropriate and comparable ways. A very small risk of angiosarcoma may have occurred as a result of vinyl chloride escaping into the environment around plants handling vinyl chloride in the past, but the evidence indicates that the current risk to the general public (if any) must be negligible.

Key terms: angiosarcoma of the liver, cancer, lung cancer, mortality, polyvinyl chloride, review, vinyl chloride monomer.

For many years the inhalation of large amounts of vinyl chloride has been recognized as potentially hazardous. Concentrations of the order of 10 000 ppm in the air induce unconsciousness and cardiac arrhythmia, while prolonged exposure to concentrations an order of magnitude lower have been liable to cause a specific pathological syndrome. This "vinyl chloride illness" has been characterized by four cardinal signs, namely, enlargement of the liver and spleen with a specific histological appearance, patchy infiltration of the skin resembling scleroderma, bony changes in the tips of the fingers described as acroosteolysis, and peripheral circulatory changes identical with the classical picture of Raynaud's disease. These pathological reactions may occur singly or together and may possibly be accompanied by other less characteristic effects. They can, however, be completely avoided if exposure never exceeds the level of a few hundred parts per million, ie, the level to which exposures were generally reduced in the mid-1960s.

One other serious effect has, however, been observed that may not be avoidable in the same relatively easy way, namely, the production of angiosarcoma of the liver. It must, indeed, be presumed that some risk of developing the disease will persist from exposure to doses that are even lower than the current industrial levels of 5 ppm or less, as vinyl chloride has been shown to act as a mutagen (23), and it cannot be assumed that a threshold exists below which no carcinogenic risk persists. Moreover, the possibility has to be considered that vinyl chloride may cause some cancers other than angiosarcoma of the liver, partly because laboratory studies have shown that it causes other cancers in animal experiments and partly because the initial studies demonstrating the production of angiosarcoma of the liver in humans were inadequate in size to exclude a material increase in the risk of cancer in common sites, such as the lung and large bowel. Since no threshold dose can be postulated, it also follows that some cancers may have been produced in the general public by the small amounts that have escaped into the general environment.

Consideration also needs to be given to the possibility that exposure to vinyl chloride over a long period may have noxious effects on humans that cannot be seen easily in animal experiments (by, for example, producing chronic respiratory disease), and, as it is a mutagen, there is also a possibility that it may act as a teratogen and cause congenital malformations in offspring.

In this review I have not examined the possibility that vinyl chloride acts as a teratogen or that it causes mutations in germ cells, as there is too little serious evidence to justify inclusion. Reviews carried out for sections of the industry by Downs et al (unpublished report to the Society of Plastic Industries Inc in 1977)

[1] Imperial Cancer Research Fund, Cancer Epidemiology and Clinical Trials Unit, Radcliffe Infirmary, Oxford, United Kingdom.

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