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IRVING R. TABERSHAW, M.D.
President

15 May. 1974

Dr. Irving J. Selikoff
Mount Sinai Hospital
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New York, New York 10029

Dear Irving:

I was struck during the course of the conference on vinyl chloride that several speakers including Hammond, Maltoni, Doll and you commented that vinyl chloride would probably demonstrate its carcinogenic potential by causing tumors at sites other than the liver. In the brief time that my colleague Bill Caffey had to present our report, the fact that we demonstrated this potential by findings, in addition to liver cancer, an increase in cancers of the lung, brain, and lymphatic system in those with greater exposure. There was also an excess of cancers of the buccal cavity and pharynx which does not appear to be exposure related.

We plan to flesh out our study by adding to the population base and by increasing our follow-up but I thought you might be interested in looking over the draft of a paper, based on our MCA study, which is now in preparation for publication. Incidentally the press release issued by the MCA was made without our knowledge or any input from us.

Thanks for the invitation to the conference. There was so much to learn, but in too short a time.

Sincerely,

Irving R. Tabershaw, M.D.

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Mortality Study of Workers in the Manufacture
of Vinyl Chloride and Polyvinyl Chloride

by Irving R. Tabershaw, M.D. and William R. Gaffey, M.D.

I. SUMMARY

Vinyl chloride in its manufacture and polymerization has been identified as a narcotizing agent (1), as a liver toxin (2), and as a vasospastic agent producing a specific occupational disease, acro-osteolysis (3). Recently, vinyl chloride has been incriminated as a carcinogen producing in a group of workers engaged in the manufacture of polyvinyl chloride a rare fatal liver tumor, hemangiosarcoma (4). Large doses of the chemical in rats produced cancer of the skin, lung and other organs (5). Unpublished but public information (6) indicates that inhalation experiments with rats in doses easily reached in manufacturing operations produces in addition to angiosarcoma of the liver, skin, kidney and other malignant lesions.

This is the first epidemiological study which suggests that in humans vinyl chloride may also be associated with cancer of multiple sites. A historical prospective mortality study of 8384 men who had had at least one year of occupational exposure to vinyl chloride before December 31, 1972 demonstrated that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphosarcoma, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers

was lower than that of the general male population, with the exception of cancers of the buccal cavity and pharynx. There was an excess of these cancers, which however was inversely related to estimated exposure. The explanation for the latter finding is not apparent.

The other major findings of the study are:

- (1) The overall mortality of the study population was approximately 75 percent of what would be expected in a comparable population of U.S. males.
- (2) No cause of death showed a statistically significant excess over what would be expected in a comparable U.S. male population.
- (3) All previously known angiosarcoma deaths in this population during the study period were found as part of the investigative procedure.
- (4) No deaths identified as angiosarcoma of the liver were found other than those previously identified.

II. INTRODUCTION

The objectives of the study were:

- (1) To compare the mortality of individuals who have worked in vinyl chloride plants with that of the general population;
- (2) To compare mortality patterns within the population of vinyl chloride workers, based upon estimated occupational exposure; and
- (3) To compare mortality among vinyl chloride workers with the mortality of other occupational groups.

The study population consisted of individuals from 34 plants who had worked for at least one year in a job involving exposure to vinyl chloride before December 31, 1972, and included retired and terminated as well as active workers. For each such worker the date of birth and an employment history were obtained, and the vital status of the worker as of December 31, 1972, was ascertained. For those found to have died, those death certificates that were available were obtained and the cause of death determined. The observed mortality was compared with that of the United States male population.

III. DATA COLLECTION

In each plant, data were collected for each worker stated by the plant management to have been employed for at least one year in a job involving exposure to vinyl chloride. In some plants, particularly those producing the monomer, this determination could be made on the basis of job titles. Usually, however, exposure was a function of both job title and the location of the job in the plant, so that the assessment of exposure had to be made on a case-by-case basis by plant officials.

Data were collected for as far back in time as complete records were kept. In most cases this covered the entire history of the plant. In others, records were kept for a fixed period such as a decade. In a few, records were kept for different periods, depending on whether the worker had died on the job or had left employment.

In most plants it was impossible to quantify exposure. However, industrial hygiene and safety personnel in each plant were able to identify certain jobs and locations as involving the highest exposures in the plant, and to classify other exposures as medium or low relative to the "high" represented by the jobs with the greatest exposure. Consequently, each exposed job in a worker's history was scored 1, 2, or 3 to indicate low, medium or high estimated exposure.

This gross classification has two major failings, as a result of the subjective nature of the estimates. The first is that the scores represent estimated relative exposure within a given plant. It is therefore possible that, in objective terms, a "high" score in one plant corresponds to a "medium" or even "low" score in another. The second is that exposures in most plants have tended to decrease over time, so that a worker with long service may have had jobs in the remote past which involved "low" exposure relative to other jobs at that time, but which might be "high" in comparison with current exposures in the same job. This subjective classification is therefore of questionable validity in characterizing the exposure of a given worker. For epidemiological purposes, however, those who have high scores can reasonably be expected, on the average, to have had the greatest exposure, while those with low scores will have had the least, even though the true exposure in each group may vary considerably from person to person.

The estimated exposure history of each worker was summarized by calculating an Exposure Index (EI). This was done by multiplying the number of months on each job by the exposure score, totalling

these overall exposed jobs, and dividing by the total number of months of exposure.

IV. FOLLOW-UP OF STUDY POPULATION

A follow-up procedure was instituted for those who had left employment and whose vital status could not be determined at the local plant, using direct mail follow-up and retail credit bureau investigations. Table I shows the vital status of the population as of December 31, 1972. Follow-up is 85 percent complete.

Those who were not found were born (and began their exposure) about 10 years before the group on which follow-up was complete, and had about half the duration of employment in exposed jobs with a slightly higher Exposure Index. Although there appears to be nothing very unusual about this group in terms of work history and exposure, it is nevertheless true that their exposures took place further back in time than that of the group successfully traced. It is therefore possible that their mortality, after a substantial latent period, might show a somewhat different pattern from that of the traced group.

All of the subsequent analysis is concerned with the 7128 workers on whom follow-up was complete. Table 2 shows their distribution by duration of exposed employment and the year in which that employment began. Although almost half the study group first entered exposed employment in 1960 or later, there are nevertheless 854 workers with 20 years or more exposure, and 1640 with 15 years or more. Table 3 shows the relationship between duration of exposure and Exposure Index (EI). There does not appear to be a close

relationship between the EI and the duration of exposure, that is workers with a higher EI do not differ substantially in duration of exposure from those with a lower EI. One implication is that in assessing the relationship between mortality and exposure, both duration and level of exposure should be examined separately, as well as in combination.

V. CALCULATION OF RISK OF DEATH

The risk of death is expressed as a Standardized Mortality Ratio (SMR), which is the ratio of the number of observed deaths in the study population to the number of deaths to be expected in a comparable population of U.S. males. SMR's were calculated for overall mortality and for 33 major cause groups.

Table 4 shows observed and expected deaths, and the SMR, for each of these causes for the total study group. In calculating the SMR's for specific causes, the 24 deaths for which no certificates were found were assumed to have the same cause distribution as those for which certificates were available.

In the standard population, each SMR would be equal to 100. Therefore, the statistical significance of the deviation of each SMR in the study population from the expected value of 100 was tested. A single asterisk indicates those SMR's which differed significantly from 100 at the 5 percent level, that is, which had a probability of .05 or less of occurring by chance. A double asterisk indicates those which were significant at the 1 percent level. SMR's based on fewer than 5 observed cases were not tested for significance.

Table 5 shows the same SMR's for workers with an Exposure Index below 1.5 versus those at 1.5 or above. The dividing point of 1.5 represents a level halfway between "low" and "medium."

Table 6 shows similar results for workers with less than 5 years exposure versus those with 5 years or more.

In order to examine the possible interaction between duration and level of exposure, the study population was divided into 4 groups on the basis of both EI (low vs high) and duration of exposure (short vs long) using the same dichotomization as Table 5 and 6.

Table 7 shows the results for short versus long exposure in the low EI group, and Table 8 shows the same comparison in the high EI group.

In each of the above tables, deaths for which certificates had not been received were assumed to be distributed as a uniform percentage of all causes. The cause specific SMR's were therefore adjusted upward by a percentage which varied in each subgroup.

IV. ANALYSIS

The overall mortality of the study population is statistically significantly lower than that of the U.S. male population. There were 352 observed deaths compared with 467 expected, for an SMR of 75.

Table 4 shows that no specific cause of death was statistically significantly greater than expected. Several, particularly heart disease, accidents and "other diseases" not detailed in the tables, were significantly below their expected values.

When the study population is divided according to intensity and duration of exposure (Tables 5 and 6) and combinations of these measurements (Tables 7 and 8) three major patterns emerge.

For malignant neoplasms as a whole, the SMR increases with increasing exposure, whether measured by level, duration, or both. In the high exposure group with 5 years or more exposure (Table 8) there are 36 observed cases and 26.11 expected.

For cardiovascular - renal diseases as a group, there are also increases in the SMR with increasing exposure, but the numbers of observed cases remain less than expected, the differences being statistically significant in all groups except the high exposure, long duration group in Table 8.

For all other causes, there are no consistent relationships with exposure.

Within the malignant neoplasms, the largest (although not statistically) significant SMR is in cancers of the buccal cavity and pharynx, with 5 observed, 2.84 expected, and an SMR of 189. However, Tables 5 to 8 show that all these cases have Exposure Indexes below 1.5, and 4 out of the 5 have less than 5 years exposure.

Cancer of the digestive system shows no excess in the study population as a whole. However, in those workers with Exposure Indexes of 1.5 or higher, there are 12 observed cases where 9.14 are expected (Table 5). In the subgroup of the above workers with 5 years or more exposure, there are 11 observed cases and 7.47 expected.

Respiratory cancer shows a slight excess in the total group, and a similar pattern for different exposure categories, with 13 observed versus 10.28 expected when the Exposure Index is 1.5 or

higher, and 12 observed versus 8.50 expected when, in addition, the duration of exposure is 5 years or more.

Malignant neoplasms of other and unspecified sites show an excess in the total group, and an increase with both level and duration of exposure (Tables 5 and 6). The relationship with exposure is more pronounced, since those with exposures of less than 5 years have fewer cases than expected.

The lymphosarcomas, although occurring at about the expected rate when the whole group is considered, are concentrated almost entirely in the high exposure long duration group. In that category there are 4 cases observed and 1.84 expected.

Cancers of the genital and urinary organs, and leukemia, have fewer cases than expected. The number of cases is too small to examine any trends.

VII. DISCUSSION

The favorable overall mortality of the study population is a phenomenon commonly observed in working populations. In view of this fact, SMR's which are higher than expected may be worthy of attention even if they are not statistically significant. This is especially true in the present study since the number of deaths from many causes is quite small, and even a relatively high SMR may not reach statistical significance.

If, in addition, a particular cause shows a consistent pattern of increase with exposure or estimated exposure, the findings are particularly interesting.

By these criteria, mortality from digestive cancer, respiratory cancer, cancer of other and unspecified sites, and lymphosarcoma,

appear to be related to exposure as estimated in this study.

In view of the association between vinyl chloride exposure and angiosarcoma of the liver, the digestive cancers were examined further to see what contribution angiosarcoma made to the observed mortality pattern.

Of the 19 digestive cancers, 7 were liver cancers, of which two were angiosarcomas according to the death certificate. However, among angiosarcoma deaths in vinyl chloride workers identified by other investigators, there were 6 which occurred in the present study population during the study period. They were all found in the course of the study, but 4 were listed on the death certificate as due to causes other than angiosarcoma. Table 9 shows these with the death certificate cause.

If there had been no angiosarcomas, Table 9 shows that the total number of digestive cancers in the high exposure group would have dropped to 8, and the number with high exposure and 5 years or more exposure would have dropped to 2, so that the mortality pattern in this cause group is due entirely to angiosarcoma.

The other cause group worth further investigation is cancer of other and unspecified sites, both because it is a heterogeneous category and because it seems, unlike the other cancers, to be more related to duration than to level of exposures.

Table 10 shows a list of the specific causes included in this category, which is essentially brain cancer and generalized cancer with primary site unknown. About 40 percent of the observed deaths were due to brain cancer. In the general male population, about 22

percent of this category is due to brain cancer, so that not only is the mortality from this cause excessive, but brain cancer is overrepresented.

The possibility exists based on the lack of specificity of some of the listed causes that some of the brain cancers were not primary, but metastases from another unidentified site such as the lung.

The cancers of the buccal cavity and pharynx are difficult to explain because of their occurrence in the low exposure - short exposure group. It is possible that this is a chance occurrence, that exposures to other substances were involved, or that the mouth and pharynx may be peculiarly susceptible because of the gaseous nature of the chemical.

VIII. POSSIBLE BIASES IN THE CALCULATION OF RISK

There are two major potential sources of bias in the study. The first is that the follow-up rate is lower than is desirable. The second is that observations of workers with long exposures followed by a long latent period are not adequately represented, so that the power of the study to detect causes of death associated with long exposure and long latency is impaired. Populations with such characteristics exist and should be investigated.

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