

A Mortality Study of Vinyl Chloride  
Workers in Japan

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Introduction

Since the discovery, in 1973, of three deaths from angiosarcoma of the liver in polyvinyl chloride (PVC) production workers of a chemical plant in the US [1], many epidemiological studies have been carried out in various countries. The results of these studies indicate the definite association between the exposure to vinyl chloride monomer (VCM) and this rare disease of the liver, and possibly other malignant neoplasm of lung, brain and lymphatic tissue [2-7].

In Japan VCM and PVC have been produced since 1949, and the production amount of VCM in 1974 reached almost 2 million tons per year. Workers who had been involved in these production process numbered about 10 thousand at the end of 1975. These workers, especially the reactor cleaners in the polymerization plants, had been exposed such a high concentration of VCM as to develop bone lesions resulting, in some cases, in the clear manifestation of acroosteolysis [8].

This retrospective cohort study was undertaken to clarify whether or not these vinyl chloride (VC) workers in Japan had experienced increased risks of dying from malignancies mentioned above and from other diseases which may be related to the occupational exposure to VCM.

Materials & Methods

The subjects of investigation consisted of male workers who had worked for at least one year before December 31, 1964 in one of 25 plants which had began producing VCM and/or PVC before 1965. The observation period was from January 1, 1950 to October 31, 1975. 4524 individuals who met the above criteria were classified according to the job they had engaged for the longest

Table 1. Major Work Activity of 4524 VC Workers and Their Vital Status as of October 31, 1975

| Type of Work   | No. of Workers | Vital Status |          |         |
|----------------|----------------|--------------|----------|---------|
|                |                | Alive        | Deceased | Unknown |
| VCM production | 900            | 853          | 44       | 3       |
| PVC production | 2546           | 2394         | 128      | 24      |
| Maintenance    | 239            | 227          | 11       | 1       |
| Warehouse      | 34             | 33           | 1        | 0       |
| Laboratory     | 578            | 558          | 19       | 1       |
| Fabrication    | 227            | 221          | 6        | 0       |
| Total          | 4524           | 4286         | 209      | 29      |

period at the termination date of the follow up (Table 1). For those workers who had been classified as PVC production, detailed job history was collected. With respect to the workers who had experienced reactor cleaning, the total amount of hours in the reactor vessels was inquired. The medical history of each member of the cohort was also investigated with the emphasis on hepatic diseases.

The vital status of those who had retired or left the companies were confirmed by referring to the municipal authorities which had the jurisdiction over the locations where these workers lived at the time of retirement. When death was confirmed, the copy of death certificate was obtained from the District Legal Affairs Bureau. The underlying cause of death was decided in accordance with the 8th revision of International Classification of Diseases (1965). Person-years was calculated for each individual from one year after the initial employment in VC job to the termination date of the follow up or to the date of death if the death had occurred prior to the completion of the follow up. The expected numbers of deaths from various causes were calculated utilizing the age-sex-specific mortality of general population in Japan in appropriate calendar years. A computer program which had been developed by Monson was used for the calculation [9].

#### Results

Within the observation period, 209 deaths occurred in the cohort and the copies of death certificate for the deceased were completely collected. The

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Table 2. Observed and Expected Deaths\*\* from Various Causes Among 4524 VC Workers Between January 1, 1950 and October 31, 1975

| Cause of Death             | PVC Workers |        |           | Other Workers |        |           |
|----------------------------|-------------|--------|-----------|---------------|--------|-----------|
|                            | Obs.        | Exp.   | Obs./Exp. | Obs.          | Exp.   | Obs./Exp. |
| All Causes                 | 128         | 147.59 | 0.87      | 81            | 109.33 | 0.74      |
| All Malig. Neopl.          | 37*         | 26.85  | 1.38      | 16            | 19.25  | 0.83      |
| Stomach                    | 16          | 11.89  | 1.35      | 4             | 8.44   | 0.47      |
| Liver                      | 6*          | 2.54   | 2.36      | 1             | 1.82   | 0.55      |
| Pancreas                   | 3           | 1.05   | 2.86      | 1             | 0.75   | 1.33      |
| Lung                       | 2           | 2.33   | 0.86      | 2             | 1.64   | 1.22      |
| Others                     | 10          | 9.04   | 1.11      | 8             | 6.60   | 1.21      |
| Benig., Unspecif. Neoplasm | 3           | 1.58   | 1.90      | 2             | 1.17   | 1.71      |
| Cirrhosis                  | 7           | 5.25   | 1.33      | 3             | 3.94   | 0.76      |

\*\* Expected deaths are based on mortality of general population in Japan.

\* Excess is statistically significant at 5% level.

vital status for 29 workers, which account for 0.6% of the total cohort, could not be confirmed (Table 1). Table 2 shows the numbers of observed and expected deaths from various causes. Workers who had been classified by their job histories as other than PVC production were small in number, so they were categorized together as others and compared it with the PVC group.

Age distribution of these two groups was similar at the entry into follow up, the average age being 28.2 for the PVC workers and 28.0 for the other workers. Average years of observation was 16.3 for both groups. The ratio of observed number to the expected in the total death was 0.87 for the PVC workers and 0.74 for the other group. The difference in the ratio between the two groups was almost explained by the difference in the mortality from malignant neoplasm. Number of deaths due to malignant neoplasm was 37 for the PVC workers and exceeded the expected number by about 10. The excess was confined to digestive organs such as stomach, liver and pancreas. The difference between observed and expected number was statistically significant solely for the malignant neoplasm of liver (observed/expected : 6/2.54).

Among 6 liver cancers one was identified as angiosarcoma of the liver by autopsy and that was stated on the death certificate. For the remaining 5 cases, only diagnoses as hepatoma (1) or as liver cancer (4) were indicated on

Table 3. Observed and Expected Deaths from Liver Cancer and Other Malignant Neoplasm for PVC Workers by Year after First Exposure and Years Worked

| Year from First Exposure | Years Worked | Liver Cancer |      |           | Other Malign. Neopl. |       |           |
|--------------------------|--------------|--------------|------|-----------|----------------------|-------|-----------|
|                          |              | Obs.         | Exp. | Obs./Exp. | Obs.                 | Exp.  | Obs./Exp. |
| 1 - 14                   | 1 - 14       | 1            | 1.35 | 0.74      | 19                   | 13.37 | 1.42      |
| 15 -                     | 1 - 14       | 2            | 0.80 | 2.50      | 9                    | 7.48  | 1.20      |
|                          | 15 -         | 3*           | 0.39 | 7.69      | 3                    | 3.46  | 0.87      |

\* Excess is statistically significant at 1% level.

the death certificate without any description of autopsy. Although the duration of employment of these 6 PVC workers distributed evenly from 1.3 to 22.6 years, the time period from the initial employment to death was more than 15 years in all but one case of 1.3 years. As shown in Table 3, three (including 1 case of angiosarcoma of the liver) of 5 cases, who had died from liver cancer 15 and more years after their initial employment in VC job, had also been engaged in VC job more than 15 years. The expected number of deaths corresponding to the above conditions was 0.39. With regard to the total malignant neoplasm other than liver cancer, the number of deaths was greater for the period less than 15 years after initial employment in comparison to the period 15 and more years. The ratio to the expected number was also higher for the period less than 15 years.

The PVC workers were subdivided into five categories; 1) reactor operation, 2) reactor cleaning, 3) dehydration and drying, 4) PVC resin bagging and 5) VCM recovery. As majority of workers shifted their job from one to another for several times, this classification did not serve as the material to estimate the level of exposure to VCM.

Then, for the estimation of relative exposure, total amount of hours worked in the reactor vessel of each individual was referred. There were 2104 workers who had experienced reactor cleaning. Among those 268 (12.7%) workers whose longest engagement was other than PVC production were included. There were 3 deaths from liver cancer among the workers who had experienced reactor cleaning. One of these 3 was died of angiosarcoma, total amount of time spent

Table 4. Observed and Expected Deaths from Various Causes by Experience of Reactor Cleaning

| Cause of Death     | Reactor Cleaning (+) |        |           | Reactor Cleaning (-) |       |           |                        |       |           |
|--------------------|----------------------|--------|-----------|----------------------|-------|-----------|------------------------|-------|-----------|
|                    | (N=2104)             |        |           | PVC Workers (N=710)  |       |           | Other Workers (N=1710) |       |           |
|                    | Obs.                 | Exp.   | Obs./Exp. | Obs.                 | Exp.  | Obs./Exp. | Obs.                   | Exp.  | Obs./Exp. |
| All Causes         | 79                   | 106.47 | 0.74      | 51                   | 54.14 | 0.94      | 79                     | 96.31 | 0.82      |
| All Malign. Neopl. | 20                   | 18.10  | 1.10      | 17*                  | 10.79 | 1.58      | 16                     | 17.21 | 0.93      |
| Liver Cancer       | 3                    | 1.68   | 1.79      | 3                    | 1.05  | 2.86      | 1                      | 1.63  | 0.61      |
| Cirrhosis          | 7                    | 3.74   | 1.87      | 1                    | 1.97  | 0.51      | 2                      | 3.49  | 0.57      |

\* Excess is statistically significant at 5% level.

Table 5. Rates of Liver Diseases in Medical History  
by Experience of Reactor Cleaning

| Reactor<br>Cleaning | hr. Worked<br>in the<br>Reactor | No. of<br>Workers | Average*<br>Years<br>Observed | Acute<br>Hepatitis |                  | Chr. Hepatitis<br>+ Cirrhosis |                  | Total Liver**<br>Diseases |                  |
|---------------------|---------------------------------|-------------------|-------------------------------|--------------------|------------------|-------------------------------|------------------|---------------------------|------------------|
|                     |                                 |                   |                               | No.                | Rate<br>per 1000 | No.                           | Rate<br>per 1000 | No.                       | Rate<br>per 1000 |
| Experienced         | 500 -                           | 969               | 12.3                          | 25                 | 25.8             | 7                             | 7.2              | 42                        | 43.3             |
|                     | - 499                           | 1135              | 11.7                          | 20                 | 17.6             | 8                             | 7.0              | 35                        | 30.8             |
| Non-Experienced     |                                 |                   |                               |                    |                  |                               |                  |                           |                  |
| PVC Workers         | -                               | 710               | 10.2                          | 11                 | 15.5             | 5                             | 7.0              | 15                        | 21.1             |
| Other workers       | -                               | 1710              | 10.2                          | 24                 | 14.0             | 10                            | 5.8              | 40                        | 23.4             |

\* Years observed is equal to years of service in the plants.

\*\* "Total Liver Diseases" include liver disease (NOS), jaundice and abnormal liver function test in addition to hepatitis and cirrhosis but exclude serum hepatitis. These diseases are counted once for an individual who have more than one liver diseases or symptoms in his medical history.

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for reactor cleaning was 879 hours. Other 2 workers died of liver cancer had worked for reactor cleaning less than 500 hours. There was no tendency that death from liver cancer concentrated in the workers who had engaged in reactor cleaning for a extended period of time. As shown in Table 4, the ratio of observed death from liver cancer to the expected was smaller for the workers with the experience of reactor cleaning than the PVC workers without experience.

With regard to the previous history of hepatic disease, rate of workers who had anamnesis of (acute) hepatitis was higher for the workers engaged in reactor cleaning, especially high for the workers with accumulated working time over 500 hours (Table 5). If abnormal liver function test, jaundice and hepatic disease (not otherwise specified) are all included, excepting serum hepatitis, 43.3 (per 1000 individuals) were affected with some kind of hepatic anamnesis for the workers having experience of working over 500 hours. For the group less than 500 hours and the non-reactor group, these figures were 30.8 and 22.7 respectively.

#### Discussion

The difficulty of clinical diagnosis of angiosarcoma of the liver, the low rate of biopsy conducted in Japan and the fact that death certificate is sometimes submitted before the completion of autopsy, all make it improbable that angiosarcoma of the liver is stated on the death certificate even if it is the cause. It is very difficult to collect medical records systematically in large population, so the study was conducted by way of the death certificate as the next to best method. As the next step, it was planned to collect the medical records of the workers whose death were identified. This second step failed except for very small number of cases. The follow up by the name and address of doctors written on the death certificate was difficult. And even if we could contact the doctors, we encountered even more difficult situation in obtaining the medical records.

On the other hand, the results of investigation conducted by "The Expert Committee of the Toxicity on VC", which is sponsored by the Ministry of Labour, provided us clinical and pathological information related to our subjects. According to that investigation, other than one case found in our cohort, the cause of 2 deaths were identified as angiosarcoma of the liver with high probability. Histo-pathological information, however, was not

available for these 2 cases. Diagnostic description on the death certificates of the 2 probable cases were liver cancer and hepatic tumor respectively. The latter was not included in the malignant neoplasm because it was classified as neoplasm of unspecified nature by the International Classification of Diseases.

Among the 7 cases of liver cancer found in our cohort, the probability of being angiosarcoma of the liver for the remaining 5 cases may be low. One of these 5 cases was examined in the above-mentioned committee and was judged as malignant tumor of extrahepatic bile ducts. For the other 4 cases, no medical records was obtained. Based on the information stated on the death certificate, it is improbable that those were angiosarcoma of the liver in 2 cases of the 4. For one case, the cause of death was identified as hepatoma on the death certificate. For another case, the metastatic lesion was diagnosed as adenocarcinoma by the exploratory excision of lymphonodi over left clavicle. Liver cancer as indicated on the death certificate was the only information available for the remaining two cases. But the term of employment in VC job was relatively short for these two cases, 1.3 and 5.5 years respectively.

There are 3 subjects (including 2 probable cases) dies of angiosarcoma of the liver during observation period. Another subject who was also a member of our cohort died in August 1976, after the termination of follow up, and was identified as angiosarcoma of the liver by autopsy. Those 4 subjects worked for PVC production more than 15 years and all experienced reactor cleaning except the one diagnosed as liver cancer on the death certificate. Considering the fact that they had been exposed to VCM for an extended period of time and sometimes with considerably high concentration, we assumed that the incidence of angiosarcoma of the liver is increasing also in our cohort. However, it is impossible to conclude in this way only from the results obtained in our study. Two cases among 3 died of angiosarcoma contributed to the abnormal excess in the period after 15 and more years from the initial employment. But this study failed to show the relationship between the mortality rate from liver cancer and the level of exposure to VC. If there had been no epidemiological studies which strongly suggest the relation of angiosarcoma of the liver to VC exposure, it is doubtful that this kind of results on the small number of cases gained serious attention.

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The investigation on the hepatic diseases in previous history was conducted as a reference on the mortality study. Because informations such as diagnostic criteria and date of diagnosis were not obtained in detail, exact incidence of liver disease was unable to be calculated. Functional and gross morphologic changes in the liver were frequently observed among VC workers, when thorough medical examination was performed [10]. It is considered that the difference in the rate of liver diseases by the experience of reactor cleaning reflects the difference in the exposed dose of VCM.

In relation to this, it is noticeable that the number of deaths from liver cirrhosis exceeded the expected for the workers experienced reactor cleaning. However, any excess of the death from liver cirrhosis is not seen in other studies [2, 3]. And alcoholic intake was not inquired in this study. The expert committee examined 3 of the 7 deaths from liver cirrhosis among the workers experienced reactor cleaning. The results denied the relationship between VCM exposure and the disease. In 2 of the 3 cases, the onset of the disease is earlier than the first exposure to VCM. Another case was lacking in symptoms specific to the hepatic insufficiency caused by VCM exposure.

For the occupational cancer in general, the latent period from the first exposure to the clinical diagnosis is considerably long. In the case of angiosarcoma of the liver by VCM exposure, the average time period is about 20 years [3, 11]. Only 28% of the total cohort had been observed more than 20 years since the initial employment. Continued follow up is necessary to clarify the whole spectrum of carcinogenic effects of VCM on the study cohort.

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