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Mortality and Cancer Rates among Workers in the Swedish PVC Processing Industry

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Personnel lists from four PVC-processing industries were collected on production of employees with at least three months of employment at the beginning of 1945 and the last day of employment December 31, 1974. Of 2073 persons, 103 could not be followed up, because they had moved abroad. The remaining persons comprise the cohort of 1970 individuals who were analyzed and compared with the national population with respect to mortality from various diseases and cancer morbidity.

The death risk from myocardial infarction is elevated in the cohort. This elevation is most clearly apparent in the subcohort which had at least two years of exposure time and where the analysis was directed at circumstances chronologically close to the time of exposure. The myocardial infarction risk related to vinyl chloride exposure is discussed in relation to earlier studies on the vascular effects of vinyl chloride. An indication of an elevated risk of morbidity and mortality from tumors in the digestive organs is also present. However, this is not statistically confirmed. A few future follow-ups of the present study are necessary in order to clarify any possible elevated risk of tumors in the PVC-processing industry.

Vinyl chloride has been shown to cause scleroderma, Raynaud's phenomenon, acroosterolysis, liver damage and liver cancer (hemangiosarcoma) (*1*) in workers exposed to vinyl chloride monomer (VCM). This has been shown in studies (*2*, *3*) performed at companies which fabricate poly(vinyl chloride) (PVC). In animal experimental studies it has been reported that inhalation of VCM causes malignant tumors in different organs in rodents (*4-6*).

In Sweden, in 1974, two cases of liver hemangiosarcoma were diagnosed in employees at a company engaged in the processing of VCM and PVC (*7*). Later another two cases occurred at the same factory.

Studies on other forms of cancer (*8*, *9*) suggest that VCM-exposed workers in the PVC fabricating industries may possibly run an elevated risk of contracting forms of cancer other than hemangiosarcoma in the liver. Earlier, an excess mortality from cardiovascular diseases was also observed (*10*) in employees in the PVC manufacturing industry.

The present retrospective cohort study was performed for the purpose of determining the pattern of morbidity and mortality in the PVC processing industry. The PVC processing industry, generally speaking, has had a lower level of exposure to VCM than the fabrication industry. In the Swedish PVC processing industry, at present, about 5000 persons are employed in production.

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Material and Methods

Information for the study was collected from four PVC processing companies. The four companies all used PVC which, after additions of various chemicals, is heat-treated for fabrication into floor covering, lace, pipes, and food packaging.

Data Collection

The following data were collected from the personnel lists at the companies: personal number, name, beginning and end of exposure (year and month) and class of exposure.

In order for a person to be included in the original cohort, at least three months of employment was required in the period beginning in 1945 and the ending December 13, 1974. The exposure was classified as follows: class 3 (high), work in the mixing department; class 2 (medium), heat treatment machines; and class 1 (low), other production departments.

The collected data were transferred to punched cards and magnetic tape for statistical processing. The magnetic tape was coordinated with the national total population and the so-called death tapes for the 1961-1976 period and checked against the cancer registry by the Central Bureau of Statistics (SCB). The personnel numbers which could not be recovered at this time were checked by the national taxation office. The original cohort included a total of 2,073 persons. Of these, 103 persons (5%) dropped out, 70 or whom had moved abroad, 5 were found in the missing persons register of the tax office, and 28 could not be traced.

Study Cohorts

For the statistical processing, the results of the cohort of 1970 persons were divided into a number of subcohorts (study cohorts): (1) all persons with at least three months of exposure (follow-up time from the beginning of exposure and through 1976); (2) all persons with at least six months of exposure excluding those who stopped before 1961 (follow-up time from beginning of exposure but no earlier than 1961 and through 1976); (3) all persons with at least six months of exposure and where the exposure began no earlier than 1961 (follow-up time from beginning of exposure and through 1976); (4) all persons with at least two years exposure (follow-up time from two years after beginning of exposure but no earlier than 1961 and through 1976 but no more than ten years after exposure stopped); (5) all persons with at least two years exposure (follow-up time from ten years after exposure began but no earlier than 1961 and through 1976).

The two latter named study cohorts were chosen in order to study whether any differences existed in the death cause pattern with respect to when the deaths occurred after the beginning of exposure. The first of the study cohorts was intended to shed light on possible causes of death which occur relatively early, e.g., accidents caused by the job. The second was intended to shed light on such death causes as occurred after a longer time had passed. Tumors caused by occupational exposure, for example, often have a long latency period, 5-10 yr or longer.

Results

The original cohort was relatively young at the beginning of exposure. The age distribution in the different exposure classes is given in Table 1. One finds various dissimilarities between the exposure classes. In class 1 (low), 41.7% were younger than 35 years at the beginning of exposure; in class 2 (average), 47.7%; and in class 3 (high), 50.6%. There

Table 1. Age distribution in original cohort at beginning of exposure

Age	% in each exposure class			
	1	2	3	1–3
< 19	1.6	2.0	8.9	2.1
20–24	7.5	14.6	14.3	9.2
25–29	13.5	15.7	21.4	14.4
30–34	19.1	15.4	17.0	18.3
35–39	17.0	13.2	10.7	15.9
40–44	13.7	12.6	9.8	13.3
45–49	11.1	12.6	8.9	11.3
50–54	8.0	7.8	5.4	7.8
55–59	5.1	3.9	1.8	4.7
60–64	2.6	2.0	1.8	2.4
> 65	0.7	0.3	0.0	0.6
No. of persons	100% (1501)	100% (357)	100% (112)	10%% (1970)

Table 2. Distribution of exposure time in the original cohort.

Months	% in each exposure class			
	1	2	3	1–3
< 5	13.1	0.3	0.0	10.1
6–23	38.4	8.4	8.9	31.3
24–59	25.0	17.4	10.7	22.8
60–119	15.3	45.7	15.2	20.8
> 120	8.2	28.3	65.2	15.1
	100% (M = 1510)	100% (M = 357)	100% (M = 112)	100% (M = 1970)

Table 3. Observed and anticipated number of deaths as of December 31, 1976.

Cohort	Number	No. of deaths		Ratio O/E	Approx. 95% confidence interval
		Observed	Expected		
Exp. class 1	1303	53	55.5	0.95	± 0.26
Exp. class 2	356	14	21.9	0.64	± 0.34
Exp. class 3	112	6	10.3	0.70	± 0.47
Exp. class 1–3	1171	73	87.8	0.84	± 0.19

Table 4. Observed and anticipated number of deaths from certain causes during the 1969–1976 period in those with at least six months of exposure including those who stopped before 1961.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	17	14.0	1.21
Digestive organ tumors 150–159	8	4.9	1.63
Cardiovascular diseases VII	22	24.3	0.91
Myocardial infarction 410.90	15	20.0	1.49
Accidents, suicide, etc. XVII	13	9.2	1.42

[a]Risk calculated from the beginning of exposure but no earlier than 1961. Study cohort 2 (1771 persons).

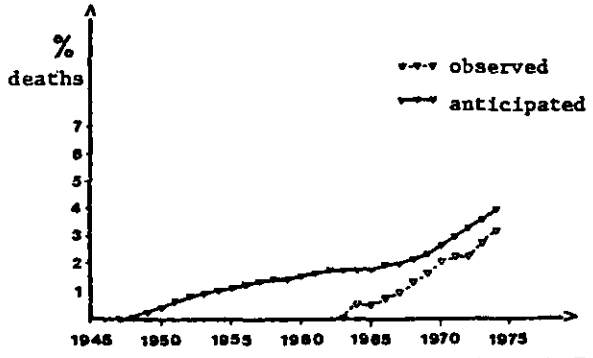

FIGURE 1. Cumulative deaths (in percent): (▽) observed; (▼) anticipated. Expected value calculated from beginning of exposure. Study cohort 1 (1970 persons). The percentage for a given year was calculated as 100 (number of persons dying through year in question divided by the number of persons beginning exposure up to and including the year in question).

were also dissimilarities in the length of exposure with respect to exposure class (Table 2). However, it should be noted that the table includes cases which were still under exposure at the final date for entrance into the cohort (December 31, 1974), for which reason, a certain bias toward short exposure times is found. Regardless of this, exposure class 3 has longer exposure times on the average.

The cohort as a whole reveals no noteworthy increase in the total risk compared with the national average, nor is there any indication of this in the subgroups making up the study cohort.

Study cohort 1, which includes everyone with at least six months of exposure and with calculation of the risk from the beginning of exposure, is somewhat remarkable in that the anticipated number of deaths is significantly higher than that observed up to 1964 (Fig. 1). This is commented on further in the discussion. Study cohort 2 (Tables 3 and 4; Fig. 2) includes persons with at least six months of exposure, excluding those who stopped before 1961. The risk calculation is made from the beginning of the exposure, but no earlier than 1961 and up to the end of the follow-up time (1976). The observed number of deaths is somewhat lower than expected, much lower in exposure class 2. Classes 2 and 3 are relatively small and are sensitive to random deviations in this type of analysis. In order for random deviations not to influence the results, the classes were combined. This is true of all study cohorts. This distribution with respect to the vari-

Table 5. Observed and anticipated number of deaths as of December 31, 1976 in those with at least six months of exposure beginning no earlier than 1961.[a]

Cohort	Number	No. of deaths		Ratio O/E	Approx. 95% confidence interval
		Observed	Expected		
Exp. class 1	1139	43	41.2	1.04	± 0.31
Exp. class 2	247	4	11.7	0.34	± 0.34
Exp. class 3	42	1	1.8		
Exp. class 1–3	1428	48	54.7	0.88	± 0.35

[a]Risk calculation from beginning of exposure. Study cohort 3 (1428 persons).

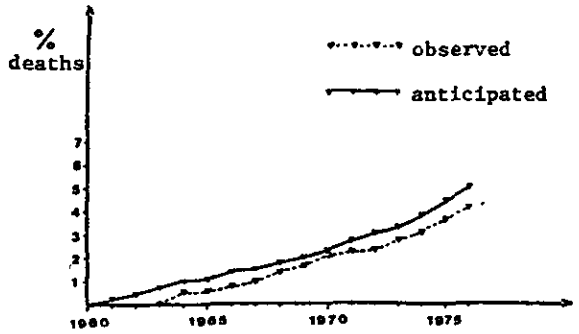

FIGURE 2. Cumulative deaths (in percent). Expected value calculated through 1961. Study cohort 2 (1771 persons). Percentage for a given year calculated as in Fig. 1.

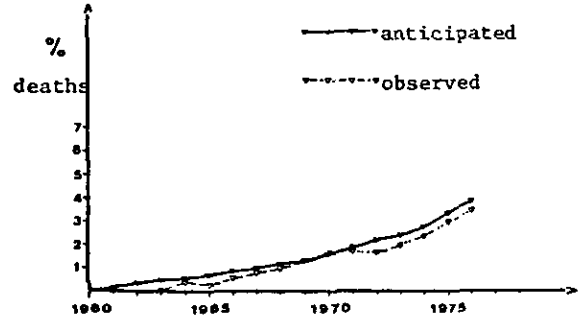

FIGURE 3. Cumulative deaths (in percent) of those who began exposure in 1960 or later. Study cohort 3 (1428 persons). Percentage for a given year calculated as in Fig. 1.

ous death causes is shown in Table 4. The observed and anticipated number of deaths during the 1961-1968 period is relatively small, only a few cases, and the death cause classification was modified as mentioned earlier in 1969, for which reason 1961-1968 period is not discussed separately. By and large, the picture is the same there as for the 1969-1976 period reported on. From Table 4, one sees that the observed number of deaths, especially those from tumors of the digestive tract, myocardial infarction and accidents, is somewhat higher than anticipated. However, the differences are not significant. Study

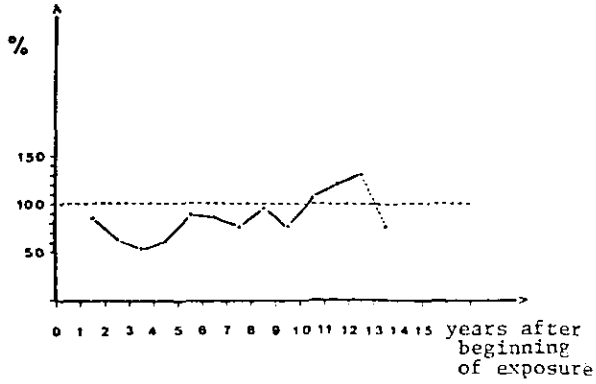

FIGURE 4. Observed death risk per year at different points of time after beginning of exposure expressed in percent of corresponding anticipated risk in those who began exposure in 1961 or later. Study cohort 3 (1428 persons).

Table 6. Observed and anticipated number of deaths from certain causes during the 1969–1976 among those with at least six months of exposure beginning in 1961 or later.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	9	9.7	0.93
Digestive organ tumors 150–159	4	3.3	1.20
Cardiovascular diseases VII	16	16.2	0.99
Myocardial infarction 410.90	14	11.2	1.25
Accidents, suicide, etc. XVII	11	7.3	1.51

[a]Risk calculated from the beginning of exposure. Study cohort 3 (1428 persons).

cohort 3 (Tables 5 and 6; Figs. 3-5) which pertains to those who began working in 1961 or later but which otherwise satisfy the same criteria as study cohort 2, displays a similar picture.

An analysis of study cohort 3 according to formula B (Figs. 4 and 5) indicates that the annual risk during the first year of exposure is somewhat lower than the anticipated one, but that after about ten years, an increased risk occurs so that the observed risk becomes higher than the anticipated.

Table 7. Observed and anticipated number of deaths from certain causes during the 1969–1976 among those with at least two years of exposure.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	5 (9)	7.4 (8.9)	0.86[b] (1.01)
Digestive organ tumors 150–159	2 (4)	2.6 (3.2)	0.78[b] (1.27)
Cardiovascular diseases VII	15 (16)	12.7 (15.8)	1.18[b] (1.01)
Myocardial infarction 410.90	11 (12)	5.4 (6.6)	2.03[b] (1.82)[b]
Accidents, suicide, etc. XVII	4 (5)	4.6 (5.1)	0.87[b] (0.97)

[a]Risk calculated from two years after beginning of exposure and no more than five years (10 years) after end of exposure. Study cohort 4 (1155 persons).
[b]$p < 0.05$.

Table 8. Observed and anticipated number of deaths from certain causes during the 1969–1976 in those with at least two years of exposure.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	9	6.0	1.51
Digestive organ tumors 150–159	4	2.2	1.85
Cardiovascular diseases VII	12	11.1	1.08
Myocardial infarction 410.90	8	4.5	1.77
Accidents, suicide, etc. XVII	2	2.5	0.79

[a]Risk calculated from 10 years after beginning of exposure. Study cohort 5 (680 persons).

Table 9. Observed and anticipated number of deaths from cancer during 1961–1976 in those with at least six months of exposure excluding those who stopped before 1961.[a]

	Observed	Expected	Ratio O/E
Malignant tumors (total)	51	44.6	1.14
Digestive organ tumors (150–159)	11	8.5	1.29

[a]Risk calculated from beginning of exposure but no earlier than 1961. Study cohort 2 (1771 persons).

In study cohort 4 (Table 7) which concerns time during ongoing exposure or a relatively short time after the end of exposure, i.e., "short-term perspective," one sees an increased death risk from myocardial infarction. Other causes are somewhat lower here than expected.

In study cohort 5 (Table 8), finally, one finds an indication of an increase in the death risk as regards tumors, but also for myocardial infarction. The differences between the observed and anticipated numbers are not, however, statistically confirmed at the 5% level.

The result with respect to mortality can be summarized as follows. In the study cohorts, overall, one finds no noticeable increase in mortality. On the other hand, there are indications of a shift in the death cause pattern compared with the national average. This shift is expressed primarily in the fact that the number of myocardial infarctions is noticeably higher during ongoing exposure or within a relatively short period of time after the end of exposure. There are also indications that the death from tumors can be elevated among persons with a long latency period (Tables 7 and 8).

In the question of cancer morbidity, there is no certain increase in study cohort 2 (Table 9 and Fig. 6). In the question of tumors of the digestive organs, in the same study cohort, 11 cases were observed as opposed to an anticipated 8.5. The difference is not statistically verified. One of these eleven tumors was liver cancer (ICD 155.0).

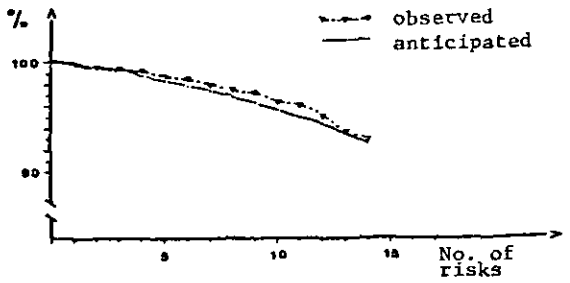

FIGURE 5. Cumulative survival probability (in percent) of those who began exposure in 1961 or later and have at least six months of exposure. Study cohort 3 (1428 persons).

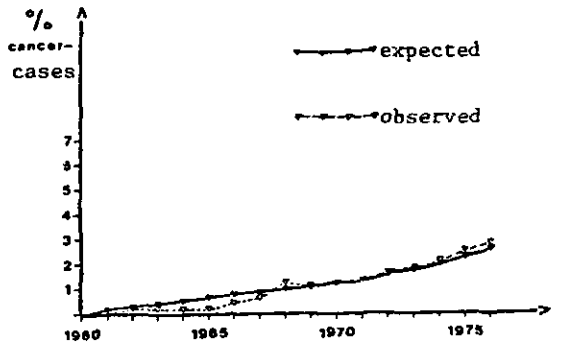

FIGURE 6. Cumulative rates of cases of all cancer (in percent). Study cohort 2 (1771 persons). The percentage for a given year was calculated as 100 (number of persons diagnosed through year in question divided by the number of persons beginning exposure through year in question).

Discussion

A noteworthy finding which arises in the analysis of the total cohort mortality (Fig. 1) is that the number of deaths at the beginning of the observation period (1947-1964) is significantly lower than one would expect in relation to the national average. This difference is so great that one cannot directly consider it to be randomly conditioned, nor can it be entirely ascribed to the so-called healthy worker effect. Theoretically, of course, the possibility exists that the selected cohort, in the question of mortality and the factors which influence said mortality, deviates from the general population. A more credible possibility is, however, that the personnel register that was available at the company involved at the time of this study was incomplete in the matter of hirings during this early period. A personnel register which, in the mid-1960's, was purged

of persons who began employment before 1960, could lead to the difference mentioned above. The companies involved reported that such a purging did not occur, so far as they knew.

If such a purging (thinning out) nevertheless occurred, this would have resulted in the elimination of persons with a long observation time at the time of follow-up. In the present study, the risk calculations were limited to beginning no earlier than 1961. This means a limitation of the analysis to pertain to the group of employees who were living at the beginning of 1961 and where the risk of an elimination is positively eliminated. This limitation, however, signifies a weakening of the analysis, since parts of the cohort with long follow-up times are excluded. Basically, this weakening signifies a poorer possibility of discovering an elevated incidence of cancer if one exists.

The myocardial infarction mortality (ICD 410.90) is elevated in the cohort. This elevation occurs most clearly in the category of the total cohort which has at least two years of employment time and where the analysis was directed at the period of time following two years after the beginning of employment and extending to no more than five years after the beginning of employment. Therefore, this involves that fraction of the mortality from myocardial infarction which chronologically is relatively closely connected to the time of employment. It is impossible on the basis of such observations to draw conclusions that the elevation was caused by exposure to vinyl chloride. The observed increase in myocardial infarction mortality is, however, so striking that it, in combination with the known facts about the toxic properties of vinyl chloride, must be given consideration. There are no reasons to assume that varying diagnostics, standards or practices in filling out the death certificates alone could provide an explanation. A natural conclusion is, therefore, that if one disregards the possibility of a random local phenomenon, the increased frequency is to be ascribed either to selection of individuals susceptible to the risk or an outbreak of risk factors in the close environment of employees. A combination of these two circumstances is, of course, also possible theoretically.

In this connection, it should be noted that many risk factors for myocardial infarction are environmentally conditioned in the fact that they constitute part of the lifestyle of the modern social environment in an industrialized country. Cigarette smoking, physical inactivity, overweight and high blood lipids constitute environmental factors which are related to social behavior. It is a well known fact that the risk of coronary vascular disease in the heart varies, inter alia, with the total load of risk factors. Among other risk factors, one can also name hereditary characteristics and high blood pressure. In this connection, there is reason to recollect that the causal network of coronary disease is multifactorial and that the disease has an environmental relationship in the broad sense. There is also reason to recall the aspect that the total risk increases when several risk factors, known or unknown, are allowed to collaborate (*11*, *12*).

It has not been possible to establish the distribution of such already known risk factors for coronary disease in the cohorts studied with respect to the national population in general. Therefore, no continued analysis of the matter of the causal relationship between close environment and heart disease morbidity can be made within the limits of this study.

Exposure classes 2 and 3 constitute subcohorts that are too small, in the present study, to allow a meaningful discussion of the myocardial infarction risks relative to the various exposure levels in the processing industry. In this connection, one should also consider the circumstance that the exposure classes in this study are based on interviews with the employees directed at the work environment at the time in question some 10 to 15 years ago. Therefore, this involves an environment which has subsequently undergone changes. Objective classification criteria in the matter of exposure, e.g., in the form of environmental measurements, do not exist. The distribution into exposure classes is, for this reason, fraught with uncertainty.

In animal experiments, it has been found that the toxicity picture in rodents chronically exposed to VCM involves the blood vessels. Besides hemangiosarcoma in the liver and the other organs (*4*, *5*) the inhalation of VCM is also believed to cause development of telangiectasis (*4*) in the liver of mice which can lead to death from hemocoele. Changes in the sinus cells have been observed in liver biopsies in VCM-exposed workers (*13*). Capillary changes in the skin of the fingers have also been observed (*14-16*), both in VCM-exposed workers with other vascular-involved diseases, such as acroosteolysis, Raynaud's phenomenon, and sclerodermia, and in VCM-exposed workers without such diseases. An over-representation of deaths from cardiovascular diseases has also been observed in a study on the PVC-fabricating industries (*10*). Animal experimental and previous medical studies of VCM-exposed populations therefore support the assumption that the increased risk of myocardial infarction observed in the present study could possibly be ascribed to VCM exposure.

As regards the mortality and morbidity from tumors, the results are uncertain. There are certain

indications of an elevation, but the differences are not statistically confirmed. One can think of two possibilities here: (1) in reality, there is no increase in the risk of tumors; (2) there is indeed an increased risk of tumors. The results neither confirm nor refute this. Tumors do not occur until after a long latency period. The majority of the persons included in the study did not begin their exposure until the 60's and 70's and therefore could not be followed for a sufficiently long time. An accurate follow-up of the present cohort during the coming five-year period should bring greater clarity into this.

In the present connection, it is of interest that in a recently published mortality study (*17*) on almost 4300 deaths in the American PVC-processing industry, an overrepresentation in cancer mortality appears to exist (all cancer), especially gastrointestinal cancer in both sexes.

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