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Mortality and Cancer Morbidity in Workers Exposed to Low Levels of Vinyl Chloride Monomer at a Polyvinyl Chloride Processing Plant

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To study whether exposure to low levels of vinyl chloride monomer (VCM) causes increased risk for cancer morbidity and death from ischemic heart disease, a cohort study was performed among 2,031 male workers at a polyvinyl chloride (PVC) processing plant who had been employed for at least 3 months during the period 1945–1980. An almost significantly increased total mortality (SMR = 116, 95% CI 99–136) was found. Deaths caused by violence or intoxication were significantly increased (SMR = 153, 95% CI 109–213), but not deaths from ischemic heart disease (SMR = 100, 95% CI 73–135). A significant increase in total cancer morbidity was observed (SMR = 128, 95% CI 101–161). Respiratory cancers were significantly increased (SMR = 213, 95% CI 127–346). Furthermore, six brain tumors (vs. 2.6 expected) were observed. This increase, however, was not significant (SMR = 229, 95% CI 84–498). No liver hemangiosarcoma was observed. Applying a latency period of ≥10 years from start of employment did not change the risk patterns. There were no significant exposure-response associations between exposure estimates for VCM, asbestos, and plasticizers and cancer morbidity.

Key words: asbestos, brain cancer, plasticizers, phthalic acid esters, respiratory cancer, ischemic heart disease

INTRODUCTION

It is well-established that vinyl chloride monomer (VCM) may induce angiosarcoma of the liver, but there have also been suggestions of increased risks for lung cancer [Buffler et al., 1979; Waxweiler et al., 1976], brain tumors [Beaumont and Breslow, 1981; Cooper, 1981], melanoma [Storetvedt Heldaas et al., 1984], and hematopoietic malignancies [Weber et al., 1981] in workers producing VCM or polyvinyl chloride (PVC). The exposure levels for VCM had, however, been very high in the latter workplaces. In contrast, the exposure to VCM has been substantially

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lower in the PVC processing industry. No excess cancer mortality or morbidity was observed in a Swedish cohort study of employees from four PVC processing plants [Molina et al., 1981]. On the other hand, a proportionate mortality study of employees in PVC fabricators showed an excess in total cancer mortality, particulary that of the digestive system [Chiazze et al., 1977]. Thus, whether low-level exposure to VCM increases the cancer incidence is not known. However, it should be remembered that there also has been exposure to other carcinogens, such as asbestos and certain plasticizers, in those working in the PVC processing industry. A much used plasticizer, di(2-ethylhexyl)phthalate (DEHP), has been regarded as carcinogenic in mice and rats by the IARC [1982].

An increased mortality due to myocardial infarction was observed in the previous Swedish cohort study of PVC-processing workers, which, hypothetically, was ascribed to a damaging effect on the blood vessels by VCM [Molina et al., 1981]. We report here on mortality and cancer morbidity in a cohort of workers from a PVC processing plant in which PVC, after addition of various chemicals, is heat-treated for fabrication into floor and wall coverings, pipes, sheets, and food packaging. The present plant is one of the four included in the previous Swedish cohort study [Molina et al., 1981]. As we have extended both the inclusion and observation period for the study and also obtained information from previously neglected company records, fewer than 50% of the subjects in the present cohort were included in the previous study.

One aim of the present study was to investigate whether there was an increased risk for cancer among employees in the PVC processing industry and whether such risks could be associated with specific chemical exposures. Furthermore, it was regarded as important to clarify whether there was an increased mortality from myocardial infarction or other cardiovascular diseases.

SUBJECTS AND METHODS

The Plant

The plant was founded in 1945. Initially, both the production and the number of employees were limited, but, since the mid 1950s, the production has been more extensive. The three main products manufactured in the plant are the following. 1) Thick film floor sheeting, floor tiles, and homogenous mats, have been produced since 1947 in calenders from PVC containing phthalic acid esters, mainly DEHP, as plasticizers. Asbestos, mainly chrysotile, used as reinforcer, was added to the PVC in the mixing department until 1977. 2) Thin film has, since 1952, been calendered from PVC, containing mostly DEHP, diisodecyl phthalate, and butylbenzylphthalate as plasticizers. The film was cut into diapers or ribbons for mat production or exported in rolls for use as packing material. 3) Pipes have, during the period 1952–1975, been extruded from PVC, containing mainly DEHP as a plasticizer. Furthermore, lead and cadmium compounds have been added as stabilizers.

Exposure Estimates

For each calendar year 1945–1980, each work operation in the plant has been classified by an occupational hygienist in cooperation with technical and safety staff of the plant, with regard to the estimated mean exposure levels of VCM, asbestos,

and plasticizers. A four-grade scale, "none," "low," "moderate," or "high" exposure level, was used.

The exposure to VCM was rather stable until 1975, when the exposure levels rapidly decreased due to the first reports of the association with liver hemangiosarcoma. Before 1975, the mean exposure level among "highly" exposed workers (workers in the mixing departments and calender operators) was estimated to be about 10 ppm, among "moderately" exposed workers (e.g., machine attendants) about 1 ppm, and among workers exposed to "low" levels of VCM (quality inspectors and packing personal) about 0.1 ppm. Based on this information, the individual cumulated exposure (ppm-years) was calculated by adding the exposure estimates for each calendar year. The cumulated exposure data were used in dose-response calculations.

The estimates for asbestos were partly based on measurements of breathing zone levels. In 1971, the mean exposure level among "highly" exposed workers (raw material transport workers, workers in the mixing departments and PVC crushing, and calender operators) was 1–3 fibers/ml, among "moderately" exposed workers (machine attendants and repairmen) >0.1–0.5 fibers/ml, and among workers exposed to "low" levels of asbestos (quality inspectors and packing personnel) up to 0.1 fibers/ml. Measurements were performed over a total of 108 hr. No measurements of asbestos were performed before 1971, but, based on the best available judgements, the time-weighted average exposure levels after 1969 were estimated to have been about 40% lower than those in the period 1956–1969. Air sampling in 1975 indicated that the mean exposure level in all exposed workplaces had decreased by a factor of 3 compared to the period 1970–1974. No asbestos was used in the manufacture after 1977. The individual cumulated exposure for asbestos (fiber-years/ml) was calculated, in the same manner as for VCM, by adding the exposure estimates for each calendar year.

The exposure levels for plasticizers were stable during the whole study period. The time-weighted average breathing zone level of phthalic acid esters among "highly" exposed workers (calender operators) was >0.5–3 mg/m^3, among "moderately" exposed workers (workers in the mixing departments and machine attendants) >0.1–0.5 mg/m^3, and among workers exposed to "low" levels of VCM (quality inspectors and packing personnel) up to 0.1 mg/m^3. The individual cumulated exposure for plasticizers (mg-years) was calculated, in the same manner as for VCM and asbestos, by adding the exposure estimates for each calendar-year.

Cohort

From the company's records, name, date of birth, address, and dates of start and end of employment were obtained for 2,042 male workers who had been employed for 3 months or more during the period 1945 to December 31, 1980 (Fig. 1). The records, however, contained no data on workers who had left employment or died before 1961.

Vital status was determined up to December 31, 1985 (Table I) for all but 11 subjects (0.5%), whose ten-digit personal identification code could not be established. Six of these subjects had been employed for less than 1 year. If a 10 year latency period was used, the total loss in follow-up was 0.7%. Thus the study cohort consisted of 2,031 subjects. Table II shows the distribution of person-years by age group and calendar year.

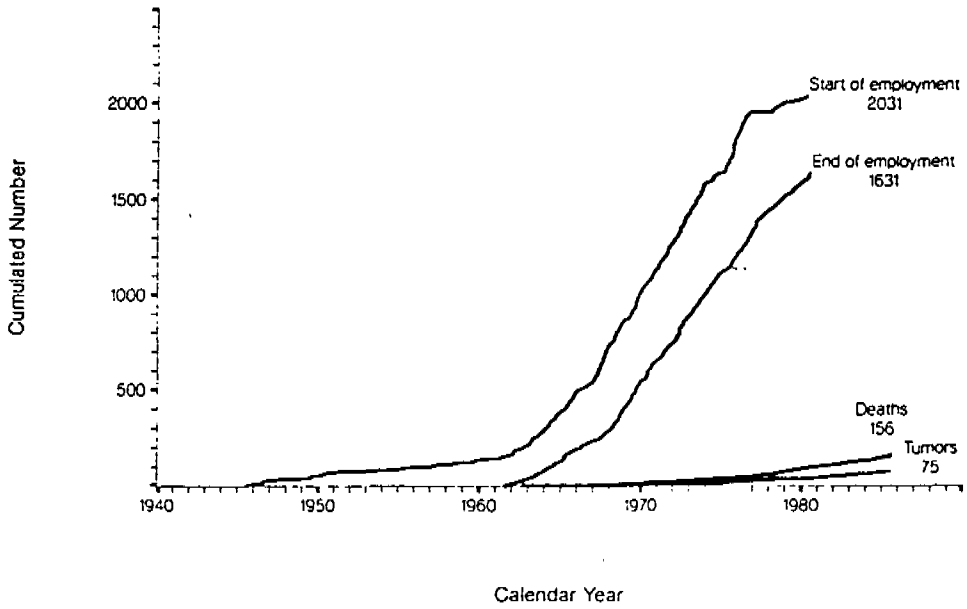

Fig. 1. Cumulative distribution of time of starting and ending of work among workers employed at a PVC processing plant in the period 1945–1980. The cumulative number of observed deaths and tumors 1961–1985 are also shown.

TABLE I. Vital Status in the Cohort of Workers in a PVC Processing Factory

	All		≥Ten years latency period	
Vital status	N	Percent	N	Percent
Living	1,726	84.5	1,536	91.8
Dead	159	7.8	108	6.5
Emigrated	146	7.1	19	1.1
Not identified[a]	11	0.5	11	0.7
Total	2,042	100.0	1,674	100.0

[a]A ten-digit personal identification code could not be established.

TABLE II. Person-Years of Observation in a Cohort of 2,031 Workers in a PVC Processing Plant

	Age (years)			
Calendar year	<30	30–59	60–79	Total
1961–1970	2,334	2,624	290	5,248
1971–1980	5,753	9,140	1,224	16,117
1981–1985	1,366	6,418	1,001	8,785
Total	9,453	18,182	2,515	30,150

Information on Causes of Death and Tumors

Information on cause of death (1961–1985) was obtained from the National Swedish Central Bureau of Statistics. The death certificates were coded according to the International Classification of Diseases (ICD) by the National Swedish Central

Bureau of Statistics, which is responsible for the coding of all Swedish death certificates. All codes were transformed to the Eighth Revision of the ICD. Death certificates regarding causes of death of special interest were obtained. A total of 50% of the death certificates were based on clinical or forensic autopsy in subjects who had died before 80 years of age. If the 10 year latency period was used, the figure was 49%.

Information on up to two tumors (coded according to the ICD, Seventh Revision) diagnosed from 1961 to 1985 was obtained from the National Swedish and the Southern Swedish Regional Tumor Registries. Case records from hospital as well as autopsies were scrutinized.

Risk Estimates

The person-year accumulation in the cohort started in 1961. Date of death, emigration or 80th birthday were used as individual endpoints. With regard to cancer morbidity, date of diagnosis of a second tumor was also used as an individual endpoint. Expected mortality for the period 1961–1985 was calculated using calendar year-, cause-, and 5 year age group-specific mortality rates for males in the county (Blekinge; about 75,000 male inhabitants). These rates were calculated from death and population counts obtained from the National Central Bureau of Statistics. Similarly, yearly morbidity rates for cancer in the period 1961–1985 for the county were obtained from the Southern Swedish Regional Tumor Register.

Cause-specific standardized mortality/morbidity ratios (SMRs) and 95% confidence intervals (CI) were calculated according to the Poisson distribution. Exposure-response relationships were assessed by analyses of SMRs over strata, based on duration of employment and the individual total cumulated exposure estimates for VCM, asbestos, and plasticizers [Breslow et al., 1983]. Each individual contributes person-years successively to each employment and exposure estimate stratum as he progresses through his employment time [Swaen and Volovics, 1987]. Thus, the exposure-response relationships were based on classified person-years and not on subjects.

The correlation between age and length of employment affects the comparability of the SMRs from each employment stratum. Furthermore, there is also an association between the cumulated exposure estimates and age. This may result in a negative bias in the SMRs, especially for those employed for a long time. Thus, to correct for the relationship between age and length of employment or cumulated exposure, an age-standardized SMR (SSMR) was calculated according to Ranstam [1984].

To clarify possible interactive effects of the three different chemical agents on cancer incidence, the distribution of subjects, observed number of tumors, and SMRs are given for the eight combinations of ever being exposed (or not) to the three agents. The term "significant" refers to $p \leq 0.05$ or to the lower limit of the 95% CI for SMR ≥ 1.00. All tests are two-tailed.

RESULTS

Mortality

During the period 1961–1985, 156 deaths were observed vs. 134.6 expected (SMR = 116, 95% CI 99–136; Table III). The cumulated number of deaths in the

TABLE III. Observed (O) and Expected (E) Mortality 1961–1985 and Specific Causes of Death in a Cohort of Workers in a PVC Processing Plant*

Cause of death		All[a]				≥Ten years latency-period[b]			
Organ	ICD-8	O	E	SMR	95% CI	O	E	SMR	95% CI
Malignant tumors	140–209	38	30.8	122	88–171	29	20.7	140	95–203
Gastrointestinal tumors	150–159	14	10.7	131	72–220	11	7.6	145	72–260
Respiratory tumors	160–163	10	6.6	153	73–280	6	4.6	130	48–284
Cardiovascular diseases	390–458	60	60.1	100	77–129	47	43.5	108	80–145
Ischemic heart diseases	410–414	44	44.0	100	73–135	36	32.3	111	79–156
Bronchitis, emphysema, asthma	490–493	4	2.0	201	55–514	3	1.3	227	47–663
Gastrointestinal diseases	520–577	7	4.6	151	61–312	3	2.7	112	23–328
Urinary tract diseases	580–599	4	1.4	291	79–745	3	0.8	389	80–1140
Violence, intoxication	800–999	37	24.2	153	109–213	16	10.6	151	89–250
All causes	000–999	156	134.6	116	99–136	105	86.5	121	100–147

*SMR, standardized mortality ratio.
[a]2,031 subjects, 30,150 person-years under observation.
[b]1,663 subjects, 12,187 person-years under observation.

cohort is plotted with regard to time in Figure 1. With regard to cause-specific mortality, there was no significantly increased risk of death in malignant tumors (SMR = 122, 95% CI 88–171), cardiovascular diseases (SMR = 100, 95% CI 77–129), or ischemic heart diseases (SMR = 100, 95% CI 73–129; Table III). Four deaths from obstructive lung diseases, vs. two expected, were observed. However, this was far from statistically significant (SMR = 201, 95% CI 55–514). On the other hand, deaths from violence or intoxication were significantly increased (SMR = 153, 95% CI 109–213).

When a latency-period of ≥10 years was applied, 105 deaths were observed vs. 86.5 expected (SMR = 121, 95% CI 100–147). The pattern of cause-specific deaths was not affected by the applied latency period.

Cancer Morbidity

A significant increase in total cancer morbidity was observed (SMR = 128, 95% CI 101–161; Table IV). The cumulated number of tumors in the cohort is plotted with respect to time in Figure 1. Among the specific cancers, there was a significant increase in respiratory cancer (SMR = 213, 95% CI 127–346), consisting of an increased incidence of both laryngeal cancer (SMR = 391, 95% CI 81–1140) and lung cancer, including one case of mesothelioma (SMR = 186, 95% CI 99–318; Table IV). The increased incidence of brain tumors did not reach a statistically significant level (SMR = 220, 95% CI 84–498). Of the six observed brain tumors,

TABLE IV. Observed (O) and Expected (E) Tumor Morbidity 1961–1985 in a Cohort of Workers in a PVC Processing Plant*

Tumor		All[a]				≥Ten years latency-period[b]			
Site	ICD-7	O	E	SMR	95% CI	O	E	SMR	95% CI
Gastrointestinal tract	150–158	19	14.9	127	78–202	14	10.6	133	70–213
Liver, bile ducts	155.	2	1.1	189	23–684	2	0.8	244	30–880
Respiratory tract	160–164	17	8.0	213	127–346	11	5.6	195	97–349
Nose, sinuses	160	1	0.2	448	11–2500	1	0.1	803	20–4470
Larynx	161	3	0.8	391	81–114	3	0.6	549	113–1610
Lung, pleura	162–164	13	7.0	186	99–318	7	5.0	141	57–290
Prostate	177	11	6.5	170	85–304	10	5.2	191	91–351
Brain	193.0	6	2.6	229	84–498	4	1.6	258	70–660
All	140–209	75	58.6	128	101–161	55	39.8	138	105–181

*SMR, standardized mortality ratio.
[a]2,031 subjects, 30,150 person-years under observation.
[b]1,663 subjects, 12,187 person-years under observation.

five were astrogliomas and one a meningeoma. Neither of the two liver tumors observed was a hemangiosarcoma.

When a latency period of ≥10 years was applied, the total cancer morbidity was of the same magnitude as without the latency period (SMR = 138, 95% CI 105–181; Table IV). The morbidity from respiratory cancer was still about doubled (SMR = 195, 95% CI 97–349), but the excess risk for lung and pleural cancer had decreased somewhat (SMR = 141, 95% CI 57–290). On the other hand, the increased incidence of laryngeal cancer reached statistical significance (SMR = 549, 95% CI 113–1610).

Dose-Response Analysis

There were no significant associations between length of employment and the incidence of respiratory cancers or total cancer incidence, regardless of whether a ≥10 years latency period was applied or not (Table V). Furthermore, there were no significant associations between the individual cumulated exposure estimates to VCM and incidence of respiratory or total cancer (Table VI). "High" cumulated exposure to asbestos (≥3.3 fiber-years/ml) was significantly associated with respiratory cancers (SSMR = 295, $p = 0.01$), but the exposure-response relationships were not statistically significant for either these tumors or total cancer incidence (Table VII). There were no significant associations between the individual cumulated exposure estimates to plasticizers and incidence of respiratory or total cancer (Table VIII).

None of the subjects in the cohort had been exposed to VCM only, 28% had been exposed to asbestos only, and 6% to plasticizers only (Table IX). Thirty-four percent of the cohort had been exposed to all three agents, but no increased cancer incidence was observed for this subcohort. However, the case of mesothelioma was from this category. Fourteen percent of the cohort had not been exposed to any of the exposure agents. The total cancer incidence was, however, increased in this group (SMR = 183, 95% CI 100–308). Finally, a total of 18% of the cohort were classified in the remaining three exposure combinations. A significant increase for respiratory cancer (SMR = 1070, 95% CI 220–3120) was observed in the subcohort of 76 subjects exposed to both asbestos and plasticizers but not to VCM.

TABLE V. Relationship Between Time of Employment and Risk of Cancer Morbidity*

Tumor		Time of employment (years)									
		<1 (mean 0.5)[a]			1–5 (mean 2.4)[b]			>5 (mean 12.3)[c]			
Site	ICD-7	O	SMR	SSMR	O	SMR	SSMR	O	SMR	SSMR	p
Respiratory tract	160–164	3	295	295	3	254	252	5	145	138	0.28
Lung, pleura	162–164	2	221	221	1	96	109	4	133	132	>0.5
All	140–209	12	155	155	12	139	145	31	132	123	>0.5

*A latency period of ≥10 years has been applied. The calculations were based on 1,663 subjects. O, observed cases. SMR, standardized morbidity ratio. SSMR, SMR standardized to the age distribution in the <1 year group. *P* for trend in SSMR.
[a]3,579 person-years at risk.
[b]3,553 person-years at risk.
[c]5,057 person-years at risk.

TABLE VI. Relationship Between the Cumulative Exposure Estimates for Vinyl Chloride Monomer (VCM) and Risk of Cancer Morbidity*

Tumor		Cumulative exposure estimates (ppm-years)									
		<0.1 (mean 0.02)[a]			0.1–1 (mean 0.4)[b]			>1 (mean 23)[c]			
Site	ICD-7	O	SMR	SSMR	O	SMR	SSMR	O	SMR	SSMR	p
Respiratory tract	160–164	6	247	247	2	161	109	3	153	165	>0.5
Lung, pleura	162–164	5	232	232	0	0	0	2	116	123	>0.5
All	140–209	26	149	149	14	155	148	15	112	105	0.3

*The calculations were based on 1,658 subjects. A latency period of ≥10 years has been applied. O, observed cases; SMR, standardized morbidity ratio; SSMR, SMR standardized to the age distribution in the <0.1 ppm-years category; p for trend in SSMR.
[a]5,543 person-years at risk.
[b]3,542 person-years at risk.
[c]3,062 person-years at risk.

DISCUSSION

The main result of the present study is an increased incidence of total cancer morbidity, and more specifically of respiratory cancers, in PVC processing workers.

Validity

No preemployment health examination was performed before 1968, when the company founded its medical health service. Even after that, there has been no focus on cardiovascular or respiratory diseases in preemployment health examinations. There is not likely to have been any self-selection against employment in the plant, but this possible bias can of course not fully be excluded. Thus there is no reason to believe that there has been any significant bias in selection of employees into the cohort affecting mortality from cardiovascular or chronic obstructive respiratory diseases. However, it is possible that workers with such diseases may have left work selectively, causing an underestimation of risk.

Since 1968, the employees have been examined routinely by chest X-ray every 5 years; no tumor has yet been diagnosed by this means. No other screening test for cancer has been performed among the workers. Thus there is no reason to believe that

TABLE VII. Relationship Between the Cumulative Exposure Estimates for Asbestos and Risk of Cancer Morbidity*

Tumor		Cumulative exposure estimate (fiber-years/ml)									
		<0.03 (mean 0.002)[a]			0.03–3.3 (mean 1.2)[b]			>3.3 (mean 13.5)[c]			
Site	ICD-7	O	SMR	SSMR	O	SMR	SSMR	O	SMR	SSMR	p
Respiratory tract	160–164	3	162	162	1	73	51	7	290	295	0.18
Lung, pleura	162–164	2	121	121	0	0	0	5	235	241	0.14
All	140–209	22	168	168	14	137	140	19	116	112	0.29

*A latency period of ≥10 years has been applied. The calculations were based on 1,658 subjects. O, observed cases; SMR, standardized morbidity ratio; SSMR, SMR standardized to the age distribution in the <0.03 fiber-years/ml category; p for trend in SSMR.
[a]3,885 person-years at risk.
[b]4,386 person-years at risk.
[c]3,875 person-years at risk.

TABLE VIII. Relationship Between the Cumulative Exposure Estimates for Plasticizers and Risk of Cancer Morbidity*

Tumor		Cumulative exposure estimate (mg-years)									
		<0.05 (mean 0.04)[a]			0.05–0.5 (mean 0.3)[b]			>0.5 (mean 2)[c]			
Site	ICD-7	O	SMR	SSMR	O	SMR	SSMR	O	SMR	SSMR	p
Respiratory tract	160–164	1	52	52	5	373	334	5	213	224	>0.5
Lung, pleura	162–164	1	58	58	2	168	158	4	194	204	>0.5
All	140–209	19	135	135	15	153	142	21	132	138	>0.5

*A latency period of ≥10 years has been applied. The calculations were based on 1,658 subjects. O, observed cases; SMR, standardized morbidity ratio; SSMR, SMR standardized to the age distribution in the <0.05 mg-years category; p for trend in SSMR.
[a]4,644 person-years at risk.
[b]3,662 person-years at risk.
[c]3,858 person-years at risk.

tumors have been diagnosed earlier in the exposed cohort than in the reference population.

Diagnostic accuracy for causes of death, as well as tumors, is important for the conclusions. Information on cause of death could be obtained for all deceased. In the cohort, 50% of the death certificates were based on clinical or forensic autopsy, which is somewhat higher than the frequency of autopsy in deceased males in the county (about 36%). Thus, there are reasons to believe that the diagnostic accuracy for causes of death in the cohort is somewhat better than average in this geographical region. The somewhat increased autopsy rate in the cohort does not seem to have caused any bias with respect to tumor diagnosis; e.g., no case of lung cancer was diagnosed by autopsy only.

Smoking is a potential confounding factor for both lung cancer and laryngeal cancer. The smoking habits in the cohort are not known. However, it is not unlikely that the number of smokers in the cohort, as well as in other groups of Swedish industrial workers [Hagmar et al., 1986; Socialstyrelsen, 1986], are somewhat higher than in the reference population. This may explain some of the observed excess risk for respiratory cancer. The exposure estimates were only partially based on measure-

TABLE IX. Relationship Between Cancer Morbidity and the Eight Combinations of the Three Exposures (−, virtually never exposed; +, exposed) for 1,660 Subjects: Vinyl Chloride (VCM), Asbestos, and Platicizers*

	All cancer						Respiratory cancer			
	VCM−			VCM+			VCM−		VCM+	
	N	O	SMR	N	O	SMR	O	SMR	O	SMR
Plasticizers−										
Asbestos−	227	14	183[a]	0	0	0	1	105	0	0
Asbestos+	472	5	79	7	0	0	0	0	0	0
Plasticizers+										
Asbestos−	99	3	180	214	5	131	1	487	0	0
Asbestos+	76	4	193	565	24	133	3	1.070[b]	2	88

*A latency period of ≥10 years has been applied. N, number of subjects; O, observed cases; SMR, standardized morbidity ratio.
[a]95% CI 100–308.
[b]95% CI 220–3.120.

ments and were mainly based on skilled, but subjective, assessments of exposure levels. Thus, the individual cumulated exposure estimates we used are, as in most retrospective cohort studies, rather crude.

Mortality

In many cohort studies among industrial workers, no increased overall mortality ratio is found. This has usually been ascribed to a "healthy worker effect" [McMichael, 1976]. On the other hand, we have, in two recent studies of workers in the chemical industry, observed increased overall mortality ratios compared with regional reference populations [Hagmar et al., 1986; Englander et al., 1988]. The almost significantly increased overall mortality in the present study is in accordance with those findings. A major cause of the overall increase is the 50% excess in violent deaths or intoxications. This was also observed in our previous studies on workers in the chemical industry [Hagmar et al., 1986; Englander et al., 1988]. The observed excess risk is probably correlated with socioeconomic factors, including alcohol abuse.

No increased incidence of deaths from cardiovascular diseases, or more specifically from ischemic heart diseases, was observed in the cohort. This is in contrast to a previous Swedish study on the PVC processing industry, including a part of the present cohort, in which a slight excess risk for myocardial infarction was indicated [Molina et al., 1981], but is in concordance with the results of a proportionate mortality study among employees of PVC fabricators [Chiazze et al., 1977]. Furthermore, the incidence of ischemic heart disease was not increased in previous studies on workers producing VCM or PVC, who were exposed to much higher levels of VCM [Doll, 1988].

Four subjects in the cohort died from chronic obstructive respiratory diseases compared with two expected. The numbers are still too small to allow any interpretation. It should be remembered, however, that only a few studies on occupational groups have shown increased mortality in chronic obstructive respiratory diseases. It has been shown that men who are not gainfully employed had a highly increased risk

of death in chronic obstructive respiratory diseases compared to gainfully employed men in Sweden [Järvholm et al., 1988]. Therefore, it has been proposed that, with respect to these diseases, other occupational groups constitute more suitable reference groups than the general population [Järvholm et al., 1988].

Cancer Morbidity

The present study showed an increased incidence of total cancer morbidity, which is in agreement with a proportionate mortality study among employees of PVC fabricators showing an excess of total cancer mortality [Chiazze et al., 1977]. On the other hand, such an increase was not observed in a previous Swedish cohort study on PVC processing workers [Molina et al., 1981]. However, the present study consists partly of the same subjects as in this latter study, but a longer follow-up period was now available.

The increase in respiratory tumors was significant. However, the SMR did not increase when applying ≥10 years latency period from start of employment, which does not strengthen the hypothesis of a causal association with the work environment in the present plant. Furthermore, no clear-cut exposure–response associations with any specific chemical agent could be established. On the other hand, the statistical power for exposure-response associations with specific tumor sites was limited by relatively few expected cases. Thus, the association between exposure to asbestos and risk for respiratory tumors, indicated in Table VII, is noteworthy, even if it does not reach formal significance. According to Doll and Peto [1985], the incidence of chrysotile-induced lung cancer increases with 1% per fiber-years/ml. Mainly chrysotile had been handled in the present plant, and the exposure levels for most workers were relatively low (mean exposure level in the "highly" exposed stratum was 13.5 fiber-years/ml). Therefore, no dramatic effects with regard to lung cancer should be expected. The subject with mesothelioma had a cumulated asbestos exposure of 17.2 fiber-years/ml and had a 26 year latency period from first day of exposure to date of diagnosis. A causal association is therefore probable in this case.

Asbestos exposure is regarded as one of the causes of laryngeal cancer [Doll and Peto, 1985]. A significant increase in that diagnosis was observed in the present study, but this was based on only three cases. The cumulated asbestos estimates for these subjects were not impressive: 6.8, 5.1, and 1.2 fiber-years/ml. Thus, whether exposure to asbestos contributed to the increased risk for laryngeal cancer is not obvious.

It is also noteworthy with regard to previously suggested associations between VCM exposure and brain tumors [Beaumont and Breslow, 1981] that the incidence of these tumors was more than doubled in our study, even if the increase was not formally significant. On the other hand, only three of the six cases of brain tumors had ever been exposed to VCM. In previous case reports, VCM exposure in PVC processing plants has been associated with hepatic angiosarcomas [Wagoner, 1983; Maltoni et al., 1984]. No such tumors were observed in our study, however.

One aim of our study was to test whether the increased cancer risks in the cohort could be associated with exposure to VCM, asbestos, or plasticizers. However, no significant dose–response associations were found, even if a tendency towards association between respiratory cancers and cumulated exposure for asbestos was observed. Several explanations for this inability to demonstrate exposure–response associations are possible. The observed excess risks may be due to nonidentified,

nonoccupational confounding factors or may be attributable to more complicated exposure interactions between chemical agents in the plant, which cannot be analyzed with our methodological approach. Alternatively, the lack of observed dose–response associations may be due to weaknesses in the applied, rather crude, exposure estimates. Furthermore, the statistical power for detecting significant exposure–response associations between chemical agents and specific tumor sites was limited in the present study by few expected cases. A follow-up study with more person-years under observation will provide an increased precision, which should clarify the risk pattern connected with employment in the PVC processing industry.

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