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A collaborative study of cancer incidence and mortality among vinyl chloride workers

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SIMONATO L, L'ABBÉ KA, ANDERSEN A, BELLI S, COMBA P, ENGHOLM G, FERRO G, HAGMAR L, LANGÅRD S, LUNDBERG I, PIRASTU R, THOMAS P, WINKELMANN R, SARACCI R. A collaborative study of cancer incidence and mortality among vinyl chloride workers. *Scand J Work Environ Health* 1991;17:159—69. A large European multicentric cohort study has been coordinated by the International Agency for Research on Cancer with the objectives of investigating the dose-response relationship between liver cancer and exposure to vinyl chloride and assessing cancer risk for sites other than the liver. A nearly threefold increase in liver cancer was detected on the basis of 24 observed deaths and 8.4 expected (standardized mortality ratio 286, 95 % confidence interval 186—425). The excess from liver cancer was clearly related to time since first exposure, duration of employment, and estimated ranked and quantitative exposures. Other cancer sites investigated on the basis of a priori hypotheses were either not in excess (lung) or apparently unrelated to the exposure variables (brain and lymphoma).

Key terms: brain cancer, cohort study, dose-response relationship, liver cancer, lung cancer, lymphoma.

Vinyl chloride (VC) is an established carcinogen for humans (1, 2), and it is also one of the few substances for which the experimental evidence of carcinogenicity was available (3) before the carcinogenic effects on humans could be demonstrated.

The concern about the hazards from exposure to this substance led to control measures which lowered the levels of exposure in excess of 500 ppm in the early 1950s to values generally below 1 ppm in industrialized countries.

In recent years, the development of laboratory techniques in investigating possible effects at the molecular level (4) renewed the interest in this substance. In addition the epidemiologic data have recently been updated (5—7) and reevaluated in a review (8).

Although occupational exposures have decreased, important scientific and public health questions remain. In 1986 the occupational program of the International Agency for Research on Cancer (IARC) invited European epidemiologists involved in research on the effects of VC to combine their efforts in a multicentric cohort study. The collaborative cohort study reported in this presentation was undertaken with the following three objectives: (i) to determine whether VC is associated with increased cancer risk at sites other than the liver, (ii) to investigate the possible exposure-response relationship between VC and liver cancer, particularly angiosarcoma of the liver, and (iii) to construct a data base which could be exploited in the future in relation to the assessment of potential risk at low levels of exposure.

In this report, we present the methods and results of this collaborative study, further details of which can be found in an IARC report (9).

Subjects and methods

Collaborators from four countries (Italy, Norway, Sweden, and the United Kingdom) participated in the cohort study and contributed a total of 14 351 subjects to the combined data base. Both existing studies and newly collected cohorts were enrolled from 19 factories. Where existing study populations were included (10—15) follow-up was extended, and/or more factories were added. In the majority of factories in the cohort there was mixed VC monomer/polyvinyl chlo-

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ride (VCM/PVC) production (12 factories), two produced VCM only, four produced PVC only, and one was a PVC-processing plant.

For the sake of homogeneity, we decided to include only subjects with at least one year of employment in the analysis, and therefore 1518 subjects (10.6 % of the combined cohort) had to be excluded. An additional 127 subjects (0.9 % of the combined cohort) were excluded for the following reasons: female gender (N = 57), out of observation period (N = 48), member of more than one cohort (N = 21), and date of first exposure unknown (N = 1). After the total of 1645 exclusions (11.5 % of the combined data base), 12 706 subjects remained for the analysis.

The vital status of the subjects included in the mortality analysis is shown in table 1, and the completeness of follow-up at 97.7 % can be considered satisfactory. For the 12 706 subjects included in the analysis, the average length of follow-up was 17 (range 10—25) years, 36 % of the cohort having a follow-up period of 20 years or more. The total number of person-years at risk was 222 746, and the distribution of person-years according to duration and the number of years since first exposure is given in table 2.

National incidence or mortality rates (men only) specific for age and five-year calendar periods were used for reference. The observation period differed by factory, the majority of subjects having been followed from 1955 (first year for which reference rates were available) or from the start of the second year of employment, whichever came first, to 1986. Two of the four countries, Norway and Sweden, were also able to provide follow-up for incidence through nation-based cancer registries, while mortality rates were computed at IARC with the use of a data base belonging to the World Health Organization (WHO). As different revisions of the International Classification of Diseases (ICD) were used over the follow-up period, a conversion table for causes of death was used and can be found in the detailed IARC report (9).

Table 1. Vital status of the cohort members.[a]

Vital status	N	%
Alive	10 981	86.4
Dead	1 438	11.3
Unknown (lost or emigrated)	287	2.3
Total	12 706	100

[a] Person-years at risk: 222 746.

Table 2. Person-years by duration of employment and follow-up.

Duration of employment (years)	Years since first exposure				Total
	1—9	10—19	20—29	≥30	
1—9	95 178	43 306	13 293	2 670	154 446
10—19	—	43 256	8 842	1 427	53 526
≥20	—	—	11 810	2 965	14 775
Total	95 178	86 562	33 945	7 062	222 746

It should be noted that for this study liver cancer was defined as ICD 155—156 (seventh revision): liver, intrahepatic and extrahepatic bile ducts, and gallbladder specified as primary or secondary; ICD 155 (eighth revision): liver and intrahepatic bile ducts specified as primary; and ICD 155 (ninth revision): liver and intrahepatic bile ducts specified as primary and liver specified as secondary. Although ideally only primary liver cancer should be chosen as the definition, the seventh and ninth ICD revisions do not permit separation of primary and secondary (as this distinction is often difficult in reality). In the eighth and ninth revisions, secondary liver cancer is classified by a four-digit code, but specification of the national mortality rates to four digits in the WHO data base is not available from all countries. Therefore, it was necessary to choose the aforementioned definition for liver cancer.

Angiosarcoma of the liver is distinguished from other types of liver cancer through histology. This type of information was sought from national investigators, and only cases histologically confirmed were included in the analyses.

For the analysis, person-years at risk were calculated with the person-years program using a modified life-table approach (16). In calculating the person-years, no censoring at old age took place, and the date of entry for the tabulation of person-years started at the beginning of the observation period according to the availability of reference rates in 1955 or on day 1 of the second year of employment, whichever occurred later.

The standardized mortality ratio (SMR) or standardized incidence ratio (SIR) and the 95 % confidence interval (95 % CI) for the SMR or SIR were calculated on the assumption of a Poisson distribution. Prior to the analysis, it was decided that four causes of death suspected a priori (ie, liver cancer, lung cancer, brain cancer, and lymphosarcoma) would be examined in detail.

The mortality analysis was performed according to several temporal variables, specifically years since first exposure, calendar period at hire, calendar period at exit, age at hire, and age at exit. In the analysis all of these variables were based on individual information available for each subject. Exposure variables were job title as autoclave worker (ever/never), duration of employment, ranked level of exposure, and cumulative exposure in parts per million-years to VCM in the air.

For the ranked level of exposure and cumulative exposure indices, job histories were required, along with exposure estimates for specific jobs and calendar periods from job-exposure matrices. The job-exposure matrices specific for calendar period were provided by industrial hygienists for 13 of the 19 factories. These matrices were developed in various ways for the different factories. For most of them, job title was used as the basic unit with which exposure was assessed, and

job histories were available for all factories except two. "Typical exposures" to VC in air were estimated as time-weighted averages by industrial hygienists using several sources of variable quality. In most factories, occasional measurements of VC provided the basis for past typical exposures, supplemented by knowledge of exposure conditions, processes, and technological changes over time. Systematic measurements taken since the mid-1970s provided the basis for more recent exposure assessments, and an indication of the variability of exposure levels between job titles.

In terms of agents to which the workers were exposed in VCM, PVC, and VCM/PVC production, VC was the main exposure, and virtually the only exposure in many of these factories. Use of butadiene was rare. In PVC processing (one factory in this study), however, additional exposures could have included PVC dust, asbestos, and other agents. All the job-exposure matrices referred only to VC exposure in air.

Each job-exposure matrix was checked and validated by two independent industrial hygienists, who were able to provide, prior to the statistical analysis, an index for the ranked level of exposure (low: <50 ppm; intermediate: 50—449 ppm; and high: ≥ 500 ppm) in which the classification of the subjects was based on the highest level to which the workers were potentially exposed, specific to their jobs and the years in which they worked, according to levels of VC recorded in the job-exposure matrices.

The same information, that is, job histories and job-exposure matrices, was used to calculate cumulative exposure in parts per million-years (exposure level from the job-exposure matrices multiplied by duration of employment) for the subjects. In some of the analyses for cancer of the liver an estimated job-exposure matrix was used for the four factories in the United Kingdom which were unable to provide their own matrices. The estimated job-exposure matrix was based on the matrices provided for the other factories in the United Kingdom. This matrix was checked with the industrial hygienist from the United Kingdom. In the following text, it is clearly noted if the analyses under discussion include this estimated matrix.

For liver cancer only, the Poisson regression analysis was performed to assess the significance of several variables simultaneously. This analysis used observed deaths and the person-years distribution for cross-classified categories of temporal and exposure variables and performed an internal comparison with the base-line categories (ie, within the cohort only) (17, 18).

Mortality results

Cause-specific mortality for the total cohort is presented in table 3. A statistically significant deficit for all-cause mortality was apparent (1438 deaths observed versus 1636.4 expected, SMR 88, 95 % CI 83—93). The following four main causes of death contributed to this deficit: (i) diseases of the circulatory system, (ii) diseases of the respiratory system, (iii) accidents, poisonings and violence, and (iv) other known causes.

For all malignant neoplasms, the SMR was 104 (95 % CI 95—114), with 445 deaths observed. However, there were two causes of death, both cancers, which showed statistically significant excesses. They were cancer of the liver with 24 observed deaths and 8.4 expected (SMR 286, 95 % CI 183—425) and cancer of an unspecified site with 24 observed deaths and 12.9 expected (SMR 187, 95 % CI 120—278). Increases which were not statistically significant were apparent for bladder cancer (21 deaths observed, SMR 146, 95 % CI 91—224), malignant melanoma (7 deaths observed, SMR 163, 95 % CI 65—335), and lymphosarcoma (7 deaths observed, SMR 170, 95 % CI 69—351).

In this report the results are not given by process. The statistically significant excess of liver cancer evident in the total cohort was mainly due to the excess in VCM/PVC production (19 deaths observed, SMR 311, 95 % CI 187—486).

Twenty-three sites were selected for analysis according to the years since first exposure, and the results for 10 of these sites are presented in table 4. Apart from liver cancer, which will be discussed in detail, there were no noteworthy patterns in risk according to this variable.

Four sites were investigated in detail for relationships with temporal and exposure variables. Of the two sites with excess risk for the total cohort, cancer of an unspecified site was not analyzed further due to the diversity of cancers found in this category; they are however discussed in a descriptive fashion in the text. Liver cancer, lung cancer, brain cancer, and lymphosarcoma were chosen a priori for further analysis. Excesses of bladder cancer in PVC production (in the United Kingdom) and of melanoma (in Norway) were not investigated further for the total cohort since they were confined to one country.

Liver cancer

No liver cancer deaths occurred before 15 years since first exposure, after which the SMR was 483 (95 % CI 208—951) for 15—19 years since first exposure, and it did not vary greatly from this level thereafter, the value always being statistically significant. In table 4, the pattern by years since first exposure is seen in 10-year groups. When only those with 15 years since first exposure or more were included in the analysis (15-year latency), the overall SMR for liver cancer was 445 (95 % CI 285—663).

Table 5 shows the SMR values for liver cancer according to the four exposure variables, without and with a 15-year latency analysis. According to job title, dichotomous as ever autoclave worker (suspected a priori as the highest risk job) versus never an autoclave worker, very high risk was experienced by those who

Table 3. Mortality by detailed cause. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval)

Cause of death[a]	O	E	SMR	95 % CI[b]
All causes (000—999)	1438	1636.4	88	83—93
All malignant neoplasms (140—207)	445	427.8	104	95—114
Buccal cavity and pharynx (140—149)	7	9.8	72	29—148
Esophagus (150)	9	12.1	75	34—142
Stomach (151)	49	45.1	109	80—144
Intestine, except rectum (152—153)	21	25.9	81	50—124
Rectum (154)	15	17.6	85	48—141
Liver and intrahepatic bile ducts (155)	24	8.4	286	183—425
Pancreas (157)	16	19.3	83	47—135
Larynx (161)	5	7.3	68	22—159
Trachea, bronchus and lung (162)	144	148.3	97	82—114
Bone (170)	3	2.5	120	25—352
Connective and other soft tissue (171)	0	1.4	0	0—265
Melanoma of skin (172)	7	4.3	163	65—335
Prostate (185)	21	20.2	104	64—159
Testis (186)	3	2.5	118	24—345
Bladder (188)	21	14.3	146	91—224
Kidney (189)	4	10.0	40	11—103
Brain (191)	14	13.1	107	59—180
Thyroid (193)	2	1.1	181	22—654
Unspecified site (199)	24	12.9	187	120—278
Lymphosarcoma (200)	7	4.1	170	69—351
Hodgkins disease (201)	7	5.3	133	53—274
Leukemia (204—207)	11	13.4	82	41—147
Other lymphatic neoplasms (202—203)	4	9.9	40	11—104
Other malignant neoplasms	27	19.3	140	92—204
Benign and unspecified neoplasms (210—239, 208)	4	6.6	61	17—155
Circulatory system (390—458)	622	712.8	87	81—94
Respiratory system (460—519)	108	140.9	77	63—93
Digestive system (520—577)	72	77.2	93	73—117
Chronic liver disease, cirrhosis (571)	35	39.7	88	61—123
Accidents, poisonings and violence (E800—E999)	114	144.0	79	65—95
Other known causes	73	127.0	57	45—72

[a] Code of the International Classification of Diseases (eighth revision) in parentheses.
[b] Based on a Poisson distribution.

were autoclave workers at some time (SMR 896, 95 % CI 447—1603). In the analysis with a 15-year latency period, a statistically significant increased risk was also apparent for those classified as "never an autoclave worker," a group which however included workers with job "unspecified" also.

Duration of employment was associated with an increasing mortality trend from liver cancer, which was statistically significant (χ^2 19.5, $P<0.001$). With a 15-year latency period, the trend was not as strong (χ^2 5.70, $P<0.025$).

A very clear exposure-response relationship was seen for ranked level of exposure and liver cancer mortality. Although the ranked level of exposure was unknown for six deaths, increasing risk at progressively increasing levels of exposure was demonstrated (χ^2 7.99, $P<0.01$). With the use of a 15-year latency period and the estimated job-exposure matrices from factories 10 through 13 from the United Kingdom, the SMR for the intermediate category (50—499 ppm) was also statistically significant (7 deaths observed, SMR 551, 95 % CI 222—1136). The risk clearly increased with increasing total cumulative exposure to VC in parts per million-years (χ^2 20.4, $P<0.001$). An analysis with a five-year lag in cumulative exposure made virtually no difference in any of the results, and therefore the data are not presented. The results of the multivariate analysis for liver cancer in an internal comparison are presented in table 6. Only two variables, years since first exposure and cumulative exposure, had a statistically significant effect on the risk of liver cancer mortality.

Risk increased steadily with increasing exposure when years since first exposure was adjusted for. The tests for interactions were not statistically significant, and the addition of a quadratic term for cumulative exposure did not improve the fit of the model. The same procedure was followed when cumulative exposure from the estimated job-exposure matrix for the factories from the United Kingdom was included, and the regression results were similar. The relative risk estimates varied slightly from the previous model, probably because of the effect of misclassification from the job-exposure matrices of the four factories whose matrices were developed from those of other factories.

Angiosarcoma of the liver

Major characteristics of the 24 liver cancer deaths certified in the mortality data as ICD code 155 (eighth and ninth revision, as no death was coded according to the seventh revision) can be seen in table 7. When

Table 4. Mortality by time since first exposure for selected sites. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval)

Cause of death[a]	Years since first exposure																			
	1—9				10—19				20—29				≥30				Total			
	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI
All causes (000—999)	207	313.9	66	57—76	529	582.5	91	83—99	471	502.6	94	85—103	231	237.4	97	85—111	1438	1636.4	88	83—93
All malignant neoplasms (140—207)	56	73.5	76	58—99	173	155.6	111	95—129	151	138.6	109	92—128	65	60.2	108	83—138	445	427.8	104	95—114
Liver and intrahepatic bile ducts (155)	—	1.5	0	0—245	8	3.2	253	109—499	11	2.8	388	194—694	5	0.9	561	182—1310	24	8.4	286	183—425
Trachea, bronchus and lung (162)	16	22.7	71	40—114	50	53.9	93	69—122	60	50.4	119	91—153	18	21.3	84	50—133	144	148.3	97	82—114
Bladder (188)	2	1.8	109	13—395	7	4.8	146	59—301	6	5.1	117	43—255	6	2.6	231	85—504	21	14.3	146	91—224
Brain (191)	2	3.4	59	7—213	6	5.3	113	42—247	2	3.4	59	7—212	4	1.0	407	111—1041	14	13.1	107	59—180
Lympho-sarcoma (200)	3	1.3	225	46—657	4	1.6	258	70—662	—	1.0	0	0—381	—	0.3	0	0—1430	7	4.1	170	69—351
Circulatory system (390—458)	67	108.0	62	48—79	223	246.2	91	79—103	209	236.9	88	77—101	123	121.7	101	84—121	622	712.8	87	81—94
Respiratory system (460—519)	8	19.9	40	17—79	30	45.0	67	45—95	47	47.5	99	73—132	23	28.6	80	51—121	108	140.9	77	63—93
Chronic liver disease, cirrhosis (571)	2	8.4	24	3—87	17	17.0	100	58—160	14	12.2	115	63—193	2	2.1	95	11—342	35	39.7	88	61—123

[a] Code of the International Classification of Diseases (eighth revision) in parentheses.

Table 5. Mortality data for liver cancer according to the exposure variables.[a] (O = observed number of deaths, SMR = standardized mortality ratio, 95 % CI = confidence interval)

Exposure variable	O[a]		SMR	95 % CI	15 years of latency[a]			
					SMR		95 % CI	
Job title								
Ever autoclave worker	11		896	447—1603	1358		678—2430	
Never autoclave worker[b]	13		181	97—130	284		151—485	
Duration of employment (years)								
1—9	4		94	26—239	205		56—525	
10—14	5		327	106—763	602		196—1406	
15—19	4		310	84—794	310		84—794	
20—24	6		714	262—1555	714		262—1555	
≥25	5		1111	361—2593	1111		361—2593	
Ranked level of exposure (ppm)								
Low (<50)	3	(4)	119	25—347	227	(244)	47—664	(67—625)
Intermediate (50—499)	3	(7)	161	33—471	250	(551)	52—731	(222—1136)
High (≥500)	12	(12)	567	293—991	719	(719)	371—1255	(371—1255)
Unknown	6	(1)	317	117—691	486	(125)	182—1079	(3—697)
Cumulative exposure (ppm-years)								
0—1999	4	(9)	99	27—254	191	(348)	52—490	(159—662)
2000—5999	4	(4)	351	96—898	460	(400)	125—1177	(109—1024)
6000—9999	4	(7)	800	218—2048	851	(1429)	232—2179	(574—2943)
≥10 000	3	(3)	1429	295—4175	1667	(1667)	344—4871	(344—4871)
Unknown	9	(1)	357	163—678	536	(100)	245—1017	(2—557)
Total	24		286	183—425	445		285—663	

[a] The values in parentheses were determined in analyses including the estimated job-exposure matrices.
[b] In Norway, the longest-held job was used. In Sweden job rotation was practiced, and no one was classified as an autoclave worker.

histology had been performed and this information was available, a liver cancer death could be classified definitely as an angiosarcoma or not. When histology had not been performed or the information was not available, it was classified "unknown" as to whether or not it was an angiosarcoma. Deaths that occurred before 1974 when angiosarcoma of the liver was first reported in relation to VC (19) may not have been investigated as thoroughly as they would have been following the 1974 report. Of the 17 deaths for which histology (pathology) information was available, 16 were histologically confirmed angiosarcomas of the liver and one was a primary liver cancer. For the remaining seven, it is unknown whether or not they were angiosarcomas of the liver. A regression analysis was performed to assess the risk of angiosarcoma of the liver. In total, 22 angiosarcomas were included, with 16 coming from the liver cancer deaths coded to ICD 155 (as seen in table 7) and six additional angiosarcomas coming from other deaths, as seen in table 8. This table shows additional liver cancer deaths, not coded as 155 in the mortality data.

In total, there were six angiosarcomas, one primary liver cancer, and five "unknown" liver cancers among the 12 additional deaths. The small numbers necessitated combining the lowest two categories of cumulative exposure (<2000 ppm-years) for stability of the base-line category. The results were similar to those obtained for the 24 liver cancer deaths in that the final model included years since first exposure and cumulative exposure. The major difference is seen in table 9, where the relative risks for angiosarcoma are higher at each level of cumulative exposure than those for liver cancer.

The absolute risk of angiosarcoma is shown in table 10, on the basis of the results of the regression analysis shown in table 9, when cumulative exposure and years since first exposure were both included in the model. At ≥25 years since first exposure and ≥10 000 ppm-years, the absolute risk was 280 per 100 000.

In summary, the results from the regression analyses indicated that, while cumulative exposure and years since first exposure had had a detectable effect on the risk of liver cancer mortality and angiosarcoma of the

Table 6. Maximum likelihood estimates for final model with cumulative exposure and years since first employment for deaths from liver cancer (N = 24). (95 % CI = 95 % confidence interval)

Variable	Relative risk	95 % CI
Cumulative exposure (ppm-years)		
<500	1.0	·
500—1999	1.2	0.1—11.4
2000—5999	4.6	1.0—21.0
6000—9999	12.2	2.5—59.6
≥10 000	17.1	3.1—93.6
Years since first employment		
0—19	1.0	·
20—24	5.6	1.4—22.4
≥25	6.8	1.7—27.4

Table 7. Characteristics of the 24 subjects who died of liver cancer. (ICD = International Classification of Diseases)

Subject	Age at hire (years)	Year of hire	Duration of exposure (years)	Length of latency (years)	Year of death	Cause[a]	ICD revision	Angiosarcoma of the liver	Histological confirmation by pathology of angiosarcoma of the liver	Total cumulative exposure (ppm-years)
1	29	1955	16	17	1973	155.0	8	Unknown	No	7 360
2	27	1957	13	15	1972	155.0	8	Yes	Yes	5 676
3	21	1959	21	21	1981	155.0	9	Yes	Yes	6 397
4	47	1953	14	32	1985	155.0	9	Unknown	No	7 000
5	30	1953	28	31	1984	155.0	9	No	Yes	8 737
6	41	1960	8	20	1980	155.0	9	Unknown	No	..
7	32	1962	20	21	1983	155.0	9	Unknown	No	5 493
8	34	1950	21	21	1972	155.0	8	Yes	Yes	18 407
9	36	1947	21	28	1976	155.0	8	Yes	Yes	13 770
10	26	1941	33	36	1977	155.0	8	Yes	Yes	27 709
11	43	1961	13	24	1985	155.0	8	Yes	Yes	404
12	45	1964	10	16	1980	155.0	8	Yes	Yes	288
13	49	1958	4	18	1976	155.0	8	Unknown	No	..
14	37	1951	18	21	1973	155.0	8	Unknown	No	1 260
15	33	1954	18	25	1979	155.2	9	Yes	Yes	5 409
16	20	1957	27	28	1985	155.2	9	Yes	Yes	4 627
17	35	1954	24	29	1983	155.0	9	Unknown	No	111
18	19	1968	3	18	1986	155.2	9	Yes	Yes	636
19	36	1951	21	28	1979	155.2	9	Yes	Yes	8 215
20	26	1950	25	31	1981	155.2	9	Yes	Yes	8 594
21	30	1962	10	17	1980	155.2	9	Yes	Yes	1 822
22	24	1950	31	33	1983	155.2	9	Yes	Yes	7 152
23	37	1965	16	19	1985	155.2	9	Yes	Yes	1 848
24	18	1966	4	18	1984	155.0	9	Yes	Yes	808

[a] Code of the ICD.

Table 8. Cases of liver cancer on the basis of cancer incidence and other information (not included as liver cancer deaths in the mortality analysis). (ICD = International Classification of Diseases)

Subject	Age at hire (years)	Year of hire	Duration of exposure (years)	Length of latency (years)	Year of death	Cause[a]	ICD revision	Site of incidence or other information	Angiosarcoma of the liver	Histological confirmation by pathology	Total cumulative exposure (ppm-years)
1	24	1951	19	19	1970	197.8	8	Cancer incidence: ICD 155.0	Yes	Yes	8 203
2	45	1961	6	8	1970	197.8	8	Death certificate: carcinoma of liver	Unknown	No	..
3	28	1966	8	8	1974	197.8	8	Death certificate: carcinoma of liver, angiosarcoma, hepatic cirrhosis	Yes	Yes	1 749
4	34	1965	10	12	1977	197.8	8	Death certificate: hepatic failure due to liver cancer	Unknown	No	..
5	18	1965	7	?	Emigrated	—	—	Cancer incidence: ICD 155.0	No	Yes	..
6	36	1957	7	7	1964	199.0		Best evidence (clinical): ICD 155.0	Unknown	No	..
7	50	1954	11	11	1965	199.0	8	Best evidence (clinical): ICD 155.0	Unknown	No	..
8	54	1969	9	10	1980	199.0	9	Cancer incidence: ICD 155.2	Unknown	No	..
9	29	1941	31	31	1972	157.9	8	Cancer incidence: ICD 155.0	Yes	Yes	28 156
10	32	1953	20	22	1975	159.0	8	Best evidence (pathology): ICD 155.0	Yes	Yes	7 673
11	43	1944	22	28	1972	227.0	8	Death certificate: hemangioendothelioma of liver, natural causes	Yes	Yes	7 114
12	42	1963	8	17	1980	571.5	9	Death certificate: hepatic failure due to hepatic fibrosis	Yes	Yes	2 658

[a] According to the ICD.

liver, age at first exposure and calendar period of exposure did not. Very clear exposure-response relationships were evident between the cumulative exposure to VC and the risk of liver cancer and angiosarcoma of the liver. Finally, an effect of misclassification was demonstrated when the estimated job-exposure matrix was included, although the effect was minimal for the angiosarcoma results.

Lung cancer, brain cancer and lymphosarcoma

The SMR for trachea, bronchus, and lung cancer was 97 (95 % CI 82—114) for the total cohort, on the basis of 144 observed deaths. The SMR values did not show any remarkable association with a particular process, and although no pattern was evident for years since first exposure, there was a statistically significant increase at 25—29 years since first exposure on the basis of 33 observed deaths (SMR 147, 95 % CI 101—207), mainly from an excess in VCM production in this time period (5 deaths observed, SMR 486, 95 % CI 158—1134). Calendar period at exit and at hire did not reveal any consistent pattern.

Fourteen deaths from brain cancer occurred in the cohort, and, although the overall SMR was not increased (SMR 107, 95 % CI 59—180), there was a statistically significant excess at ≥30 years since first exposure on the basis of four observed deaths (SMR 407, 95 % CI 111—1041) (table 4). The excess was confined to the calendar period of hire of 1945—1954 and was the most evident for VCM/PVC production. Analyses by calendar period of exit, age at hire, and age at exit did not reveal any patterns of risk for brain cancer mortality.

Table 9. Maximum likelihood estimates for the final model with cumulative exposure and years since first employment for the deaths from angiosarcoma of the liver (N = 22). (95 % CI = 95 % confidence interval)

Variable	Relative risk	95 % CI
Cumulative exposure (ppm-years)		
<2000	1.0	·
2000—5999	6.8	1.1—41.7
6000—9999	24.7	4.1—150.1
≥10 000	45.4	7.3—281.1
Years since first employment		
0—19	1.0	·
20—24	4.7	1.0—22.8
≥25	6.2	1.4—29.0

Table 10. Absolute risk of angiosarcoma of the liver per 100 000.

Years since first employment	Cumulative exposure (ppm-years)			
	<2000	2000—5999	6000—9999	≥10 000
0—19	1.0	6.8	24.4	44.8
20—24	4.7	32.0	115.6	212.5
≥25	6.2	42.2	152.3	280.0

A detailed analysis of the seven deaths from lymphosarcoma showed no pattern in the SMR values according to years since first exposure. All seven deaths occurred in VCM/PVC production, and for this process alone there was no excess apparent by calendar period of hire or exit or age at hire or exit.

In table 11, the SMR values for lung cancer, and in table 12 those for brain cancer and lymphosarcoma, are shown according to the exposure variables. The analyses by job title, duration of employment, and cumulative exposure showed no relationship with any of the three sites. Neither was lung cancer associated with the ranked level of exposure, while brain cancer was slightly in excess in the high category of exposure. Lymphosarcoma showed a slight increasing pattern of mortality with increasing category of ranked level of exposure, but the entire analysis was based on four deaths only.

Table 11. Mortality data for lung cancer according to the exposure variables.[a] (O = observed number of deaths, SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval)

Exposure variable	O[a]	SMR[a]	95 % CI[a]
Job title			
Ever autoclave worker	25	97	63—143
Never autoclave worker[b]	119	97	80—116
Duration of employment (years)			
1—9	73	95	75—120
10—19	51	107	79—140
≥20	20	83	51—129
Ranked level of exposure (ppm)			
Low (<50)	37	94	66—130
Intermediate (50—499)	33	116	80—163
High (≥500)	35	98	68—136
Unknown	39	87	62—119
Cumulative exposure (ppm-years)			
<50	20 (37)	98 (110)	60—151 (77—151)
50—499	32 (49)	101 (101)	69—143 (75—134)
500—1999	14 (18)	101 (85)	55—169 (51—135)
2000—5999	11 (16)	83 (74)	42—149 (43—121)
6000—9999	7 (10)	141 (152)	57—290 (73—280)
≥10 000	2 (2)	106 (94)	13—384 (11—339)
Unknown	58 (12)	93 (80)	71—120 (41—139)
Total	144	97	82—114

[a] The values in parentheses were determined in analyses including the estimated job-exposure matrices.
[b] In Norway, the longest-held job was used. In Sweden job rotation was practiced, and no one was classified as an autoclave worker.

Table 12. Mortality data for brain cancer and lymphosarcoma according to the exposure variables. (O = observed number of deaths, SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval)

Exposure variable	Brain cancer			Lymphosarcoma		
	O	SMR	95 % CI	O	SMR	95 % CI
Job title						
Ever autoclave worker	2	85	10—307	3	661	136—1931
Never autoclave worker[a]	12	112	58—196	4	147	40—377
Duration of employment (years)						
1—9	8	106	46—208	6[b]	484	178—1053
10—19	3	78	16—228	1	116	3—648
≥20	3	183	38—535	—	0	0—1230
Ranked level of exposure (ppm)						
Low (<50)	3	91	19—265	1	127	3—705
Intermediate (50—499)	1	42	1—235	1	176	4—983
High (≥500)	4	128	35—328	2	234	28—846
Unknown	6	141	52—306	3	310	64—907
Cumulative exposure (ppm-years)						
<50	—	0	0—204	1	233	6—1296
50—499	4	162	44—414	1	156	4—868
≥500	4	120	33—308	1	142	4—794
Unknown	6	110	40—239	4	288	78—736
Total	14	107	59—180	7	221	89—455

[a] In Norway, the longest-held job was used. In Sweden job rotation was practiced, and no one was classified as an autoclave worker.
[b] All six deaths in the periods 1—4 years.

Cancer of unspecified site

Twenty-four deaths in the cohort were classified as malignant neoplasms of unspecified sites (ICD 199), giving a statistically significant excess (24 deaths observed, SMR 187, 95 % CI 120—278). Additional information, such as cancer incidence data, was available for 20 of the 24 deaths. Three subjects had liver cancer and were therefore included in table 8. It was unknown, however, whether they had angiosarcoma of the liver since no histological information was available. No other clear excess of a particular cancer among those classified as cancer deaths of an unspecified site was apparent.

Cancer incidence results

For the 2643 subjects from the four factories in Norway and Sweden included in the cancer incidence analysis, the total number of cancers observed was 127 (SIR 107, 95 % CI 89—127), and their distribution by site is shown in table 13 (reported for one or more observed deaths). The only statistically significant excess was for liver cancer, on the basis of seven observed cases (SIR 303, 95 % CI 122—623). Suggestive increases were found for stomach cancer (13 cases observed, SIR 150, 95 % CI 80—256), lung cancer (22 cases observed, SIR 152, 95 % CI 95—230), melanoma (8 cases observed, SIR 184, 95 % CI 79—362), and brain cancer (8 cases observed, SIR 159, 95 % CI, 68—312).

Although the lung cancer increase was not statistically significant, it was investigated in more detail as other studies have suggested increased risk for lung cancer. There was no excess according to process type or category of years since first exposure. A slight excess was suggested for < 15 years of employment, while the SIR values were close to 100 for 15—19 and ≥ 20 years of employment. For the ranked level of exposure, the risks in the high and low categories were virtually identical. According to cumulative exposure, no exposure-response was apparent (results not presented in tabular form). Without statistical significance and with little apparent relationship to VC exposure, some indication of increased lung cancer risk remained for one PVC-processing plant and one Norwegian VCM/PVC production plant. The national investigator for the PVC-processing plant attributed the excess to exposure to asbestos, which was utilized in the process (7), while the excess remained unexplained in Norway.

Discussion

This collaborative study was carried out with the main purpose of analyzing exposure-response relationships between exposure to VC and liver cancer and investigating whether exposure to VC could increase cancer risk for sites other than the liver.

The results confirmed the association between exposure to VC and liver cancer. The excess of liver cancer mortality was associated with duration of employment, and a clear association with ranked level of exposure was found. The results were strengthened by the regression analyses, which indicated that the risk of liver cancer depended on cumulative exposure and years since first exposure.

Twenty-two subjects had histologically confirmed angiosarcoma of the liver, and the regression analyses demonstrated that the risk was mostly influenced by cumulative exposure to VC. The relative risks were higher at each level of cumulative exposure than those for all liver cancer deaths, but it must be remembered that the same 16 angiosarcoma deaths were included in both analyses. The approximate incidence rate of angiosarcoma of the liver in Norway, for example, based on 1953—1988 data, was 1 in 10 million per year (personal communication from A Andersen, 1989). Others have estimated the annual incidence at 1 to 2 in 10 million (20, 21).

Given 222 746 person-years at risk accumulated by this cohort, with an annual incidence of angiosarcoma of the liver of 2 per 10 million in the general population, the overall expected figure for the cohort would be 0.045. The rarity of this tumor supports the use of internal comparisons to assess the significance of exposure variables.

Table 13. Cancer incidence, based on data for four factories in Norway and Sweden, by detailed cause. (O = observed number of cases, E = expected number of cases, SIR = standardized incidence ratio, 95 % CI = 95 % confidence interval)

Cancer site[a]	O	E	SIR	95 % CI[b]
Buccal cavity and pharynx (140—148)	5	4.2	119	39—277
Stomach (151)	13	8.7	150	80—256
Intestine, except rectum (152—153)	8	8.9	89	39—176
Rectum (154)	2	5.9	34	4—123
Liver and intrahepatic bile ducts (155)	7	2.3	303	122—623
Pancreas (157)	3	4.3	70	14—203
Larynx (161)	2	1.6	122	15—441
Trachea, bronchus and lung (162)	22	14.5	152	95—230
Melanoma of skin (190)	8	4.4	184	79—362
Prostate (177)	16	18.0	89	51—144
Testis (178)	1	2.2	45	1—252
Bladder (181)	7	7.9	88	36—182
Kidney (180)	4	5.4	74	20—188
Brain (193)	8	5.1	159	68—312
Thyroid (194)	3	0.9	327	67—955
Lymphosarcoma and other lymphoma (200, 202)	1	3.6	28	1—154
Multiple myeloma (203)	1	1.9	53	1—297
Other malignant neoplasms	16	11.9	135	77—219
All malignant neoplasms (140—205)	127	119.0	107	89—127

[a] Code of the International Classification of Diseases in parentheses.
[b] Based on a Poisson distribution.

The exposure estimates used for the ranked level of exposure and cumulative exposure indices were based on the reconstruction of past exposures, and they appeared to be an efficient tool for investigating exposure-response relationships. Although the job-exposure matrices utilized for the analysis were often based on rough estimates and thus resulted in a certain degree of imprecision, the results demonstrate exposure-response relationships for the carcinogenicity of VC. A recent study also estimated cumulative exposure to VCM, PVC, and butadiene and found that only cumulative exposure to VCM had any effect on liver cancer risk (6).

No increase was evident for lung cancer mortality, nor was there any association with the exposure variables, including ranked and cumulative exposure indices. It should be noted that the power of the study would allow detection of a statistically significant (at the 5 % level, one-sided) SMR for lung cancer of 114 with 80 % probability.

A slight increase in lung cancer was suggested by the incidence data, which corresponded to about 10 % of the mortality data. There was no apparent relation between lung cancer incidence and VC exposure. In one factory of the four included in the incidence analysis, a case of pleural mesothelioma was reported, and exposure to asbestos has been documented for the PVC-processing plant (7).

Two other sites investigated for excess risk were brain cancer and lymphosarcoma according to the a priori hypotheses. The results from this collaborative study did not suggest an effect of exposure to VC on mortality from brain cancer, although the power of the study only permitted detection of an SMR of 182 or more, which could be labeled as statistically significant with 80 % probability. The excess at ≥ 30 years since first employment was, however, an indication that an effect of exposure cannot be fully dismissed. For lymphosarcoma, although an excess was suggested, the small numbers and missing information on exposure variables for some of the subjects prohibited interpretation in relation to exposure to VC.

None of the other causes of death was in excess; instead, some statistically significant deficits were apparent. The deficit in total mortality was probably due to the healthy worker effect, both in the hiring of healthy workers compared with the general population and in a survival effect within the cohort due to the criteria for inclusion of employment for one year or more.

These results are very similar to those reported recently in the United States (6). In that study only liver cancer was in excess for the cohort of VCM workers (SMR 333, 95 % CI 202—521), with no statistically significant excess of lung cancer (SMR 115, 95 % CI 95—139), brain cancer (SMR 145, 95 % CI 79—248) or hematopoietic cancers (SMR 78, 95 % CI 48—121). In the nested case-referent analysis, liver cancer risk increased with increasing cumulative exposure (estimated as duration times categorized exposure level). Of the 19 liver cancers, 12 were angiosarcomas, and for this subgroup only, unlike our results, was the positive dose-response evident.

Concluding remarks

The results of this multicentric collaborative study on workers in the VC industry indicate that exposure to VC is associated with an increase in liver cancer. An exposure-response relationship was observed for both ranked and estimated cumulative exposure. The relationship was even more evident when only liver angiosarcoma was analyzed.

No significant excess of mortality was found for the other sites suspected a priori to be affected by exposure to VC. Although the incidence of lung cancer was slightly increased, neither it nor lung cancer mortality appeared to be associated with any of the exposure variables. Brain cancer and lymphosarcoma mortality, although showing slight increases, did not appear to be consistently associated with exposure, although the small numbers prohibited firm conclusions.

An increased risk of bladder cancer and melanoma of the skin was detected which did not appear to be related to exposure in that the association with employment in the VC industry was confined to one country only.

No increased mortality was observed for the other main causes of death.

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