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PREFACE

During the 1980s, the National Institute for Occupational Safety and Health (NIOSH) has helped to protect and preserve the health of workers in developing countries. The World Health Organization (WHO) is also dedicated to this end, and through its Programme of Action on Worker's Health has sought to protect and promote the health of working populations throughout the world.

In reaching toward these objectives, NIOSH and WHO have been able to collaborate on several projects. One project has now resulted in this text, A Joint Publication on Teaching Epidemiology in Occupational Safety and Health. This volume focuses on the need to train occupational epidemiologists in the recognition and evaluation of occupational diseases and injuries. It is a training tool that uses the case approach to instruct epidemiolgists. It is with pride that we publish this book of case studies as an aid to both epidemiologists and the many workers who will benefit from their services.

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TEACHING EPIDEMIOLOGY IN OCCUPATIONAL HEALTH

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-- = NOT APPLICABLE; 1 = LOW; 2 = MEDIUM; 3 = HIGH

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OTHER CONCEPTUAL ISSUES				
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-- = NOT APPLICABLE; 1 = LOW; 2 = MEDIUM; 3 = HIGH

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CASE CONTROL				
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SCREENING			1	2
SURVEILLANCE				
LATENCY	3	3		2
PERSON-YEARS		2		
EXPOSURE ASSESSMENT	3	1	3	1
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CROSS SECTIONAL	3	2	3	3
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PROPORTIONAL				2
CASE CONTROL				
OTHER CONCEPTUAL ISSUES				
CLUSTER INVESTIGATION	3			1
SCREENING	1			1
SURVEILLANCE	1	2	2	
LATENCY				
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EXPOSURE ASSESSMENT	3	1	2	2
CHOOSING A COMPARISON POPULATION		1		
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DATA ANALYSIS				
SIGNIFICANCE TESTING				2
CONFIDENCE INTERVALS				
STRATIFIED ANALYSIS				2
REGRESSION				
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VINYL CHLORIDE AND CANCER*

PART 1

In January 1974 the B.F. Goodrich Company notified the United States National Institute for Occupational Safety and Health (NIOSH) that four cases of angiosarcoma of the liver (ASL) had occurred since 1967 in a work force of about 500 long-term workers at a polyvinyl chloride (PVC) production plant in Louisville, Kentucky, USA.

Case number	Age at diagnosis, race, sex	Date of diagnosis	Date of first PVC exposure	Total years of exposure
1	43 white, male	8-67	7-52	15
2	36 white, male	5-70	11-55	13
3	49 white, male	3-73	12-48	16
4	58 white, male	12-73	11-45	28

Although only four cases occurred over a 10-year period (1964-1974), ASL is so rare a tumour that a causal relationship was strongly suspected. The expected incidence of ASL in the general population was derived from the US National Cancer Institute's Third National Cancer Survey (1969-1971) which indicated that only about 27 cases occur per year in the entire population of 200 million in the United States of America.

Question 1

Calculate a crude mortality ratio for ASL in long-term PVC polymerization workers at this plant in the past 10 years. Assume 10 years of observation during which the workers were at risk for developing cancer.

Crude mortality ratio = _____

Within just a few days, additional observations were reported which supported the association between vinyl chloride exposure and the development of ASL. First, an Italian study, the preliminary results of which had been presented at the Xth International Cancer Congress at Houston, USA, in 1970, were published in 1971 and had found that rats given long-term inhalation exposure to work-place concentrations of vinyl chloride monomer (VCM) developed not only ASL, but also angiosarcoma at other sites, as well as other malignant tumours (lung, renal). (Viola et al., 1971) Second, detailed clinical and pathological reviews of the four human cases of ASL showed that all four had similar clinical illnesses and similar pathological lesions involving portal hypertension and portal fibrosis in addition to ASL.

Question 2

What further questions are raised both by the finding of four cases of ASL at one plant and by the appearance of ASL and other tumours in rats exposed to VCM?

* By Henry Falk, Richard Waxweiler, & Clark Heath, 1975. Revised 1985

Before proceeding, some background information concerning VCM/PVC is necessary. VCM is a gas ($CH_2 = CHCl$) produced largely through chlorination of ethylene, a byproduct of the petroleum industry. When polymerized, VCM forms PVC, one of four major polymer plastics widely used in the modern world (the other three are polystyrene, polypropylene, and polyethylene). PVC can take various physical forms (liquid, solid, rigid, flexible) depending on chemical additives used (copolymers, plasticizers).

PVC has been produced commercially since the 1930's. Since the Second World War, its production has steadily increased throughout the world, production in the USA in 1974 amounting to 3.5 million tons. As a plastic, it has multiple uses varying from floor tiles and seat covers to toys, water pipes, and tires. VCM until recently was considered a relatively inert gas and as such was widely used as a spray can propellant.

Over one million workers in the USA have some kind of contact with VCM/PVC. These workers can be considered in the following three categories:

1) VCM production. In January 1974, VCM was being produced in 12 different plants in the USA, employing a total of about 1000 workers. The chemical process took place in an essentially closed system of vats and pipes. Workers were directly exposed to VCM only when leaks occur in the system.

2) PVC polymerization. According to the methods used before 1973, the VCM gas, liquified under pressure, was transferred by tank car to polymerization facilities. There were 37 such plants in the USA, as of January 1974, employing a total of about 20 000 workers. In the polymerization process, VCM was introduced into large reactor vessels where polymerization took place under heat and pressure, often in the presence of chemical additives. Following the reaction process, the newly-formed PVC was drained from the vessel. However, residual polymer builds up on the vessel walls, requiring periodic removal, partly by water jet and partly by hand. Cleaning by hand entails workers entering the vessels and spending considerable time in an atmosphere containing increased amounts of VCM. While workers entering reactors are now carefully protected from VCM exposure, in the past little or no protection was thought necessary. Considerable direct exposure to VCM may also occur when workers handle freshly polymerized PVC beyond the reactor vessel. Such fresh PVC may retain substantial amounts of unreacted VCM within its polymer structure, releasing VCM into the air in the process of packing and shipping.

3) PVC fabrication. From polymerization facilities, PVC in various physical forms is shipped to numerous manufacturing concerns throughout the country for fabrication into diverse consumer products. Use of PVC in such fabrication plants varies greatly. Depending upon amounts of PVC used, the ways in which it is used, and the working conditions involved, workers may well be exposed to residual VCM released from PVC plastic. In all, about one million workers are employed in PVC fabrication plants. Many of the plants are small, employing only a handful of workers in each plant.

Question 3

a) Given these facts, what phase of the VCM/PVC industry would be best suited for an epidemiological study of VCM health effects? Why?

b) What is the purpose of conducting further epidemiological studies in this population?

c) What kind of study might be undertaken and why?

d) What criteria would you suggest for selecting groups of workers for study?

PART 2

NIOSH chose to conduct a retrospective cohort mortality study of workers at PVC polymerization plants. The study was designed to follow polymerization workers from the time they entered the industry until the end of December 1973, and to compare observed cause-specific mortality among such workers with that expected based on known USA white male cause-specific mortality rates. Four plants were selected for the study on grounds of length of operation, accessibility of records, and probable ease of followup.

1. B. F. Goodrich, Louisville, Kentucky (where the four original cases had occurred),
2. B. F. Goodrich, Avon Lake, Ohio,
3. General Tire, Ashtabula, Ohio, and
4. Firestone, Pottstown, Pennsylvania.

Since a cohort study itself would take several years to complete, an initial rapid assessment of mortality patterns was undertaken, using available information in medical and insurance records at each plant.

A quicker approach is the proportional mortality study. In a study of proportional mortality rates, the proportion of deaths due to a specific cause (here ASL), in the exposed population, is compared to the proportion expected in a comparison population. In a cohort study, the incidence rate of disease (or the mortality rate from a specific disease) is compared between the exposed and the comparison populations. Proportional mortality studies can be based on available data, while cohort studies require extensive follow-up of cohort members.

From the records available at the selected plants, 144 deaths were identified. This figure includes workers who had died after retirement, as well as workers who had died on the job. All were white males. For each death, the age at death and the date of death were available. Using this information, a proportional mortality analysis was performed to determine if any particular causes of death were unduly represented when compared with what might be expected for white males in the USA as a whole dying at the same ages in the same years. The expected proportions, derived from US mortality rates and adjusted for age and year of death, are shown for specific causes of death in Table I, together with the observed numbers of deaths.

Table I. Proportional mortality ratio

Cause of death	Observed number of deaths	Expected proportion	Expected number of deaths	Observed/ expected ratio
Cardiovascular	63	.460	_____	_____
Cancer	31	.160	_____	_____
Pulmonary	10	.050	_____	_____
Digestive tract	3	.050	_____	_____
Liver/Biliary	* 4	.005	_____	_____
Leukemia/Lymphoma	4	.020	_____	_____
Brain	4	.010	_____	_____
Other	6	.025	_____	_____
Cirrhosis of liver	4	.025	_____	_____
Accidents	7	.020	_____	_____
All other causes	39	.335	_____	_____
Total	144	1.00	_____	_____

* Note that specific cancer sites are subsets of the total 31 cancer deaths.

Question 4

a) Calculate the expected number of deaths and an observed/expected mortality ratio for each diagnostic category.

b) How would you interpret the results?

c) How might the results be misleading?

THE COHORT STUDY

The cohort study was conducted by abstracting all available medical and work-history information on each worker, past and present, ever to work at each of the four plants. The specific jobs performed by each worker, the dates of starting and ending each job, and the age at the start of employment were recorded. Each worker was then traced to determine cause of death.

Question 5

What means might have been used to achieve follow-up of each worker?

The next step in the cohort study involved construction of a table of person-years at risk for disease for members of the cohort. Observed and expected mortality was then compared for specific causes of death within the cohorts using these person-year totals as denominators. The basic principles by which the cohorts were assembled can be illustrated by reviewing the work histories of 10 different hypothetical workers.

Worker No. 1: Began work in 1944 at 20 years of age. Had worked up to the present in PVC polymerization.

Worker No. 2: Began work in 1944 at 20 years of age. Worked until August 1949 as a pipefitter and left that employment.

Worker No. 3: Began work in 1944 at the age of 35 years. Had worked up to the present in PVC polymerization.

Worker No. 4: Began work in 1944 at 20 years of age. Died in 1969. Worked in PVC polymerization.

Worker No. 5: Began work in 1944 at 20 years of age. Had worked to the present in administration, becoming vice president in charge of sales.

Worker No. 6: Began work in 1946 at the age of 52 years. Died in 1947. Worked in PVC polymerization.

Worker No. 7: Began work in 1972 at 21 years of age. Had worked to the present in PVC polymerization.

Worker No. 8: Began work in 1944 at 20 years of age. Worked for three weeks in PVC polymerization and then was drafted into the Army. Returned in 1954 at the age of 30 years and worked in PVC polymerization until October 1956 when he ceased that employment.

Worker No. 9: Began work in 1944 at the age of 40 years. Worked in PVC packing and shipping. Retired in 1969.

Worker No.10: Began work in 1965 at the age of 20 years. Had worked to the present in PVC polymerization.

Question 6

A modified life-table method is used to determine the total number of person years at risk of developing disease stratifying by age and decade of observation. The chart is listed below.

a) Complete the following chart to show person-years at-risk for developing disease for all these ten persons. The person-years contributed by Workers Nos. 1 and 2 have been entered for illustration purposes. (For sake of simplicity, consider partial years as whole years).

Decade of observation

Age in years	1944-1953 Workers No.	1954-1963 Workers No.	1964-1973 Workers No.	Total
20-29	1-10 2-10			
30-39		1-10 2-10		
40-49			1-10 2-10	
50-59				
60-69				
Total				

b) Why do person-years continue to accumulate after the worker leaves work or retires?
c) When would the person-years stop accumulating?
d) How is this information to be used?
e) What would be the effect of loss to follow-up?

PART 3

Obviously, different workers have different work histories and hence contribute unequally in terms both of exposure to VCM and of latency since their first VCM exposure. Some have worked directly in polymerization for many years (Workers Nos. 1, 3 & 4), others for shorter time periods (Workers Nos. 6, 7, 8 & 10). Some have had less direct contact with polymerization (Workers Nos. 2, 5 & 9), again for varying periods of time. To make the cohort study as meaningful as possible, it is necessary to give particular attention to the mortality experience of workers closely exposed to VCM over a substantial period of time, with an initial exposure long enough ago to allow for reasonable carcinogenesis latency. The review of the actual work histories of the initial four cases is a useful starting point for establishing criteria of job category, exposure duration, and latency. The following chart has been completed for the ten hypothetical workers. After examining this information, learning about the natural history of cancer, and investigating the work practices, the investigators decided on requirements for entry into the cohort. Entry into the cohort required five years of VCM exposure in a production areas of the plant, and ten years of latency.

Age in years	1944-1953 Workers No.	1954-1963 Workers No.	1964-1973 Workers No.	Years of exposure	Total
20-29					0
30-39		1-10 2-10 4-10		30	
40-49		3-5	1-10 2-10 4-6	31	
50-59		3-5 9-10	3-5	20	
60-69			3-5 9-10	15	
Total years of exposure	0	50	46	96	

Question 7

How would this chart of "high-risk" person-years compare with one in which all person-years are included regardless of exposure, latency, and job category?

Question 8

What workers were eliminated? Why?

Question 9

a) What is the effect of including Workers Nos. 6 and 7 in the "high-risk" chart?
b) What is the effect of including Worker No. 10 in the "high-risk" chart?
c) How is latency to be defined for Worker No. 8?

Assuming a criterion of five-years' exposure, the total person-years at risk for disease in the actual cohort are shown by age in Table II for persons with less than and more than ten years' latency. Follow-up was virtually complete (1287 out of 1294 members of the ten-year latency group). In these two groups, a total of 5 and 35 cases of cancer were observed. Included for comparison are 1965 age-specific mortality rates for cancers of all sites in US white males.

Table II. Total person-years at risk for disease

Age in Years	Person-years at risk disease for workers with latency of less than 10 years	more than 10 years	Expected age specific cancer mortality per 100 000	Expected number of cancer deaths for latency of less than 10 years	more than 10 years
20-29	8444	38	13		
30-39	4619	3065	28		
40-49	2180	5668	91		
50-59	508	2681	300		
60-69	40	1078	712		
70-79	0	171	1223		
80+	0	20	1710		
		Total expected deaths			
		Total observed deaths		5	35
		SMR (O/E X 100)			

Question 10

a) For each latency group, calculate the expected numbers of deaths in each age category, and then an overall standardized mortality ratio (SMR).

b) How do you interpret these results in terms of cancer risk among persons exposed to VCM?

The actual computation of expected numbers of cases was far more complex than the above illustrations suggest. Person-years at risk for disease were counted using 5-year rather than 10-year groupings by age. Expected numbers of deaths were calculated using mortality rates for 5-year periods from 1940 to the present, rather than a single set of rates for a given median year (1965). The results of these calculations are shown in Table III.

Table III. Number of deaths among workers with five or more years VCM exposure and ten or more years latency

Cause of death	Observed	Expected	Standardized mortality rate
Cardiovascular	57	54.7	_____
Cancer	35	23.5	_____
Pulmonary	12	7.7	_____
Liver/Biliary	7	0.6	_____
Leukemia/Lymphoma	4	2.5	_____
Brain	3	0.9	_____
Other	9	11.8	_____
Cirrhosis Of liver	2	4.0	_____
Pulmonary disease (excluding cancer)	6	3.4	_____
Violent deaths	13	14.2	_____
All other causes	22	26.5	_____
Unknown cause	1	---	--
Total	136	126.3	_____

Question 11

a) Why is it preferable to use mortality rates from several different time periods rather than from one year in computing expected mortality?

b) Why are 5-year groupings by age preferable to 10-year groupings?

Question 12

a) Compute an SMR value for each cause-of-death category.

b) How would you interpret these results?

c) How might the results be affected if different criteria were used for exposure (1, 2 or 10 years instead of 5) or for latency (5 or 15 years instead of 10)?

Question 13

What further studies should be undertaken in light of these results?

Question 14

If a repetition of this study would yield a negative result in another country, what reasons for this could you think of?

INSTRUCTOR'S NOTES
VINYL CHLORIDE AND CANCER

OBJECTIVES

1. How to deal epidemiologically with a cluster of rare disease.
2. How to choose the appropriate study design.
3. How to choose the appropriate study population.
4. Introduction to the proportional mortality ratio.
5. Introduction to the cohort study including the concept of person years.
6. Understanding latency and exposure categorization.

PART 1

Answer 1

Calculate a rough value of crude mortality ratio of ASL for long-term PVC polymerization workers at this plant in the past 10 years, assuming 10 years at-risk for each worker and a US population of 200 million.

Crude mortality ratio = Cases/person-years (exposed) = 4/(500X10) = 0.0008
Cases/person-years (general population)=27/(200 000 000) = 0.00000135
= x 5926 excess

Instructors note — Make sure that the students are familiar with the definition of person-years at risk. "At risk" refers to years of observation when the person is eligible to develop the disease of interest.

Answer 2

What further questions are raised both by the finding of four cases of ASL at one plant and by the appearance of ASL and other tumours in rats exposed to VCM?

a. PVC industry - So far, cases were from just one plant. Are other plants involved? Is this an industrywide problem? Are there special risk-factors besides VCM exposure at the Louisville plant?

b. Diagnosis - Rare tumours are easily misdiagnosed. Would a careful review of records reveal more cases than are initially apparent? What is the true risk for exposed workers? Are there precursor stages of ASL which could be identified (e.g. liver damage)?

c. Outcomes - The animal studies suggest that a multiplicity of tumours result from VCM exposure. Is this true for exposed persons also?

d. Public health - PVC is widely used. What risk is there, if any, for 1) consumers, 2) persons living near VCM/PVC production or fabrication facilities or for persons employed in the many industries which manufacture PVC-containing products? It might be useful to ask one or more students to review the process in advance, and to comment on the major sources of exposure, and exposure levels in his or her country.

Answer 3

a) Given these facts, what phase of the VCM/PVC industry would be best suited for an epidemiological study of VCM health effects? Why?

Considerations

1. Exposure - studied populations should have had exposure to VCM.
2. Population size - sufficient size to provide some acceptable power to the study (add power calculation).
3. Records - available records and tracking of the population. The workforce in the polymerization phase would be the best to study, given the size of the workforce and their extent of exposure.
4. Latency.
5. Same plant/industry wide - cluster problem.

b) Why conduct further epidemiological studies of this population?

There are three answers to this: 1) to quantify the magnitude of the cancer excess in the population in which the cluster was originally observed; 2) to determine whether other malignant or nonmalignant diseases are also in excess, other than the original sentinel tumour; 3) if one wanted to confirm the association between vinyl chloride and ASL, independent of the original cluster, one would theoretically need to exclude the original cases or go to an entirely new study population. If the presenting tumour had been more common, this would be more necessary than with an extremely rare tumour such as ASL.

c) What kind of study might be undertaken? Why?

The discussion should address at least three issues involved in choosing the most appropriate study design. First, what are the advantages of basing the study upon exposure (cohort approach) or disease (case-referent approach)? Second, should the period of observation be prospective or retrospective? A prospective approach would allow the collection of high quality exposure data, but would be expensive and would not provide results for at least ten years. Third, should the measure of disease be cancer incidence (morbidity) or death (mortality)? For angiosarcoma, mortality approximates to morbidity because of the lethality of the disease.

To return to the issue of whether a cohort or case-referent study design is preferable, the latter is usually said to be more efficient if the disease is rare. However, a cohort study in this highly exposed group of workers could be used to quantify the excess, initially apparent, as a cluster. Alternatively, a case-referent study in a defined geographical area, e.g. a nation, could be conducted if there were a means of identifying cases. This approach might miss the contribution of a rare exposure if there are other, more common causes of the disease.

d) What criteria would you suggest for selecting groups of workers for the study?

Since cancers are likely to require a long latent period after the first chemical exposure, only those plants in operation for many years should be studied, and preferably those making pure PVC (and relatively few copolymers). Particular attention should be given to the workers involved, first, in reactor-cleaning and, second, in direct handling of fresh PVC. Attention should be given to the ultimate size of the cohort, to the feasibility of retrieving records at given plants, to the ease of tracking workers in particular areas, and to the existence of industrial hygiene that would characterize prior exposure.

If positive findings come from the study of polymerization workers, consideration might be given to a study of less exposed phases of the industry and of the consuming public.

PART 2

Answer 4

a) Calculate the expected number of deaths and an observed/expected mortality ratio for each diagnostic category.

Table IV. Proportional mortality ratio

Cause of death	Observed number of deaths	Expected proportion	Expected number of deaths	Observed/ expected mortality ratio
Cardiovascular	63	.460	66.24	0.95
Cancer	31	.160	23.04	1.35
Pulmonary	10	.050	7.20	1.39
Digestive tract	3	.050	7.20	0.42
Liver/Biliary	4	.005	0.72	5.56*
Leukemia/Lymphoma	4	.020	2.88	1.39
Brain	4	.010	1.44	2.78
Other	6	.025	3.60	1.67
Cirrhosis of liver	4	.025	3.60	1.11
Accidents	7	.020	2.88	2.43*
All other cases	39	.335	48.24	0.81
Total	144	1.000	144.00	1.00

* Significant $p = 0.05$, using a "simple" Chi-square test, i.e. $\frac{(\text{observed number} - \text{expected number})^2}{\text{expected number}}$

A more accurate test would be the Mantel-Haenszel summary chi square used on age standardized data. This, however, requires age data which are not given in this problem.

b) How would you interpret the results?
There is an excess of cancer (especially of the liver and brain) and also an excess for accidents.

c) How might the results be misleading?

1. A proportional mortality analysis compares proportions and not rates. If mortality rates for causes other than cancer were relatively low among PVC workers, the proportion of cancer deaths might appear excessive without any real increase in rates.

2. The 144 deaths may not be representative of all deaths within the cohort.

3. Data came from medical and insurance records at each plant. No independent appraisal or review of cause of death was made.

4. The comparability was somewhat controlled in being restricted to white males and adjusted for age and year of death. However, there is always some concern about comparing a healthy working population to general US population mortality data.

ANSWER 5

5. What means have been used to achieve follow-up of each worker?

Records of company, union, pension, Veterans Administration, social security, state motor vehicle, credit bureau.

ANSWER 6

6. a) Complete the following chart to show person-years at-risk for these ten persons. The person-years contributed by workers No. 1 and 2 have been entered for illustration purposes.

Note: The purpose of this exercise is to practice calculating person-years at risk. Do not worry about excluding anyone by title, work history, or latency.

Age in years	1944-53 Workers Nos.	1954-63 Workers Nos.	1964-73 Workers Nos.	Total person-years
20-29	1-10 2-10 4-10 5-10 8-10		7-2 10-9	61
30-39	3-5	1-10 2-10 4-10 5-10 8-10		55
40-49	3-5 9-10	3-5	1-10 2-10 4-6 5-10 8-10	66
50-59	6-2	3-5 9-10	3-5	22
60-69			3-5 9-10	15
Total person-years	72	70	77	219

b) Why do person-years continue to accumulate after the worker quits or retires?

A worker is continually followed and is at risk of developing the disease even after quitting, retirement, or lack of further VCM exposure. Note that for study purposes, he is only followed after he has achieved sufficient exposure and latency as defined by the study (in this case five years exposure and ten years latency).

c) When would person years stop accumulating once adequate exposure time has been acquired?

1 - When the worker dies. Note that if the worker dies prior to a sufficient latency period, he is not included in the study.
2 - When the study ends; in this case 1973.

d) How is the life-table information to be used?

Person-years are accumulated as the denominator for rate calculations.

e) What would be the effect of loss to follow up? Consider fewer person-years for any statum selection, and different accuracy of diagnosis in different geographical areas.

PART 3

Answer 7

How would this cohort of "high-risk" person-years compare with one in which all person-years are included, regardless of exposure, latency, and job category?

It contains less than half the total person-years, none from the early decades and none for persons in their the age group 20-29. This cohort definition (five years' exposure, ten years' latency) is arbitrary, but reasonable. It can be changed as circumstances warrant it.

Answer 8

What workers were eliminated? Why?

No. 5 - administrative job; no VCM exposure.
No. 6 - insufficient exposure time; insufficient latency.
No. 7 - insufficient exposure time; insufficient latency.
No. 8 - insufficient exposure time.
No.10 - insufficient latency.

Answer 9

a) What would be the effect of including each worker in the high-risk chart?
No. 6 - dilute the overall person-year total with two years without representing an appreciable risk of a work-related cancer, and his death would falsely exaggerate mortality in whatever his cause of death category was, again being unlikely to be job-related illness.

No. 7 - dilute the overall person-year total without representing appreciable risk of a work-related cancer.

No. 10 - again, dilute the person-year total without having sufficient latency to be eligible of a work-related cancer.

b) How is latency to be defined of Worker No. 8?

Worker No. 8 does not meet the five years' exposure criterion necessary to be included in the "high-risk" chart. Therefore, defining latency is meaningless in this case.

In general, latency is defined as the interval of time ending with death (or study end date, whichever come first) and beginning with the first exposure.

Answer 10

a) For each latency group, calculate expected numbers of deaths in each age category, and then an overall standardized mortality ratio (SMR).

Age in years	Expected number of cancer deaths for latency of less than 10 years	more than 10 years
20-29	1.098	0.005
30-39	1.293	0.858
40-49	1.984	5.158
50-59	1.524	8.043
60-69	0.285	7.675
70-79	0	2.091
80+	0	0.342
Total expected deaths	6.184	24.172
Total observed deaths	5	35
SMR (O/E X 100)	80.85	144.79

b) How do you interpret these results in terms of cancer rates among persons exposed to VCM?

These results indicate fewer cancer deaths than expected in the short latency group (reflecting the fact that one needs to be healthy to hold a job [Healthy worker effect]), but more than expected for long latency, perhaps indicating oncogenic effects of VCM or other work- place chemicals. Also, the excess of cancer is not merely a result of the four liver cancers alone. The SMR applies specifically to this cohort, and cannot be directly extrapolated to other cohorts (past or present), although it is a good indicator of risk in similarly exposed groups.

Answer 11

a) Why is it preferable to use mortality rates from several different time-periods rather than from one year in computing expected mortality?

For some causes of death (e.g., stomach or lung cancer), mortality rates have changed greatly over the past several decades.

b) Are 5-year groupings by age preferable to 10-year groupings?

Since the risk of death from particular causes may change markedly with age, especially at older ages, the use of individual year- groupings is preferable.

Answer 12

a) Compute the SMR value for each cause-of-death category.

Cause of death	Observed	Expected	SMR	95 % Confidence limits +
Cardiovascular	57	54.7	104	79-135
Cancer	35	23.5	149*	104-207
Pulmonary	12	7.7	156	80-272
Liver/Biliary	7	0.6	1167**	467-2404
Leukemia/Lymphoma	4	2.5	160	51-386
Brain	3	0.9	333	85-907
Other	9	11.8	76	35-145
Cirrhosis of liver	2	4.0	50	8-165
Pulmonary disease (excluding cancer)	6	3.4	176	64-384
Violent deaths	13	14.2	92	49-157
All other causes	22	26.5	85	52-126
Unknown cause	1			
Total	136	126.3	108	90-127

+ For the ratio of an observed value of a Poisson variable to its expectation.
* p = 0.05
** p = 0.01 Poisson chart 99% confidence intervals 41-343.

b) How do you interpret these results?

Cancer mortality is significantly increased. Numbers are small, however, and only liver tumours show statistically significantly excesses. Excesses present for lung, leukemia, and brain may deserve further study. The SMR for total cancer is remarkably similar to the simplified illustration (149 versus 145) and the overall results are basically similar to those obtained in the proportional mortality analysis. For validity and comparability arguments, see note 4c above.

c) How might the results be affected if different criteria were used for exposure (1, 2, or 10 years instead of 5) or for latency (5 or 15 years instead of 10)?

Longer exposure and latency criteria might have increased the SMR values, but at a loss of numerical/statistical strength. Shorter periods would increase numerical strength, but dilute the results.

Answer 13

What further studies should be undertaken in light of these results?

While mortality excesses may be too small to warrant similar cohort studies in less exposed workers or in general population groups, a detailed study of individual cancer cases in polymerization workers may be useful. Specific clinical, pathological, and work-history features of such cases (especially liver, and possibly brain and lung) may provide further clues to etiology. Additional animal-exposure experiments are also needed. Studies on other vinyl chloride related diseases are desirable.

Answer 14

If a repetition of this study yielded a negative result in another country, what reasons for this could you think of?

For example, lower exposure levels, too short exposure times, poor record-keeping system, population at risk too small.

Reference

Viola, P.L., Bigotti, A. Caputo, A. Oncogenic response of rat skin, lungs and bones to vinyl chloride. Cancer research, 31; 516-522 (1971).