

VINYL CHLORIDE AND CANCER

Objectives:

After completing this exercise, the participant should:

1. understand the concepts and the calculation of proportionate mortality ratio (PMR) and standardized mortality ratio (SMR);
2. be able to discuss the strengths and weaknesses of the retrospective cohort study design;
3. understand the concept of, and be able to calculate, person-years at risk;
4. be familiar with the issues involved in selecting an appropriate study population.

Part I

In January 1974 the B.F. Goodrich Company notified the National Institute for Occupational Safety and Health (NIOSH/CDC) that 4 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.

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

Although only 4 cases occurred over a 10-year period (1964-74), ASL is so rare a tumor that a causal relationship was strongly suspected. Expected incidence of ASL in the general population was derived from the National Cancer Institute's Third National Cancer Survey (1969-71) which indicated that only about 27 cases occur per year in the entire United States population.

Two measures of association commonly used in occupational epidemiology are the STANDARDIZED MORTALITY RATIO (SMR) and the PROPORTIONATE MORTALITY RATIO (PMR). Like the relative risk and odds ratio, the SMR and PMR are both ratios wherein the value (rate, odds, etc.) from some study or index population is divided by the value from some comparison or reference population. In this context, the value from the study population is considered the "observed" value, while the value from the reference population is considered the "expected" value. Hence all 4 measures of association may be thought of as 'observed divided by expected', or O/E.

The SMR is a ratio of mortality rates:

$$\begin{aligned}
 \text{SMR} &= \frac{\text{mortality rate in the study population}}{\text{mortality rate in the reference population}} \\
 &= \frac{\# \text{ observed deaths} / \text{person-years at risk in study pop.}}{\# \text{ deaths} / \text{person-years at risk in reference population}} \\
 &= \frac{O}{E} = \frac{\# \text{ observed deaths in study population}}{\# \text{ deaths expected based on mortality rates in reference pop.}}
 \end{aligned}$$

As a practical matter, the SMR can also be calculated as O/E, where O = the observed number of deaths in the study population, and E = the number of deaths expected to have occurred in that study population, based on mortality rates from some reference population. (Some prefer to express the SMR by multiplying the ratio by 100, but we will not do so in this exercise). The SMR is usually adjusted for age.

QUESTION 1: Calculate the expected number of deaths and the SMR for ASL in long-term PVC polymerization workers at this plant in the past 10 years, assuming a U.S. population of 200 million and 10 years of observation during which the workers were at risk for developing cancer. Calculate the SMR.

$$\text{Expected \#} = (\text{Rate in reference pop.}) \times (\text{Study Population}) \times (\text{Years})$$

=

SMR =

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 reported 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 tumors (lung, renal). Second, detailed clinical and pathologic review of the 4 human cases of ASL showed that all 4 had similar clinical illnesses and similar pathologic lesions involving portal hypertension and portal fibrosis in addition to ASL.

QUESTION 2a: From the data given above (the finding of 4 cases of ASL at one plant and by the appearance of ASL and other tumors in rats exposed to VCM), what can be said about the causal association between VCM and ASL?

QUESTION 2b: What further questions are raised by these findings?

Before proceeding, some background information concerning VCM/PVC is necessary. VCM is a gas ($\text{CH}_2 = \text{CHCl}$) produced largely through chlorination of ethylene, a byproduct of the petroleum industry. When polymerized, VCM forms PVC, one of 4 major polymer plastics widely used in the modern world (the other 3 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 World War II, its production has steadily increased throughout the world, production in the U.S. in 1974 amounting to 7 billion pounds. 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 1 million workers in the U.S. have some kind of contact with VCM/PVC. These workers can be considered in the following 3 categories.

- 1) VCM production. As of January 1974, VCM was being produced in 12 different plants in the U.S. employing a total of about 1,000 workers. The chemical process takes place in an essentially closed system of vats and pipes. Workers are directly exposed to VCM only when leaks occur in the system.
- 2) PVC polymerization. The VCM gas, liquified under pressure, is transferred by tank car to polymerization facilities. There were 37 such plants in the U.S. as of January 1974, employing a total of about 20,000 workers. In the polymerization process, VCM is introduced into large reactor vessels where polymerization takes place under heat and pressure, often in the presence of chemical additives. Following the reaction process, the newly-formed PVC is 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, ways in which it is used, and working conditions involved, workers may well be exposed to residual VCM released from PVC plastic. In all, about 1 million workers are employed in PVC fabrication plants. Many of the plants are small, employing only a handful of workers each.

QUESTION 3a: Given these facts, what phase of the VCM/PVC industry would be best suited for an epidemiologic study of VCM health effects? Why?

QUESTION 3b: What kind of study might be undertaken and why?

QUESTION 3c: Assuming that a workplace-based study will be conducted, what practical considerations are important for selecting worksites?

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Part II

NIOSH/CDC 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 through December 1973, and to compare observed cause-specific mortality among such workers with that expected based on known U.S. 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 follow-up.

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

Since the cohort study itself would take several months to complete, an initial rapid assessment of mortality patterns was undertaken, using available information in medical and insurance records at each plant. From these records, 144 deaths were identified. Included were workers who died after retirement, as well as workers who died on the job. All were white males. For each death, age at death, and cause and date of death were available.

Recall that the SMR is a ratio of mortality rates. In contrast, the PMR is a ratio of proportions, specifically the proportion of all deaths in a population which are ascribed to a particular cause.

$$\text{PMR} = \frac{\text{the proportion of deaths in the study population due to Cause X}}{\text{the proportion of deaths in the reference population due to Cause X}}$$

Notice that the PMR does not require knowledge of the mortality rate in either population, it just requires knowledge of the number of deaths in the study and reference populations. Although an SMR usually provides a more reliable measure of association than a PMR, the data needed to calculate the PMR are almost always more readily available than are the data needed to calculate an SMR.

As a practical matter, sometimes it is more convenient to calculate the PMR as O/E, where O = the observed number of deaths from Cause X in the study population, and E = the number of deaths from Cause X expected to have occurred in that population, based on the proportionate mortality of Cause X in the reference population.

$$\text{PMR} = \frac{O}{E} = \frac{\text{observed \# of deaths in the study population due to Cause X}}{\text{expected \# of deaths in the study population based on proportionate mortality due to Cause X in reference population}}$$

Expected proportions, derived from U.S. mortality rates and adjusted for age and year of death, are shown for specific causes of death in the table below, together with observed numbers of deaths.

Table 1. Proportionate mortality study of 4 PVC Polymerization Plants

<u>Cause of death</u>	<u>Observed # deaths</u>	<u>Expected proportion</u>	<u>Expected # deaths</u>	<u>O/E ratio (PMR)</u>
Cardiovascular	63	0.460	_____	_____
Cancer*	31	0.160	_____	_____
• Pulmonary	10	0.050	_____	_____
• Digestive Tract	3	0.050	_____	_____
• Liver/Biliary	4	0.005	_____	_____
• Leukemia/Lymphoma	4	0.020	_____	_____
• Brain	4	0.010	_____	_____
• Other	6	0.025	_____	_____
Cirrhosis of Liver	4	0.025	_____	_____
Injuries	7	0.020	_____	_____
Other Causes	39	0.335	_____	_____
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ALL CAUSES	144	1.00	_____	_____

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

QUESTION 4a: Calculate the expected number of deaths and an observed/expected mortality ratio for each diagnostic category.

QUESTION 4b: How would you interpret the results?

QUESTION 4c: Since the PMR is based on proportions, how might the results be misleading?

QUESTION 4d: How may the method of identifying deaths been biased?

The PMR, though imperfect, is readily calculable and frequently useful in providing direction for further investigation. Further investigation may involve a cohort study capable of yielding the data necessary to compute an SMR.

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 4 plants. The specific jobs performed by each worker, the dates starting and ending each job, and the age at 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 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 #1: Began work in 1944 at age 20. Has worked to the present in PVC polymerization.
- Worker #2: Began work in 1944 at age 35. Has worked to the present in PVC polymerization.
- Worker #3: Began work in 1944 at age 20. Worked until August 1949 and quit. Worked as a pipefitter.
- Worker #4: Began work in 1944 at age 20. Died in 1969. Worked in PVC polymerization.
- Worker #5: Began work in 1944 at age 20. Has worked to the present in administration. Is now vice president in charge of sales.
- Worker #6: Began work in 1946 at age 52. Died in 1947. Worked in PVC polymerization.
- Worker #7: Began work in 1972 at age 21. Has worked to the present in PVC polymerization.
- Worker #8: Began work in 1944 at age 20. Worked 3 weeks in PVC polymerization and then was drafted into the Army. Returned in 1954 at age 30 and worked in PVC polymerization until October 1956 when he quit.
- Worker #9: Began work in 1944 at age 40. Worked in PVC packing and shipping. Retired in 1969.
- Worker #10: Began work in 1965 at age 20. Has worked to the present in PVC polymerization.

Tables of person-years at risk, such as Table 2 below, may be used to determine the total number of person years at risk of developing disease stratifying by age and decade of observation.

QUESTION 6: Complete Table 2 to show person-years at-risk for developing disease for each of the 10 persons. The person-years contributed by Workers #1-3 have been entered for illustration purposes. (For sake of simplicity, consider partial years as whole years, births as on Jan. 1, and quitting of jobs or deaths as on Dec. 31.)

Table 2. Accumulated Person-Years at Risk

Age	Decade of Observation			Total Person-Yrs
	1944-1953	1954-1963	1964-1973	
20-29	#1-10 #3-10			
30-39	#2-5	#1-10 #3-10		
40-49	#2-5	#2-5	#1-10 #3-10	
50-59		#2-5	#2-5	
60-69			#2-5	
Total				
Person-Years				

QUESTION 6b: Why do person-years continue to accumulate after the worker quits or retires?

QUESTION 6c: When would the person-years stop accumulating?

QUESTION 6d: How might the information in this table be used?

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Part III

Obviously, different workers have different work histories and hence contribute unequally to the table in terms both of exposure to VCM and of latency since first VCM exposure. Workers #1, 2, and 4 had worked directly in polymerization for many years and had the highest exposure to VCM. Workers #6, 7, 8, and 10 also worked directly in PVC polymerization, but had exposure for shorter time periods. Workers #3 had less direct contact with polymerization for varying periods of time. To assess those at highest potential risk, we decide to limit our table of person-years to workers with direct exposure to VCM over a substantial period of time, with initial exposure long enough ago to allow for reasonable carcinogenesis latency. Based on our review of the initial cases, we decide that entry into the cohort requires 5 years of direct VCM exposure and 10 years of latency. The latency period is defined as the delay between exposure to a disease-causing agent and the appearance of manifestations of the disease. The period of latency is counted from the day of first exposure to the agent in question. The following table has been completed for all 10 hypothetical workers.

Table 3. Accumulated Person-Years at High Risk

Age	Decade of Observation			Total Person-Yrs
	1944-1953	1954-1963	1964-1973	
20-29				0
30-39		#1-10 #3-10 #4-10		30
40-49		#2-5	#1-10 #3-10 #4-6	31
50-59		#2-5 #9-10	#2-5	20
60-69			#2-5 #9-10	15
Total	0	50	46	96
Person-Years				

QUESTION 7: How does Table 3 which includes only "high-risk" person-years compare with Table 2 in which all person-years are included regardless of exposure, latency, and job category?

QUESTION 8: Which workers were eliminated? Why? What would be the effect of including them in the "high-risk" chart?

To determine if 10 years latency is indeed needed to develop ASL, we split latency into the two categories: <10 years and 10+ years latency. Follow-up was virtually complete. Five cases of cancer were observed in the <10 year latency group and 35 cases were observed in the 10+ year latency group. Assuming a criterion of 5-years' exposure, total person-years at-risk for disease in the actual cohort are shown by age in the following table for persons with less than and more than 10 years' latency. Included for your use in calculating expected number of deaths per person-years at-risk in each age group are 1965 age-specific mortality rates for cancers of all sites in U.S. white males.

Table 4 (next page) was constructed by a method analagous to Table 2, that is by adding up the person-years at risk for all 1294 workers with at least 5 years of exposure, regardless of latency.

QUESTION 9: Using Table 4, calculate the expected number of deaths for each age and latency category, and then an overall standardized mortality ratio (SMR) for each latency group.

QUESTION 10: How do you interpret these results in terms of cancer risk among persons exposed to VCM?

Table 4. Standardized Mortality Ratio for Cancer-Related Deaths

Age	Person-Years At-Risk for Disease for Workers with > 5 Years Exposure and Latency of		Expected* Age Specific Cancer Mortality Rate/100,000/yr	Expected Number Of Cancer Deaths For Latency of	
	<10 years	10+ years		<10 years	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		_____	_____
		SMR (O/E x 100)		_____	_____

* Expected deaths adjusted for cause and calendar year.

We just calculated an SMR according to the formula:

$$SMR = \frac{\text{observed \# deaths}}{\text{expected \# deaths}}$$

The actual computation of expected numbers of cases is far more complex than the above illustrations suggest, but, fortunately, computers perform these calculations more accurately and quickly than humans. Person-years at risk for disease were computed using 5-year rather than 10-year groupings by age. Expected numbers of deaths were computed 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 computations are shown in the Table 5.

QUESTION 11a: Why is it preferable to use mortality rates from several different time periods rather than from one year in computing expected mortality?

QUESTION 11b: Why are 5-year groupings by age preferable to 10-year groupings?

Table 5. Number of Deaths Among Workers
With 5+ Years VCM Exposure And 10+ Years Latency

<u>Cause of Death</u>	<u>Observed</u>	<u>Expected*</u>	<u>SMR</u>
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	_____
Other Known Causes	22	26.5	_____
Unknown Cause	1	--	--
ALL CAUSES	136	126.3	_____

* Expected based on U.S. white male rates adjusted for age and calendar year.

QUESTION 12a: Using Table 5, compute an SMR value for each cause-of-death category.

QUESTION 12b: How would you interpret these results?

QUESTION 12c: 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: In light of these results, what further questions remain to be answered? What studies would you propose to answer these questions?

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Part IV - CONCLUSION

The published paper by Waxweiler et al. from which this case study was drawn provides additional information on the histopathology of the liver, brain, and lung cancers observed in this cohort.

The following chronology details the regulatory history of vinyl chloride and illustrates the concurrent processes of research and regulation.

- MAY 70 Dr. P.L. Viola of Italy reports that high concentrations of vinyl chloride caused cancer in rats.
- AUG 72 Dr. Cesare Maltoni of Bologna, Italy, finds angiosarcoma and various tumors in experimental animals exposed to vinyl chloride concentrations as low as 250 ppm (parts-per-million).
- JAN 73 NIOSH requests information on possible hazards associated with occupational exposure to 23 chemical substances, including vinyl chloride.
- 22 JAN 74 NIOSH informs OSHA that since 1971 four PVC workers in one B.F. Goodrich plant died of angiosarcoma of the liver.
- 15 FEB 74 OSHA holds a fact-finding hearing at which the Maltoni data are presented.
- 05 APR 74 Emergency Temporary Standard (ETS) for VC is promulgated which reduces the Permissible Exposure Limit (PEL) from 500 ppm to 50 ppm and establishes other requirements for monitoring and respiratory protection.
- 15 APR 74 Industrial Bio-Test Laboratories of Northbrook, Illinois presents data indicating that 2 out of 200 mice exposed to VC concentrations of 50 ppm for 7 hour per day, 5 days per week for about 7 months had developed angiosarcoma of the liver.
- 10 MAY 74 OSHA proposes a VC standard which would reduce employee exposure to "no detectable level" as measured by sampling and analytical methods sensitive to 1 ppm with an accuracy of $1\text{ppm} \pm 50\%$. The proposal calls for regulated areas with limited employee access. Exposure monitoring, engineering controls, medical surveillance and training are also required. Respiratory protection (respirator use) would be permitted while engineering and work practice controls are being implemented or where exposures exceeded the PEL even after feasible engineering controls are instituted.

- 25-28 JUN,
08-11 JUL 74 OSHA holds public hearing.
- 21 AUG 74 Dr. Joseph K. Wagoner (Waxweiler's coauthor) presents results of SMR study to Subcommittee on the Environment of the U.S. Senate Commerce Committee.
- 04 OCT 74 OSHA publishes final standard.
- 31 JAN 75 U.S. Court of Appeals, 2nd Circuit upholds VC standard stating that in the area of safety OSHA is not restricted to the status quo but may promulgate standards which require improvements in existing technologies and the development of new technologies.

Clearly, the urgency and potential seriousness of the problem prompted the rapid completion of the cohort mortality study and the concurrent regulatory activity. By August 21st, 14 cases of biliary and liver cancers had been identified among workers at the four plants, eleven of which were later confirmed as angiosarcomas. In addition, reports of seven cases in Europe had been received by NIOSH (West Germany (2), Czechoslovakia (2), United Kingdom, Norway, and Sweden, one each).

References

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