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Occupational Epidemiology

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There is no analogue to the HWE in a proportional mortality analysis, since by definition the total number of deaths expected must be equal to the total number of deaths observed. However, the HWE probably has some influence on cause-specific proportional mortality ratios. SMRs for all cancers tend to be higher than SMRs for all other causes, usually by 10 to 20%. Therefore, even if there is no absolute excess of cancer among a group of deceased persons, for methodologic reasons an excess of 10 to 20% might be expected. Note that in the realm of rate ratios, this is a very weak association.

Also, SPMRs tend to be more interpretable for uncommon causes of death than for common causes. If the rate of some uncommon disease such as lung cancer is increased by, say, 200%, the SMR and the SPMR will each reflect this increase. However, if a common illness such as circulatory disease is increased by 200%, the SMR will still reflect this increase, while the SPMR will be increased considerably less. Also, whereas SMRs for two or more causes are essentially independent of each other, SPMRs for two or more causes are interdependent, since the sum of the expected numbers must equal the sum of the observed numbers.

In spite of these limitations to SPMR analyses, they are most useful and provide information that usually differs little from that obtained in an SMR analysis. It is especially instructive to do SPMR and SMR analyses on the same data, so as to evaluate interpretation of the results of these two methods of analysis.

B. Example — Rubber Workers

Consider again the data in Table 6.1. In assessing whether a specific cause of death is in excess, one might look only at causes for which the SMR is greater than 100. If this criterion is used, only leukemia and cancers of the stomach, large intestine, and bladder are in excess among the entire group of rubber workers. However, it might be argued that because of the HWE (or because of some other bias), SMRs greater than the "all-causes" SMR should be considered to be in excess. Intuitively, one assesses such excess by dividing each cause-specific SMR by the all-causes SMR to obtain a "corrected" SMR (CSMR).[29]

The results of such a division are illustrated in Table 6.17. In Column I are the same SMRs as in Table 6.1 (note that the SMRs differ slightly because the analyses were carried out at different times). In Column II are the CSMRs. CSMRs less than 100 are seen only for diseases other than cancer or cardiovascular disease. In Column III are the SPMRs from a proportional mortality analysis. By definition the all-cause CSMR and the SPMR are 1.00.

It can be seen that the CSMR and the SPMR for the several causes illustrated are similar. Part of the similarity no doubt is due to the relatively weak associations between disease and working in the rubber industry. However, under any of the three methods used to compute expected numbers, one would wish to investigate further death from bladder cancer and the lymphatic and hematopoietic cancers.

There is one tendency in Table 6.17 that may be of interest. For diseases of old persons, e.g., bladder cancer and stroke, the CSMR is higher than the SPMR. For diseases of young persons, e.g., brain cancer and external causes of death, the SPMR is higher than the CSMR. Whether this tendency is a general property of the CSMR and the SPMR is unknown. If it is a general property, it no doubt results from the way the weights differ between a SMR computation and SPMR computation, i.e., person-years vs. numbers of deaths.

C. Example — Vinyl Chloride Workers

In 1974, three cases of angiosarcoma of the liver among vinyl chloride workers were reported.[24] Later in the same year, the results of two epidemiologic studies were reported. In one, a standardized proportional mortality analysis was conducted of the causes of death among 161 deceased persons, most of whom had worked at the same plant as the three with angiosarcoma.[25] In the second, a standardized mortality ratio

Table 6.16
STANDARDIZED MORTALITY RATIOS (AND OBSERVED DEATHS) ACCORDING TO PLANT DIVISION IN WHICH EMPLOYEES EVER AND USUALLY WORKED[a]

	All causes		All cancers	
Division	Ever	Usual	Ever	Usual
"Laid Off"	—	81 (319)	—	69 (44)
Chemical	74 (161)	74 (68)	85 (32)	80 (13)
Aerospace	74 (711)	81 (282)	92 (155)	89 (55)
Tires	79 (1968)	91 (1345)	92 (393)	93 (265)
Industrial products	76 (1600)	81 (796)	84 (309)	94 (159)
Services	83 (2238)	84 (1638)	90 (405)	94 (305)
Rubber reclaim	75 (315)	72 (93)	94 (68)	100 (22)
Processing	79 (833)	87 (536)	98 (177)	111 (117)
Total [b]	—	82 (5079)	—	94 (980)

[a] Data differ slightly from those presented in Table 6.1.

Table 6.17
NUMBER OF DEATHS OBSERVED AMONG RUBBER WORKERS AND RATIOS OF OBSERVED TO EXPECTED ACCORDING TO THREE METHODS

		Observed/expected[a]		
Cause of death	Observed deaths	I	II	III
All causes	4982[b]	0.82	1.00	1.00
All cancer	980	0.94	1.17	1.17
Digestive	364	0.98	1.22	1.21
Bladder	48	1.22	1.52	1.45
Brain	30	0.80	1.00	1.00
Lymphatic and hematopoietic	106	1.13	1.42	1.44
CNS vascular	493	0.91	1.13	1.07
Circulatory	2445	0.83	1.03	1.01
External	278	0.62	0.77	0.86
All other causes	786	0.65	0.74	0.77

[a] Excludes 97 deaths of unknown cause.
[a] I Expected numbers based on 5-year age-time specific mortality rates for U.S. white males (SMR/100).
II Expected ratios in I have been divided by 0.82 (all causes SMR/100) and by 0.98 to correct for 97 deaths of unknown cause (CSMR/100).
III Expected numbers based on 5-year age-time specific proportional mortality ratios for U.S. white males (SPMR/100).

Table 6.18
OBSERVED AND EXPECTED DEATHS AMONG VINYL CHLORIDE WORKERS IN A PROPORTIONAL MORTALITY STUDY*

Cause of death	Observed	Expected	SPMR*
All causes	161	161.0	100
All cancer	41	27.9	150
Digestive	13	8.3	160
Liver and biliary	8	0.7	1100
Lung	13	7.9	160
Brain	5	1.2	420
Other	10	10.5	95
CNS vascular	8	9.5	80
Circulatory	66	68.6	96
External	22	24.5	90
All other causes	24	30.5	79

* Expected numbers based on proportional mortality ratios for United States white males.
† SPMR = Standardized proportional mortality ratio = 100 × observed/expected.

analysis was conducted on the mortality among 8384 men who had worked with vinyl chloride, including those at the same plant as above.[21] Among these 8384 workers were 352 who had died, including most of the 161 included in the above report.

In Table 6.18 are presented the results of the SPMR study. A 50% excess of cancer was seen, which was due entirely to cancers of the liver, the lung, and the brain. In Table 6.19 are presented the results of the SMR study. As compared to the general population, there was essentially no excess of cancer. However, the CSMR was (102/75) × 100 or 136. There were large excesses of cancers of the liver and of the brain. For respiratory cancer, while the SMR was close to 100, the CSMR was 140.

Thus the two studies reported similar results, even though one was smaller and based simply on a SPMR analysis. In this study an analysis according to age and year of death of persons with cancer was also done (Table 6.20). As can be seen, while there is no trend with age at death, there is a steady increase in the SPMR with year of death. This suggests that many more persons will die from cancer because of exposure to vinyl chloride.

The judgment as to whether the excesses of specific causes of death are likely to be causal is based on reason rather than any statistical significance. There can be little doubt that vinyl chloride (or some closely related compound) is responsible for the angiosarcoma. This disease was extremely rare before it was discovered among vinyl chloride workers. The rate ratio among vinyl chloride workers must be in the 1000s. The disease occurred mainly in the men who worked for many years (10+) cleaning the reactors; these men accumulated a high dosage of exposure to vinyl chloride. While angiosarcoma association is at the top of the highly likely to be causal group. This nothing in epidemiology (or any science) is ever absolutely certain, the vinyl-chloride-angiosarcoma association is at the top of the highly likely to be casual group. This was so after the first three cases of angiosarcoma were identified.

With respect to cancers of the brain and of the lung, a causal interpretation of the association is not possible at the moment. Both are relatively common cancers and are based on much smaller rate ratios. The cause of most of lung cancer is known, and the excess seen here could conceivably be due to cigarette smoking. The cause of most of brain cancer is not known.

It is mainly of scientific interest whether vinyl chloride exposure leads to brain or

Table 6.19
OBSERVED AND EXPECTED DEATHS AMONG VINYL CHLORIDE WORKERS IN A MORTALITY STUDY*

Cause of death	Observed	Expected	SMR
All causes	352	467.3	75
All cancer	79	77.2	102
Digestive	19	21.7	88
Liver	7	1.7	412
Respiratory	25	23.9	105
Brain	7	2.5	280
Other	10	9.3	108
CNS vascular	13	24.5	57
Circulatory	142	178.8	79
External	52	91.7	57
All other causes	66	95.1	69

* Expected numbers based on mortality rates for United States white males.

Table 6.20
OBSERVED AND EXPECTED DEATHS FROM ALL CANCERS AMONG VINYL CHLORIDE WORKERS IN A PROPORTIONAL MORTALITY STUDY ACCORDING TO AGE AND YEAR OF DEATH

Characteristic	Category	Observed	Expected	SPMR
Age of death	<50	11	7.6	140
	50—59	17	8.1	210
	>60	13	12.2	110
Year of death	<1965	12	11.4	110
	1965—69	10	7.3	140
	1970	19	9.2	210

lung cancer. Exposure must be reduced because of its highly likely role in causing angiosarcoma. If some lung and brain cancer are also prevented, so much the better.

IV. CASE-CONTROL STUDIES WITHIN A COHORT

On occasion, personnel records may be available for a cohort of employed persons, but it may be too expensive to review all of the records to determine the work history of each person. Some sample of the records is selected to be reviewed. Since a primary interest in such review is to determine association between work and disease, priority is given to reviewing the work histories of persons with one or more diseases of interest. For purposes of comparison, the work histories of "controls" are also determined.

A. Procedure

In this discussion, it is assumed that mortality data for the entire cohort are available. Initial analyses proceed as described in Section II of this chapter, including Tables 6.1 to 6.13. If one or more causes of death are found to be in excess and if there is

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Chapter 9
CURRENT PROBLEMS IN OCCUPATIONAL EPIDEMIOLOGY

I. INTRODUCTION

The purpose of occupational epidemiology is to provide information on human health that can be used to prevent human illness. As time goes by data accumulate on the relationship between occupational exposures and human diseases. Some of these data can be interpreted unequivocally and can provide a firm basis for a change in behavior. Other data are subject to more than one interpretation or may be challenged as to veracity. As indicated throughout these pages, data by themselves provide no indication as to whether or not they reflect true processes in human populations.

In this chapter a variety of problems related to occupational exposures are considered. These problems are illustrated by referring to recent literature in occupational epidemiology. The intent is to provide an overview of general problems rather than to provide a detailed review of specific issues. Excellent reviews of the known and suspected effects of exposure to substances used in industry can be found in the Criteria Documents published by the National Institute for Occupational Safety and Health (NIOSH) and in the reports of the International Agency for Research in Cancer (IARC).[1,2]

For each of the studies reviewed in this chapter, the collection, analysis, and interpretation of the data are presented and the meaning of the results is discussed. Some of the studies are models on how to conduct research; some of the studies illustrate problems in methodology that should be avoided. All of the studies illustrate the realities encountered in conducting research in occupational epidemiology and in interpreting the results of that research.

II. OCCUPATION AND REPRODUCTIVE EFFECTS

Exposure to substances used in industry may lead to effects on the reproductive system in men or in women or may lead to an effect on the unborn fetus. Few data have been published on the general relationship between occupation and problems of reproduction. Until recently few pregnant women have been exposed to industrial environments. Any effects on male workers are difficult to detect. Any effects on fetuses have not been studied to any extent.

A. Vinyl Chloride and Fetal Deaths

In October 1974, interviews were conducted with male workers exposed to vinyl chloride monomer (VCM), polyvinyl-chloride (PVC) or rubber.[3] Questions were asked about the interviewee's health as well as about the outcomes of pregnancy of the workers' wives. The fetal death rate subsequent to exposure for VCM was higher among the families of exposed men than among the families of controls (Table 9.1).

This study is difficult to classify. It is not a retrospective cohort study, because workers were not followed either in retrospect or in prospect for the occurrence of fetal deaths. It is not a case-control study, because subject selection was not based on presence or absence of fetal deaths. It is best thought of as a cross-sectional study where exposure is presence or absence of a history of VCM exposure and disease is presence or absence of having had fetal death. A potential problem is that there may have been a differential rate of termination of employment according to exposure-disease status. The data seen in Table 9.1 could result if exposure to VCM did not

Table 9.1
FETAL DEATH RATES AMONG FAMILIES OF MEN EXPOSED TO VINYL CHLORIDE MONOMER AND AMONG FAMILIES OF CONTROLS

	Fetal death rate*			
	Prior to exposure		Subsequent to exposure	
Group	Crude	Standardized	Crude	Standardized
Exposed	10.1	6.1	16.5	15.8
Controls	6.9	6.9	8.8	8.8

* Number of fetal deaths per 100 pregnancies.

lead to increased fetal death, but if controls with fetal deaths terminated at a higher rate than exposed workers with fetal deaths. This can be thought of as selection bias.

Selection bias also was possible because not all workers eligible for the study were interviewed. The data in Table 9.1 could have resulted if exposed workers with a history of fetal deaths selectively agreed to participate in the study.

Because the interviews were not conducted blindly, observation bias was possible. The data in Table 9.1 could result if workers with exposure to VCM over-reported, or if controls under-reported, the occurrence of fetal deaths.

No information on smoking of mothers is presented. Smoking is known to be associated with an increased fetal death rate.[4] The data in Table 9.1 could have resulted from confounding by smoking if the wives of VCM workers smoked more than the wives of controls.

The primary procedure used in the analysis was direct standardization of rates, because the age distribution differed between exposed and control groups. Because the standard used was the age-distribution of the controls, the crude and standardized rates for controls in Table 9.1 were identical. For the exposed, there was a substantial reduction in the standardized rate prior to exposure. This occurred because the exposed group was older than the control group, and because the rate of fetal deaths increased with age (Table 9.2).[4]

In this example the standardization behaved well, since the age-standardized rates as well as the age-specific rates showed essentially no differences in fetal death rates between the exposed and the control groups. However, the potential difficulties of direct standardization with respect to small numbers can be seen. If there had been more controls in the <20 category, and if there had been two or three fetal deaths among the seven exposed persons in the <20 category, that stratum would have contributed heavily to a high standardized rate among the exposed group. In such a situation, it is best to limit the analysis to overlapping age-strata in which there are sufficient numbers, e.g., ages 20 to 29. In any standardization procedure attention must be given to the elements being standardized.

The meaning of this single study is unclear. Some of the criticisms raised above must be viewed as far-fetched. The likelihood of selection bias seems remote. The possibility of observation bias is more real, inasmuch as the interviews were conducted shortly after the carcinogenic properties of vinyl chloride were announced. If anything, the fetal death rate of 8.8% in controls seems low, suggesting that they may have not been stimulated sufficiently to recall previous miscarriages in their wives. It seems unlikely that the smoking habits of the wives of these two groups of workers would differ; even

Table 9.2
FETAL DEATH RATES PRIOR TO EXPOSURE AMONG FAMILIES OF MEN EXPOSED TO VINYL CHLORIDE MONOMER AND AMONG CONTROLS ACCORDING TO AGE OF FATHER

		Age of father					
	Group	<20	20—24	25—29	30—34	≥35	All
Number of pregnancies	Exposed	7	44	56	27	14	148
	Control	31	80	38	6	4	159
Fetal death rate*	Exposed	0.0	4.5	12.5	18.5	7.1	10.1
	Control	6.5	5.0	10.5	16.7	0.0	6.9

* Number of fetal deaths per 100 pregnancies.

if wives of exposed men smoked more, the association between smoking and fetal deaths is weaker than the association seen in this study.

As suggested by the above paragraph, the meaning of the results of this study is a matter of opinion, not of science. Different persons will raise different criticisms or different defenses. Certainly the results of this one study are not definitive.

With respect to future public health policy, it is not a major concern whether vinyl chloride exposure to men tends to increased fetal deaths among their offspring. The association between VCM and angiosarcoma is many times stronger and therefore VCM exposure must be reduced. Such reduction would be expected to minimize any adverse effects of VCM on the reproductive system.

However, it is of public health concern that VCM might affect pregnant women directly. In order to address this concern, studies must be made of pregnant women exposed to VCM and of their children.

B. Paternal Occupation and Childhood Cancer

1. Children in Quebec

"In reviewing, for other purposes, a small sample of birth and death certificates of Quebec children, the impression emerged of a large number of fathers in petrol-related occupations when the cause of death was cancer."[6] To quantify this impression, the occupation of the father was obtained from the birth certificate of 386 children under the age of 5 who died from cancer. For comparison purposes, two matched controls per case were selected — the preceding and succeeding child in the birth certificate registry. As seen in Table 9.3, approximately twice as many cases had fathers with potential exposure to petrol and other hydrocarbons. The odds ratio is $(71 \times 697) \div (75 \times 315) = 2.1$. The 95% confidence interval of the odds ratio is 1.5 to 3.0.

Selection bias is an unlikely explanation since paternal occupation was not ascertained until after cases were defined. Observation bias could have led to these results. The authors admit to a prior notion that petro-related occupations were related to childhood cancer. In classifying a father's occupation, it is possible that occupations difficult to classify were coded as petrol-related for cases but not for controls. However, the authors state that occupation was coded by a person who was blinded as to case-control status. Thus, for this reason, observation bias was not possible.

Confounding by some factor related to occupation and childhood cancer could always be an explanation. However, no data on potential confounding factors were available from the birth certificate, except for age. The mean paternal age for both cases and controls was 31.4. Further, little is known as to determinants of childhood cancer.

Table 9.3
OCCUPATION OF FATHER AT TIME OF BIRTH AMONG CHILDREN DYING OF CANCER IN QUEBEC AND AMONG CONTROL CHILDREN

Occupation of father	Children with cancer	Control children
Motor-vehicle mechanic	28	27
Machinist	24	29
Other hydrocarbon exposure	19	19
Other	315	697
Total	386	772

Odds ratio = 2.1

The data can be criticized if they include the cases upon whom the initial impression was based. It may be that the initial impression was correct, but was based on a sample of children with cancer who were simply atypical because of chance. In order to test the correctness of the impression, independent data should be evaluated. It is not stated in this report whether or not this was done.

In the analysis of data a large number of occupations were coded. The data in Table 9.3 are derived from a much larger Table. The association with hydrocarbon-related occupations is partially a result of looking through a number of occupations and grouping those which appear to be related to hydrocarbon exposure. However, this grouping seems to have been done without regard for disease status; for example, among the "other hydrocarbon exposure" grouping were three cleaners among controls and only one among cases.

A criticism might be made that a matched analysis was not done. However, if the controls were matched to cases for purposes of control of confounding, the lack of a matched analysis would only dilute any association between exposure and disease. The occurrence of an odds ratio of 2.1 (instead of 1.0) could not be attributed to the non-matched nature of the analysis. Further, the matching was done essentially for purposes of convenience rather than of control of confounding. A matched analysis was not called for.

It is difficult to interpret the results of a single study such as this. While the association is probably real in this population at this time, it is not necessarily causal. The fact that the association is statistically significant does not mean that it could not have *occurred by chance*. The *only* change in behavior dictated by this study should be to collect further data.

2. Children in Finland

In response to the above study, an analysis was done of data collected in a Finnish study of childhood cancer. Cases were children under the age of 15 who developed, rather than died from, cancer. One control for each case was selected; the control was the child born immediately before the case in the same maternity welfare district. Paternal occupation was routinely recorded for all children at the first visit of the mother to the maternity welfare center. As seen in Table 9.4, there was no association of paternal hydrocarbon exposure with childhood cancer. The 95% confidence limits of the odds ratio of 1.0 were 0.8 and 1.3.

The data in this study indicate no association between paternal hydrocarbon exposure and childhood cancer. Criticisms must be directed at factors that may have led to the failure to detect a true association, should one have existed.

Table 9.4
OCCUPATION OF FATHER AT TIME OF CONCEPTION AMONG CHILDREN DEVELOPING CANCER IN FINLAND AND AMONG CONTROL CHILDREN

Occupation of father	Children with cancer	Controls
Hydrocarbon exposure	109	109
Other	743	743
Total	852	852

Odds ratio = 1.0

Random misclassification must be considered. With respect to disease, little misclassification is likely. Few children with the diagnosis of cancer do not have the disease; few children without the diagnosis have latent disease. However, the determination of petrol exposure in the father is not a precise procedure. It is possible that some fathers said not to have exposure in fact did and vice versa. However, in order for an odds ratio of 1.0 to result from random misclassification, there would have to be no relationship between true paternal occupation and classified paternal occupation. This seems unlikely.

Selection bias could have led to these results, assuming that paternal exposure to hydrocarbons led to childhood cancer, only through a rather convoluted process. Cases who had fathers with hydrocarbon exposure would have had to be selectively excluded from the study or controls who had fathers with hydrocarbon exposure would have had to be selectively included. Inasmuch as the data were collected prior to any hypothesis as to hydrocarbon exposure of childhood cancer, this possibility seems remote. For the same reason, there seems to be little likelihood that paternal occupation was ascertained differently from cases and controls.

In order for confounding bias to have led to data in which there was no association between exposure and disease, negative confounding must have occurred. Some factor that was a cause of childhood cancer would have had to be more common among the controls than among the cases. Since little is known as to the causes of childhood cancer, such a factor would be difficult to identify. There is known to be a weak association between prenatal X-ray and childhood cancer.* If there were more X-rayed children among fathers with *no* hydrocarbon exposure, negative confounding would be possible. However, the association between childhood cancer and prenatal X-ray is very weak (OR ~ 1.5) and could not mask a true odds ratio of 2.1.

3. Comment

These two studies led to data that are not compatible on statistical grounds. The 95% confidence limits do not overlap and thus it is quite unlikely that results such as these would result simply because of random variation in the selection of two samples from the same universe. However, the data from these studies are not at all atypical of data collected in the epidemiologic setting. It is relatively common for two studies to lead to grossly different results that do not seem to be explainable for methodologic reasons.

Whenever an association is first reported, as in the Quebec study, it is reasonable to report the association and to comment briefly on the possible meaning. If there is broad general truth to the association, this will be quickly recognized and substantiat-

ing data will soon be assembled. There is no need for the authors either to defend their data against detractors or to announce their wide generalizability. The authors of the Quebec study behaved in a proper conservative manner by recommending only that further investigation be done.

When the results in Quebec became known, persons with interest in the general problem considered how to examine further the relationship between paternal hydrocarbon exposure and childhood cancer. Among these persons were those who believed that the association was causal, those who believed that the association was nonsense, and those who were agnostic. Each type of person considered the possibility of collecting further data: some may have wanted to collect confirmatory data, some may have wanted to collect contradictory data, and some wanted simply to collect data. There is no necessary connection between a person's opinion as to the truth of some association and his desire to collect data that confirms or refutes the association. However, it might be supposed that there will be a tendency for true believers to collect contradictory data. Agnostics will not necessarily collect true data, for their seeming neutrality may only be a mask covering some hidden bias.

The first data to appear after the initial report of some association tend to be the result of expedience rather than of a desire to confirm or refute the association. The Finland paper resulted from an analysis of data collected for another reason and presumably free of bias. Had this paper been authored by representatives of the oil industry, there would be a natural reaction that the industry was out to cover-up the harmful effects of paternal occupation. However, if a confirmatory paper had been published by representatives of the oil industry there would be a strong desire on the part of the general scientific community to believe the causal nature of the association.

As time passes, other data will appear on the relationship between paternal exposure to hydrocarbons and childhood cancer. One might expect that data that show no association will be viewed as being "uninteresting" and will not be published, while data that show an association will be published. These are emotional human responses to data. However, it seems unlikely that there is a strong tendency in science for such preferential publication of data that show association. As in this situation, whenever a positive study appears, a negative study frequently follows.

The judgment as to the ultimate truth as to whether the exposure causes the disease is not a matter of adding up the positive and the negative studies. Each study must be considered as to its merits. It is possible that all studies are correct; the exposure may cause the disease in one population but not in others. It is not necessary that universal truth be the final result of the consideration of the results of a number of scientific studies.

With respect to the specific association between paternal hydrocarbon exposure and childhood cancer, the question is still undecided. There is no obvious reason to fault one or the other study. While on general principles it would be wise to limit exposure to hydrocarbons, there is as yet no need to set a specific standard of exposure because of likely damage to the future children of a man exposed to petrol.

C. Summary

Much work is needed in general on the etiology of birth defects and specifically on the possible role of occupation. I believe that epidemiologic surveillance systems on industrial populations are ideally suited to such study. The outcome of birth occurs close in time to the exposure; a number of medical visits and insurance payments take place during a pregnancy and delivery; any abnormality of the child usually is apparent at or shortly after birth.

Epidemiologic surveillance systems on industrial populations should be designed so as to incorporate data on pregnancies among wives of male workers. At the preemployment history, information may be obtained as to previous reproductive history. If pregnancy expenses are paid by a company-supported insurance program, data on the pregnancy and its outcome should be readily available from the insurance company and/or the hospital.

Because any adverse outcomes of pregnancy related to work are likely to be of relatively low frequency, large amounts of data will be necessary to detect any association. Therefore, it seems reasonable that groups of companies within specific industries pool their data or share their findings. Much of the data collected will be routine and of little interpretive value. However, if an abnormality of pregnancy is caused by some parental work exposure, it should be detected as soon as possible. Elimination of the responsible substance has the potential to lead in a relatively short time to elimination of the adverse health effect. This contrasts with the years or decades needed to demonstrate the successful elimination of an occupational carcinogen.

III. OCCUPATION AND RESPIRATORY CANCER

Currently, there is concern over the role of chemicals in the etiology of cancer. It is hypothesized that long-term low-level exposure to environmental pollutants may be responsible for a high percentage of cancer.[9] However, it is difficult to study this question in the general population; no records exist on past exposures to these pollutants and doing prospective cohort studies would be expensive and of questionable feasibility. Persons working in industry are exposed to higher levels of many chemicals; some rough estimate can usually be obtained as to past exposure; the conduct of retrospective cohort studies on industrial populations is relatively inexpensive and feasible. Therefore, much can be learned about the role of chemicals in the development of human cancer by studying industrial populations.

There is a wide spectrum of current knowledge as to the relationship between industrial exposure to chemicals and cancer. For some substances there is an unquestioned relationship between a substance and a cancer; standards of exposure to the substance exist, are enforced and seem to be effective. For some industrial settings there is agreement that the general exposure is harmful even though there is no specific association between a substance and a disease. Standards in the setting are aimed at general environment rather than specific exposure. In other settings there is a contested association between exposure and disease; to some observers an association represents cause and effect while to others the association is an example of bias. Finally, there are situations in which the data are conflicting and most agree that no conclusions are possible at the moment.

In this section the relationship between occupation and respiratory cancer is considered. For some occupational exposures, there is a clear-cut causal association with respiratory cancer. For other exposures, excess respiratory cancer has been reported but disagreement exists as to whether the association is causal.

A. Nickel and Respiratory Cancer

In 1949 on the basis of clinical reports, cancers of the nose or lung among workers exposed to nickel were classified as industrial diseases.[10] To quantify this association, a study was done of the occupation of 15,247 men who died from lung cancer, from nasal cancer, or from other causes.[11] This study was done of deaths between 1938 and 1956 in an area of Great Britain where a nickel refinery was located.

The data were collected by a review of death certificates. Cause of death was coded in accordance with standard procedures; the occupation of each decedent was that

listed on the death certificate. The relationship between cause of death and occupation is given in Table 9.5. Excesses of nasal cancer and of lung cancer among decedents in the nickel industry are apparent.

It is difficult to construct a realistic argument that the associations seen in Table 9.5 are the result of bias. All deaths of men residing in this area were included; therefore there was no selection. Selection bias could have resulted if men who were employed in the nickel industry and who died from "other causes" migrated from Great Britain before death, but this seems unlikely. There is also no reason to believe that nasal and lung cancers were over-certified as the cause of death in men who worked in the nickel industry. Confounding by cigarette smoking could be considered for the excess of lung cancer, but is extremely unlikely. In those years a very high proportion of British males smoked; therefore even if nickel workers smoked more than other workers, the amount of confounding possible was minimal. Cigarette smoking has little, if any, effect on nasal cancer.

A question can be raised as to the basic study design and the way the data were analyzed. The data were based solely on death certificates. No follow-up was made of a group of nickel workers and no mortality rates were available. The study was essentially a proportional mortality study in which the percentage of nasal and lung cancers were compared among various groups of workers.

Crudely, the proportion of nasal cancer among nickel workers was 0.065 [13/(13 + 48 + 139)]. Among "other" employees the proportion was 0.00064 and among all employees the proportion was 0.0016. The ratio of the proportion of cancer among nickel workers to the proportion among "other" employees was 100:1. If the ratio is computed relative to the "total" group, it is 40:1. Irrespective of which group is used for comparison, the excess nasal cancer among nickel workers is apparent. The proportion of lung cancer among nickel workers (0.24) was also substantially higher than the proportion among "other" workers (0.05).

Because of the strong association between employment in the nickel industries and cancers of the nasal sinuses and lung, the study design and analysis could be simple. The error introduced by the use of proportional mortality is perhaps 10 to 30%; the error introduced from the lack of age-standardization is also small. These errors can have little effect on the 4000% excess of nasal cancer or the 500% excess of lung cancer among nickel workers. The causal nature of the association can readily be accepted.

However, the determination of a safe level of exposure to workers in nickel refineries is much more difficult. Safety cannot be considered to be achieved until no excess nasal or lung cancers occur. For nasal cancer, because of its rarity, this means no cases must occur among nickel workers. For lung cancer, which is largely determined by cigarette smoking habits, some nonzero number must be expected among any group of persons who smoke.

In 1970, the occurrence of deaths among a cohort of nickel workers was reported.[11] Eight hundred and forty-five men who had been employed in a nickel refinery in South Wales were followed from 1939 through 1966. Excess nasal cancer among nickel workers was suspected in 1927 and the refining process was changed between 1925 and 1933.[11-13] Therefore, it was of particular interest to determine whether any excess nasal or lung cancer had occurred in men first exposed after 1925.

Because this was a retrospective cohort study, the observed number of deaths could be compared to the number expected based on national death rates. The results are presented in Table 9.6. No nasal cancer occurred in men who were first employed after 1924; only a slight excess of lung cancer was seen in these men. It might be concluded that the change in process led to the prevention of nickel-induced cancer.

However, in 1977 an updated follow-up was presented (Table 9.7).[12] Among men

Table 9.5
CAUSE OF DEATH AMONG PERSONS EMPLOYED IN NICKEL AND IN OTHER INDUSTRIES IN GREAT BRITAIN

Industry of employment	Cause of death		
	Nasal cancer	Lung cancer	Other causes
Nickel	13	48	139
Other Refining	1	54	606
Steel	3	121	2,055
Coal-mining	2	73	2,729
Other	6	503	8,894
Total	25	799	14,423

Table 9.6
OBSERVED/EXPECTED CAUSES OF DEATH AMONG NICKEL WORKERS ACCORDING TO YEAR OF FIRST EMPLOYMENT; FOLLOW-UP 1939 to 1966

Year of first employment	Cause of death		
	Nasal cancer	Lung cancer	Other causes
<1925	30/0.11	105/13.9	263/208.7
1925—29	0/0.01	4/2.3	23/23.7
1930—44	0/0.02	4/3.8	44/33.9

who started employment between 1925 and 1929, one case of nasal cancer occurred. An excess of lung cancer was seen in both groups of men who were first employed after 1925. While this excess is relatively much smaller than that observed in men who started working before 1925, it suggests that some workers employed after 1924 developed lung cancer because of their work.

In this example, data on men who started working between 1925 and 1929 are being evaluated in 1977 to determine whether or not nickel workers develop excess cancer. It might be assumed that the risks to workers of today will be no higher than the risks to the workers in 1925. However, it seems clear that one cannot conclude that the changes instituted in nickel refining around 1925 were sufficient to prevent the development of work-related nasal or lung cancer.

The specific agent responsible for the excess cancers is not known. While both nickel and nickel carbonyl gas are carcinogenic,[12] excess nasal and lung cancer has also been observed in men exposed mainly to nickel ore dusts.[14] Had controls been instituted in 1925 only against elemental nickel and nickel carbonyl gas, the reduction in excess respiratory cancer might have been much less.

A parallel to the nickel cancers may be seen in vinyl chloride. The excess occurrence of a rare cancer (angiosarcoma of the liver) was recognized on clinical grounds.[15] Clinical recognition was possible because the disease had few other causes and had a very high rate ratio associated with the exposure (100+). The process of producing vinyl chloride has been changed so that exposure is greatly reduced.[16] However, it is unknown as to whether these controls will prevent the occurrence of angiosarcoma.

Also, the possible excess occurrence of cancers of the lung and of the brain among

Table 9.7
OBSERVED/EXPECTED CAUSES OF DEATH AMONG NICKEL WORKERS ACCORDING TO YEAR OF FIRST EMPLOYMENT; FOLLOW-UP 1934 TO 1971

	Cause of death		
Year of first employment	Nasal cancer	Lung cancer	Other causes
<1925	56/0.17	128/18.4	368/378.0
1925—29	6/0.03*	9/3.6	51/48.3
1930—44	0/0.03	0/5.5	69/54.9

* One man developed nasal cancer but died from heart disease.

workers exposed to vinyl chloride have been reported in a proportional mortality study.[12] If vinyl chloride leads to these cancers, the rate ratio is many times less than that for angiosarcoma. Further, these cancers are much more frequent among the general population and might be expected to occur among vinyl chloride workers for noncausal reasons. It may be difficult to demonstrate that the occurrence of one of these diseases in a vinyl chloride worker is not due to vinyl chloride exposure.

Also, it should be clear that at the moment the decision as to the "safe" level of exposure to vinyl chloride is a matter of opinion rather than of science. In one study no excess cases of angiosarcoma, lung cancer, or brain cancer were reported.[13] It is possible that workers at this plant were exposed to safe levels of vinyl chloride. However, it is also possible that insufficient time has passed for any vinyl chloride-induced cancer to develop. The setting of a standard of exposure to vinyl chloride had to be based on a process of negotiation between government and industry. The standard must be conservative, i.e., because of the uncertainty associated with what is a safe level of vinyl chloride, the standard should, if anything, be too low.

B. Coke Ovens and Respiratory Cancer*

In 1962, a collaborative study of the mortality experience of steelworkers was initiated by the U.S. Public Health Service, the Graduate School of Public Health of the University of Pittsburgh, and three large steel companies.[14] The purpose of the study was to assess conflicting reports of excess illness among certain groups of steelworkers.

As of 1953, there were 59,072 men employed in seven steel plants in Allegheny County, Pennsylvania. In 1962—64 an attempt was made to determine the vital status as of 1/1/62 of each of these men. There were 32,263 men who were still employed, 6346 who had retired, but were alive, 15,650 who had left employment but were alive, and 4716 who were deceased. Only 97 men could not be located.

As seen in Table 9.8, the observed mortality among this group was 82% of that expected on the basis of Allegheny County rates. Among all steelworkers, there was no overall excess of cancer.

The next step was to break down the study group of steelworkers according to their usual area of employment.[15] So as to minimize the difficulties associated with persons changing jobs, an analysis was done including a man in a given work area only if he worked there for at least 5 years. In order to eliminate the over-estimation of expected deaths, the death rates of men who worked in each work area for at least 5 years were

* This section is taken from a paper in a symposium on the environment in *Environmental Law*.[16] See also Chapter 3.

Table 9.8
OBSERVED AND EXPECTED DEATHS AMONG STEELWORKERS*

Cause of death	Observed	Expected	SMR†
All causes	4716	5766.8	82
All cancer	1008	1091.4	92
CNS vascular	365	464.3	79
Heart disease	1906	2311.3	82
External	474	450.5	105
All other causes	963	1449.3	66

* Expected numbers based on mortality rates for Allegheny County, Pennsylvania.
† SMR = Standardized mortality ratio = 100 × observed/expected.

Table 9.9
OBSERVED AND EXPECTED DEATHS FOR ALL CAUSES AND ALL CANCERS AMONG STEELWORKERS EMPLOYED AT LEAST FIVE YEARS IN SPECIFIED WORK AREAS*

		All causes		All cancer	
Work area	Race	Obs.	Exp.	Obs.	Exp.
Coke plant	White	130	130.8	29	28.3
	Non-white	96	78.7	40	19.6
Cold reducing mills	White	71	70.7	17	14.6
	Non-white	14	6.3	1	1.4
General labor	White	102	81.6	16	18.4
	Non-white	49	46.1	14	11.4
Maintenance	White	377	318.4	76	70.1
	Non-white	16	14.3	3	3.8
Merchant mills	White	253	266.9	63	59.1
	Non-white	28	42.4	5	10.7

* Expected numbers based on mortality rates for all steelworkers who worked at least 5 years.

compared to the rates of all steelworkers in the study who worked at least 5 years. The results of this analysis are presented in Table 9.9.

Among all causes of death, no "healthy worker effect" is seen, since the mortality rate used for comparison was that of all steelworkers rather than that of a general population. Moderate excesses of death are seen among nonwhite workers in the coke plant and the cold reducing mills and among white workers in the general labor and maintenance areas. With respect to all cancer, however, a striking excess is seen among nonwhite workers in the coke plant. Most of this excess was found to be due to lung cancer.

Several questions were raised by this finding: