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Epidemiologic Problems Associated with Exposure to Several Agents

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Simultaneous exposure to many potentially hazardous agents in the environment is the rule, yet there have been few studies that have addressed the issue of interactions of these agents in modifying disease outcomes, even though such interactions may potentially be important in terms of policy-making. Epidemiological methods may be an important way to identify interaction effects, especially for chronic disease outcomes. Some examples of epidemiologic investigations of this problem are given, and a matrix method used to evaluate the contribution of nineteen chemicals to the risk of liver angiosarcoma in vinyl chloride workers is discussed.

Introduction

The theme of this Symposium is epidemiologic studies as a scientific basis for environmental policy-making. Perhaps one may best illustrate the strengths of chronic disease environmental epidemiology over other sciences and its frailties in policy-making by focusing on studies of exposures to multiple agents. The strength of epidemiology lies in its ability to identify high risk populations and suggest leads for agents that should be studied individually in the laboratory. On the other hand, when experimental data exist for an agent, epidemiology can corroboratively extend the findings to the human experience. Chronic disease epidemiology has also been most useful in suggesting synergistic effects from multiple agents, particularly in the area of cardiovascular disease and cancer. The limitations of epidemiology such as sample size, confounding variables, etc. are compensated by the integration of epidemiologic results with those of other disciplines.

Before one can detect health effects from low doses of several agents, one must be able to detect the effects of high doses from one or more agents. The most likely place to find high levels of exposures to toxic agents is in the occupational setting. Thus the problems of occupational epidemiology may serve as a starting point to illustrate the types of and the minimal degree of difficulties one may expect to encounter in nonoccupational environmental epidemiology.

The clear determination of a causal agent solely from epidemiology has been rare in chronic disease occupational epidemiology. The major reason is the lack of good retrospective exposure data. Consequently, this paper reviews how occupational epidemiology proceeded in a few selected cases without retrospective exposure data and integrated with other disciplines in arriving at an etiology; secondly, it describes more recent methods for improvisation and use of retrospective exposure data, and lastly, points out some techniques for and value in considering multiple agents simultaneously.

Historical Perspective

Historically we have documented epidemiologically only environmental carcinogens with substantial relative risks. Today, through our hindsight, many of the well accepted carcinogens identified in the industrial setting are taken for granted as having been "single agent" studies. On the contrary, there were no uranium miners exposed only to radon daughters, and no chemical workers exposed only to bischloromethyl ether or vinyl chloride monomer.

The association between radon daughter expo-

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sure and lung cancer can be traced back to 1879, when Harting and Hesse (*1*) noticed an excess of fatal pulmonary neoplasia among Erz Mountain miners. The mines in the Erz Mountains had been worked at various times for silver, cobalt, bismuth, nickel, arsenic, radium, and finally uranium. In the early 1900's, pneumoconiosis in combination with arsenic and cobalt was assumed to be the specific etiologic factor (*2*) responsible for the neoplasia. No type of radiation was thought to play a causal role until 1924 (*3*).

As of 1944, radionuclides with short half lives, such as the radon daughters polonium-218 (^{218}Po), bismuth-214 (^{214}Bi), lead-214 (^{214}Pb) were not considered to be dangerous. Thus it is not surprising that in a lead editorial on lung cancer that year in the Journal of the National Cancer Institute, Lorenz (*4*) downplayed the effect of the short halflife radon daughters and instead reviewed the radiobiology of radon itself. He concluded that radon could not possibly be the responsible carcinogen among the Erz Mountain miners. Meanwhile United States uranium mining, which first began to flourish in 1948, resulted in exposures to miners of free silica dust, sulfur, iron, nickel, lead, arsenic, antimony and other elements in addition to radon and the radon daughters.

Shortly thereafter, in 1951, Bale (*5*) determined theoretically that although radiation from radon would not be substantial, the radiation from radon daughters would be 20 times that of radon and could have a significant effect. From theoretical calculations was born the hypothesis that radon daughters were the agent responsible for the excess lung cancer risk among the Erz Mountain miners. It was only after this discovery that a technique was developed for field measuring radon daughters in uranium mines and that the extensive epidemiologic studies began.

It appears that exposures to nickel, iron, and arsenic were never seriously considered etiologically, either in the studies of the Erz Mountain miners or of the United States uranium miners, because they were "low" and never really accepted as carcinogens until much later. Free silica exposures were high enough to cause silicosis (*6*), and exposure levels tended to correlate somewhat with those of radon daughters based solely on amounts of mine ventilation. In spite of the "scar cancer" theory held by some that associated silicosis with predisposition to lung cancer, the fact that no epidemiologic evidence existed in other populations associating the two diseases removed silica from consideration as the carcinogen. The strong dose-response relationship between lung cancer and working level months of radiation exposures from radon daughters in various types of mines further precluded attempts ever being made to correlate any other exposures among the miners.

The epidemiologic story of bischloromethyl ether began in 1962, with the recognition of three cases of lung cancer, all in individuals under 37 years of age, occurring among chemical operators in one building (*7*). According to a company list, persons working in that building were exposed to 103 chemicals, including some pesticides. This list was sent to a research group who suggested further investigation of some of the agents based on their similarity to other carcinogens. Bischloromethyl ether and chloromethyl ether were not suspected. Subsequently, a toxicologist at another institution reviewed the list and noted ten of these 103 chemicals were likely to be carcinogens. Two in particular—bischloromethyl ether and chloromethyl ether—were very likely carcinogens on theoretical grounds.

The subsequent experimental data established that chloromethyl ether and more so bischloromethyl ether were indeed potent carcinogens when inhaled. It appears that the three other simultaneous epidemiologic studies elsewhere relating bischloromethyl ether to lung cancer, together with the animal data, and the epidemiologic study of the plant where the original problem was found, resulted in none of the other substances ever being considered as even partly responsible for the epidemic.

The events leading to the recognition of the human carcinogenicity of vinyl chloride are similar. An initial discovery of a cluster of cases of angiosarcoma of the liver combined with the experimental carcinogenicity of vinyl chloride formed an impelling indictment. The weight of the evidence precluded investigation of other compounds present in the same industry.

There is little dispute that radon daughters, bischloromethyl ether (BCME) and vinyl chloride are human carcinogens. More importantly, however, the historic scientific mood that very few agents caused cancer has changed to the acceptance that numerous occupational carcinogens may be present, even simultaneously. This acceptance undoubtedly accounts for the more recent consideration of multiple agents in the occupational epidemiology literature. However, if a new theory were to arise today concerning the carcinogenic contribution of another component of the occupational environment of uranium miners, BCME workers or vinyl chloride polymerizers, or concerning a new carcinogen in an altogether different industry, one would be faced with the major problem of environmental cancer epidemiologic

studies—a lack of retrospective exposure data.

During the long latency period between exposure and cancer, substantial interim qualitative and quantitative variations in industrial exposures may occur due to worker mobility and raw material and industrial process changes. Industries are approaching this problem with increasingly sophisticated environmental monitoring systems. Thus with our changing awareness, we are today making the industrial hygiene measurements which will allow multiple exposure chronic disease studies, 10 to 20 or 40 years from now. However, the epidemiologist studying today's health effects is dependent upon exposure data gathered when the prevailing philosophy was to measure—if at all—only those environmental components thought to be dangerous. The result is the paucity of multiple agent studies in occupational cancer or occupational health today. Therefore, the problem facing the occupational epidemiologist is how to improvise and how to analyze retrospective exposure data. A review of such improvisations and analyses in the occupational epidemiology literature is in order.

Improvisation and Use of Retrospective Exposure Data

Multiple exposures have been considered as some combination of severity and duration of exposure based on a nominal, dichotomous, ordinal or relative scale. The rarity in the literature of consideration of both duration and severity of exposure is underscored by a recent review of published articles that found only one of the two parameters was considered 75% of the time (*8*).

More enlightening than the types of classifications are the techniques invoked to assess these multiple exposures. Schemes for classifying workers begin with detailing the employee's work history by time spent in specific departments, areas or jobs within a plant (Fig. 1). These data are usually available from personnel records, but may be supplemented with interviews of coworkers and supervisors. Interviewing spouses appears to be a poor source of such data even for such simple criteria as presence or absence of a film badge (*9*).

Either from this step or on the basis of other documents such as union contract agreements, the next step is enumerating all departments, areas or jobs within a facility. This list then becomes the basis for the most difficult step: classification of each department, area or job by exposure. Once accomplished, it is then a straightforward task to link the detailed personal work histories to arrive at personal exposure classifications.

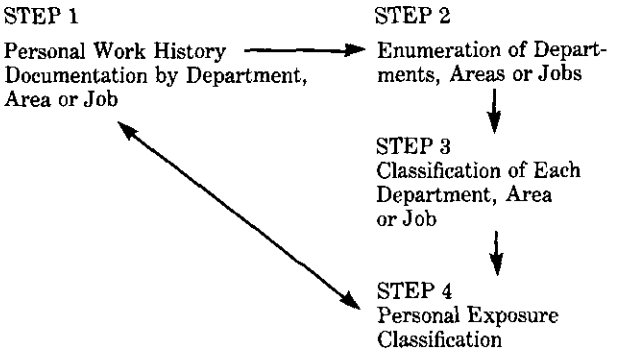

FIGURE 1. Scheme for classifying workers by exposure in industry.

There have been a few epidemiologists fortunate enough to study worker populations belonging to a chemical company that had the foresight back in the 1950's and earlier to measure simultaneously the air levels of various chemicals such as arsenic (*10, 11*) and vinyl chloride. In lieu of such data, the following examples illustrate attempts to overcome the difficulties associated with Step 3 in Figure 1. In a stomach cancer case control study, Blum, et al. (*12*) classified hundreds of unique rubber worker jobs into 20 common production processes. He then used the individual judgments of three industrial hygienists who were not plant employees to arrive at high, moderate, low or no potential exposure categories for four agents. These ratings, which pointed toward an association with talc exposures (Table 1), were based on the possibility for exposure from knowledge of the processes, not on detailed data documenting their actual existence.

In a slightly different manner, I used a six-point ordinal scale of exposures to each of 19 chemicals which was developed by panels of company supervisors safety engineers, and other employees, (Table 2). For each chemical each job was assigned a severity of exposure for each calendar year. The

Table 1. Odds ratio by potential exposure for stomach cancer: case control study in a rubber plant.[a]

High or moderate exposure	Carbon black	Polycyclic hydrocarbons	Nitrosamines	Talc
Ever vs. never	1.49	1.10	1.30	2.41[b]
2 yrs vs. never	1.29	1.08	1.64	2.48[c]

[a]Data of Blum (*12*).
[b]$p < 0.01$.
[c]$P < 0.05$.

Table 2. Exposure ratings.

Rating	Definition
0	No exposure
1	*Minimal exposure to low levels (Chemical in building*—not handled, low vapor pressure and dust level, probably works on different floor)
2	Moderate exposure (Works around the chemical, but exposure is minimal)
3	Works in areas where subject to occasional high excursions (Normally exposure is minimal but occasional spills, leaks, or dust exposure may occur
4	Works in areas where level is high (Exposure levels in the area are frequently high. Might consider that some risk is involved if chemical is very toxic)
5	*Intimate contact—skin or high inhalation (such as poly* cleaners, handling slurry)

Table 3. Job-exposure dictionary: chemical exposure levels specific for job identification number and calendar year for a *given chemical.*

Job identification number	Chemical exposure levels						
	1942	1943	1944	1945	1946	. . .	1973
1	0	0	0	2	2		2
2	5	5	5	5	5		5
3	2	2	1	1	0		0
.							
.							
.							
.							
.							
84	4	4	4	1	1		1

entire matrix in Table 3 represents just one of the chemicals. These exposures then varied over time and over job within the facility as did processes, raw materials, products or even ventilation as judged by company personnel. The chemicals listed in Table 4 were fairly widely distributed throughout the plant, so there were numerous jobs that had exposures to some of the chemicals but not others. Expected and observed doses based on duration multiplied by severity of exposure to each chemical were then calculated and compared between the angiosarcoma cases and noncases. Suprisingly, vinyl chloride monomer was not the only chemical associated with angiosarcoma.

Axelson proceeded beyond relying on the memory and judgment of people to assess historical exposures (*13*). Using records of the State-owned Swedish Railroad, he reconstructed annual herbicide use by brand name and chemical components from 1957 to 1971 (Table 5). For some years the only available data were the types of herbicides and total amount of herbicides consumed. For other years, the actual amount of each of 12 herbicides consumed was available. Using a case control design nested within a cohort study, he was able to detect elevated relative risk for cancer by duration, but not severity of exposure for each of the two herbicide components of major concern, phenoxy acids and aminotriazole.

One of the most thorough retrospective exposure reconstructions was carried out by Arp (*14*) in a study of a rubber plant. Using purchasing records of raw materials to find out what substances came into various areas of the plant, quality control reports to determine the chemical composition of those materials, production records to determine the recipe or composition of each product along with the amount produced, ventilation records, time motion study and detailed job description data to determine which chemicals were handled on which jobs and historical environmental sampling data, along with various other documents, he was able to reconstruct back to 1920 which jobs in which years included exposures to xylene, benzene, all coal-based solvents and petroleum-based solvents. These jobs were divided into primary exposures, constituting direct handling of the solvents, and secondary exposures constituting routine use of the solvent in the work area without direct use or handling by the person with that job title. He validated this technique by successfully predicting and confirming which jobs in the plant were currently using the solvents. This is a very time-consuming process, but perhaps the only way to determine the relevant historical exposures of recently occurring cancer deaths.

Somewhat similar large-scale efforts which are dependent on industry cooperation are underway in the oil refinery, shipbuilding and aluminum reduction industries.

It is noteworthy that all four of the studies cited have used some form of case control design nested within retrospective cohorts. The major advantage to this nested design is not in statistical power but in minimizing the cost associated with detailing work histories and exposures.

Multiple Agent Analyses

Finally, it is illustrative to review a few studies that considered individual chemicals while simultaneously controlling for exposure to other chemicals. In the vinyl chloride investigation, we found that angiosarcomas in the chemical plant studied were highly associated with exposure to two chemicals, vinyl chloride monomer ($p = 0.004$) and caprylyl chloride ($p = 0.005$). When each chemical

was examined conditional on the exposure of the other, the caprylyl chloride association disappeared ($p = 0.9$) but that for vinyl chloride monomer persisted ($p = 0.05$) (*15*). This predictable result corroborated our experimental knowledge of vinyl chloride monomer carcinogenicity.

Similarly, Axelson, in his case control study of a parish in Sweden that contained a copper smelter, looked at numerous etiologic agents (*16*). He first looked in detail at arsenic exposures for lung cancer, cerebral vascular disease and cardiovascular disease. He classified all of the jobs within the smelter in this parish, based on four levels as determined by a plant engineer. He found a nice dose-response curve for lung cancer and positive associations for cardiovascular disease and cerebrovascular disease. But he went a step further. He also had the jobs within the smelter rated for exposures to a number of other metals. For cerebrovascular disease he found a relative risk of 3.1 for arsenic and 4.5 for copper. The arsenic effect disappeared when he controlled for copper exposure (relative risk = 0.4). However, the association with copper persisted (relative risk = 1.7, $p = 0.07$) when he controlled for arsenic exposure. The suggestion of synergistic hypotheses from multiple exposure studies is seen in Ott's studies (*10, 11*) of arsenic workers and vinyl chloride workers from the same plant (Table 6). It is important that such results be further investigated.

These latter examples are illustrative of the hypothesis generation or refinement that is common in other areas of epidemiology but often overlooked in occupational epidemiology. Testing synergistic hypotheses may be the most important contribution of epidemiology because they are not commonly tested experimentally. Who knows what

Table 4. Observed and expected cumulative dose differences for liver angiosarcoma cases.[a]

Chemical	Observed dose	Expected dose	Average observed-expected dose difference	p value
Acrylonitrile	18,168	63,371	-4,520	0.000
Acetylene	23,133	14,920	821	0.161
Acrylates	83,381	41,466	4,192	0.015[b]
Butadiene	2,580	47,072	-4,499	0.000
Caprylyl chloride	114,930	37,297	7,763	0.003[b]
Chlorinated solvents	46,840	44,744	210	0.440
Mercuric chloride	31,782	12,766	1,902	0.067
Methanol	121,533	60,141	6,139	0.016[b]
Vinyl chloride monomer	214,526	120,362	9,416	0.002[b]
Vinylidene chloride	47,372	47,828	-46	0.498
Vinyl acetate	58,413	24,314	3,410	0.033[b]
PVC dust	93,446	121,617	-2,817	0.056

[a]Case days = 64,929; cohort days = 83,381.
[b]$p < 0.05$ and dose ratio = 1.0.

Table 5. Available information about amount of herbicides consumed 1957–1971 on Swedish railways.[a]

Trade name	Active compounds	Herbicides consumed, tons									
		1957	1958	1959	1960	1961	1962 . . .	1968	1969	1970	1971
Totex	Atrazin	57.1	X								
Ureabor	Disodium tetraborate + Monuron		X	X	X						
Karmex	Diuron					X					
Telwar	Monuron			X	X	X	0.29				
Primatol A	Atrazin			X	X	X	3.7				
Emisol 100	Amitrol		X	X	X	X	7.2	1.4	1.2	1.3	0.9
Emisol 50	Amitrol					X					
Weedex tel	60% Amitrol + 40% Monuron					X	28.8				
Weedex Kar	60% Amitrol + 40% Diuron						3.8	21.3	21.4	20.2	19.6
Totalex extra	Atrazin + dichloropropionic acid + 2,4-D + 2,3,6-TBA							4.5	4.5	4.2	
Uridal	Diuron + dichloropropionic acid								4.0	3.2	
Total amount of different herbicides (X)		52.8	51.5	40.0	45.0						

[a]From Axelson (*13*).

Table 6. Observed and expected deaths among chemical plant workers.[a]

	Ratio observed/expected		
	Arsenic exposed[b]	Vinyl chloride exposed	Arsenic and vinyl chloride exposed
All causes	85/102.5	79/89.1	10/11
Respiratory system cancer	17/5.2	4/5.2	3/0.6
Other malignant neoplasms	11/12.3	9/10.2	4/1.3

[a]Data of Ott et al. (*11*).
[b]Includes a few people also exposed to vinyl chloride.

additional carcinogens or cocarcinogens might have turned up among the uranium miners or BCME chemical workers had attempts been made to assess multiple occupational exposures.

Such analyses will take on increasing importance in the future. However, as most regulations requiring industrial hygiene sampling are quite recent compared with the long induction-latent period of cancer, epidemiologists must turn to historical corporate records for exposure estimates. Records I have mentioned earlier have been kept by many corporations for decades for business purposes. Thus, if further research substantiates the utility of such data to occupational or environmental epidemiology, then regulatory agencies will soon be focusing on the corresponding issues of their retention and public access.

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