Who Should Provide Research Initiative and Support?

by Lewis H. Kuller*

The study of low dose environmental exposure is a major concern for epidemiologists. The problem is a special example of a common source epidemic with either single or continuous exposure. Usually the most common source investigations begin with an epidemic, cluster of cases. However, environmental studies often start with an exposure that is considered to be potentially hazardous and a search for cases. The relatively low attack rate and also relative risk requires large sample sizes for testing hypotheses. The incubation period from exposure to onset of the disease may be very long, and therefore the exposure dose is difficult to define. Many of the diseases of interest also have multiple etiologies, and the amount of disease attributed to the specific environmental exposure may be relatively small (the attributable risk). Many of the other potential etiological agents also share common host characteristics with the environmental agent of interest further confounding the analysis. The identification of specific, unusual characteristics of disease such as rare histological type or location, or host characteristic may be a valuable approach to the study of environmental agents. The cost of doing environmental studies are substantial. Various resources are currently being utilized. There are several problems associated with many of these nongovernmental resources. One possible solution to the availability of a large funding source for environmental research, independent of special interest groups, may be a consumer-oriented tax on adverse personal health behavior, such as alcohol consumption and cigarette smoking.

Introduction

The interest in this topic, “Who Should Provide Research Initiative and Support?”, evolved from three observations: (1) The concern by reviewers of grant proposals related to epidemiological studies of low dose environmental effects: a fundamental question has been raised about the utility or the cost benefit of doing extensive low dose environmental epidemiological studies when the results of such studies are likely to be negative or equivocal. (2) The apparent desire to spend relatively large amounts of money to modify the environmental problems associated with low dose effects in the absence of solid evidence of health risks: the presumed effects on the population at risk is generally based on health effects at a much higher dose and the extrapolation of a dose response curve to the low dose effect. (3) The relative decline in federal support for health related research and the corresponding increase dependency on support from special interest groups such as major industrial concerns, trade organizations, foundations, and lobbyists.

Several groups have recently discussed the need for epidemiological studies of environmental health effects. Some of my colleagues in toxicology and experimental biology have considered the mouse and rat a close relative to man and have decided that except for a slight weight adjustment, extrapolation from one species to another is biologically sound. Others have decided that cell culture techniques may be a satisfactory replacement for human observations. I do not believe that a dialogue about the merits of cell culture, mouse toxicological studies or even human clinical observations as compared to epidemiology is useful. Each approach has a specific merit and must be used conjointly in order to resolve the complex problems of the environment and human health.

*Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15261.

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do, however, believe that the ultimate and important question is the relationship between a specific environmental agent and the exposed human, not necessarily the mouse. Human experimental studies, such as carefully done clinical trials, or even laboratory controlled experiments will remain the gem of the health research area. The trials of killed poliomyelitis vaccine by Dr. Jonas Salk and Tommy Francis culminated the years of laboratory and observational epidemiological research and were the beginning of the end of a great health problem. The fluoridation trials are an important example of the types of environmental experimental epidemiological studies which are possible to do and result in extremely important public health results.

Why are environmental epidemiological studies expensive? Why are the results of such studies often equivocal and confusing? An environmental epidemiological problem is a special case of a common source epidemic investigation. We may either investigate a single exposure, such as the atomic bomb radiation effects, or a continuous exposure as in the occupational situation or in the continuous exposure to air pollutants, or toxic chemicals. In the classical common source exposure investigation the epidemiologist begins with an observed epidemic of disease (Table 1). He notes an increased frequency of disease above that which would be expected. The distribution of the disease that is identified is measured in relation to time and the population at risk. Based on these observations a common source, rather than person to person, zoonotic, or other indirect exposure is suggested. The investigator then begins an intensive effort, the detective work, to determine the source of the epidemic, agent, and mode of transmission. The investigator begins with cases and works back to the source. Once the probable source and agent have been identified only then does the epidemiologist search for the remaining potential population at risk. The key to the problem is often the identification of the epidemic, that is, the surveillance of disease within a population. The initial investigation is often relatively small and limited to the cluster of cases identified initially as the epidemic. The approach is basically a case control type of study. The careful definition of the case is often also a key to the solution of the puzzle. Similarly, the solution to the problem often depends on the observation of repeat common source outbreaks of similar diseases, rather than the identification and search for disease among all exposed. It would be extremely unlikely for health departments to do a detailed investigation of all individuals who ate at a C rated restaurant. An outbreak of gastrointestinal disease might be traced to a specific restaurant or food source and ultimately to some specific environmental problem at the source.

The success of the investigation is therefore based on: (1) that the specific disease can be identified, (2) that the incubation period from exposure to disease is relatively brief, and (3) that the common source accounts for a fairly substantial percentage of all disease being studied, that is, a high attributable risk. The contrast between the previously described investigation of a common source epidemic and many of the current environmental epidemiological studies is apparent. First, most of the environmental investigations begin with an exposure, rather than disease outbreak. The search is really for the epidemic, that is, disease rather than exposure. Fortunately most individuals exposed to a disease agent do not develop clinical disease. The so-called attack rate will rarely approach 100% unless the dose of the agent is very great or the pathogenicity of the agent, that is, ability to cause disease among those exposed, is severe. Most environmental investigations therefore require very large sample sizes in order to identify the relatively few individuals who will develop the disease given the exposure. Second, the incubation period from exposure to onset may be very long—measured in years, rather than days. The population must therefore be followed for long periods of time or we must resort to the classical historical perspective types of study designs. The so-called historical perspective study is plagued by the inability to clearly define the exposure dose, especially for many of the long

| Table 1. |
|------------------|--------------------------|
| Common source epidemic | Environmental exposure |
| Identification of “epidemics” | Unusual level of exposure to environmental agent |
| Definition of disease by examination of cases | Identification of population at risk and exposure dose |
| Interview to identify common source | Measurement of physiological variable or disease incidence |
| Comparison of cases and controls | Attempt to adjust for confounding variables |
| Identification of specific agents and possible dose-response relationship | Verification of “dose effect” in other populations |
| Estimation of “attack rate” or incidence in total exposed cohort | |

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incubation period diseases. The criteria for the measurement of exposure many years ago is often the basis of the argument about low dose effects. The third basic problem is related to the attributable risk estimations for most of the common diseases, such as lung cancer, heart attack and stroke and many of the other chronic diseases. The majority of the diseases have multiple etiologies other than the environmental agent. The attributable risk associated with the environmental exposure may be small. The relatively low attributable risk percentage results in a small difference in incidence of disease between the potentially exposed population and suitable controls and an even smaller difference within the exposed cohort. Only when the relative risk is high and the cohort exposed is fairly well defined, is it generally possible to clearly identify the epidemic related to the environmental exposure. Unfortunately, such situations generally apply to relatively high dose effects rather to the more common low dose effects of community environmental exposures. Unfortunately in many situations we are searching for a 10% or may be 50% increase in risk following exposure, that is a relative risk of may be 1.1 to 1.5. This small relative risk plus the low attributable risk previously mentioned requires a very large sample size for study (Table 2). Sample size and long incubation period require considerable costs for followup. Yet we could argue that a 10% excess risk associated with a very high prevalence of the environmental exposure could result in a substantial increase in the number of cases of a disease in a population.

Unfortunately, to make matters even more difficult, the exposure is often confounded by differential exposure to other risk factors. The population at risk (exposed) may have characteristics that also increase the risk of the disease of interest. For example, the distribution of cigarette smoking, air pollution and specific occupational exposures may all cluster within certain low socioeconomic and so called blue collar populations (Table 3). The ability to separate air pollution from occupational exposures and cigarette smoking and risk of lung cancer or chronic obstructive pulmonary disease has been extremely difficult (Fig. 1). In order to reduce the cost of these studies, investigators have presumed that the distribution of these confounding variables, such as occupation and cigarette smoking, are similar among those environmentally exposed and not exposed. Their solution to the problem is either not measure the confounding variables or do it so crudely as to result in a meaningless measurement.

Several solutions to these problems have been suggested. The first, as proposed by Dr. Enterline and others, is to study primarily occupational groups that have much higher levels of exposure and greater ease of followup. If an excess of a disease is identified in these occupational groups, then studies of the general population, that is, nonoccupationally exposed and therefore presumably at lower dose, would be considered, or some mathematical model would be developed to relate high to low dose exposures. I would tend to agree that the occupational studies have a better defined population, have greater exposure, and may well be the first line of study. There are several problems with this approach. The sample sizes in many occupational studies are too small to identify the risk associated with some of the less common types of diseases especially some of the cancers (Table 4). Rarely have the occupational longitudinal studies been able to identify a disease risk not previously identified from either clinical or case control studies. The longitudinal occupational studies therefore tend to be more verification than the identification of new environmental exposures. There may be more susceptibles in the general population, such as women, children, elderly, or those with other chronic diseases who may be at risk to an exposure that would not be observed in an occupational setting. For example, Aronow (4) has proposed that low dose carbon monoxide exposures are associated with decreased exercise

Table 2. Estimated sample size for cohort study \( a = 0.05 \) (two sides) and \( \beta = 0.05 \) for relative risk of 1.5, based on various estimates of incidence of disease in "now exposed."

| Incidence | Sample size each group |
|-----------|------------------------|
| 5/1000    | 25,755                 |
| 10/1000   | 12,796                 |
| 20/1000   | 6,315                  |
| 30/1000   | 4,155                  |
| 50/1000   | 2,427                  |
| 1/100     | 1,131                  |
| 3/100     | 267                    |

Table 3. Age-adjusted cigarette smoking rates for white male residents \( \geq 35 \) years of age of Lawrenceville and the South Hills, 1978.

|          | Never smoked, % | Ex-smoker, % | Current smoker, % | Total, % |
|----------|-----------------|--------------|------------------|----------|
| Lawrenceville | 21.9          | 31.3         | 46.8             | 100      |
| South Hills   | 34.1          | 38.8         | 27.1             | 100      |
| Difference   | 12.2\(^a\)    | 7.5\(^b\)    | 19.7\(^b\)       |          |

\(^a\)Data of Weinberg (1).
\(^b\)Significant at 0.1% level.
Table 4. Probability of developing site-specific cancer in 20 years: white men, age 50.

| Cancers                  | Probability, % | Sample size detect a 1.5 relative risk |
|--------------------------|----------------|----------------------------------------|
| All cancers              | 13.9           | 805                                    |
| Lung cancer              | 3.8            | 3,536                                  |
| Colon and rectum cancer  | 2.2            | 7,261                                  |
| Prostate cancer          | 1.7            | 9,744                                  |
| Bladder cancer           | 1.0            | 14,711                                 |
| Stomach cancer           | 0.5            | 29,610                                 |
| Leukemia                 | 0.4            | 37,060                                 |

aData of Seidman (2).  
b$\alpha = 0.01, \beta = 0.10$; data of Schlesselman (3).

tolerance among patients with severe angina pectoris. Studies of occupational groups exposed to high levels of carbon monoxide, let us say 50-75 ppm, may not demonstrate any health effects because of the absence of patients with angina pectoris from this cohort, or the fact that such patients are relatively few in the occupational setting and would not be identified by the usual followup techniques. In spite of these limitations, the use of the occupational cohort studies should not be minimized.

Another approach is to select sentinels of disease. In the classical epidemiological common source epidemics, such sentinels of disease may be specific types of bacteria, such as the typing of Salmonella or Shigella. A common serotype among those with disease or subclinical disease and also at the environmental source is a valuable and powerful measurement of an environmental exposure. In the current environmental epidemiological studies it is some times useful to identify diseases which are relatively rare or have unusual pathologic characteristics as a sentinel of exposure to specific environmental agents, such as mesothelioma in relationship to asbestos exposure and angiosarcoma in relationship to vinyl chloride. Even though these diseases are rare, we might consider that any individual with the disease belongs to the “epidemic” cohort, and that study of these individuals may identify other sources of environmental exposure. Similarly, other investigators have suggested using other specific markers such as chromosomal aberration or biochemical measurements.

Figure 1. Plot of white male lung cancer incidence rates by median income for geographic areas of Allegheny County, Pennsylvania, 1970. Numbers in parentheses are area numbers. Correlation coefficient = 0.6109.
rather than specific diseases as an indicator of exposure. The increased prevalence of a marker is not proof of association with disease. The marker may be present long before clinical disease becomes apparent. Identification of the marker would substantially shorten the observed "incubation period" necessary for followup, and if the prevalence of the marker such as a chromosomal aberration is much higher than the ultimate disease, leukemia, the sample size would be substantially reduced. The cost of the study would be less even if the specific marker test is relatively expensive.

The great hope for the epidemiologist is the identification of the steps from exposure to the biochemical change or cellular change to clinical disease. Unfortunately the history of the identification of early markers in relationship to subsequent disease has not been promising. Thus, in recent years, sputum cytology, CEA antigen and α-fetoprotein have not been as sensitive and specific as initially predicted.

The second question is, who pays the cost? The shrinking health research dollar and the inflationary costs of studies will certainly result in a decrease in both the number and scope of future investigations.

A large number of studies are being supported by other than the usual federal health research sources (Table 5). These include: (1) single industry or company financed occupational studies, (2) support from industry wide trade organization, such as the Electric Power Research Institute and the National Egg Board, (3) studies by foundations, and (4) studies initiated by labor unions and other consumer organizations.

Financial support for environmental research from any of these sources have certain restrictions. Industry support is obviously goal-specific. The industry or company, such as a steel company, is interested in determining the potential health hazards related to a specific exposure within the industry. The recent explosion in industrial epidemiological studies seems to be generated by a desire to stay at least one step ahead of NIOSH and OSHA regulations and the numerous criteria statements which are being published. Excellent industry-supported studies have been done especially here at the Graduate School of Public Health in the Department of Biostatistics and Industrial and Environmental Health Sciences. Unfortunately the support of these studies is some times predicated on the interest of the company and not necessarily on the specific merits of the issues. Most of these studies have also been limited in their scope to reviews of occupational records and mortality followup. Recently there has become a tendency for companies to acquire their own "in-house epidemiologist" as a way of better controlling the output and cost. Such an approach, if it continues, could clearly lead to biased studies whether intended or not. Few of these studies will probably expand beyond the company population, due to publication restrictions once a particular problem with these studies has been deduced, at least in those studies being conducted by university groups.

Support of research by so called industrial trade organizations is also apparently growing in popularity. The "consumer" or industrial producer is taxed a smaller amount of money which is then marked for research usually related to the industrial product. The Electric Power Research Institute apparently has a small hidden tax on electric bills. The National Egg Board collects money based on the shipments of crates of eggs. This approach to collecting research funds has certain merits that will be discussed later. A relatively large amount of funds can be generated at a minimal cost to any single individual. The funds can generally be utilized for goal-directed important research of particular interest to both the company and the consumer. The basic problem again is that this type of research tends to be very goal-specific as defined by the industrial organization and is often tailored to the specific value of the products. The Egg Board research, for example, has come under considerable scrutiny because of the belief that the research is primarily aimed at proving the value of the egg yolk. It is unlikely that the research supported by the Electric Power Research Institute is oriented primarily at turning on light switches. However, the research is generally not investigator-oriented and therefore in some way may stifle the intellect of the investigative research community. Also this research tends to be short term as compared to the necessary long

Table 5. Funding of environmental research and studies.

| Source                        | Problem                                                                 |
|-------------------------------|-------------------------------------------------------------------------|
| Industry                      | Short-term, limited population; specific goal-directed; potential bias  |
| Trade organizations           | Short-term; specific goal-directed; bias                                |
| Foundations                   | Limited support; time restrictions                                      |
| Labor unions and consumer     | Short-term, limited population; specific goal-directed; potential bias  |
| government                    | Political realities of less money and competition; high cost of environmental studies; may be insufficiently goal-directed |
term epidemiological studies often necessary for major environmental problems.

The foundations have played a role in public health research and teaching. The Rockefeller Foundation was responsible for the early development of public health schools in the United States. The work of the National Foundation for Infantile Paralysis in the development of the Salk vaccine is well known. The Mellon Foundation supported the development of the University of Pittsburgh Graduate School of Public Health. Foundation support will probably continue to play a vital role in public health and in environmental research. However, foundation support is often short term and subject to the vagaries of the "board of directors" or review committee.

Finally, pressure from labor unions and consumer organizations has resulted in another source of support for environmental research. In this case as part of a labor agreement a certain amount of funds are set aside for research into a specific problem. Again, the research is very goal-specific, often related to a specific company or industry, and not a general environmental problem.

The above sources of research support will continue to play a major role in environmental research. I believe, however, that the major source of support will continue to depend on the federal research program, such as the National Institutes of Health, Environmental Protection Agency, and the National Institute of Occupation, Safety and Health. There are several reasons for these assumptions. First, as noted, much of the funds from the other sources are generally restricted to specific industry and occupational groups. Second, are usually very goal specific, that is a contract to do a specific job, and thirdly, of relatively short duration. It is doubtful whether major environmental research programs within universities, or other health centers can survive strictly on such funds.

Continued federal support for our environmental epidemiological research is obviously related to the quality of the research proposals and the availability of the funds. Two aspects of study designs have recently created very thorny problems for the support of these studies.

The first problem has also been previously discussed and relates to the inability to measure the individual's exposure. Many of the earlier environmental studies were of the so-called ecological type, in which the distributions of rates within a community or over time were compared in relationship to estimated environmental exposures. As noted, it is unlikely that such studies will resolve the low dose-effect problem. They are all confounded by numerous other differences between the communities, as well as difficulties in estimating doses within defined populations. The occupational longitudinal studies have also provided relatively crude estimates of exposure dose. Support for future epidemiological studies of low dose effects will probably require a better estimate of environmental exposure especially low dose effects. This will include more careful measurements of the occupational, community, and home environmental exposures. Occupational epidemiological studies will require good industrial hygiene measurement. Better estimates of air and water pollutants will be required, and at least some sampling by personal monitoring of the environment will probably be necessary. The measurement of the home environment that is indoor pollution will probably be an extremely difficult and complex problem.

The second concern has also been briefly mentioned in the introduction. Studies of low dose effects, even with relatively large sample sizes and adequate power, have a good chance of failing to demonstrate any adverse effect (Table 4). Some investigators seem to panic at the thoughts of an expensive "negative" study. Some federal agencies have gone as far as to basically decide that negative epidemiological studies are of little value. Basically, if you don't have a positive result you're fired! Scientific review groups responsible for allocation of funds are not easily disposed to supporting low dose effect studies that have a high probability of finding no effects. It does seem to me that there is an important place for such studies. Many citizens are frightened by the potential health effects of low level environmental exposure. For example, small increases in radiation exposure, such as been noted in Cannonsburg, near Pittsburgh, or in relationship to Three Mile Island, have conjured up the fear of many cases of leukemia, cancer, congenital malformations and developmental abnormalities. Some individuals feed this fear with inaccurate data and numerous press reports. Newspaper reporters unable to obtain data from available studies often publish preliminary and inaccurate information and add to the citizens' concern. The hysteria associated with the reporting of the exposure probably has a far greater health effect on the public than the potential low dose physical effect. The ability to determine clearly the estimated health impact from low dose effect would be extremely important for the physical as well as mental health of the population. The study designs to test these low dose effects must be biologically sound. The length of followup has to be adequate to cover the proposed incubation period. The
estimation of dose must be reasonably determined both within the exposed population and between the exposed and controls. The sample size should be large enough given an estimated relative risk to have at least a reasonably good power. The relative risk estimates should be based on the best current available data.

These studies are very expensive and I believe will not be supported by currently available federal research dollars. We will therefore be left with three choices: (1) to accept the fact that low dose epidemiological studies are not cost-effective and accept toxicological, animal experimental and the mathematical extrapolation from high dose studies in humans, (2) to modify the epidemiological research methodology to reduce cost but still have studies reasonably capable of obtaining useful information, and (3) to develop other sources of funding.

As an epidemiologist and public health physician, I would have a hard time accepting the first premise. Other scientist seem to agree. The possibility of errors is very large; and some effects can only be measured in man. There are great difficulties in measuring low dose effects by animal experimental studies and toxicological studies. The world is not divided into good and bad environmental effects. There is a critical grey zone that requires careful studies in man. Possibly we should return to the more classical common source type of investigation, rather than the more extensive longitudinal studies that begin with environmental exposure and proceed to disease. There would obviously be exceptions to this sequence. Conceivably the great cost of environmental studies would be reduced if the investigators followed the usual track of common source epidemics and began with disease outbreaks. Improved surveillance of so-called “long incubation period” diseases, such as cancer, heart disease, congenital malformation, developmental abnormalities, and other diseases may increase the likelihood of identifying specific epidemics. Surveillance specifically aimed at rare cancer sites or occurrence at unusual ages such as the young adult within selective communities with subsequent followback to determine potential environmental exposures may be a more feasible approach. Changes in the prevalence or incidence of a specific developmental abnormality in relation to time or place, may be related to an environmental exposure. The Atlanta Congenital Malformation Registry has recently noted an apparent epidemic of ventricular septal defects. Other investigators have utilized the study of chromosomal aberration among both spontaneous and induced abortions as markers of environmental exposure. These surveil-

lance systems require: (1) the identification of an epidemic, that is an increase in the frequency of a disease as compared to changes in reporting or ascertainment; (2) careful followback studies to identify the possible environmental and occupational exposures (which may be particularly difficult in long incubation period diseases) and (3) followup industrial hygiene studies to determine the potential exposure doses. This approach is similar to a classical common source epidemic investigation. Again the basic difference is in relation to the incubation period and the type of exposure.

One of the growing problems with these types of studies is the confidentiality questions that are increasingly limiting the investigators to the available data sources, such as mortality statistics, incidence data, hospital records, birth certificates, etc. One always wonders how John Snow would have responded if the water company and health department had told him that their records were confidential. We recently had an experience in which the gas company told us that the date in which a home was switched from coal burning to natural gas was confidential.

Finally, a more adequate source of funding is necessary. If it is logical to tax the consumer for electric power and use the funds to support the Electric Power Research Institute, and for the Egg Board to tax each crate of eggs, then producer-related health research taxes might be considered. The obvious approach would be a tax on the sources of environmental pollution or on known health hazards. A tax on certain industrial processes known to cause pollution in the environment might be considered inflationary and also likely to decrease the competitive position of an American industry. The steel industry is reported to be in deep trouble already and would probably be quite unhappy if an additional tax were added to their product, even if relatively modest, especially if the funds were used for research not directly related to the industry. The use of fines for pollution as a source of health research would be unstable and also might lead to more enforcements in order to obtain more money. The old speed trap towns would be replaced by the environmental monitoring patrol.

A tax on dangerous consumer products would have certain appeal (Table 6). Cigarette smoking is probably the single largest source of personal environmental pollution. Representative Drinan recently introduced legislation to add a 10 cent tax to cigarettes. He estimated a yield of about $4-5,000,000,000. My own estimates which were conceived prior to his announcement were more conservative, about $2,500,000,000. He apparently
Table 6. Estimated yield from a tax on cigarettes and alcohol.

| Source | Estimated cigarette smokers | Estimated alcohol consumption | Adult population, ≥ 17 | Total consumption | Tax at $1/gallon | $416,611,360 | Oz/gallon | 128 | Oz/drink | 0.5 | Tax per drink | 0.3g | Tax at 1¢/drink | $1,372,800,000 |
|--------|-----------------------------|-------------------------------|------------------------|------------------|-----------------|----------------|-----------|-----|----------|-----|--------------|-----|----------------|-----------------|
| Cigarette | Smoking | Alcohol | 85,000,000 | Smoking | Average 1 pack/day | 85,000,000 | Packs per year × 365 | 31,025,000,000 | Tax 10¢ per pack | = $3,102,000,000 |
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