Exposure Registries

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ABSTRACT. Exposure registries are new tools for use as part of the public health response to toxic occupational and environmental exposures. These registries can help fill a gap that currently exists in the effective handling of problems following the revelation of an exposure situation. In the past, such a tool was lacking and potentially high-risk groups may not have received needed services. Recent legislation, however, has mandated the establishment of exposure registries. These registries can help provide the basis for a unified response to what historically has been described as a fragmented and ineffective approach to managing high-risk cohorts and assessing the impact of toxic substances. Certain exposure registries are now mandated by law (PL 96-510), and they have a place alongside other disease control and public health tools. Their establishment and use is not without problems, but the gain from them could be substantial. They fill a gap in the current public health response to problems of groups found to be at increased risk of exposure to toxic substances.

CONTEMPORARY LIVING has unintended byproducts, including occupational exposures, environmental contaminants, and chemical and radioactive wastes. Revelations in the 1960s and 1970s led to public awareness of numerous incidents of occupational and environmental insults.[1-3] Unsuspecting workers or residents sometimes learned that their work or place of residence had exposed them to a deleterious environmental substance, and ultimately, in some cases, a disease resulted from such exposure.[4,5] Some critics have maintained that the response of governmental agencies and corporations are sometimes tentative and inadequate.[5-7] Today there are few effective programs to clarify such potential risk situations and the resulting needs.[6,7]

Groups of people thought to be exposed to environmental substances, and who may be at increased risk for subsequent diseases, may suffer due to deficient research and service responses to their problems.[5-7] Reasons for such deficiencies include an array of uncertainties: difficulties in determining who were exposed, to what, and with what current and future effects. Methodologic limitations in the ascertainment of the long-term effects of low-level multiple exposures to toxins have been a persistent research question for the past two decades. Combined exposures to low levels of hazardous substances and certain diseases, e.g., cancer, with long latency periods and low incidence often defy effective study. Proposed studies to investigate these situations exhibit little statistical power. Chance clusterings of cases complicate the assessment and interpretation of exposure-disease relationships. Even if aware of these technical limitations, affected people apparently want definite studies to determine if they have been exposed or if they are diseased. Many citizens apparently believe that relatively simple tests of exposure or disease are available and it is only callous or recalcitrant bureaucrats who will not provide

them.[6,7] Additionally, the potentially exposed workers or residents have experienced dwindling property values, reduced credit ratings, cancellation of insurance coverage, hiring discrimination, and psychological sequelae.[7,8]

The fears engendered by potential exposures often give way to distrust because of inconsistent or insensitive or delayed responses from corporations or government agencies involved at all levels.[6,7] This problem is due in part to the fact that people at risk of exposure or disease have needs and concerns (medical, economic, social, legal, and psychological) that cross lines of responsibility of many institutions and are exacerbated due to the lack of definable remedies.

One approach that may meet some of the research and service needs of high-risk populations is the registration of exposed persons, i.e., establishment of exposure registeries. This is a relatively new approach, in contrast to the more established disease or outcome registries, e.g., cancer registries. Exposure registries are the enrollment of persons exposed, or likely to have been exposed, to an occupational or environmental toxin and the subsequent following, and in some cases, managing of those groups. The purposes and functions of exposure registries[9–14] may be summarized as follows:

(1.) to delineation of the population at risk
(2.) to follow-up of a cohort to ascertain exposure-disease associations
(3.) to follow-up of a cohort to ensure the institution of appropriate primary and secondary prevention, and medical surveillance
(4.) to follow-up of a cohort to allow for appropriate social, legal, and economic support
(5.) to demonstrate societal concern for the cohort and provide a base for political action relevant to the exposure
(6.) to notify a cohort of an exposure, preventive measures, or therapeutic advances, which were not understood or known at the time that the registry was established

Exposure registries are not always useful in etiologic research. With diseases with low prevalence following low-level exposures, exposure registries are not very effective tools because exposure classification is often difficult; the statistical power of prospective studies is low and the time period of study may be impractically long.

For some situations where there are indeterminate exposures, registries may provide opportunities to determine the exposure-disease association and risk. Also, where practical prospective studies can be designed, registries can be of use in establishing hypotheses. There are many questions when considering an exposure registry for etiologic research. How can exposed persons be adequately differentiated from non-exposed persons? What group could serve as a comparison group so that the disease experience of the exposed group can be evaluated? How long should the group be followed? These questions can become quite technical, but often, even the most basic questions are the hardest to resolve: What are the exposure and disease of concern?

In addition to the social and scientific issues that governmental or private officials face in considering whether to establish a registry, are questions of who will fund, staff, and use such a registry; for how long; and to what end. Many officials anticipate overwhelming "volunteer bias," "litigation bias," and subsequent misclassification of registrants. Exposure registries also carry with them the implied promise that something will be done, and often, governmental and private agencies are not able to make a commitment. Once established, responsible officials worry about whether there will be a policy and funding commitment to maintain such registries. Even with these problems exposure registries may have value.

History of exposure registries

Registration of exposed persons is a standard procedure for addressing some infectious and communicable diseases. Examples include: quarantining of exposed persons, identification and location of sexual contacts, and the listing of people at a church picnic where a foodborne outbreak was suspected.[14]

Chronic diseases are also appropriate for exposure registries because of the long time period between exposure and the need to follow exposed persons. The forerunner of contemporary exposure registries is the long-term follow-up of atomic bomb survivors that began in 1950.[15] This involved the registration and prospective study of the populations of Hiroshima and Nagasaki. One component of this effort to trace atomic bomb survivors, the Life Span Study, was organized to include 100,000 individuals who were followed to determine effects of exposure.

Other efforts in the early 1950s involved notifying, following, and screening persons at risk of thyroid cancer due to therapeutic thymus irradiation.[16] This activity also constituted an exposure registry. The current effort to locate and follow mothers, daughters, and sons exposed to diethylstilbestrol also constitutes an exposure registry.[17]

What might be considered the ideal situation for an exposure registry was exemplified by the establishment in 1976 of the Michigan Polybrominated Biphenyl (PBB) follow-up registry.[18] About 4,600 persons were initially enrolled, interviewed, and studied for acute and subacute adverse health outcomes. This represents the ideal in exposure registries because the exposure occurred over a relatively short period; PBB is toxic to animals both acutely and chronically, is persistent for a lifetime, and it is measurable.

In the occupational field a number of *de facto* registries have been established. Workers exposed to aromatic amines are followed by corporations or government agencies and are screened for bladder cancer.[19–21] Researchers at the National Institute for Occupational Safety and Health (NIOSH) currently maintain registries of workers exposed to kepone, dibromochloropropane, and dioxin. In addition to these formalized registries, there are three other "occupational" identifica-

tions of "at-risk" persons, which are similar to registries. First, regulations of the Occupational Safety and Health Administration (OSHA) require employers to send to NIOSH the personnel records of all employees exposed to various OSHA-regulated substances upon termination of the employee's employment, including retirement or death, or in the event the employer ceases business without a successor.[22] There is, however, very little compliance with this requirement. Second, various OSHA standards (and NIOSH criteria documents) require that employers maintain employee exposure records, some for as long as 30 yr.[22] Third, *de facto* exposure registries have been created in the lists of individual surviving members of retrospective cohort mortality studies compiled by scientific investigators.[9] These lists, the results of vital status determinations, inherently constitute registries; however, the registrants are not aware of their risks or membership in such registries.

An effort has been proposed in legislation pending before Congress that would require surviving members of positive studies to be notified individually of their risks.[23,24] This has the effect of confirming registry membership. Although such an effort (notification) is not necessarily intended as a registry, there are many similarities: notifications often subsequently lead to ongoing medical surveillance for the lifetime of the cohort; and they are costly; they are labor intensive. Less similar is the fact that notifications may utilize loose criteria for exposure classification and may not involve an active or interactive relationship with those notified.

In addition to the Occupational Safety and Health Act of 1970, two pieces of legislation have been the cornerstone in the establishment of exposure registries: (1.) the Health Services Research, Health Statistics, and Health Care Technology Act of 1978 (Public Law 95-623) and (2.) the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (Public Law 96-510). The Health Services Research, Health Statistics, and Health Care Technology Act mandated that the National Center for Health Statistics (NCHS) study the issues in establishing a federal system to assist in locating individuals who have been or may have been exposed to hazardous substances, determining the effect of such exposures on their health, and helping them obtain access to appropriate medical care and treatment.[25,26] The study resulted in 12 recommendations, 5 of which are pertinent to the establishment or operation of exposure registries:

(1.) Develop adequate documentation of data files and computer programs that have widespread research utility.

(2.) Improve the timeliness of epidemiological studies of exposed populations.

(3.) Develop improved risk assessment methodologies and analytical technology for the detection and monitoring of hazards in the environment.

(4.) Institute efforts for coordinating environmental and health monitoring programs and for expanding the study of population subgroups that display an unusually high or low incidence of disease-specific morbidity or mortality.

(5.) Study the resource requirements involved in establishing a network of coordinated screening and diagnostic services for individuals with suspected exposure to hazardous substances.

The law (PL 95-623) also mandated the study of incidence, prevalence, distribution, and effects of environment-related disease in populations. Subsequently, a report[26] was released that presented a plan for these studies. The report describes the major data collection systems within the environmental health area and discusses problems inherent in using this database to associate human health effects with environmental exposures.

Most significantly, in 1980, exposure registries were mandated by the legislation that created CERCLA, often referred to as "Superfund." CERCLA also created a new agency of the Public Health Service, the Agency for Toxic Substances and Disease Registry (ATSDR). This agency is required to implement the health-related authorities of the act, among which is the requirement, "in cooperation with the States, establish and maintain a national registry of serious diseases and illnesses and a national registry of persons exposed to toxic substances."[27] The intent of Congress in drafting this mandate is not specified in the legislative history of the law. Hence, whether it is for etiologic research or for broader public health purposes is left to be determined by the way the law is applied.

"In December 1982, the Environmental Defense Fund, joined later by the Chemical Manufacturers' Association and the American Petroleum Institute, filed suit against the Secretary of Health and Human Services, seeking declaratory and injunctive relief relating to the implementation of Section 104(i) of P.L. 96-510 that created ATSDR and that contained the requirement for the establishment and maintenance of national registries."[27] In May 1983, the government signed a consent decree that, among other things, required the administrator of ATSDR to conduct a peer review, to be completed within one year, or the methods to be used to establish such registries.[27] A document entitled "Criteria and Methods for Establishing and Maintaining Exposure and Outcome Registries for Environmental Health Problems" was drafted by the Centers for Disease Control (CDC) to fulfill the requirement of the consent decree. The document proposes criteria for the establishment of nonoccupational environmental disease and exposure registries to be established under PL 96-510. It also presents discussions of the strengths and limitations of exposure and disease registries.

The top priorities for registries for the ATSDR, as stated in the document, are:

(1.) Persons exposed outside the workplace to:
- (A.) Persistent, measurable levels of hazardous agents in which animal studies or other evidence predicts significant adverse effects in humans, or
- (B.) Hazardous agents for which current methods exist to prevent an adverse outcome; or

(2.) Persons with outcomes of interest where measurements of exposure to hazardous agents are available.[27]

Implicit in the document was the rationale that the questions regarding registries should be confined to determining their appropriateness for research on exposure-disease relationships. Broader public health goals aimed at responding to the needs and concerns of exposed populations, who were drawn into the risk labeling process, were not addressed in the document.

In a subsequent document entitled "National Registry Proposal," drafted by ATSDR and the topic of a public meeting, an interpretation of when an exposure registry should be established was proposed.[28] "The ultimate purposes of a registry of persons exposed to toxic substances are to provide service to registrants and to facilitate the development of new scientific knowledge. Besides identifying and keeping track of exposed persons, a registry should coordinate the clinical and research activities that involve its registrants. Since many researchers may propose using registrants as study participants, the registry should be the focal point of coordination. By maintaining a comprehensive data base on all exposed persons, a registry should try to collect information that satisfies multiple needs. Besides playing an important role in assuring uniformity and quality of the collected data, a registry should ensure that data collection is not duplicative in studies in order to reduce the overall burden to exposed or potentially exposed persons."[28]

This document also proposes criteria for when a registry should be established, who should be included, levels of follow-up, and when follow-up of a registry cohort should be terminated.

Proposed model for use of exposure registries

A registry provides a structured and orderly approach to help handle the problem of identifying and maintaining communication with persons exposed to toxic substances. Amidst the uproar that almost inevitably follows the revelation of perceived exposure situations there is a need for structure and an organized and sensitive response. Harris[6] proposed the following five steps that would provide a practical and sensitive framework for responding to new-found hazards:

(1.) The construction of an algorithm for local health agencies to use when responding to perceived pollutant hazards,

(2.) The suggestion in the algorithm of a lead agency to coordinate providing accurate information to concerned citizens and the media,

(3.) A history-taking to determine all citizens' concerns and the implications the incident has for them,

(4.) The development and implementation of an effective mechanism to inform concerned citizens of the state of current knowledge, including risk, routes of exposure, thresholds, and testing procedures,

(5.) Diffusion of decision making responsibility for testing, cleanup, and site location from specific political agencies (such as health departments) to a broader community base.

Using this more coordinated approach to incidents should allow for a truer perspective on the need for a registry. With such a perspective, decisions can be made with less emotion and more consideration.

An exposure registry would fit into the framework of Harris.[6] As part of the response to a perceived hazard a tentative definition of those affected by exposure would be determined, and a tentative categorical listing of people, defined by time and place characteristics such as residence or job type, would be developed. Efforts would be made to identify the hazardous substances present, determine whether exposure could have occurred, and when and via what routes. This information will help prevent further exposures.

Because many of the conclusions drawn from these questions would be speculative or subjective, a broad criterion for the decision to establish a registry would suffice. The criterion, in the form of a question, would be: Is it likely that some people were exposed to a harmful substance? If the answer is "yes," a limited term registry could be established. The purpose of the registry could be to develop a structure for bringing order to the situation and to identify individuals requiring services and programs. This may only be a short-term need. Hence, a registry might be valuable for a limited time, after which it should be closed. The registry need not be a collection of information in a "permanent" record. As the situation changes, new objectives and goals for the registry may be developed to address more long-term problems. The value of a registry must be assessed at intervals to ensure that objectives still hold and are being met. If they are not, objectives should be revised or the registry closed. Long-term registries are also likely, and should result only from periodic appraisals of the need for the registry. These registries need continuity of funding, objectives, and personnel if they are to be effective.

In addition to deliberations about the creation of a registry, the following factors should be considered: (1.) the possibilities for primary and secondary prevention (exposure mitigation, chemoprevention, screening) or therapeutic trials that might be useful, and (2.) a plan for the transfer of registry information and surveillance responsibility to the primary health care system. The existence of prevention possibilities need not be prerequisites for establishing registries. In many cases asymptomatic registrants will seek medical assurance of whether they show signs of exposure and signs of effects. In some cases such medical assurance will be given, in others it will only be possible to provide counseling and follow-up.

Transfer of information to the primary medical care delivery system. It is unlikely that exposure registries could provide all of the counseling and medical surveillance services that registrants might need. The magnitude of such a task is large and costly. Moreover, the use of a registry to coordinate the provision of medical service delivery may result in fragmentation of individuals' health services. Therefore, primary care

practitioners should be involved in the management of high-risk cohorts. Occupational and environmental risk information generally is not considered by primary care practitioners for a number of reasons.

(1.) Historically, medical training has not encouraged this kind of awareness. Few primary care practitioners take even a rudimentary occupational history. Still, many physicians do not take such a history.[29]
(2.) Historically, occupational and environmental risk information has been compartmentalized in company records or scientific papers and segregated from the worker and his physician.
(3.) The implications for disease control that could result from knowing occupational and environmental risk information have not been clarified.

These uncertainties and the practical limitations of health insurance plans cause primary care physicians to shy away from treating patients with occupational or environmental exposures.

All three of these hindrances are essentially problems of information linkage: informing workers and physicians and transferring information found in one area to another. It should not be difficult to ensure that information on various exogenous risk factors for an individual be transferred from a registry to those who provide primary care. When this information is factored into the individual's health maintenance and promotion plan, there can be appropriate surveillance, and clinical manifestations can be more easily linked to predisposing risks.

Therefore, registered persons can have information utilized where it may be the most beneficial to their medical care, without establishing new medical care structures. To make such an approach work, registry managers will have to communicate risk information to primary care practitioners *and* information on surveillance, biological markers, diagnosis, treatments, and results of epidemiological analyses pertaining to the ongoing follow-up of the cohort.

Technical developments: Biological markers and chemoprevention. Two recent developments may make exposure registries more appropriate as opportunities for primary and secondary prevention programs: (1.) the identification of preclinical or premalignant biological markers of exposure or outcome, and (2.) the development of methods of chemoprevention of disease.[30-32] The former makes it increasingly possible to document exposure to the individual, thus enabling researchers to more precisely study long-term effects and benefits of prevention strategies.[30] The latter is the administration of micronutrients or drugs to persons at risk and, in a premalignant state, to alter the risk and impede progression of the disease.[31,32] In terms of research, the evaluation of the effectiveness of chemoprevention may be possible by measuring the resulting changes in frequency of some preclincial marker rather than waiting for the actual disease outcomes to manifest. In this case exposure registries are not only useful for the purpose of assessing disease outcomes, but also for managing high-risk populations and evaluating the efficacy of management strategies.

Responsibility for the registry. The funding and management of registries could involve companies, professional groups, or state and federal sources. A primary source would be Superfund, which mandates exposure registries. The funding of screening and surveillance programs could be through each individual's health care insurer, although there is no mechanism for doing this at this time. There may be need for legislation to promote third-party cooperation and to provide funding for those with no health care insurance or program. Chemoprevention and other intervention trials could be funded through various federal research programs, by pharmaceutical corporations, or other private sources, after approval of research protocols by the registry involved.

Impact of registries

The impact of registries on registrants is manifold. Registrants may have concerns about confidentiality and stigmatization from being from an "affected" community. These concerns will be heightened if the possibility of linkages of registries exist. In other cases, the mere existence of a registry for a particular community or occupational group may lead some to conclude that a group has been impacted adversely by the exposure, even if no impact has been demonstrated. Groups suspected of being exposed to potentially harmful substances with possible long-term effects need responses that show that there is genuine concern for their fears and needs. Such people need expert counseling, clear information about timely efforts at responding to the crisis, and continuous follow-up. A registry could be a vehicle for this type of response if registries were seen not only as research opportunities, but as venues for public health action and societal response to these problems.

On the other hand, registrants who are seeking to exert political or social pressure can take advantage of the fact that registration is an act that defines a group with common characteristics. This is a necessary step in effecting political and social change. For registrants in exposure registries, this may be useful in securing ongoing services of medical surveillance, counseling, antidiscriminatory measures, and judicial redress. Such pressures may also secure environmental controls and other means of primary prevention.

People who have learned of an exposure with unknown but frightening implications often have needs which are not met because of the inability of governmental or private sector programs to respond, or because the people have false expectations. Although a registry may be an appropriate response, it can also appear to provide a solution, when in fact it does not. A registry could become a political sop provided to give an appearance of dealing with an environmental crisis when other, more politically difficult, but better, solutions are in order.

Registries have varied impacts on society as a whole, although these impacts are difficult to assess. Registries

may provide the opportunity to elucidate the extent and depth of pollutant-related disease so that the true dimensions of the problem can be seen and so that appropriate preventive, remedial, or remunerative actions can be taken. However, registries that misclassify individuals on the basis of exposure, or that involve pollutants of minor or irrelevant toxicities can lead to the improper inclusion of many individuals in studies, leading to false conclusions. These registrants could believe that mere inclusion in a registry entitled them to make claims, demands, and remonstrances, despite lack of proof of any significant exposure. Registries must fully inform registrants of the significance of their exposure to prevent actions which are inefficient, costly, disruptive, and unfair to certain sectors of society such as the defendant in resulting litigation or government agencies.

Balancing the costs of pollution vs. the production costs in protecting against them is a major policy question of our times.[33] Too often in such discussions one side of the equation has not been adequately determined. For example, in monitoring occupationally or environmentally related disease, the focus should not be limited to rates of disease but should include biomedical, psychosocial, economic, and legal effects. An exposure registry could be a framework in which to monitor the extent and impact of occupationally or environmentally related disease by active follow-up of cohorts involved. This has not been generally attempted and, consequently, there is little information on the value of this approach. The various studies of occupational cohorts that comprise *de facto* registries provide good opportunities to study the impacts of pollutant-related disease.[21,34,35] One reason for not utilizing this approach is that health and disease registries have been the domain of the biomedical community and not of social scientists and economists. A potential value of the registry is to encourage full use of the data.

Conclusions

The registration and follow-up of individuals at risk from occupational and environmental disease has been mandated by legislation. Registries are useful tools for delineating high-risk populations, and provide a framework for an evaluation of the range of impacts that result from the investigation of toxins. The fact that registries are limited in identifying some types of disease/exposure associations does not detract from their utility in addressing other broad public health problems of high-risk cohorts.

Exposure registries do not have to be considered as permanent records. Rather, registries should have an ongoing evaluation component. Exposure registries may be of limited terms. Periodic analysis of information and re-evaluations of the necessity for registries are imperative, otherwise they do not represent a very effective response to problems.

Exposure registries should not exist separately from the primary medical care system. Rather, they should have a strong interactive role in channeling relevant risk information to the primary care provider.

Developments in biological markers could allow for the establishment of better criteria for registry membership and indications of early disease. Also, the registries established in the next 5–10 yr should be seen as opportunities for pilot studies (trials) of various chemopreventive agents and other interventions, particularly with regard to cancer. Such approaches would be beneficial to registrants and researchers.

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