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Challenges to retrospective exposure assessment

by Patricia Stewart, PhD¹

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Retrospective exposure assessment has become a crucial component in the interpretation of occupational epidemiologic results. Many advances have been made over the last 2 decades, but substantial progress is still necessary to reduce the misclassification of exposure. The efforts needed include evaluating the validity and reliability of assessment methods, better documentation of the methods, use of exposure determinants to estimate exposure levels more accurately and reliably, and an increase in the understanding of industrial hygiene and biological measurement data and questionnaires, their limitations, and how to use them best. In addition, better characterization of exposures is necessary. This need includes evaluating dermal and ingestion hazards, incorporating nonoccupational sources of exposures, particularly hobbies, evaluating the effect of multiple chemicals, and exploring different exposure metrics.

Key terms epidemiology, occupation.

Retrospective exposure assessment is a fairly recent phenomenon in the investigation of chronic disease in the workplace, and only in about the past 10 years has it become a recognized component of occupational epidemiologic studies. The industrial hygienist has therefore become an increasingly important member of the interdisciplinary team investigating this type of disease. The role of the industrial hygienist is hampered, however, because there are no standardized methods to estimate historical exposure levels. In part, this is because the appropriate estimation method for a study is dependent on the type of information that is available, which varies from study to study. There is a lack of standard methods also, however, because the validity or reliability of the methods has been studied very little. The few studies that have examined validity or reliability have found that a considerable amount of misclassification occurs, which, when applied to hypothetical situations, has a substantial effect on observed disease risks (1—2).

Retrospective exposure assessment is a process used primarily for epidemiologic studies, but it can also be used to document exposures for worker compensation claims or toxic tort cases. The methods used to assess exposures for these 3 purposes are determined primarily by the source of the exposure information. If the source is the employer, a more technical and possibly more precise approach can be taken than if the information is

coming from the study subject. The approach using employer information is represented in this paper by the cohort study; the second approach, from the study subject, is represented by the population-based case-control study.

This report describes several areas that need more attention in the field of retrospective exposure assessment. These areas can be thought of as improving current estimation methods, improving the use of exposure data, and improving the characterization of exposures.

Improving current estimation methods

One of the top priorities in the area of retrospective exposure assessment is the evaluation of the validity and reliability of current estimation methods because methods are not likely to be improved until it is known where they perform poorly. Validity can be evaluated indirectly by using estimates developed for a disease or study to investigate exposure-response relationships with a different, known health effect [eg, evaluating silica estimates developed for the investigation of lung cancer by examining their relationship with silicosis (3)]. Validity can be evaluated directly by reconstructing historical exposure levels (4) or using historical monitoring data (5). The

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most valid approach is probably the latter, but it is not thought to be feasible in most cases because too few monitoring data are usually available to use some of them on a validation study. Yet removing the data from use in the study is not necessary. If the estimation method is evaluated before the estimates are developed for a study, the measurement data can first be used to evaluate the method and then be incorporated into the study (5). The determination of validity is, however, problematic when the gold standard is "alloyed" (6), such as when historical air measurement data are nonrandom. (See the section Improving the Use of Exposure Data.) Reliability (or reproducibility) can be evaluated by using multiple assessors or by comparing the estimates with estimates developed from a different estimation method.

Validity and reliability measures, such as percent agreement, kappa, and correlation statistics, that measure overall agreement are useful, but overall agreement provides only limited information. Exploring the performance of estimation methods in more detail to determine when the methods perform well and when they do not can provide information that can be used to pinpoint areas where improvement is needed. Areas that should be explored include different exposure situations [eg, level of exposure, type of job, presence or lack of sensory indicators (odor, dust) or health effects, physical state of the agent, route of exposure, and date of exposure] and different assessment situations [eg, type of exposure information used, experience of the assessor (2)]. Publishing the results of these types of investigations will identify areas that need improvement and should, consequently, stimulate research in these areas.

One of the primary goals of validity and reliability investigations is to improve assessment methods. The methods for assessing exposure levels have changed very little since the earliest studies and one of the major reasons for this lack of change is probably due to the lack of documentation as to how the estimates were developed. A review of occupational cohort studies showed that most provide only a short paragraph on the assessment process (7). This practice means that each investigator new to exposure assessment gets little guidance from reviewing other studies. It also means that progress with improving estimation methods has been slow. Finally, the lack of documentation limits the credibility of the study and the interpretability of the results. Two recent cohort studies that are an exception to this practice are a study of semiconductor workers and a study of acrylonitrile workers. For each, several exposure assessment reports (5, 8–13) accompanied the epidemiologic analysis (14, 15). These reports provided detailed documentation on how the exposure estimates were developed. Assessments made for population-based case-control studies have traditionally been even less well documented. A recent study provides an illustration, however, of

good documentation (unpublished observations). These studies should help to improve the field of exposure assessment.

The lack of documentation in most published studies makes it difficult to know exactly how the estimates were developed, but it appears that most investigators have compared the exposure situations or "exposure profiles" of jobs without measurements to those of jobs with measurements. This suggests a deterministic approach (ie, estimation is based on physical and chemical principles). More attention has recently been paid to this area both in retrospective exposure assessment and in industrial hygiene practice in the current workplace (16, 17). It seems reasonable therefore to assume that this approach will be used to assess exposure levels in the next millennium.

In theory, if one could identify all the exposure determinants (ie, the factors that influence exposure levels) for any given job (ie, an exposure profile) and the impact of the determinants on exposure levels, the exposure level could be assessed. Although identifying all the determinants of all chemical and physical agents for all jobs is not possible, it may be possible to estimate the effect of the most important determinants for some jobs well enough for epidemiologic purposes. A review of determinants described in the literature suggests that at least 4 general classes of determinants can be identified: determinants associated with the agent (such as physical state and particle size), meteorological conditions (temperature and humidity), the worksite (type of operation, process equipment and controls), and the individual worker (frequency and duration of a task and the use of protective equipment) (17).

Several of these determinants (eg, use of protective equipment) have been found in multiple studies across numerous industries. It is possible that a comprehensive evaluation of the studies published to date could already reveal certain patterns that could then be used to develop a model to assess historical exposure levels. It is unlikely, however, that there will be a single model that accurately predicts exposure levels for all jobs. Rather it is likely that many models will be needed, depending on the type of process, job and other factors. Approaches using artificial intelligence or fuzzy logic may provide a mechanism for more accurate and more efficient assessments.

Developing estimates from a deterministic-based model has several advantages. First, many cohort and population-based case-control studies rely on interview data. Using a deterministic model means that it would be necessary to ask only questions on the determinants in the model, many of which could probably be answered by respondents. Second, use of determinants in questionnaires would allow information to be obtained that is specific to the individual, overcoming the traditional prob-

lem of assuming homogeneous exposure levels in a heterogeneously exposed group of workers with the same job title. Third, if there were recognized and accepted determinants for given jobs, the questionnaires used to obtain the determinant information for these jobs could become standardized. Such standardization would decrease the resources needed for the design of questionnaires in future studies. This practice would also increase the comparability of the information collected across studies. Fourth, the use of determinants would increase the accuracy of the exposure assessments by identifying what exposure variables should be considered in the estimation process, in contrast to the current practice of each assessor considering what he or she thinks is important. Fifth, it would increase the likelihood of developing standardized estimation methods. This would increase the reliability of the estimates within and across assessors and would increase the comparability of the epidemiologic results across studies. Sixth, if models were developed they could be computerized. If the questionnaires incorporating the determinant information were also computerized, the efficiency of the assessor could be dramatically increased because the assessment process could then be automated. This is not to say that automated computation of exposure levels could be done on all jobs. Certainly, however, it is likely it could be done on the more common agents for more commonly evaluated jobs such as pesticides and farming, oil mists and machinists, and asbestos and brake-repair workers.

Finally, the identification of determinants and the use of models could significantly change the current practice of industrial hygiene in the workplace. The current practice presumes that the only way to estimate exposures is to measure them. Because of the tremendous number of resources that is necessary to measure exposures, most workplaces are unlikely to ever have a comprehensive data base of exposures to all agents for all jobs in the workplace. An alternative to this approach is to use models to predict exposure levels. This approach requires much fewer resources (18) and allows the expenditure of resources on protecting workers rather than measuring exposures. Not only would it have a tremendous impact on the current workplace, it would develop an invaluable data base for future epidemiologic studies. Moreover, estimates made at the time of the exposure are likely to be much more accurate than estimates developed years later, so that the accuracy and the credibility of the estimates would be greater. Such an approach has been successfully implemented in a large chemical company in the United States (17).

In conjunction with or as a separate approach to deterministic models, it may be possible to estimate exposure levels using personal and area monitoring and computer simulations. As computer software packages become more sophisticated, it may be possible to

develop a computer software program that estimates concentrations in a work area from area and personal measurements taken at different locations in the work area. The program could be similar to those used by meteorologists to measure temperature gradients across a large geographic area. If better information could be obtained on how area concentrations relate to personal exposures, this methodology could be a possible future technique, particularly to estimate personal exposure levels for jobs for which the exposures arise from the general air rather than from the performance of a task.

Improving the use of exposure data

Exposure data can cover a broad range of data. In this paper only 3 types will be discussed: air measurements, biological measurements, and questionnaires. The first 2 are predominantly used in cohort studies; the 3rd is used in both cohort and population-based case-control studies. Other types of exposure data also have limitations, but usually these limitations are less crucial to the estimation process because the data are less crucial.

Almost all assessment methods and evaluations of validity rely on air monitoring data. Yet there are several concerns about monitoring data that need further attention in the future. First, air monitoring data can be the source of considerable misclassification due to unrepresentative sampling, inappropriate sampling and analytic techniques, incomplete documentation, and other factors. In the future, the industrial hygienist collecting the data should ensure that complete documentation is provided with the measurements (eg, sampling and analytic method, duration, personnel or area, date, location, etc). The industrial hygienist assessing retrospective exposures must then carefully consider this information to ensure the appropriate use of the measurement. This practice is particularly important when the monitoring data are from different sources. Comprehensive documentation and analysis will allow the industrial hygienist to understand whether merging the different data sets will result in errors in the estimates or how the data can be modified to reduce the error. Reducing error in the estimates is critical because a small amount of error in the estimates can have a substantial effect on risks of disease observed in an epidemiologic study (18).

In some studies the industrial hygienist uses measurement data from sources other than the employer, because of the scarcity or lack of employer measurements. Often times, these supplementary data come from government agencies. These data sets usually include small employers or unusual industries or jobs that are not likely to be the subject of a published report, so they can be important sources of information, particularly in popula-

tion-based case-control studies. Researchers have expressed concern, however, that these data may represent worst-case scenarios and are not comparable to representative measurements taken by employers. This difference could result in biased exposure estimates if the data were taken at face value, even if they are not merged with employer data. Estimates biased upward could result in disease risks being associated with exposure levels higher than the levels at which the risks actually occurred, thus increasing risks to workers. It is important, therefore, to determine whether this perception is true. Even if it is, if government data rank jobs similarly to representative data, it is possible that the data could provide useful information for the assessment of exposure levels. More work needs to be done in this area.

Another source of information on exposure is biological monitoring data. Some studies have actually used biological results to classify subjects in an epidemiologic study (19, 20). It is unusual, however, to have biological data; to have enough for an epidemiologic study is the exceptional case. The collection of biological data is, nonetheless, becoming more common, and this trend is likely to continue over the next millennium. It is not currently obvious how such data can be incorporated into exposure assessments based on air monitoring data. Certainly, many biological markers of exposure (eg, blood lead) can be converted into likely air exposure levels, but it is not clear how such a conversion would be done if dermal exposure were also a contributor. It is also not clear how to use biological data on substances that have long half-times in the body, because the biological concentration can reflect both current and historical exposures. The way to extrapolate an individual worker's biological concentration into a population's exposure is also unclear because of metabolic differences and differences due to work practices. Moreover, it does not seem particularly satisfying to convert an estimate of dose into an estimate of exposure. Biological monitoring results could be used to validate the estimate, but this use has some of the same problems as using the data to estimate airborne exposures. Thus using biological data with air monitoring data is problematic at this time. Careful thought should be given to this issue.

The 3rd major source of exposure information is the questionnaire. Although questionnaires are used in cohort studies, they are often used by industrial hygienists who can follow-up unclear or contradictory responses with further questions. In the population-based case-control study, however, the interviewer is not usually an industrial hygienist and is therefore less likely to recognize when additional probing is necessary or how to do it. As a result, job-specific questionnaires have been used that obtain detailed information on the work environment and work practices of a worker (21, 22). This procedure allows an assessment specific to that particular worker.

One difficulty with this individual-specific approach arises when the study subject is not available for interview either because of having died or having been lost to follow-up. A proxy is therefore needed, but spouses are not likely to know what the workplace is like. An alternative source of workplace information could be work colleagues (4). Another area needing attention related to questionnaires is memory recall. Exposure assessment is heavily dependent on a person's memory, particularly in the case-control design; yet little work has been done to investigate the ability of people to recall the workplace. It is not clear what information can be queried or how to best get it. It is crucial that we know what types of information people can accurately report, what types are likely to be inaccurate, and what questionnaire design techniques can increase accuracy.

Improving the characterization of exposures

The measurement data available for retrospective exposure assessment has almost exclusively been airborne measurements. Dermal exposures cannot only be a significant source of exposure for some chemical agents when the agents are in the liquid state, but also when they are in the vapor state (23). Yet few epidemiologic studies have assessed dermal exposures. If a substance is a particulate or a liquid with a low vapor pressure and a long half-time, wipe samples of surfaces can be used to assess exposures (24). Where the substance has been a volatile liquid, however, only a very basic characterization, such as yes or no (21, 25) or frequency of exposure (5), has been done.

Recently a model for estimating dermal exposure levels has been suggested (26). This model accounts for the area of skin contact, the amount deposited on the skin, the number of contacts per day, the fraction absorbed through the skin, and the weight fraction of the substance in the mixture. Limitations to this approach and to dermal measurements in general were described. Once an estimate of dermal exposure is developed, however, it is not apparent how to use it with inhalation estimates. As a minimum, future epidemiologic analyses should include stratification of risks from one route of exposure by those of the other route (15).

There are other sources of exposure that have generally been ignored in the occupational epidemiologic study. To my knowledge there has been no epidemiologic study that has accounted for ingestion hazards. Yet the ingestion of metals from contamination on hands and cigarettes has long been recognized. Attention should also be paid to estimating exposure levels from nonoccupational sources. These can include hobbies, diet, ambient

air, water, soil, and showering. As a minimum, the industrial hygienist should take the lead in estimating exposure levels arising from hobbies.

Epidemiologic analyses have generally examined disease risks in relation to employment in an industry or department (such as nickel smelting), or in relation to a single agent, such as asbestos, or a class of substances otherwise not distinguished (eg, organic solvents). This simplistic approach has found numerous associations in the past, but it is also likely that many associations have been missed because of this approach. Evaluating classes of agents has been justified on the basis that a similar chemical structure is likely to result in similar health effects, making an additive model appropriate. There are, however, likely to be interactions among agents that are not structurally, or even physiologically, related that can also affect health outcomes. For example, in one study, formaldehyde by itself was not related to nasopharyngeal cancer, but in the presence of particulates an exposure-response relationship was found (27). The difficulty for the investigator doing an assessment is that there are often hundreds of chemical and physical agents in a workplace to which a person can be exposed. Although the feasibility of assessing the quantitative levels of all chemical and physical agents may be impractical, at least a qualitative evaluation should be made and used in the epidemiologic analysis.

Even when an assessment to multiple agents has been done historically, rarely has the epidemiologic analysis accounted for these multiple agents. The earlier mentioned semiconductor study is a notable exception (14). In this study, because many workers had exposure to several of the 14 chemical and physical agents evaluated, the investigators used a cluster analysis to identify which agents generally occurred together. These clusters were the "classes" of chemical agents that were evaluated for associations with the health outcome. A useful description of other approaches for analyzing the effect of multiple agents has been described elsewhere (28).

Another area that should be given more thought is that of the exposure metric used. Traditionally, 8-hour time-weighted averages have generally been used, probably because of their use in the regulatory area. These may not, however, be appropriate for a particular disease. Peaks or the average intensity excluding peaks (29) could be important even for chronic diseases. Similarly, in most mortality studies long-term average exposure estimates (eg, annual) are often developed, assuming that cumulative exposure is the correct measure of exposure. The disease mechanism may, however, depend on a threshold being exceeded, so that episodic events and the time between the events may be more important than the average daily exposure.

With the exception of assessments based on biological monitoring or radiation studies, most occupational

epidemiologic studies have used a job-exposure matrix approach in which all subjects holding a specific job is given the same exposure level. This approach is used because there are rarely enough monitoring data to estimate individual workers' exposure levels. Recent work indicates that workers with the same job can vary considerably in their exposures levels (30), and work practices are likely to be a major contributor to this variability. The job-specific questionnaires described earlier (21, 22) obtain data on people's work practices, but considerably more effort is needed to understand the effect of work practices on exposure levels. Such information, in conjunction with gene susceptibility studies, may provide additional insight into exposure-disease associations. Caution, however, must be taken in how these data are used to minimize "blaming the victim" when high exposures are measured or disease is observed.

Finally, almost every study is likely to have some feature that can be investigated as a methodologic issue. Investigators should be alert to such opportunities and conduct as many such studies as feasible. Publishing the results, discussing the impact of the findings on studies, and identifying follow-up areas would substantially improve retrospective exposure assessment in the next millennium.

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