7. Retrospective exposure assessment

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7.1 Introduction

Retrospective exposure assessment concerns the reconstruction of past exposure in epidemiological studies. It has often been applied in occupational epidemiological studies and perhaps less so in environmental epidemiological studies, and hence the methodology in the former is better developed. The quality of a study depends to a large degree on the accuracy, validity, and reliability of the exposure estimates, and these may be reduced the further back in time a study goes. A poor assessment will lead to misclassification of exposure that will decrease the power of a study to detect an association between exposure and disease (see Chapter 12).

7.2 Determination of feasibility

Little information has been provided on evaluating the feasibility of a study. There are several exposure assessment considerations, however, that should be evaluated. In a sense, a feasibility study can be thought of as a 'mini' study, that is, the same components of an exposure assessment process must also be evaluated in a feasibility study. These components are: identification of the exposure being evaluated, selection of the exposure metric (e.g. cumulative exposure), the collection and availability of exposure information (measurement and non-measurement), the development of exposure groups, the assessment of exposures, and the evaluation of the validity/reliability of the estimation process. In conceptual terms, the same components of the assessment process are present in assessment of environmental exposures as they are in industry-based studies. The exposure assessment components are presented in the following in the general order in which they are done, although there is much overlap across the components and much of the process is iterative.

If, however, it is determined that one of these components has serious deficiencies that cannot be overcome by other means (e.g. in an industry-based study job histories do not specify where individuals worked and there are few long-term workers available for interview), serious consideration should be made as to whether useful information can be obtained in the absence of an exposure assessment or in the presence of serious misclassification.

Two other issues affect the feasibility of a study. One is related to statistical power. Power should be assessed not only on the prevalence of the exposure and the number of study subjects, but also on the exposure level. If the estimates of disease risk used in the power calculation were obtained from studies that were primarily among high-exposed subjects, the study under consideration must have similar exposure levels to achieve those risks, otherwise the power will be overestimated. In addition, assumptions on the degree of misclassification may be used to simulate the loss of power in order to provide a more realistic estimate of the true power of a planned study.

A further issue is that of the representativeness of a population. The exposure experience of the study group does not have to be representative of the general population. The key to studying an unusual population, however, is to appropriately interpret the results and relate them to what would be expected in other populations.

7.3 Selection of an agent and the exposure metric

In theory, selection of the exposure and the exposure metric should be based on the toxicological mechanism of the exposure being studied. In the case of some exposures, however, the exposure to be estimated may not be the exposure of interest. For example, a sampling and analytic technique may not have been developed for the exposure of interest. There may only be historic measurement data on substances other than the substance of interest. The specific causative agent may not be known (such as the aetiologic agent in wood dust that causes respiratory function loss) or there may be multiple causative agents in the mixture (such as polycyclic aromatic hydrocarbons and lung cancer).

For most agents the exposure–disease relationship for identifying the appropriate exposure metric is not known or only poorly understood. For chronic disease, cumulative exposure is generally thought to be the best metric, but average exposure or highest exposure is sometimes evaluated. For acute diseases, such as asthma, other metrics may be more appropriate, such as the frequency of exposure above a particular threshold. If dermal route makes a significant contribution to the total exposure, this route should also be assessed (see Chapter 9). Selecting only one metric can be risky when the toxicological mechanism is not known. Different metrics often rank subjects differently and therefore will have different disease risks. It is recommended that multiple metrics be developed to allow exploration of different mechanisms.

7.4 Types of information for exposure assessment and its collection and organization

There are three major types of information that are crucial to assessing exposures: work or residential histories, measurement data, and descriptive (non-measurement) data.

7.4.1 Work and residential histories

A work history can be defined as a chronological inventory of all jobs that were performed by the subject during his or her employment in a company (in the case of industry-based studies) or lifetime (in the case of population-based studies of chronic disease). The work history is useful because it places the study subjects in an environment that provides a logical starting point for investigation. A history can be obtained from the employer (e.g. personnel records), from union records, medical records, from the study subjects themselves, or from their proxies (Bond *et al.* 1998). Obtaining work histories from the subjects is obviously more problematic if the study covers a long time period, because some of the subjects may be deceased or untraceable, possibly resulting in selection bias. The use of proxies is also problematic because they may not have complete knowledge of the subject's history. Records used must be carefully examined to ensure that they are complete, both as far as the subjects covered and the coverage of individual subjects.

Merely the presence of a work history, however, does not mean that good information on jobs is available. A recent trend in industry, but one that has existed for many years to some extent, has been to 'generalize' job titles, that is, to make them less specific to the task(s) being performed. As a result, vague terms, such as 'operator' may be used for specific jobs that in a chemical plant, for example, previously may have been called reactor operator, distillation operator, or utility operator. Even if changes in the jobs (and dates) are designated accurately, but individuals with the same title performed different tasks with different agents or exposure levels, substantial misclassification can occur. Thus, it may be necessary to collect more information by asking company personnel or workers where the individuals worked, or from records, such as foreman reports, union lists, and maintenance reports.

In population-based studies, an occupation may be characterized best by job title and branch of industry or line of business of the employer. A detailed description of each job in terms of duties and processes may improve the coding of jobs according to standard classifications and may also facilitate expert evaluations of exposure (see Section 7.4.2).

The counterpart of work histories in environmental studies are residential histories. These histories can be problematic because the subjects may have moved residences more often than jobs and the subjects may not be able to recall details, such as street and house numbers.

7.4.2 Measurements in the workplace or in the environment

Measurement data are often available for industry-based studies, but rarely for population-based studies. Measurement data can provide information both on the presence of an agent and its intensity, but without appropriate accompanying documentation on how they were taken and under what circumstances they can be misleading or useless.

It is often useful for the study investigators to take measurements of current exposures (see Chapter 5). An investigator should consider such an approach when at least some of the conditions are similar, for at least part of the period under study, to those measured. Measuring current exposures can allow comparison of measurement techniques across plants if more than one worksite is in the study; provide exposure data for jobs that had not been monitored; provide greater understanding of the variability of exposures (particularly in high variably exposed jobs such as maintenance); and confirm the historical measurements. In contrast to industry-based studies, personal exposure measurements of the general population are generally not available. Nor is it usually feasible to collect such measurements because the population is distributed over a much larger geographic area than a worksite and many worksites are no longer in existence. Routinely collected environmental measurements are sometimes available and could be used to create exposure indices. Measurements from the literature may be helpful, but their availability is generally limited. Their usefulness can be enhanced, however, by evaluation determinants of exposure (see Section 7.7). If measurement data are not available, it may be that only qualitative exposure assessments are feasible.

Environmental measurements are more 'ecologic' than measurements on occupations in the sense that there are fewer and they are used often to represent the exposures of a much larger population over extended areas.

7.4.3 Direct exposure questions

Direct exposure questions are used in case–control or cross-sectional studies where no measurement data are available. Such information is collected by either self-administered questionnaire or by interviews (see Chapter 2). Responses may be prompted by a closed format addressing specific agents or broad classes of chemicals like 'Have you ever worked with (chemical)?'. A list of specific exposures that is queried in this manner is called an exposure checklist. Such listings may contain rather general terms like 'dusts' or 'solvents' but also specific chemicals. The alternative to checklists is to ask open-ended questions such as 'What chemicals were you exposed to?'. Responses to these types of questions, however, are more vulnerable to differential recall of exposures than are prompted responses (Teschke *et al.* 2000). Furthermore, the analysis is complicated by the fact that the degree of specificity of the reported substances varies between subjects, some recalling specific chemicals and others reporting only general classes of materials. While subjects may know the common names of substances they have used, they are not likely to know the chemical names of agent exposures. As a result, it has been concluded that self-reports of occupational exposures alone, without other information, are not sufficiently accurate to warrant their sole use in most community-based studies (Ahrens 1999).

The usefulness of such questions increases if they are asked within the context of an activity. Further details about calendar time, frequency, or intensity of exposure can be questioned in order to allow an exposure–response analysis.

7.4.4 Job, process, and residential descriptions

Measurement data on its own, however, has limited usefulness. To ensure proper interpretation, the data needs to be placed within the context of the job and workplace. For example, high measurement results should be evaluated in light of tasks, controls, and other conditions. Thus, a third important type of data is descriptive data about the worksite. The job may be described in terms of services provided, products manufactured, tasks, and materials being produced, processed, or handled. A work history can be supplemented by detailed descriptions of each job task, referring to the department or process. Furthermore, each workplace may be characterized by a description of its physical layout like the type of environment (indoors/outdoors, room size, ventilation), use of protective measures, and the type of equipment or machines that were used. A short description of the activities of colleagues next to the respondent can give useful information, too.

However, three practical aspects impose severe restrictions on this need for more information. First, the ability of respondents to recall details of job tasks that have been performed in the distant past is limited. Second, broad open-ended questions may not result in responses relevant to the exposure assessment. Third, the number of specific questions that can be included in a general job history is limited by the fact that each question has to be repeated for each job. This can be time consuming since the number of job periods that can be expected in population-based studies ranges between 5 and 8 periods on average (Jöckel *et al.* 1992, 1998).

In industry-based studies, some of this information may be described in company records (e.g. job descriptions or task analyses, engineering plans, medical problems, plant layouts). In other cases, it may be necessary to interview workers. Many details, however, can be obtained by job-specific questionnaires (JSQ), administered to individuals who held a specific job or worked in an area of interest, to supplement the work histories (Joffe 1992; Tielemans *et al.* 1999). Depending on the focus of the study and on the exposure of interest, JSQs can be developed for specific job tasks, occupations, and/or industries. For example, a JSQ for welders dealt with the metals welded, preparation of metal surface (cleaners, solvents, abrasives), filler metals used, kinds of fluxes, inert gases, or electrodes in the Montreal study (Gerin *et al.* 1985). This approach was extensively used in a case–control study in Montreal covering multiple cancer sites and 294 exposures or agents (Siemiatycki *et al.* 1981; Gerin *et al.* 1985).

The JSQs in this study were meant to deal more specifically with certain manual professions that are reported frequently. The JSQs served as an aid for the interviewers to ask the technical questions relevant to the exposure assessment. In lung cancer case–control studies that were conducted in Germany between 1988 and 1996, 33 JSQs were used to assess exposure (Ahrens *et al.* 1996; Jöckel *et al.* 1998; Pohlabeln *et al.* 2000). Exposures (yes/no) and intensities (low, moderate, high) were inferred from specific job tasks and, partly, from agents or materials that were reported. The reported frequency of tasks performed was an essential basis for the quantification of exposures. Questions of a closed format were used as much as possible to reduce the laborious, costly, and less standardized task of individual coding of exposures by a team of experts. Presumed exposures of a certain job were addressed by appropriate specific and knowledge-based questions in the corresponding JSQ and were used to verify exposure or non-exposure in order to increase the specificity of the assessment.

Similarly, in studies of the environment, for example, studies of air pollution, it is crucial to collect descriptive data of the environment like industrial emission sources, traffic density, domestic heating, and weather conditions (see Chapter 3). For indoor air pollutants such as domestic radon decay products, information about the housing construction, ventilation habits, heating system, and duration of stay at home need to be recorded.

7.4.5 Biologic measurements

The advances in molecular biology have widened the scope of epidemiological research by using measurement in biological samples as indicators of internal exposure, early biological effects, or susceptibility to disease. However, many currently available biomarkers of exposure have only limited applications, because (a) they often do not reflect historical exposures due to a short biological half-life, (b) there are uncertainties as to what the biomarker is measuring, (c) they may be affected by the disease process, (d) they may be confounded and affected by problems of shipment or laboratory measurements, (e) their availability is restricted because they often require invasive procedures, for example, to obtain blood or tissue, (f) the response rate may be low, and (g) they can be very expensive (see Chapter 11).

Nevertheless, biomarkers of exposure can provide valuable quantitative information for agents that have a long persistence in humans, as in the case of certain metals that can be measured in urine or blood (Merzenich *et al.* 2001) or in the case of measurement of dioxins in blood (Flesch-Janys *et al.* 1998). In the latter study, production department-specific dose rates were derived from blood levels and working histories of a subgroup of chemical workers by applying a first-order kinetic model. These dose rates were used to estimate exposure levels for all cohort members.

Biological markers of exposure may also be used to validate exposures that were assessed in an interview and may be used to improve questionnaires (see Chapter 2). In the investigation of exposure–disease relationships biomarkers of exposure may be more suitable for prospective cohort studies, while in case–control studies of chronic diseases questionnaires still remain the primary source of exposure data.

7.5 Collection and processing of data/quality control/training

The need for standardization and documentation of the exposure assessment process has been recognized. The construction, validation, and standardization of questionnaires are often neglected and the valuable body of knowledge and experience from other sciences, such as psychiatric disorders, intelligence, or pain, is ignored. Some key issues and recommendations, which should be part of the standardization procedure, have been described by a working group of the IEA (IEA European Questionnaire Group 1998 [http://www.dundee.ac.uk/iea/EuroQuests.htm]) (see Chapter 2).

Moreover, as validated instruments are rare, the investigator should seek to adopt established instruments that have been successfully used in previous studies. Whenever possible, structured closed-ended questions and checklists rather than open-ended questions should be used. A standardized application of such instruments, including training of interviewees and development of an interviewer manual, is also important (Fink 1995). Modern technological achievements like computer-assisted interviews may help to further standardize the application of instruments, facilitate complex conditional jumps, and integrate plausibility checks and aids for interviewers for specific questions. All steps of the data collection process need to be documented and may be entered into a database immediately to allow a continuous monitoring and quality control of the data collection process.

Training of coders (see later) should also be done. Once the data has been collected, the next step is organization. Organization of data is a time-consuming but extremely important part of the exposure assessment process because of the large volume of information usually collected.

7.6 Development of exposure groups

An important component of the exposure assessment process is the development of exposure groups. One of the first steps prior to developing exposure groups is to code the jobs (and industries). To do so, in industry-based studies it is usually necessary to standardize the job titles for spelling, abbreviations and word orders to allow easy sorting and grouping. Once completed, a single 'standardized' job or department title can be used to describe all jobs (or departments) in that group. A compilation of the 'standardized' titles and the original titles is called a job dictionary.

After standardization, coding of jobs and industries is done to make direct use of this information in the epidemiologic analyses and to facilitate exposure assessment. Coding may enhance the ability to distinguish particular occupational subgroups by cross-classifying job titles and industries. In addition, coding is usually necessary to apply a job-exposure matrix (JEM) (see Chapter 8). Coding of jobs is usually done according to standard classification systems. Coding of residences is done using global positioning systems (GPS).

Assessing exposures to groups, rather than to individuals, is generally more efficient because individual assessments require multiple measurements on all or most of the study subjects (a situation rarely found) and extensive resources. Grouping also tends to be more efficient than individual assessments, because it results in less attenuation of the exposure–response relationship, unless the between-worker variability within the group is large (see Chapter 12). Exposure groups can be developed during the epidemiologic analysis or the exposure assessment phase.

The goal of developing exposure groups is to group subjects with similar exposure levels to the same agent(s). Large differences among the groups (contrast) result in less attenuation of the exposure–response relationship. Two approaches can be followed for grouping. In one, the smallest unique grouping is made. Thus, for a study of acrylonitrile workers, 3600 unique job/department/plant groups were developed across eight plants and estimates were developed for each group (Stewart *et al.* 1998). In the epidemiologic analysis, the subjects were divided into five exposure groups, which provided the contrast among the groups (Blair *et al.* 1998). Other investigators prefer to develop fewer groups with a larger number of members, but this procedure may increase the risk of heterogeneously exposed workers within the groups. To prevent this occurrence, between- and within-group variability can be evaluated by measurement data (see Chapter 6). Such an evaluation requires, however, the availability of repeat measurements, which are not always available.

In general, it is best to keep exposure groups as unique as possible (Fig. 7.1). It is recommended that various jobs be kept as separate groups rather than grouping

> It is 'preferable to start by accumulating information in as much detail as possible; the detailed information (can) always be summarized, whereas by starting with only a comparatively coarse stratification there (is) no opportunity of breaking down the results on a more detailed basis should this later prove to be necessary' (Fay and Rae 1959).

Fig. 7.1 A lesson to be kept in the forefront of exposure assessment.

multiple jobs, because of other, unanticipated analyses. The first epidemiologic analysis may provide leads that are followed up long after the original results are published. The original exposure groups may not be appropriate for the newer analyses, because individuals within the original exposure groups may not be homogeneous for the second exposure. A new grouping of jobs would therefore be required. For example, correlation coefficients between dust and allergen levels in a bakery ranged from 0.57 to 0.86 when comparing average, cumulative, and peak exposure levels (Nieuwenhuijsen *et al.* 1995). The job title may be the unit of specificity for the exposure groups, but in some studies even more refinement may be necessary. In a study of bakeries, the job was the primary variable explaining variability of inhalable dust, whereas in the same population, the job and particular worksite (bakery) was important for wheat allergens, and the worksite alone was important for α-amylase allergens (Houba *et al.* 1997). The median between- and within-worker variability was found to be significantly different for continuous vs. intermittent processes, mobile vs. stationary workers, and general vs. local sources (Kromhout *et al.* 1993), which suggests some determinants that should be considered. Other determinants may be department, process, job assignment (e.g. board operator), area or location, tasks, equipment, craft, product, process container, batch or lot, project, production unit, controls, and sources of the contaminant. Careful consideration of these determinants of exposure (and possibly others) is likely to substantially reduce the variability of exposures within an exposure group (see Chapter 6). A description of these determinants for a job is called a job exposure profile.

In addition to the exposure determinants, the availability of measurement and descriptive data affects the grouping. For example, in a study of pneumoconiosis among coal miners, measurement data existed for some, but not all, occupation/mine/year exposure groups (Seixas *et al.* 1991). Where measurement data were available, the occupation/mine/year combinations comprised the exposure groups. Broader exposure groups (occupation/year, mine/year (within occupational group) and year (within occupational group)) were developed where data was not available.

Exposure groups are usually developed with a single or a small number of exposures in mind. This approach presupposes single agent causality. In circumstances where it is difficult to identify single agents or where multiple agents may be acting together, using a cluster analysis may be warranted. For example, workers in the semi-conductor industry study were found to have exposures to 14 chemical and physical agents, with a high correlation among the exposures (Hines *et al.* 1995). The researchers identified the exposure profile of each study subject and developed three exposure groups based on similar exposures to the 14 agents. Two other descriptions of the process of developing exposure groups have been described (Loomis *et al.* 1994; Quinn *et al.* 2001).

Evaluation of environmental exposures are based on similar concepts in that homogeneous exposure groups need to be developed. However it has been rarely applied. Use of cluster analysis should also be considered.

7.7 Quantification of exposure levels

The goal of the estimation process is to accurately develop exposure estimates for the exposure groups. Exposures can be estimated qualitatively (yes/no), semi-quantitatively (low, medium, or high; or on a scale, say, of 1–4), or quantitatively (in measurement units such as milligram per cubic metre) and can be developed for a JEM or for individuals. Qualitative assessments will not be discussed here. Typically, industry-based studies and retrospective case–control studies were based on JEMs. Recently, with the development of JSQs, assessments are being made on individuals. A decision on which approach to use is dependent on the information available. The level of detail in the work histories plays a crucial role as to how specific the estimation can be. If, for example, in an industry-based study, exposures vary considerably within department and vary little across departments, but only information on department is known of the subjects, it is inefficient to spend much time developing quantitative exposure levels. Similarly, if few measurement data are available for the period under study or some measurements are available but the effect of changes in the workplace cannot be estimated, semi-quantitative estimates may be the best the investigator can do.

In most studies investigating chronic disease, exposure levels have changed over time due to changes in technology (pollution controls), work practices, government regulations, or other reasons. In such cases, for practical reasons estimates are developed for years or even time periods (multiple years) rather than for smaller units of time, although in studies of acute or short-term adverse health effects, such as reproductive effects, smaller time units, such as months, may be appropriate. Development of time periods may be done by evaluation of the measurement data: statistically or by observation. Researchers of the dusty trades industry plotted measurement results against time (Rice *et al.* 1984). Any plot in which all measurements were higher or lower than previous or subsequent measurements was considered to represent a distinct time period if supported by descriptive data.

The measurement data may be so few, however, that other sources of information, such as engineering and production records and published emission data or interviews, are needed to identify time periods. If developing semi-quantitative estimates each exposure group is assigned a score that reflects a differing exposure level. This approach is easier and faster than the quantitative approach and is often assumed to be more credible than quantitative estimates. Caution must be taken, however, to ensure that the scores assigned to the exposure groups accurately reflect the differences in exposure to minimize misclassification; otherwise lack of an association could result from misclassification due to inappropriate scores. There are two primary disadvantages to semi-quantitative estimates. Often, the scores are not defined in terms of measurement units, so that the study's usefulness for risk assessment is limited. The second disadvantage is that because the method is less specific than the quantitative approach, it tends to encourage a superficial evaluation of exposures and little documentation of the assessment process. This disadvantage is easily overcome, of course, but it requires discipline by the assessor.

Scores have been based on a variety of exposure metrics or a combination of different metrics. Sometimes frequency of exposure has been used as the criterion (exposed 5 days a week = high, 1–3 days a week = medium, and < 1 day a week = low). Intensity, type of contact (direct, indirect), pattern of exposure (continuous or intermittent), and other types of descriptors have also been used. Well-documented studies identify the determinants evaluated and the weights assigned to these determinants to calculate scores. The weights can be estimated from measurements on the study subjects or from the literature. In a study of pesticide applicators, for example, weights from 0 to 9, developed from the literature, were assigned to tasks, application method, use of controls, work and hygiene practices, protective equipment, and the occurrence of spills and were evaluated (see Chapter 16).

Quantitative estimation can be difficult and time consuming, and the credibility of the estimates is often questioned. Moreover, usually some measurement data is required to perform quantitative assessments, although they do not have to be on the jobs or at the worksites under study. This type of assessment provides the best information for risk assessment and is more likely to allow the exploration of different exposure metrics. More care is taken when developing the estimates, because error in the estimation process is more visible.

Quantitative estimation requires several steps. The data may have to be cleaned, for example, by examining frequencies of the various data fields, standardized (e.g. spelling, abbreviations, word order), and measurements below the limit of detection treated. Summary statistics (arithmetic means and standard deviations, geometric means and standard deviations) should be developed by location and year; the duration and type of measurement (personal, area); the source of the data; the sampling and analytic method; 'representativeness' of the measurements; and so on to provide insight into the variability of the data and an overview of the exposure scenarios. For example, in a study of silica workers, different sampling and analytic methods were used. A conversion factor was applied to the results of one method to maximize comparability to the second method (Rice *et al.* 1984). In contrast, in a study of ethylene oxide workers, the authors excluded the measurements of a method with fewer measurements because the variability of the measurements differed by method (Hornung *et al.* 1994).

Examination of the measurements should be done without regard to the exposure groups because it can provide insight into how the exposure groups should be developed. Once the exposure groups and time periods have been identified, the exposure levels can be estimated for each unique exposure group/time period. Prior to assigning the exposure, first, it may be useful to develop a table of measurement means by exposure group and time to get the overall picture of the exposure scenarios. The means should then be evaluated within the context of the descriptive data and determined whether they are reasonable. If so, the measurement means or medians can be used directly as the exposure estimate. Once it is determined which means to use, the remaining empty cells (i.e. exposure group/time periods) can be completed. This is perhaps the most difficult part of the exposure assessment process.

Statistical modelling can be used to estimate exposure levels for exposure group/time periods when measurements are not available (see Chapter 6). In such approaches, determinants of exposures in the workplace, as well as those associated with measurement data, for example, personal vs. area measurements, the duration, the sampling method, and the like are identified, either through observation or questionnaires. In a study of asphalt workers the tasks of mastic laying and of oil gravel paving, and years before 1997 were significant variables for predicting bitumen fume, bitumen vapour, and benzo(a)pyrene (Burstyn *et al.* 2000). Other determinants (e.g. application temperature in non-mastic paving, type of sample (i.e. area sample), and various sampling methods) were significant for one or two of these substances.

Non-statistical deterministic modelling also can be used to estimate exposure levels. Determinants that are thought to influence exposure levels are identified from the literature, from observation, or analogy from similar situations. Each value of the determinant is assigned a weight, which is used to modify the measurement mean. In a study of flight attendants, investigators modified cosmic radiation measurement data from an existent database using taxi time, ascent and descent time, the cruise altitude, and time at the cruise altitude (Grajewski *et al.* 2002).

Unmeasured conditions can be recreated or estimated from other worksites. In a study of embalmers, historical conditions were simulated by varying the amount of formaldehyde concentration in the embalming fluid, the type of procedure (autopsied and intact), and differing levels of exhaust ventilation (Hornung *et al.* 1996). Investigators of a study of workers dealing with man-made mineral fibre used a deterministic model by identifying a set of 'job exposure elements' common to all jobs (Quinn *et al.* 2001). The elements included: distance from the source, duration of the exposure, and the intensity of the physical effort required by the job. These were used to estimate the exposures for those jobs that lacked air measurements by comparing the elements of the unmeasured job to the elements of the measured jobs.

It may be possible to use measurement data for an agent that is likely to reflect similar relative exposure levels to a second agent. In this instance two agents must be used throughout the process in the same relative quantities and be affected by the same environmental conditions to the same degree, resulting in the same ratio (between the two agents) across jobs and over time. It is important to confirm that these two assumptions are met.

In environmental studies qualitative and semi-quantitative assessments suffer the same limitations and have the same strengths as they have in industry-based studies but are generally less sophisticated in the assessment process than occupational studies. Semi-quantitative assessments have been done on distance from waste sites for solid waste contaminants (Knox 2000). Studies of air pollution have used measurement data of air contaminants from fixed sources. In some studies, recent measurements are linked to acute diseases, such as hospital admissions for respiratory disease (Atkinson *et al.* 2001). The use of current measurement data is more suitable if the disease is acute than if it is more chronic, such as birth defects, cancer, or mortality. Some investigators, however, have utilized historic measurements for air (Vena 1982; Jöckel *et al.* 1992; Pope *et al.* 2002) and water contaminants (Bove *et al.* 1995) that have approximated the time period of interest. In a study of breast cancer and triazine exposure, the level of contamination from groundwater and tap water measurements, the number of acres on which triazine application was likely, and the amount of pesticide used by applicators were scored for each county and the latter were assigned low, medium, or high exposure categories (Kettles *et al.* 1997). In an environmental study of arsenic and skin cancer around a power plant, emission levels, weather data, and topography were used to model the exposure (see Chapter 3).

As in occupational studies models can be developed based on correlation between the two substances over a known period of time to predict the exposure levels in the unknown period (Goldberg *et al.* 2001). Few environmental studies have been conducted that have incorporated environmental measurements on the study subjects (or over a small geographic area) and generally these have been indoor studies (Mahaffey *et al.* 1993; Brauer *et al.* 2001; Smedje and Norback 2001).

7.8 Accuracy and reliability

Wherever possible estimates should be evaluated for their accuracy and reliability. Evaluating the accuracy of retrospective exposure assessment is usually difficult, if not impossible, because it is rarely possible to determine what the true exposures were. Biologic measurements are limited as a gold standard not only because they usually do not exist, but also because most agents of interest have a relatively short half-life in the human body. Moreover, there may be differences in how individuals metabolize substances, and there may be non-occupational sources of exposures, or exposure to agents may have occurred in other jobs and the agents are still stored in the body. Airborne (or dermal) measurement data can result in biased estimates due to non-representative sampling. Furthermore, when measurement data are scarce it may be more efficient to use them to estimate the exposures than to use them in a validation study.

In the embalmers study mentioned previously (Hornung *et al.* 1996), measurements were collected from five funeral homes that had not been evaluated in the original study and compared to the predicted values obtained from applying the model. In the acrylonitrile study, an evaluation of the estimation methods was done prior to developing the estimates (Stewart *et al.* 1998). Job/time period combinations were identified for which measurements existed. Estimates were developed for these combinations and compared to the measurement data. The accuracy of the estimates can be evaluated by comparing the exposure estimates to measurements in other facilities, either as reported in the literature or by obtaining measurements from similar facilities. The operations, however, should be similar to those of the facility under investigation, and differences do not necessarily reflect incorrect estimates. A study of car and bus mechanics compared measurements in an inspectorate database to the exposure estimates (Plato *et al.* 1995).

Indirect validation can be done by evaluating the risk to a disease known to be caused by a particular agent using estimates developed for another investigation. For example, confidence in silica estimates developed for a lung cancer study increased when an exposure–response relationship was found with silicosis in the same population (Dosemeci *et al.* 1994). It must be noted, however, that this method does not validate the estimates if the true exposure–response relationship in the population is not known.

Validation studies require that different indicators of exposure are obtained for the same subjects. Often a detailed and more accurate exposure assessment is only possible for a subset of subjects within a study. Such information may, however, be exploited for the whole study, as in the example of a case–control study on asbestos and lung cancer, in which the intensity of exposure for a subsample of the study subjects was assessed by a panel of experts. The information on duration of exposure in the original study was combined with the expert assessment of duration and intensity using a new method called two-phase paradigm (Pohlabeln *et al.* 2002; Schill and Drescher 1997). Applying this method the efficiency of the study was increased because it gave more precise risk estimates for the expert assessment by compensating for the smaller numbers in the subsample.

Reliability, defined as the reproducibility of exposure estimates, can also be examined and together with validity of specific methods is discussed in more detail in Chapter 8.

7.9 Recommendations

Use of quantitative estimates has often been the most challenged, because of the mistaken perception that it contains more misclassification than does a semi-quantitative approach. It is not usually recognized, however, that developing a small number of exposure groups with a semi-quantitative approach (e.g. low, medium, and high, or a score of 1–4) is likely to result in much greater error than quantitative estimates. This is because the semi-quantitative approach assumes that all subjects within an exposure category have the exact same exposure level and that the relationship among the exposure levels for the subjects within each exposure category is the value assigned to the categories. Thus, all subjects assigned a score of 3 are assumed to have an exposure that is 3 times the exposure level of those subjects assigned a score of 1 and 1.5 times the exposure level of those assigned a score of 2. Usually the variability of exposures at a worksite is much greater than these differences assume. In addition, even if the relationships are correctly estimated, this approach can result in two individuals with nearly the same exposure level falling in two different categories because they are on the high end of the lower category and the low end of the higher category. Also, two individuals assigned to the same category may be on the extreme ends of the category. Therefore, semi-quantitative scores may also be interpreted as representing a rank order and be analysed accordingly, for example, using dummy variables for each level.

Quantitative assessment appears to be more prone to error than the other methods, but it should be recognized that it is unlikely that the subjects were truly exposed to the estimate assigned. Nevertheless, it is likely that the differences between the subjects' estimated exposure levels and the truth are less than for semi-quantitative estimates. Thus, we recommend that quantitative assessment be made whenever possible.

In most studies the information available varies across jobs or time periods, so that it may not be possible to use the same estimation methods for all estimates. In such a case, several methods may be used. Even when a single estimation method is used, confidence in the estimates can vary by the number of measurements, the type (area or personal), duration, or variability of the measurements, the amount of information known about the job, and other variables. Estimates of lower confidence can be a source of misclassification and therefore it is useful to assign a confidence score to each estimate. A sensitivity analysis can determine if estimates of low confidence affect the disease risk estimates.

Typically, documentation of the estimation procedure is crucial to allow others to interpret better the epidemiologic results and to increase the credibility of the study. Each of the assessment components should be discussed in the documentation in enough detail to provide the reader with an understanding of what was done and why. Examples of good documentation have been published and should include each of the steps described in this chapter (Stewart *et al.* 1998; Glass *et al.* 2000; Quinn *et al.* 2001).

References

Ahrens, W. (1999). *Retrospective assessment of occupational exposure in case–control studies.* Landsberg. ecomed Verlagsgesellschaft. 1–124. Fortschritte in der Epidemiologie.

Ahrens, W., Jöckel, K.-H., Pohlabeln, H., Bolm-Audorff, U., *et al.* (1996). Assessment of exposure to asbestos in a case–control study of lung cancer: comparison of supplementary questionnaires and an exposure check-list. *Occupational Hygiene*, **3**, 125–36.

Atkinson, R. W., Anderson, H. R., Sunyer, J., Ayres, J., Baccini, M., *et al.* (2001). Acute effects of particulate air pollution on respiratory admissions. *American Journal Respir Crit Care Med*, **164**, 1860–66.

Blair, A., Stewart, P. A., Zaebst, D. D., Pottern, L., Zey, J. N., Bloom, T. F., Miller, B., Ward, E., and Lubin, J. (1998). Mortality of industrial workers exposed to acrylonitrile. *Scandinavian Journal of Work Environment and Health*, **24**, 25–41.

Bond, G. G., Bodner, K. M., Sobel, W., Shellenberger, R. J., *et al.* (1988). Validation of work histories obtained form interviews. *American Journal of Epidemiology*, **128**, 343–51.

Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., and Savrin, J. E. (1995). Public drinking water contamination and birth outcomes. *American Journal of Epidemiology*, **141**(9), 850–62.

Brauer, M., Ebelt, S. F., Fisher, T. V., Brumm, J., Petkau, A. J., and Vedal, S. (2001). Exposure of chronic obstructive pulmonary disease patients to particles: respiratory and cardiovascular health effects. *Journal of Exposure Analysis and Environmental Epidemiology*, **11**, 490–500.

Burstyn, I., Kromhout, H., Kauppinen, T., Heikkila, P., and Boffetta, P. (2000). Statistical modeling of the determinants of historical exposure to bitumen and polycyclic aromatic hydrocarbons among paving workers. *Annals of Occupational Hygiene*, **44**, 43–56.

Dosemeci, M., McLaughlin, J. K., Chen, J.-Q., Hearl, F., McCawley, M., Wu, Z., Chen, R.-G., Peng, K.-L., Chen, A.-L., Rexing, S. H., and Blot, W. J. (1994). Indirect validation of a retrospective method of exposure assessment used in a nested case–control study of lung cancer and silica exposure. *Occupational and Environmental Medicine*, **51**, 136–8.

Fay, J. W. J. and Rae, S. (1959). The pneumoconiosis field research of the national coal board. *Annals of Occupational Hygiene*, **1**, 149–61.

Fink, A. (ed.). (1995). *The complete survey kit.* Thousand Oaks, London, Sage Publications, New Delhi.

Flesch-Janys, D., Steindorf, K., Gurn, P., and Becher, H. (1998). Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environmental Health Perspectives*, **106**(Suppl. 2), 655–62.

Gerin, M., Siemiatycki, J., Kemper, H., Eng, B., *et al.* (1985). Obtaining occupational exposure histories in epidemiologic case–control studies. *Journal of Occupational Medicine*, **27**, 420–6.

Glass, D. C., Adams, G. G., Manuell, R. W., and Bisby, J. A. (2000). Retrospective exposure assessment for benzene in the Australian petroleum industry. *Annals of Occupational Hygiene*, **44**, 301–20.

Goldberg, M. S., Burnett, R. T., Brook, J., Bailar, J. C. III, Valois, M.-F. and Vincent, R. (2001). Associations between daily cause-specific mortality and concentrations of ground-level ozone in Montreal, Quebec. *American Journal of Epidemiology*, **154**(9), 817–26.

Grajewski, B., Waters, M. A., Whelan, E. A., and Bloom, T. F. (2002). Radiation dose estimation for epidemiologic studies of flight attendants. *American Journal of Industrial Medicine*, **41**, 27–37.

Hines, C. J., Selvin, S., Samuels, S. J., Hammond, S. K., Woskie, S. R., Hallock, M. F., and Schenker, M. B. (1995). Hierarchical cluster analysis for exposure assessment of workers in the semiconductor health study. *American Journal of Industrial Medicine*, **28**, 713–22.

Hornung, R. W., Greife, A. L., Stayner, L. T., Steenland, N. K., Herrick, R. F., Elliott, L. J., Ringenburg, V. L., and Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. *American Journal of Industrial Medicine*, **25**, 825–36.

Hornung, R. W., Herrick, R. F., Stewart, P. A., Utterback, D. F., Feigley, C. E., Wall, D. K., Douthit, D. E., and Hayes, R. B. (1996). An experimental design approach to retrospective exposure assessment. *American Industrial Hygiene Association Journal*, **57**, 251–6.

Houba, R., Heederik, D., and Kromhout, H. (1997). Grouping strategies for exposure to inhalable dust, wheat allergens and α-amylase allergens in bakeries. *Annals of Occupational Hygiene*, **41**, 287–96.

IEA European Questionaire Group (1998). Epidemiology deserves better questionaires. http://dundee.ac.uk/iea/EuroQuests.htm

Jöckel, K.-H., Ahrens, W., Wichmann, H.-E., Becher, H., *et al.* (1992). Occupational and environmental hazards associated with lung cancer. *International Journal of Epidemiology*, **21**, 202–13.

Jöckel, K.-H., Ahrens, W., Jahn, I., Pohlabeln, H., *et al.* (1998). Occupational risk factors for lung cancer: a case–control study in West Germany. *International Journal of Epidemiology*, **27**, 549–60.

Joffe, M. (1992). Validity of exposure data derived from a structured questionnaire. *American Journal of Epidemiology*, **135**, 564–70.

Kettles, M. A., Browning, S. R., Prince, T. S., and Horstman, S. W. (1997). Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. *Environmental Health Perspectives*, **105**, 1222–7.

Knox, E. G. (2000). Childhood cancers, birthplaces, incinerators and landfill sites. *International Journal of Epidemiology*, **29**, 391–397.

Kromhout, H., Symanski, E., and Rappaport, S. M. (1993). A comprehensive evaluation of within- and between-worker components of occupational exposure to chemical agents. *Annals of Occupational Hygiene*, **37**, 253–70.

Loomis, D. P., Peipins, L. A., Browning, S. R., Howard, R. L., Kromhout, H., and Savitz, D. A. (1994). Organization and classification of work history data in industry-wide studies: An application to the electric power industry. *American Journal of Industrial Medicine*, **26**, 413–25.

Mahaffey, J. A., Parkhurst, M. A., James, A. C., Cross, F. T., Alavanja, M. C. R., *et al.* (1993). Estimating past exposure to indoor radon from household glass. *Health Physics*, **64**, 381–91.

Merzenich, H., Hartwig, A., Ahrens, W., Beyersmann, D., *et al.* (2001). Biomonitoring on carcinogenic metals and oxidative DNA damage in a cross-sectional study. *Cancer Epidemiology, Biomarkers and Prevention*, **10**, 515–22.

Nieuwenhuijsen, M. J., Lowson, D., Venables, K. M., and Newman Taylor, A. J. (1995). Correlation between different measures of exposure in a cohort of bakery workers and flour millers. *Annals of Occupational Hygiene*, **39**, 291–8.

Plato, N., Tornling, G., Hogstedt, C., and Krantz, S. (1995). An index of past asbestos exposure as applied to car and bus mechanics. *Annals of Occupational Hygiene*, **39**, 441–54.

Pohlabeln, H., Jöckel, K.-H., Brüske-Hohlfeld, I., Möhner, M., *et al.* (2000). Lung cancer and exposure to man-made vitreous fibers: results from a pooled case–control study in Germany. *American Journal of Industrial Medicine*, **37**, 469–77.

Pohlabeln, H., Wild, P., Schill, W., Ahrens, W., Jahn, I., *et al.* (2002). Asbestos fibreyears and lung cancer: a two phase case–control study with expert exposure assessment. *Occupational and Environmental Medicine*, **59**, 410–14.

Pope, C. A. III, Burnett, R. T., Thun, M. J., Calle, E. E., Krewski, D., Ito, K., Thurston, G. D. (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air polution. *Journal of the American Medical Association*, **287**(9), 1132–41.

Quinn, M. M., Smith, T. J., Youk, A. O., Marsh, G. M., Stone, R. A., Buchanich, J. M., and Gula, M. J. (2001). Historical cohort study of US man-made vitreous fiber production workers: VIII. Exposure-specific job analysis. *Journal of Occupational and Environmental Medicine*, **43**, 824–34.

Rice, C., Harris, R. L. Jr., Lumsden, J. C., and Symons, M. J. (1984). Reconstruction of silica exposure in the North Carolina dusty trades. *American Industrial Hygiene Association Journal*, **45**, 689–96.

Schill, W. and Drescher, K. (1997). Logistic analysis of studies with two-stage sampling: a comparison of four approaches. *Statistical Medicine*, **16**, 117–32.

Seixas, N. S., Moulton, L. H., Robins, T. G., Rice, C. H., Attfield, M. D., and Zellers, E. T. (1991). Estimation of cumulative exposures for the National study of Coal Workers' Pneumoconiosis. *Applied Occupational and Environmental Hygiene*, **6**, 1032–41.

Siemiatycki, J., Day, N. E., Fabry, J., and Cooper, J. A. (1981). Discovering carcinogens in the occupational environment: a novel epidemiologic approach. *Journal of the National Cancer Institute*, **66**, 217–25.

Smedje, G. and Norback, D. (2001). Incidence of asthma diagnosis and self-reported allergy in relation to the school environment—a four-year follow-up study in school children. *International Journal of Tuberculosis and Lung Disease*, **5**, 1059–66.

Stewart, P. A., Zaebst, D., Zey, J. N., Herrick, R., Dosemeci, M., Hornung, R., Bloom, T., Pottern, L., Miller, B. A., and Blair, A. (1998). Exposure assessment for a study of workers exposed to acrylonitrile. *Scandinavian Journal of Work Environment and Health*, **24**, 42–53.

Teschke, K., Smith, J. C., and Olshan, A. F. (2000). Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *American Journal of Industrial Medicine*, **38**, 385–8.

Tielemans, E., Heederik, D., Burdorf, A., Vermeulen, R., *et al.* (1999). Assessment of occupational exposures in a general population: comparison of different methods. *Occupational and Environmental Medicine*, **56**, 145–51.

Vena, J. E. (1982). Air pollution as a risk factor in lung cancer. *American Journal of Epidemiology*, **116**(1), 42–56.