

Assessment of exposure in occupational epidemiology

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KAUPPINEN TP. Assessment of exposure in occupational epidemiology. *Scand J Work Environ Health* 1993;20 special issue:19–29. Recent progress in assessing exposure in occupational epidemiology studies is reviewed. Traditional methods based on surrogate and qualitative measures of exposure are no longer sufficient for searching for new risks, quantifying risks, and learning about their mechanisms. More sophisticated methods and exposure indices are needed that are aimed at estimating the exposure-response relation. Prospective studies, case-referent studies within cohorts, and community-based case-referent studies applying interviews of the subjects or confirming exposures from workplaces are designs favoring exposure assessment. Exposure modeling is expected to improve the quality of estimates in industry-based studies. Job-exposure matrices have proved useful, especially in analyses of large studies, provided that they are applied so that misclassification does not significantly bias the results. Misclassification of exposure should be regularly assessed and controlled in epidemiologic studies. Good documentation of the information used and studies on methodological validity and reliability are needed to develop exposure assessment.

KEY TERMS — dose-response, exposure index, exposure-response, job-exposure matrix, misclassification, model, retrospective, review.

Valid and reliable exposure assessment is becoming increasingly important in occupational epidemiology. There are several reasons. First, new risks are more difficult to detect because of lower exposure levels and confounding due to multiple exposures. Second, the emphasis in epidemiology is shifting gradually from qualitative risk identification to quantitative risk assessment, which focuses on estimating exposure-response relationships. Third, the growing research activities on the mechanisms of action (“molecular epidemiology”) require accurate exposure assessment (1, 2).

As a rebound to the growing challenges, the amount of data on exposures keeps increasing, creating a potential for improving the quality of exposure assessment. Exposure assessment methods have developed rapidly over the past few years, and several reviews on the progress are available on this topic (1, 3–6).

In this review I discuss the exposure-related aspects of the life cycle of an epidemiologic study, starting with selecting the topic and planning the study, proceeding to collecting the data, assessing the exposure, statistically analyzing and interpreting the results, and ending with reporting and documenting. The methods of exposure assessment depend significantly on the study design and are therefore dis-

cussed separately for industry-based and community-based studies. Some methods, such as job-exposure matrices, have been applied in studies of various designs and sizes, from small to nationwide register-linkage studies. The review of the methods is followed by a discussion of the misclassification of exposure, which is the main bias in exposure assessment and one of the key issues in the future development of occupational epidemiology.

Exposure aspects of planning a study

Knowledge of the exposures to be studied is useful already in the very early phase of a study, when the objective is being chosen. Selection criteria have been proposed for studies on occupational cancer, and many of them concern exposure (7). The following factors are likely to contribute to the relevance of the study: large number of exposed workers, high level of exposure, good quality of available data on exposure, large expected number of cases attributable to exposure, appropriate time elapsed since first exposure, rising trend in the extent of exposure, and good possibilities to control confounding exposures.

Exposure assessment has previously often been considered a separate issue that does not contribute directly to the epidemiologic framing of the study hypothesis. In many cases a limited dialogue between the professionals was sufficient for the detection of new occupational hazards. However, the recent needs to quantify exposures require that exposure assessment become an integral part of an epidemiologic study already in the planning phase, where the bases for the success or failure of the study are created.

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The ultimate goal of any ambitious epidemiologic study is the assessment of the causal relation between the occurrence of a disease and an exposure (ie, a universal relation, which is independent of calendar time and geographic place, but which may be conditional on the characteristics of the population under study). In general terms, the object of research in epidemiology is the occurrence relation between the outcome (eg, disease) and the determinant (eg, exposure to an agent) (8). In practice, this goal often reduces to modeling the exposure-response relation. The effect of exposure can be modified (enhanced or reduced) by other factors. In addition, the empirical relation can be confounded (distorted) by an incomparability originating from the design or methods of the study. A study can address many relations simultaneously, but they are usually studied one by one with the aim of reaching an unconfounded exposure-response relation. The principal task of exposure assessment is to serve this basic goal. Exposure assessment is therefore best integrated into the study, if it can be derived from the occurrence relation under study. Therefore the occurrence relation must be well defined conceptually. Naturally, the assessment procedures adopted should also be feasible. Figure 1 outlines the steps of planning exposure assessment and the feasibility evaluation from this theoretical point of view.

Exposure assessment should address the relevant and well-defined exposures. In collecting the necessary information for assessing exposures, replies are expected and sought to such questions as "Which agents should be assessed?" "Should agents be assessed individually or is aggregation acceptable?"

"Which physical phases (eg, gas, liquid, solid) of an agent and which routes of exposure (eg, inhalation, dermal absorption, ingestion) should be considered?" "Is the mean exposure during the workday or work year appropriate or should high peak exposures be emphasized?" "What is the minimum level of exposure to be considered?" "Is there a clear contrast in the level of exposure within the population projected for the study?" "How far back in time should exposures be assessed?" Finding the answers to these questions requires insight into toxicology, industrial hygiene, epidemiology, and statistics, and therefore a multidisciplinary team should generally carry out the exercise.

The general guidelines for the extent of exposure assessment can be inferred from the occurrence relation which relates the risk of outcome to the determinants, the modifiers, and the confounders. A complete assessment should cover all three of these sets of factors to enable the estimation of an unconfounded and unmodified (or modified) exposure-response relation. In practice, the team has to make the selection out of all occurring agents on the basis of such factors as the suspected effect of the agents, prevalence of exposure, and time since first exposure (9).

The next step is to select the relevant indices of exposure. The alternatives range from simple surrogates of exposure to sophisticated measures of internal dose (10). For each agent under study, it is possible to address the agent as such or address its more specific characteristics in relation to the route of exposure, the physical phase of exposure, or the continuous-peak nature of exposure. Combining differ-

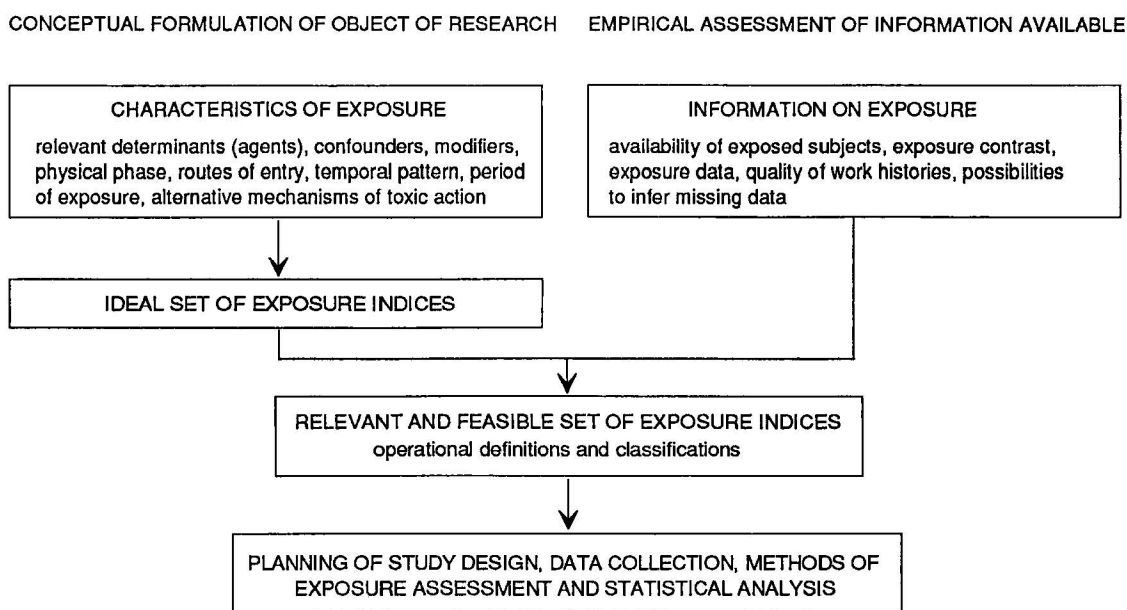


Figure 1. Planning for exposure assessment in occupational epidemiology studies.

ent agents should be avoided because it can lead to misclassification and "dilution" of the true effect. If one deals with genuine heterogeneous mixtures (eg, diesel exhaust, tobacco smoke), isolation is not possible; instead, one needs to use a marker as a surrogate measure (11). The relevance of peak exposures in studies of chronic diseases has been reported to be restricted mainly to situations in which the rates of elimination and repair do not follow first-order kinetics (12). Thermodynamic potency has been proposed as a guideline for the assessment of concentration peaks of gases and vapors (13).

When the entity of assessment has been defined, there are still many qualitative (eg, exposed, unexposed, unknown), semiquantitative (eg, low, moderate, high), and quantitative ways to classify it. The quantity-related variables fall into the following three broad classes: indices of level, indices of time, and combined indices of level and time. There is some empirical justification for preferring the use of combined indices, which may reflect the true effective dose more accurately than the level- and time-based indices. However, use of the simplest combined index, cumulative exposure (time integral of the level of exposure; often simplified to the product of the mean level and duration of exposure), can be criticized for its omission of the latency period required by many chronic diseases. Several improvements have been suggested to overcome this fallacy, for example, weighting the exposure by the time between the disease and exposure (14), comparing cumulative exposure between different "time windows" (15), and using mathematical models to identify the optimal expression of cumulative exposure (16). General selection criteria derived from the principles of causal inference have been suggested (17), but still the most valid index usually remains unknown and is likely to vary from agent to agent. Many researchers have ended up using several indices to learn about different aspects and patterns of risk.

The selection between exposure indices is likely to gain in the future from research on pharmacokinetic models. These models predict theoretically the dose of the target organ on the basis of external exposure, absorption, distribution, excretion, and metabolism. They are therefore potentially useful in the development of epidemiologic exposure indices, quantitative risk assessment, and the epidemiologic evaluation of mechanistic hypotheses derived from laboratory studies (18). A general conceptual model has been proposed (19), and specific models are available for many agents, such as asbestos, solvents, beryllium, ionizing radiation, ozone, dusts, silica, and coal. (See reference 16.) The development in the formulation of study hypotheses is likely to shift the emphasis in occupational epidemiology from simple hypothesis testing (acceptance-refusal) to parameter estimation of the occurrence relation, where the central issue is the fit of empirical data with alternative mechanistic hypotheses.

Another area of theoretical development is the simulation of the exposure-response relation. Simple calculations show that selecting an invalid index of exposure can even lead to an observation of a decreasing exposure-response relation even though the true one is increasing (17). Correlations vary widely between the commonly used exposure indices (20), and a deeper understanding of the biases influencing the observed exposure-response relation are still largely unexplored.

When the object of the study has been conceptually well defined, one has to deal with the relevance and feasibility problems, for example, which population and follow-up period would be the most informative from the point of view of the objectives of the study, is there a clear exposure contrast within the study population, are the necessary records available, accessible, reasonably complete and accurate enough, is it possible to collect the information needed to calculate the preferred exposure indices, how should the missing information be dealt with, and how should exposures be defined and classified in practice. The exposure experts may contribute to these issues through their knowledge on such topics as the occurrence of exposure, the level of exposure, the variability of exposure, the initial year of exposure, and the occurrence of confounding exposures.

Some study designs tend to provide more information on the exposure-response relation than others. However, there is much overlap between different designs. Any kind of study may provide excellent information, if unlimited resources are available. On the other hand, a good design may fail if the study is too small or is poorly conducted. Priority designs from the point of view of exposure assessment are generally studies which address future (prospective) or current (cross-sectional) exposures, because they often allow exposures to be measured directly. Planning schemes, such as the one presented in figure 1, also work best in these designs. Exposure assessment of past (retrospective) exposures is more problematic because exposure estimates are based more on subjective judgments. Because most chronic diseases are studied retrospectively, the emphasis in the following sections is on methods used in the assessment of historical exposures.

Methods of exposure assessment in industry-based studies

The principal designs of industry-based studies are the cohort study and the case-referent study nested within the cohort. The advantage of these designs is that the study population comes from a small number of workplaces and the number of occupations and agents to be considered in exposure assessment is therefore limited. Workplace visits are usually feasible, and even additional measurements can be made. The nested case-referent study (figure 2A) has

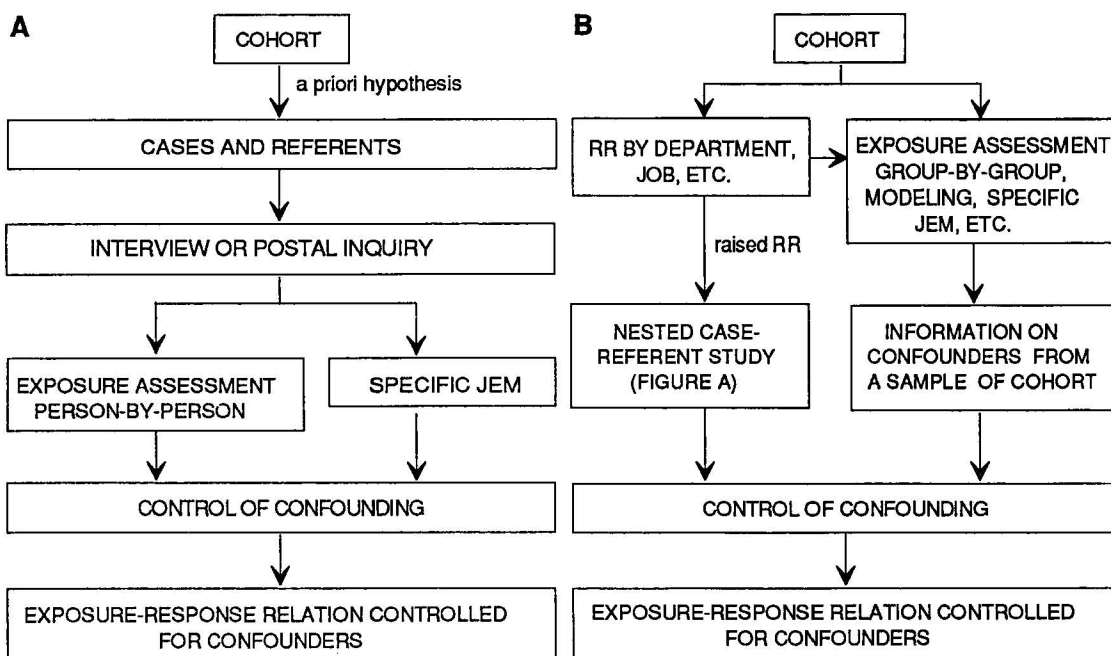


Figure 2. Examples of industry-based study designs favoring the estimation of unconfounded exposure-response relations: A: case-referent study nested within a cohort; B: cohort study optionally followed by a case-referent study. (JEM = job-exposure matrix, RR = relative risk)

perhaps the largest potential in revealing a valid exposure-response relation as the ultimate goal of the study. The number of subjects to be assessed is usually much smaller than in cohort studies, and more emphasis can therefore be put on obtaining reliable information on total work history, confounders, and workplace exposures. The exposures can be assessed either person by person or by a job-exposure matrix specific for time period and plant. (See, eg, reference 21.) Although the quality of exposure estimates may be high in this design, problems of power arise because of the small number of exposed cases if the disease of interest is rare.

The traditional cohort study utilizes work histories and various exposure-related records collected from plants (22). Job titles can be transformed to exposure estimates with the use of a job-by-job evaluation, exposure models, or a specific job-exposure matrix. (See, eg, reference 23 and figure 2B.) If the cohort is large and the exposures to be assessed are multiple, this procedure is laborious. Occupational confounders can be controlled by assessing them from workplace data, and the nonoccupational confounders from data obtained from a sample of the cohort. If the interest concentrates a priori on one or a few specific outcomes, it is possible to avoid collecting work histories for all members of the cohort and constructing job-exposure matrices for all jobs and periods by proceeding directly to a nested case-referent study.

Estimating exposure in cohort studies usually relies on incomplete individual work histories obtained from plant records. Information on jobs held outside the workplaces is usually not available. Use of a single job (eg, first, longest, last) as a surrogate for exposure distorts the observed risk estimates. For example, using cumulative exposure to formaldehyde in only one job title could lead to a serious attenuation of the observed exposure-response relation in a cohort study (24). The effect of incomplete work histories is the most pronounced in cohorts with high turnover and in cross-sectional study designs. The coverage of work histories has been reported to be the least accurate among deceased and old subjects, and such inaccuracy can lead to an artificial flattening or drop in the high domain of the exposure-response function (25). The completeness of the exposure history depends also on the agent: the coverage is more complete for plant-specific or relatively rare agents than for agents occurring widely also outside the plant. These inherent problems of a traditional cohort study can be overcome by collecting complete work histories from the subjects or their next-of-kin, a tedious process for large cohorts, or by using a nested design, in which complete work histories need to be collected only for the cases and their referents.

The methods used for exposure assessment in cohort studies depend strongly on the availability of exposure data. If comprehensive data are available,

retrospective exposures can be estimated with statistical (stochastic) modeling in which missing data are replaced by values from a model fitted with the data from historical industrial hygiene measurements. (See, eg, references 26 and 27.) Statistical models can include terms derived from factors that significantly influence the level of exposure, such as the type of product and ventilation (28). When the jobs to be assessed comprise several specific tasks with a varying level of exposure, the measurement data often concern tasks rather than jobs. In this case one has to know the share of worktime between different tasks in a job and calculate the 8-h time-weighted average (TWA) exposure for jobs from task-specific measurement data. This approach has been called the task-specific TWA model of job exposures, and it has been successfully applied, for example, to estimate gasoline exposure among transportation workers (29). Prior to adopting any model, the researchers should critically evaluate the exposure data for possible biases and representativeness. Validity aspects of exposure data have been reviewed earlier for industrial hygiene measurements of air contaminants (30) and biological monitoring (31, 32).

In most cases exposure data cover only a small fraction of the jobs and periods to be assessed. An industrial hygiene survey is sometimes feasible to acquire additional information on recent exposures in jobs of interest. However, the level of exposure has usually changed over the years. In such cases the only direct way of obtaining new information on historical exposures is measurements in simulated circumstances, or in plants which have not undergone changes. Simulation surveys have been carried out, for example, in a granite shed (33), in rock wool and slag wool plants (34, 35), and in embalming facilities (36).

If no additional measurement data can be obtained, there are several methods with which to estimate the missing exposures. Interpolation of missing values from job- and plant-specific means has been used to estimate dust exposure in granite sheds (37). The exposures in jobs or plants may also be so similar that incomplete measurements can be generalized to concern all unmeasured situations (38, 39). If an agent occurs simultaneously with a measured agent, a conversion factor can be used in exposure assessment (40). Methods based on the experience of an expert or plant personnel are also popular, but they usually employ ranks or other ordinal exposure scales, which provide a less accurate basis from which to calculate an exposure-response relation.

A new approach in the estimation of historical exposures is deterministic modeling, which, distinct from statistical modeling, does not include a random term (41, 42). Significant changes in exposure circumstances at workplaces often take place during short periods due to changes in process, work, premises, ventilation, personal protection, or other factors. These changes tend to lead to stepwise rises

or drops in the temporal exposure profiles of workers. If the significant factors determining the level of exposure can be identified and assessed, it is possible to construct a deterministic model to calculate the required exposure indices. The general source-receptor model of exposure can be used as a theoretical framework in the construction of models (29). The deterministic approach has been used to reconstruct historical exposures of man-made mineral fiber production workers (43), painters (44), resin manufacture workers (40), welders (45), and phenoxy herbicide and chlorophenol production workers (46). The advantage of the deterministic approach is that it can be used when only very few measurement data are available. This method is likely to be less accurate than measurement-based statistical modeling methods. However, it probably provides more consistent exposure estimates than its conventional alternative, expert judgment, when exposures are assessed in complex situations.

The validity, reliability, and documentation of exposure assessment are important factors contributing to the quality of a study. It is difficult to evaluate validity in retrospective studies because the true exposures are unknown. Qualitative exposure assignments (yes/no) can be validated to some extent by comparing the exposure estimates based on the work histories from the company records to the estimates derived from the total work histories collected from a sample of the cohort (47). Quantitative estimates have been cross-validated against biological monitoring data (eg, in reference 48), a subset of air monitoring data (eg, in reference 28) and air monitoring data in simulated situations (34). When exposure models are used, the effect of the range of values for each input variable on the estimated level of exposure can also be studied by statistical sensitivity analysis (49). A further problem is the tendency of the results of validation studies to be study-specific and difficult to generalize. In spite of these difficulties, new studies on this issue would be welcome to guide the development and use of exposure assessment methods.

The reliability (repeatability) of the results of exposure assessment may depend on the assessor, but also on the amount of data available and the assessment method used. Reliability problems may be less serious in industry-based studies than in community-based studies, in which the exposure information available is often scarce and the result of estimation is therefore more dependent on the knowledge and skill of the assessor(s).

The documentation of exposure assessment is becoming increasingly essential in modern epidemiology. Detailed documentation of used information and inference rules forces the assessor to work carefully, increases the credibility of the findings, enables reanalyses of the data, and facilitates the reuse of information in other studies. A computerized data-base system, called the job-exposure profile system, has

been recently developed for documenting plant, job, and exposure information for industry-based studies (50). Careful assessment and documentation also require more time, a fact that should be taken into account in the planning of the schedule and in the financing of the study.

Methods of exposure assessment in community-based studies

Community-based studies refer to case-referent studies in which the source population resides in a specified geographic area. Examples of two case-referent designs that have been informative from the point of view of exposure are presented in figures 3A and 3B. The first design is from a large cancer study in which living cancer cases and their hospital and population referents were interviewed, followed by an exposure assessment made by a team of experts (51). The second design is from a liver cancer study in which both the cases and referents were deceased and exposure information had to be collected from the next-of-kin. Contacting companies helped improve the accuracy of the exposure assessment, and surveying the work histories with a general job-exposure matrix extended its coverage (52).

The collection of work histories and other relevant information through interviews or postal inquiries offers both advantages and disadvantages as com-

pared with the use of employer records, which is typical of most industry-based studies (47). The advantages include the possibility to tailor the questions to concern the hypotheses of interest, the ability to explore individual work practices, and the opportunity to query subjective signs and symptoms of exposure, such as the occurrence of odor or irritation. By these methods total work histories can be collected instead of partial ones, and also information can be obtained on nonoccupational confounders. Work histories collected in interviews of the study subjects themselves have been reported to agree well with the standard records collected for pension purposes (53).

It is recommendable that exposure experts be used in the development and interpretation of questionnaires and in testing that the chemical and other special vocabulary is understandable by the subjects. The informativeness of the queries increases if the chronological work histories can be supplemented by occupation- and exposure-specific information. Portable computers facilitate the use of hierarchical questionnaire structures, with which certain replies automatically trigger specific questions relevant for the assessment of exposures (54). An alternative to collecting information on specific topics is to recontact the respondent by sending the keyed-in work history for corrections with additional questions. This method has been called SCORE (self-corrected occupational report) (1). Contacting previous employers is laborious but feasible to ascertain the occurrence

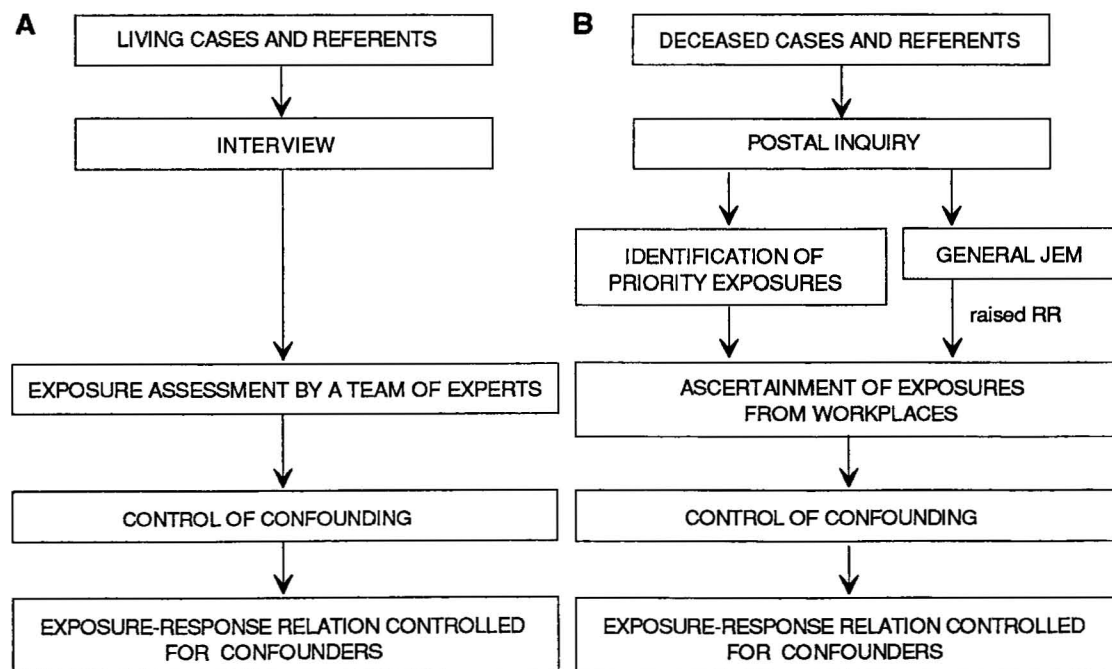


Figure 3. Examples of community-based study designs favoring the estimation of unconfounded exposure-response relations: A: case-referent study with interview and exposure assessment based on judgment by a team of experts; B: case-referent study with postal questionnaire and exposure assessment based on judgment by a team of experts supplemented by a survey using a general job-exposure matrix. (JEM = job-exposure matrix, RR = relative risk)

of exposure and to learn more about its characteristics.

Vital status influences the quality of exposure assessment in community-based studies. Living subjects are a definite advantage for exposure assessment because surrogate respondents are generally unable to recall the complete work history of the subject, and the information supplied may lack important details. The validity of work histories and other exposure-related information depends on the age of the surrogate respondent, the relationship to the subject, the duration of the shared life with the subject, and the degree of detail requested. The characteristics of the job matter, the longest-lasting and last jobs, are also recalled better than short and distant jobs (55). Comparability of information between the cases and referents can be improved, for example, by matching or controlling for vital status and by using suitable blinding techniques.

The validity and reliability of exposure assessment methods in community-based studies have been insufficiently studied. The large spectrum of industries and jobs to be covered and the lack of direct measurement data on exposures often lead to the use of a team of raters instead of only one. Trained assessors of the same team may reach a 95–98% agreement rate, but the agreement is generally poorer if assessors outside the team are used (56). Documenting inference rules is also important in community-based studies because the results may be sensitive to the opinions of the assessors. Using accurate conceptual and operational definitions of the agents to be assessed and their minimum levels of exposure is one way to improve the consistency and validity of exposure assessment (57).

Job-exposure matrices in exposure assessment

A job-exposure matrix is, in principle, a cross-tabulation of a list of job titles with a list of agents to which workers carrying out the jobs may be exposed. One element (cell) of a job-exposure matrix usually indicates the probability and level of exposure to an agent within a job. All elements form a set of rules, by which information on jobs collected in epidemiologic studies can be converted to information on potential exposures. Since 1980, when the first computerized job-exposure matrix was reported, the obvious facility of their use has raised much interest among researchers, and the job-exposure matrix technique has been extensively discussed. (For reviews, see references 58–60.)

Job-exposure matrices can be classified as general or specific. A general job-exposure matrix covers all jobs or occupations of a general (nationwide) classification, whereas a specific matrix is restricted to job titles occurring within an industry, or even within one facility. The agents included in the exposure di-

mension of the matrix are selected and defined according to the interests of the persons constructing the matrix. The number of agents included can also vary widely, ranging from one to several hundreds. Even though most job-exposure matrices deal mainly with chemical exposures, there are no restrictions as to the type of exposure. Any work-related factor, such as shift work, sedentary work, physical stress, smoking, lifting, or psychological stress, can, in principle, be analyzed with this technique. Specific job-exposure matrices often include time as a third dimension to allow for temporal changes in exposure. This feature is rare in general job-exposure matrices, which address time only as a few long periods or not at all.

General job-exposure matrices have been used mainly as a tool of exposure assessment in large community-based studies and in register-based cohort studies covering many or all industries. They save time in large studies and are often the only feasible method. Another advantage is that they can be used in all studies applying job codes similar to those of the job-exposure matrix. They are also completely “blinded” and assess subjects consistently irrespective of outcome. The main disadvantage of general job-exposure matrices is that their uncritical use may lead to serious misclassification of exposures, which tends to mask the risks under study. Construction of a new general job-exposure matrix requires extensive knowledge in occupational hygiene and may take as long as one to three years, a fact which should also be taken into account when the possible saving of time in exposure assessment is being considered.

The first general job-exposure matrix was constructed in the Harvard School of Public Health, Boston, in the United States, in the late 1970s (61). It included 500 industry-specific occupations and 334 chemical agents. The next large matrix was constructed in the Environmental Epidemiology Unit of the Medical Research Council (MRC) in Southampton, in the United Kingdom (62). It covered 669 industry-specific occupations and 50 chemical, physical, or other agents. These two matrices have been evaluated against self-reported exposures from The Netherlands (63). The MRC matrix biased the risk estimates less towards unity than did the Harvard version. Use of the highest category of exposure (high probability and level) provided clearly more valid results than the use of all exposed categories against nonexposure. The MRC matrix was evaluated simultaneously with the Dutch study also with Finnish data assessed by a group of hygienists as a criterion (64). The highest exposure category was valid for many agents with a low prevalence of exposure, whereas aggregating all exposed categories strongly biased the results on rare agents and moderately biased those on common agents. The degree of bias depended also on the individual agent. Applicability of the MRC matrix across countries was considered to be rather good because exposures re-

late much more strongly to jobs and industries than to countries. Other general job-exposure matrices have been constructed, for example, in Sweden (65) and in Italy (66).

A different type of general job-exposure matrix, including 160 chemical agents, was generated as one result of a large community-based study carried out in Montreal, Canada (67). This matrix used direct empirical information (*a posteriori*), whereas the Harvard and MRC matrices were based on the knowledge and experience of the constructors (*a priori*). The validity of posterior job-exposure matrices is potentially high because of their empirical starting point, and they may turn out to be useful in the future.

Experience on job-exposure matrices indicates that the general matrices may be valuable tools for assessing exposure in large studies covering a wide range of industries or jobs. Their validity depends on the job-exposure matrix used and, especially, on the way the grading of exposure is applied. Simulation experiments show that the use of continuous variables for the probability and level of exposure instead of the dichotomies or trichotomies typical of job-exposure matrices diminishes bias and allows various options for transforming and analyzing the data (68). The rate of misclassification, which is a major concern in the use of general job-exposure matrices, can also be controlled by stratification or statistical modeling. Additional dimensions and the use of empirical data in the construction of a job-exposure matrix generally improve validity and decrease misclassification bias. Premises and assumptions made in the construction of job-exposure matrices are rarely documented, and this lack of documentation complicates the reporting of the study and the adjustment of job-exposure matrices to specific purposes. The job-exposure matrix technique, which was developed for the exposure analysis of chemical agents, may offer a new outlook also for the assessment of other job-related risk factors in large studies, for which other methods have so far been unfeasible.

Many industry- and plant-specific job-exposure matrices have been constructed during the last several years (60). Some of them are multidimensional and so specific that their performance approaches exposure assessment in industry-based studies. The estimates and inference rules of any systematic exposure assessment in an industry-based study virtually form a job-exposure matrix, and the distinction between these two is a matter of definition. Therefore the validity and reliability aspects discussed earlier in the context of industry-based studies also concern specific job-exposure matrices.

Misclassification of exposure

Misclassification can occur with all study designs, and it can concern any of the basic elements of an

epidemiologic study: the outcome, exposure, or the covariates (confounders, modifiers). From the point of view of exposure assessment, exposure misclassification and covariate misclassification are of major concern. The nature of misclassification can be either nondifferential or differential. In nondifferential misclassification, exposure is misclassified similarly among subjects with and without outcome. In differential misclassification, exposure is overestimated or underestimated in relation to the outcome status. It is also important to distinguish between qualitative misclassification (exposed-unexposed) and quantitative misclassification (eg, light-moderate-heavy exposure) because their effects differ.

The basic source of exposure misclassification is the variability of qualitative and quantitative exposure between workers belonging to the same observational group or category of determinant (often called "homogeneous exposure group"). Recent calculations indicate, however, that only a small part of these groups can, in practice, be considered homogeneous as to exposure. In the analysis of a large measurement data base (69), individual mean exposures varied up to twofold for 25%, from two- to tenfold for 45%, and over tenfold for 30% of the groups formed from job titles. An intermittent process increases the between-worker variability of exposure as compared with a continuous process, but this difference explains only 13% of the variability. The rest is probably explained by the mix of specific tasks and work practices of the individuals comprising the group (70). These findings suggest that even if the qualitative exposure status (yes/no) and the group means were unbiased, it would be difficult to produce an unbiased exposure-response relation without individual exposure data or information on tasks and work practices. Ideally, repeated measurements from the same workers should be available because within-worker (day-to-day) variability is often high also. The use of biological monitoring data from individual workers, whenever available, partially solves the problems related to the between-worker variability, but new problems related to the biological variability between- and within-workers may arise (71).

The effects of misclassification are formally predictable. Nondifferential misclassification of the outcome or exposure tends to bias the risk measure towards the null value (see, eg, references 72, 73), but in rare cases it may even raise the risk measure (74, 75). Misclassifying confounders can bias the results in both directions so that a positive confounder, when misclassified, tends to cause a bias away from the null value and a negative confounder towards the null value (76). If misclassification concerns only the quantity of exposure, the estimate of relative risk is not biased, but the exposure-response relation tends to disappear (77). However, quantitative and qualitative misclassification often occurs simultaneously, biasing both the (mean) risk estimate and

the exposure-response relation. Differential misclassification is more complicated, and there is no general tendency towards the null value. (See, eg, reference 72.)

The factors influencing misclassification bias are well known. The magnitude of the bias is related to the true relative risk, the prevalence of exposure, and the sensitivity and specificity of the exposure assessment. Correction formulas that calculate the true relative risk have been derived for simple 2×2 tables when misclassification concerns outcome (78), exposure (72, 73), exposure and outcome (78), exposure and covariates (79, 80), quantitative exposure classes (2×N table) (80, 77), and quantitative classes of exposure and covariates (81, 82). Formal corrections are usually based on assumptions concerning sensitivity and specificity. The corrected values are not necessarily better than the uncorrected ones, and formal correction procedures are therefore rarely used, or they are used only to indicate the direction and crude magnitude of the misclassification bias.

Preventing misclassification is preferable to formal correcting procedures. To diminish misclassification, the best feasible methods should be used to assess exposure and collect work histories. Persons with uncertain exposures can be excluded in the selection of the groups to be studied or they can be analyzed as a separate group. Known mathematical relationships between the prevalence of exposure, sensitivity, specificity, and the magnitude of bias can be used to identify critical errors in assigning exposures. It has also been proposed that statistical air sampling from representative workers should be used instead of homogeneous exposure groups in prospective and cross-sectional studies to minimize quantitative misclassification (71). Various blinding techniques are probably the best means with which to avoid differential misclassification.

Mathematical formulas derived for misclassification bias indicate that improving the quality of exposure assessment, with methods as accurate as possible, reduces misclassification bias and thus increases the validity of the final risk estimates. However, this process raises the costs of the study. Five methods of collecting occupational exposure information in community-based studies have been compared as to their statistical power and costs (83). For example, assessing the exposures of 1000 subjects to 160 agents was estimated to cost USD 60 000 if the job titles were abstracted from routine records and analyzed by a job-exposure matrix, USD 230 000 if the work history from an interview was analyzed by a job-exposure matrix, and USD 450 000 if a team of experts analyzed interview-based work histories. The statistical power for detecting a twofold risk was only 0.2–0.4 for the routine records plus job-exposure matrix, 0.4–0.6 for the interview plus job-exposure matrix, and 0.9–1.0 for the interview plus the team of experts. The cost-efficiency of the routine record-based approach was the best in this comparison, but

detecting twofold and lower risks is in many cases impossible because it requires large numbers of cases and referents, which are generally available only for relatively common outcomes in nationwide or other large registers. The apparently expensive use of interviews and a team of experts was the most feasible method, and slightly more efficient than the job-exposure matrix analysis of interview-based work histories. Even though these results cannot be generalized to all specific routine records, interviewing procedures, job-exposure matrices, or study designs, they suggest that epidemiologic studies profit from the high quality of the exposure assessment. Moreover, investing in exposure assessment may be the only way in the future for occupational epidemiology to identify new risks, quantify the effects of risks, and learn about the underlying toxicologic mechanisms.

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