Exposure Assessment in Risk Assessment

Robert F. Herrick, Sc.D.

National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226

The assessment of exposure is an important component of the risk assessment process. Exposure information is used in risk assessment in at least two ways: 1) in the identification of hazards and the epidemiologic research investigating exposure–response relationships and 2) in the development of population exposure estimates. In both of these cases, the value of a chemical risk assessment is enhanced by improvements in the quality of exposure assessments. The optimum exposure assessment is the direct measurement of population exposure; however, such measurements are rarely available. Recent developments in methods for exposure assessment allow estimates to be made that are valid representations of actual exposure. The use of these exposure estimates to classify exposures correctly enhances the likelihood that causal associations between exposure and response will be correctly identified and that population risks will be accurately assessed.

Introduction

Chemical risk assessment is founded upon the premise that exposure causes risk. The presence of exposure indicates potential risk. In the simplest case, for example, those without exposure are subject to some background level of risk of an adverse health outcome, whereas those who are exposed may experience some increment of risk above background. The quantitative risk assessment seeks to describe the nature of the association between exposure and the response which constitutes the additional risk.

Exposure assessment is an important component of the overall risk assessment process. The information derived from exposure assessment may be used at two points, at least, in quantitative risk assessment. The first is in research, particularly in the human epidemiologic studies that are important for hazard identification and the assessment of exposure/dose–response associations.[1] In these studies, valid exposure assessment is essential to identify these associations and to establish evidence that the associations are causal in nature. The criteria that are applied to evaluate the likelihood of a causal association (e.g., the strength of the exposure–response association, the presence of an exposure–response trend, and a clear temporal relationship between exposure and development of the effect) all require at least an indirect assessment of exposure.[2]

The second use of exposure information is as a classification variable when risk assessment models are used to estimate population risks. In this case, exposure status is an independent variable used in a predictive model to estimate population risks, so error in exposure assessment will result in error and uncertainty in the risk estimates. The quality and predictive value of quantitative risk assessments are enhanced, therefore, by improvements in the assessment of exposure.

The Exposure/Dose–Response Continuum

The discussion of exposure assessment in quantitative risk assessment can begin by examining the concept of exposure itself. Particularly for the case of environmental contact with chemicals, exposure can be viewed as part of a process through which a chemical produces a toxic response or health effect. When the chemical is, in fact, the cause of the observed effect, the pathway from source to response may be termed a causal continuum. As shown in Figure 1, there are several components of this pathway, of which exposure is one.

Ambient Concentration

The pathway starts at the source of the chemical itself. For our purposes, the source may be considered to be the point of release of the chemical into the environment. The source may be a stack releasing sulfur dioxide (SO_2) into the atmosphere, an outfall from a sewage treatment facility, a furnace in a foundry, or a new carpet in an office building. When a source has released a chemical, the chemical's presence in the environment is characterized as an ambient concentration. It may be described in units such as mass per volume, e.g., milligrams of particulate material per cubic meter of air (mg/m^3) or micrograms of chloroform per liter of drinking water ($\mu g/L$). All measures of ambient concentration are defined in such terms of units of the contaminant per unit of the environmental matrix.

Exposure

The ambient concentration is an environmental measure, which is independent of any human interaction. When people come into contact with a chemical through an environmental medium, the process is termed exposure. The factor that distinguishes between ambient concentration and exposure is

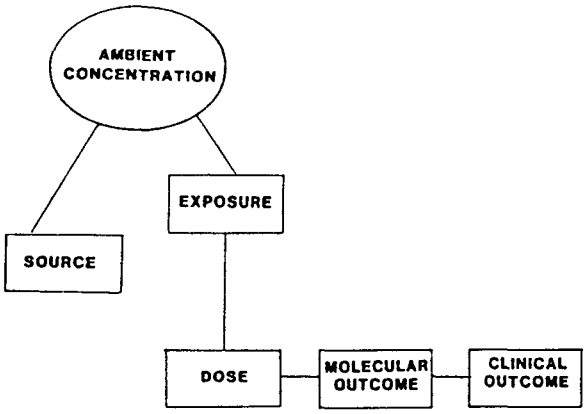

FIGURE 1. Conceptual model of causal association in occupational epidemiology.

the human interaction with the environment. Just as a tree falling in the forest may release energy in the form of sound waves, it is noise only if there is someone there to hear it. By the same logic, the presence of a contaminant in an environment does not necessarily constitute exposure, unless there is a receptor in the environment to come into contact with the contaminant. Exposure is the result of human contact with an ambient concentration of a chemical. Following the causal pathway in Figure 1, we reach the center concept of exposure resulting from human interaction with the environment.

When exposure is considered as a component of the causal continuum, it is helpful to think of it in terms of a process, rather than an event. Although there are momentary events and short-term exposures that may cause adverse health effects, most risk assessments should consider exposure to be a process occurring over time. Exposure can then be regarded as a dynamic process in three dimensions: composition, magnitude, and time.

Composition of Exposure

Accurate exposure assessment requires a complete understanding of the composition of exposure. If we are to correctly identify associations between exposure and effect, the true composition of the exposure must be known. In epidemiologic studies, the incomplete or inaccurate assessment of the composition of exposure may result in the failure to identify a causal association between exposure and response, or erroneous attribution of cause through confounding or effect modification. In a recent study of exposure to the industrial chemical 1,3-butadiene, we discovered that the analytical method which had been used historically to measure exposures to this chemical may have incorrectly included measurements of compounds other than butadiene along with the actual butadiene exposure. The source of this uncertainty was the incomplete resolution of these compounds in the gas chromatographic analysis.[3] The result of this lack of analytical specificity could be overreporting of the true butadiene exposure, which would result in errors in describing the exposure–response relationship if this exposure data were used in a quantitative risk assessment. Another example of the importance of knowing the composition of exposure comes from animal studies of SO_2 exposure and aerosols. Atmospheric particles smaller than 1 μm in diameter were found to strongly potentiate the irritant effect of SO_2 compared with exposure to gaseous SO_2 alone or in combination with large-diameter particulate material.[4] If the true composition of these mixed atmospheres were not known, including the gaseous SO_2 and the aerosol size distribution, the actual exposure–response relationship between SO_2 and pulmonary irritation would be obscured.

Magnitude of Exposure

Another characteristic of exposure that must be assessed is its magnitude. The accurate quantitation of the level of exposure is an essential component in the assessment of risk. Methods to measure the level of exposure are the subject of several full disciplines spanning methods derived from air pollution, industrial hygiene, and a range of occupational and environmental health sciences. The methods for assessment of chemical exposures are usually driven by, and limited by, the laboratory practice of analytical chemistry. The measurements made using these methods usually reflect what is possible analytically rather than what may be the best information for studying the association of the exposures and health effects. For example, painters using epoxy-based coatings may be exposed to aerosols containing epoxy resin molecules which have two functional epoxy groups each. These reactive epoxy groups are responsible for a range of toxic effects associated with epoxy resins, such as sensitization and mutagenesis.[5] Epoxy paints are prepared for application by mixing the resin with a curing agent that reacts with the epoxy groups. The mixture that constitutes the painters' exposure contains some epoxy resin molecules which have begun to react with the curing agents in the mixture, forming polymeric chains. These chains still contain available (unreacted) epoxy functional groups, however, and a measurement method that is sensitive only to the unreacted DGBA molecule can seriously underestimate the effective total epoxy exposure.[6] Limitations such as these may become apparent when we consider exposure as it is related to dose as a cause of effects in biological systems.

Exposure Over Time

The third dimension that can be applied to exposure is time. Exposure is a process occurring over time, and the first two characteristics (composition and magnitude) change over time. Accurate assessment of exposure must recognize the dynamic nature of exposure over time and consider the effect of these changes on the nature of the exposure–response

relationship. Monitoring techniques available today, for example, allow continuous monitoring of chemical exposures in real time. In studies such as an investigation of the association between ozone levels and respiratory function in children, continuous monitoring for ozone revealed that the concentration in the hour preceding pulmonary function testing was the strongest predictor of effect as compared with exposure levels averaged over other time intervals, as well as cumulative exposure.[7] In chronic diseases such as cancer, cumulative lifetime exposure to compounds such as asbestos and benzene have been strongly associated with disease risk.[8,9] In these studies of chronic effects, exposure levels changed dramatically over the time during which the study subjects were exposed. Exposure assessment to document the changes in the level of exposure over time was essential in developing accurate exposure estimates to correctly classify study subjects in the epidemiologic analysis.

The time at which a subject's exposure occurred can be important in investigations of the exposure/dose–response process. The age of an individual at the time of exposure, or during the period over which exposure occurs, is a factor which could influence the likelihood that exposure will result in a health effect. It is known from animal studies, for example, that younger animals are more susceptible to the induction of cancer from exposure to polycyclic aromatic hydrocarbons than are older animals.[10] Therefore, age at the time of exposure should be considered as a variable in evaluating these associations. The time sequence of exposures may also be a determinant to be considered in an exposure assessment. If exposure to an agent that is a promoter of a carcinogenic response takes place after an initiating event, the eventual health outcome could be very different than if the order of exposure were reversed. An exposure assessment that identified the occurrence of both exposures without noting their time sequence could obscure the actual association between exposure and risk.

Dose

In our efforts to improve the quality of exposure assessment, it is important to recognize that exposure itself is not the proximate cause of a biological change or a health effect. Exposure is a process that results from human interaction with an ambient concentration of a contaminant. The assessment of exposure is an environmental measurement; we need to recognize that exposure is not the same as dose, although they are closely related. As shown in Figure 1, exposure and dose are related parts of the causal continuum, but there are important differences between the two. For our uses, dose can be considered to be a measure of an agent at a receptor site in a living system.[11] The molecular site at which biochemical events take place is not accessible for direct measurement. Although we do not have the ability to directly measure the quantity of a toxin directly at its point of action, we can make a measure of exposure that is representative of and correlated with dose. In this manner, we can determine exposure as the environmental precursor of dose. Using this as our operational definition, we can refine our methods of exposure assessment to optimize the value of exposure as a dose measure.

In studies that seek to evaluate the association between exposure and effect, exposure should be assessed as the best possible surrogate or marker of dose. This means that exposure measures must consider factors that will mediate the pathway between exposure and dose (e.g., the characteristics of exposure itself such as composition and magnitude over time) and the characteristics of the exposed population. Factors such as the age and gender distribution of an exposed population can have a very significant effect on the relationship between the exposure and the dose to critical biological units between individuals in the exposed population. Occupational factors, such as contact with other chemicals on the job, can have a significant impact on the nature of an exposure–response association, e.g., the synergistic effect of polycyclic aromatic hydrocarbons and sunlight in the risk of photosensitization and skin cancer among roofers and highway construction workers.[12] Factors related to lifestyle and personal behavior can have a substantial impact on exposure–response associations, as in the case of smoking among asbestos–exposed workers. Exposure assessment must be comprehensive in approach, recognizing the characteristics of the exposure of primary interest, of other potentially confounding exposures, and the characteristics of the exposed populations that will influence the association between exposure/dose and response. When exposure assessments are optimized to identify exposure correctly and to classify study subjects based upon exposures that are relevant to the effect being observed, the power of study to identify an association and to establish evidence that it is causal in nature is enhanced.

Exposures of Populations

In hazard identification and epidemiologic research, or in risk estimation, the quality of the exposure information is an important determinant of the quality of the risk assessment. When a causal relationship between exposure/dose and response has been identified, or when evidence for such an association is being evaluated, assessment of exposure as a valid indicator or surrogate of dose is essential. The goal of an exposure assessment, therefore, is to provide an accurate exposure value for each member of the population of interest. One approach to obtain this is to assess exposure by direct measurement for each individual in the population. This has been done in some well-defined populations, usually in occupational settings, when the outcome of interest is an effect with a short period of induction or latency, such as a level of enzyme activity or a molecular end point. Studies such as these can be conducted cross-sectionally allowing individual exposure and effect measurement for each study subject.

This can be a powerful approach to research and risk assessment because exposure measurement techniques can be used that continuously monitor the level and pattern of personal exposure over time.[13] In most situations, this sort of direct measurement is not possible, and some method for estimating exposures from limited information must be employed.

The simplest exposure assessment for a population is the dichotomous classification into exposed and unexposed groups. Members of the population of interest can be classified on the basis of ever having been in a situation of potential exposure to the contaminant(s) of interest. Examples of such dichotomous classification could be 1) ever having lived with a smoker (yes or no), 2) ever having worked in a chemical production facility, or 3) ever having lived in an area served by a particular municipal water supply system. A simple classification system such as this offers the advantage that it is likely to distinguish individuals between the two categories correctly. There are a number of disadvantages to such a system. Specifically, it is qualitative in nature, providing very little information about the nature and magnitude of exposure. By using such a surrogate measure of exposure, the amount of misclassification may be low, but the value of the exposure classification for risk assessment is limited. However, this sort of classification has been useful in investigating associations between employment in particular industries and disease, e.g., studies of cancer of the respiratory tract among coke oven workers.[14]

A variety of exposure assessment methods may be considered as semiquantitative approaches. These techniques are an improvement over the simple, dichotomous classification because they attempt to classify members of a population based upon the magnitude of exposure on a relative scale. A common assessment technique is to use duration of exposure as a marker for total, cumulative exposure. The extent to which total length or duration of exposure accurately represents total exposure is limited by the homogeneity of exposure level between members of the study population, as well as over time. If all members of the population have the same level of exposure and if that level is constant over time, then a ranking of population members by total duration of exposure would be identical to ranking by cumulative exposure. These conditions of constant, homogeneous exposure over time are rarely met, however, and the use of duration of exposure as an exposure assessment outcome can result in substantial misclassification.[15] In cases where information has been available to examine both duration of exposure and some other exposure classifier which accounted for differences in exposure between individuals and over time, duration has been found to be an inferior predictor of risk.[8,9]

In recognition of the variability in exposure between individuals and over time, exposure assessment strategies have been developed employing ordinal ranking systems to classify individuals into categories based upon level of exposure. These approaches are frequently used when a limited amount of measured exposure information is available. In such cases, an exposure value measured for a portion of the study population may be assigned to others in the population who are considered to be similar in terms of factors that determine their exposure. This approach offers the advantage of allowing examination of the nature and shape of the exposure/dose–response relationship, as the exposure classes have a numerical value associated with each of them. The major disadvantage of this approach is that errors in the assignment of individuals to the classes and errors in the ranking values used for the classes tend to create exposure misclassification which dampens the apparent relationship between exposure and response, provided the classification errors are random.[16,17]

The most quantitative approach to exposure assessment (short of making individual personal exposure measurements) is to develop a strategy to assign unique exposure values for each member of the study population over the period of interest. This approach has been employed when there is at least some measured exposure information that will support the development of a predictive model to estimate exposures for individuals and time periods where measured exposures are not available. The available information on the levels of exposure and the characteristics of the members of the study population can be used to develop statistical models that predict exposures. Although this approach to exposure assessment requires sufficient measured data to support the development of a predictive model, it has the advantage of generating point estimates of exposure that can be used for quantitative risk assessment.[8,18]

Exposure Misclassification

If we consider exposure as a risk factor for the development of a health effect or disease, the nature of an association between risk and effect can be fully and correctly evaluated only when the risk and effect measures are valid. Incorrect assessment of either exposure or effect results in misclassification that can obscure true associations and lead to error or uncertainty in risk assessment.

Exposure misclassification is most likely to be nondifferential in nature; that is, errors in exposure classification will occur throughout the study population, without regard to health or outcome status. In the simplest case, members of a study population who are truly exposed may be incorrectly classified as unexposed, and some exposed are classified as unexposed. In this case, the net result will be a bias in the study findings toward the null hypothesis of no association between exposure and response. In more quantitative exposure assessments, such as the assignment of individuals to rank-ordered categories based upon cumulative lifetime exposure, nondifferential misclassification between adjacent exposure categories can have an attenuating effect on an exposure–response trend, if one, in fact, exists.[19] Even when

the exposure misclassification rate is only 20%, the true estimate of risk among the exposed can be substantially greater than the apparent relative risk. This holds whether the misclassification is between a simple exposed/unexposed dichotomy or by some more-quantitative exposure classes. A misclassification rate of 20% would not be at all surprising in epidemiologic studies, particularly when exposures must be estimated based upon a historical reconstruction for some members of a study population. In the few studies where estimates of historical exposures were compared with actual measurements of exposure from the past, agreement within 20% between estimates and measurements of past exposure would be considered very good. In many cases, much larger differences have been observed.[20]

Summary and Conclusions

Valid exposure assessment is an essential part of quantitative risk assessment. The incorporation of exposure information in hazard identification and research enhances the likelihood that these activities will correctly identify etiologic associations between exposure and response and accurately determine the strength of these associations. When a quantitative risk assessment is conducted to estimate population risks, accurate assessment of exposure will improve the validity of the risk estimates. Direct measurements of human exposures would be the most accurate assessment of exposure. Although such measurements are frequently not available, new approaches to exposure assessment are being developed to provide accurate exposure estimates for populations. These improvements in exposure assessment methodology offer the prospect for advances in the practice of quantitative risk assessment.

References

1. McClelland, R.O.: Health Effects of Diesel Exhaust: A Case Study in Quantitative Risk Assessment. Am. Ind. Hyg. Assoc. J. 47(1):1–13 (1986).
2. Lilienfeld, A.M.; Lilienfeld, D.E.: Foundations of Epidemiology. Oxford University Press, New York (1980).
3. Fajen, J.M.; Roberts, D.: Occupational Exposure of Workers to 1,3-Butadiene. Presentation No. 443 at the American Industrial Hygiene Conference, Orlando, FL (1990).
4. Amdur, M.O.; Dubriel, M.; Creasia, D.A.: Respiratory Response of Guinea Pigs to Low Levels of Sulfuric Acid. Environ. Res. 15:418–423 (1978).
5. Hine, C.H.; Rowe, V.K.; White, E.R.; et al.: Epoxy Compounds. In Patty's Industrial Hygiene and Toxicology, Vol. 2A, Toxicology, pp. 2143–2257. G.D. Clayton and F.E. Clayton, Eds. John Wiley & Sons, New York (1981).
6. Herrick, R.F.; Ellenbecker, M.J.; Smith, T.J.: Measurement of the Epoxy Content of Paint Spray Aerosols: Three Case Studies. Appl. Ind. Hyg. 3:123–128 (1988).
7. Spektor, D.A.; Lippmann, M.; Lioy, P.J.; et al.: Effects of Ambient Ozone on Respiratory Function in Active, Normal Children. Am. Rev. Resp. Dis. 137:313–320 (1988).
8. Dement, J.M., Harris, R.L., Symons, M.J.; Shy, C.M.: Exposures and Mortality Among Chrysotile Asbestos Workers. Part I.: Exposure Estimates. Am. J. Ind. Med. 4:399–419 (1983).
9. Rinsky, R.A.; Smith, A.B.; Hornung, R.; et al.: Benzene and Leukemia. N. Engl. J. Med. 316:1044–1050 (1987).
10. Homburger, F. (Ed.): The Physiopathology of Cancer. S. Karger, Basel, New York, London (1976).
11. Doull, J.: Factors Influencing Toxicology. In: Casarett and Doull's Toxicology, p. 70. J. Doull, C.D. Klaassen, and M.D. Amdur, Eds. Macmillan Publishing, New York (1980).
12. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard — Occupational Exposure to Coal Tar Products. DHEW (NIOSH) Pub. No. 78-107. NIOSH, Cincinnati, OH (1978).
13. Schulte, P.A.; Boeniger, M.; Walker, J.T.; et al.: Biological Markers in Hospital Workers Exposed to Low Levels of Ethylene Oxide. Mutat. Res. 278:237–251 (1992).
14. Lloyd, J.W.; Lundin, F.E.; Redmond, C.K.; Geiser, P.B.: Long-Term Mortality Study of Steelworkers. V. Respiratory Cancer in Coke Plant Workers. J. Occup. Med. 13:53–68 (1971).
15. Checkoway, H.: Methods of Treatment of Exposure Data in Occupational Epidemiology. Med. Lav. 1:48–71 (1986).
16. Marshall, J.R.; Priore, R.; Graham, S.; Brasure, J.: On the Distortion of Risk Estimates in Multiple Exposure Level Case–Control Studies. Am. J. Epidemiol. 113(4):464–473 (1981).
17. Kromhout, H.; Oostendorp, Y.; Heederik, D.; Boleij, J.S.M.: Agreement Between Qualitative Exposure Estimates and Quantitative Exposure Measurements. Am. J. Ind. Med. 12:551–562 (1987).
18. Griefe, A.L.; Hornung, R.W.; Stayner, L.G.; Steenland, K.N.: Development of a Model for Use in Estimating Exposure to Ethylene Oxide in a Retrospective Cohort Mortality Study. Scand. J. Work Environ. Health 14(Suppl. 1):29–31 (1988).
19. Checkoway, H.; Savitz, D.A.; Heyer, N.J.: Assessing the Effects of Nondifferential Misclassification of Exposures in Occupational Studies. Appl. Occup. Environ. Hyg. 6:528–533 (1991).
20. Stewart, P.A.; Herrick., R.F.: Issues in Performing Retrospective Exposure Assessment. Appl. Occup. Environ. Hyg. 6:421–427 (1991).