neurologic exams and neuropsychological test batteries are designed to confirm and classify functional problems in individuals selected on the basis of signs and symptoms identified by the patient, family, or other health professionals. Their usefulness in detecting low baserate impairment in workers or the general population is generally thought to be limited, decreasing the usefulness of clinical assessment approaches for epidemiologic risk assessment.

Second, neurologic exams and neuropsychologic test batteries were developed to assess the functional correlates of the most common forms of nervous system dysfunction: brain trauma, focal lesions, and degenerative conditions. The clinical tests were validated against these neurologic disease states. With a few notable exceptions, chemicals are not believed to produce impairment similar to that from trauma or lesions; neurotoxic effects are more similar to the effects of degenerative disease. There has been insufficient research to demonstrate which tests designed to assess functional expression of neurologic disease are useful in characterizing the modes of central nervous system impairment produced by chemical agents and drugs.

b. Case reports. The first type of human data available is often the case report or case series, which can identify cases of a disease and are reported by clinicians or discerned through active or passive surveillance, usually in the workplace. However, case reports where exposure involved a single neurotoxic agent, although informative, are rare in the literature; for example, farmers are likely to be exposed to a wide variety of potentially neurotoxic pesticides. Careful case histories assist in identifying common risk factors, especially when the association between the exposure and disease is strong, the mode of action of the agent is biologically plausible, and clusters occur in a limited period of time.

Case reports are inexpensive compared with epidemiologic studies and can be obtained more quickly than more complex studies. However, they provide little information about disease frequency or population at risk, but their importance has been clearly demonstrated, particularly in accidental poisoning or acute exposure to high levels of toxicant. They remain an important source of index cases of new diseases and for surveillance.

c. Epidemiologic Studies. Epidemiology has been defined as "the study of the distributions and determinants of disease and injuries in

human populations" (Mausner and Kramer, 1985). Knowing the frequency of illness in groups and the factors that influence the distribution is the tool of epidemiology that allows the evaluation of causal inference with the goal of prevention and cure of disease (Friedlander and Hearn, 1980). Epidemiologic studies are a means of evaluating the effects of neurotoxic substances on human populations, but such studies are limited because they must be performed shortly after exposure if the effect is acute. Most often these effects are suspected to be a result of occupational exposures due to the increased opportunity for exposure to industrial and other chemicals. Frequently, determining the precise dose or exposure concentration can be difficult in epidemiological studies.

 Cross-sectional studies. In crosssectional studies or surveys, both the disease and suspected risk factors are ascertained at the same time, and the findings are useful in generating hypotheses. A group of people are interviewed, examined, and tested at a single point in time to ascertain a relationship between a disease and a neurotoxic exposure. This study design does not allow the investigator to determine whether the disease or the exposure came first, rendering it less useful in estimating risk. These studies are intermediate in cost and time required to complete compared with case reports and more complex analytical studies but should be augmented with additional data.

(2) Case-control (retrospective) studies. Last (1986) defines a casecontrol study as one that "starts with the identification of persons with the disease (or other outcome variable) of interest, and a suitable control population (comparison, reference group) of persons without the disease." He states that the relationship of an "attribute" to the disease is measured by comparing the diseased with the nondiseased with regard to how frequently the attribute is present in each of the groups. The cases are assembled from a population of persons with and without exposure, and the comparison group is selected from the same population; the relative distribution of the potential risk factor (exposure) in both groups is evaluated by computing an odds ratio that serves as an estimate of the strength of the association between the disease and the potential risk factor. The statistical significance of the ratio is determined by calculating a p-value and is used to approximate relative risk.

The case-control approach to the study of potential neurotoxicants in the

environment provides a great deal of useful information for the risk assessor. In his textbook, Valciukas (1991) notes that the case-control approach is the strategy of choice when no other environmental or biological indicator of neurotoxic exposure is available. He further states: "Considering the fact that for the vast majority of neurotoxic chemical compounds, no objective biological indicators of exposure are available (or if they are, their half-life is too short to be of any practical value), the case-control paradigm is a widely accepted strategy for the assessment of toxic causation." The case-control study design, however, can be very susceptible to bias. The potential sources of bias are numerous and can be specific to a particular study. Many of these biases also can be present in crosssectional studies. For example, recall bias or faulty recall of information by study subjects in a questionnaire-based study can distort the results of the study. Analysis of the case-comparison study design assumes that the selected cases are representative persons with the disease—either all cases with the disease or a representative sample of them have been ascertained. It further assumes that the control or comparison group is representative of the nondiseased population (or that the prevalence of the characteristic under study is the same in the control group as in the general population). Failure to satisfy these assumptions may result in selection bias, but violation of assumptions does not necessarily invalidate the study results.

An additional source of bias in casecontrol studies is the presence of confounding variables, i.e., factors known to be associated with the exposure and causally related to the disease under study. These must be controlled either in the design of the study by matching cases to controls on the basis of the confounding factor or in the analysis of the data by using statistical techniques such as stratification or regression. Matching requires time to identify an adequate number of potential controls to distinguish those with the proper characteristics, while statistical control of confounding factors requires a larger study.

The definition of exposure is critical in epidemiologic studies. In occupational settings, exposure assessment often is based on the job assignment of the study subjects, but can be more precise if detailed company records allow the development of exposure profiles. Positive results from a properly controlled retrospective