study should weigh heavily in the risk assessment process.

(3) Cohort (prospective, followup) studies. In a prospective study design, a healthy group of people is assembled and followed forward in time and observed for the development of disease. Such studies are invaluable for determining the time course for development of disease (e.g., followup studies performed in various cities on the effects of lead on child development). This approach allows the direct estimate of risks attributed to a particular exposure since disease incidence rates in the cohort can be determined. Prospective study designs also allow the study of chronic effects of exposure. One major strength of the cohort design is that it allows the calculation of rates to determine the excess risk associated with an exposure. Also, biases are reduced by obtaining information before the disease develops. This approach, however, can be very time-consuming and costly.

In cohort studies information bias can be introduced when individuals provide distorted information about their health because they know their exposure status and may have been told of the expected health effects of the exposure under study.

A special type of cohort study is the retrospective cohort study in which the investigator goes back in time to select the study groups and traces them over time, often to the present. The studies usually involve specially exposed groups and have provided much assistance in estimating risks due to occupational exposures. Occupational retrospective cohort studies rely on company records of past and current employees that include information on the dates of employment, age at employment, date of departure, and whether diseased (or dead in the case of mortality studies). Workers can then be classified by duration and degree of exposure. Positive results from a properly controlled prospective study should weigh heavily in the risk assessment process.

d. Human Laboratory Exposure Studies. Neurotoxicity assessment has an advantage not afforded the evaluation of other toxic end points, such as cancer or reproductive toxicity, in that the effects of some chemicals are short in duration and reversible. This makes it ethically possible to perform human laboratory exposure studies and obtain data relevant to the risk assessment process. Information from experimental human exposure studies has been used to set occupational exposure limits, mostly for organic solvents that can be inhaled. Laboratory exposure studies have contributed to risk assessment and the setting of exposure limits for several solvents and other chemicals with acute reversible effects.

Human exposure studies sometime offer advantages over epidemiologic field studies. Combined with appropriate sampling of biologic fluids (urine or blood), it is possible to calculate body concentrations, examine toxicokinetics, and identify metabolites. Bioavailability, elimination, doserelated changes in metabolic pathways, individual variability, time course of effects, interactions between chemicals, and interactions between chemical and environmental/biobehavioral processes (stressors, workload/respiratory rate) are factors that are generally easier to collect under controlled conditions.

Other goals of laboratory studies include the indepth characterization of effects, the development of new assessment methods, and the examination of the sensitivity, specificity, and reliability of neurobehavioral assessment methods across chemical classes. The laboratory is the most appropriate setting for the study of environmental and biobehavioral variables that affect the action of chemical agents. The effects of ambient temperature, task difficulty, rate of ongoing behavior, conditioning variables, tolerance/sensitization, sleep deprivation, motivation, and so forth are sometimes studied.

From a methodologic standpoint, human laboratory studies can be divided into two categories-betweensubjects and within-subjects designs. In the former, the neurobehavioral performance of exposed volunteers is compared with that of nonexposed participants. In the latter, preexposure performance is compared with neurobehavioral function under the influence of the chemical or drug. Within-subjects designs have the advantage of requiring fewer participants, eliminating individual differences as a source of variability, and controlling for chronic mediating variables, such as caffeine use and educational achievement. A disadvantage of the within-subjects design is that neurobehavioral tests must be administered more than once. Practice on many neurobehavioral tests often leads to improved performance that may confound the effect of the chemical/drug. There should be a sufficient number of test sessions in the pre-exposure phase of the study to allow performance on all tests to achieve a relatively stable baseline level.

Participants in laboratory exposure studies may have been recruited from

populations of persons already exposed to the chemical/drug or from naive populations. Although the use of exposed volunteers has ethical advantages, can mitigate against novelty effects, and allows evaluation of tolerance/sensitization, finding an accessible exposed population in reasonable proximity to the laboratory is difficult. Naive participants are more easily recruited but may differ significantly in important characteristics from a representative sample of exposed persons. Naive volunteers are often younger, healthier, and better educated than the populations exposed environmentally, in the workplace, or pharmacotherapeutically.

Compared with workplace and environmental exposures, laboratory exposure conditions can be controlled more precisely, but exposure periods are much shorter. Generally only one or two relatively pure chemicals are studied for several hours while the population of interest may be exposed to multiple chemicals containing impurities for months or years. Laboratory studies are therefore better at identifying and characterizing effects with acute onset and the selective effects of pure agents.

Neurobehavioral test methods may have been selected according to several strategies. A test battery that examines multiple neurobehavioral functions may be more useful for screening and the initial characterization of acute effects. Selected neurobehavioral tests that measure a more limited number of functions in multiple ways may be more useful for elucidating mechanisms or validating specific effects.

Both chemical and behavioral control procedures are valuable for examining the specificity of the effects. A concordant effect among different measures of the same neurobehavioral function (e.g., reaction time) and a lack of effect on some other measures of psychomotor function (e.g., untimed manual dexterity) would increase the confidence in a selective effect on motor speed and not on attention or nonspecific motor function. Likewise, finding concordant effects among similar chemical or drug classes along with different effects from dissimilar classes would support the specificity of chemical effect. For example, finding that the effects of a solvent were similar to those of ethanol but not caffeine would support the specificity of solvent effects on a given measure of neurotoxicity.

## 2. Animal Studies

This section provides an overview of the major types of end points that may be evaluated in animal neurotoxicity