The risk assessor also should know that there are different levels of concern based on the magnitude of effect and reversibility of some neurotoxic effects. Neurotoxic effects may be irreversible, i.e., cannot return to the state prior to exposure, resulting in a permanent change in the organism, or reversible, i.e., can return to the pre-exposure condition, allowing the organism to return to its state prior to exposure. Clear or demonstrable irreversible change in either the structure or function of the nervous system causes greater concern than do reversible changes. If neurotoxic effects are observed at some time during the life span of the organism but are slowly reversible, the concern is also high. There is lesser concern for effects that are rapidly reversible or transient, i.e., measured in minutes, hours, or days, and appear to be associated with the pharmacokinetics of the causal agent and its presence in the body. Reversible changes that occur in the occupational setting or environment, however, may be of high concern if, for example, exposure to a short-acting solvent interferes with operation of heavy equipment in an industrial plant. The context of the exposure should be considered in evaluating reversible effects. The risk assessor should note that once damaged, neurons, particularly in the central nervous system, have a limited capacity for regeneration. Reversibility of effects resulting from cell death or from the destruction of cell processes may represent an activation of repair capacity, decreasing future potential adaptability. Therefore, even reversible neurotoxic changes should be of concern. Evidence of progressive effects, i.e., those that continue to worsen even after the causal agent has been removed; or delayed effects, i.e., those that occur at a time distant from the last contact with the causal agent; or residual effects, i.e., those that persist beyond a recovery period; or latent effects, i.e., those that become evident only after an environmental challenge or aging, have a high level of concern. Environmental challenges can include stress, increased physical or cognitive workload, pharmacological manipulations, and nutritional deficiency or excess.

Neurotoxic effects can be observed at various levels of organization of the nervous system, including neurochemical, anatomical, physiological, or behavioral. At the neurochemical level, for example, an agent that causes neurotoxicity might inhibit macromolecule or transmitter synthesis, alter the flow of ions across

cellular membranes, or prevent release of neurotransmitter from the nerve terminals. Anatomical changes may include alterations of the cell body, the axon, or the myelin sheath. At the physiological level, a chemical might change the thresholds for neural activation or reduce the speed of neurotransmission. Behavioral alterations can include significant changes in sensations of sight, hearing, or touch; alterations in simple or complex reflexes and motor functions; alterations in cognitive functions such as learning, memory or attention; and changes in mood, such as fear or rage, disorientation as to person, time, or place, or distortions of thinking and feeling, such as delusions and hallucinations. At present, relatively few neurotoxic syndromes have been thoroughly characterized in terms of the initial neurochemical change, structural alterations, physiological consequence, and behavioral effects. Knowledge of exact mechanisms of action is not, however, necessary to conclude that a chemically induced change is a neurotoxic effect.

Neurotoxic effects can be produced by chemicals that do not require metabolism prior to interacting with their target sites in the nervous system, i.e., primary neurotoxic agents, or those that require metabolism prior to interacting with their target sites in the nervous system, i.e., secondary neurotoxic agents. Chemically induced neurotoxic effects can be direct, i.e., due to an agent or its metabolites acting directly on target sites in the nervous system, or indirect, i.e., due to agents or metabolites that produce their effects primarily by interacting with target sites outside the nervous system, which subsequently affect target sites in the nervous system. Excitatory amino acids such as domoic acid damage specific neurons directly by activating excitatory amino acid receptors in the nervous system, while carbon monoxide decreases oxygen availability, which indirectly kills neurons. Other examples of indirect effects of chemicals that could lead to altered structure and/or function of the nervous system include cadmium-induced spasms in blood vessels supplying the nervous system, dichloroacetate-induced perturbation of metabolic pathways, and chemically induced alterations in skeletomuscular function or structure and effects on the endocrine system. Professional judgment may be required in making determinations about direct versus indirect effects.

The interpretation of data as indicative of a potential neurotoxic effect involves the evaluation of the

validity of the data base. This approach and these terms have been adapted from the literature on human psychological testing (Sette, 1987; Sette and MacPhail, 1992) where they have long been used to evaluate the level of confidence in different measures of intelligence or other abilities, aptitudes, or feelings. There are four principal questions that should be addressed: whether the effects result from exposure (content validity); whether the effects are adverse or toxicologically significant (construct validity); whether there are correlative measures among behavioral, physiological, neurochemical, and morphological end points (concurrent validity); and whether the effects are predictive of what will happen under various conditions (predictive validity). Addressing these issues can provide a useful framework for evaluating either human or animal studies or the weight of evidence for a chemical (Sette, 1987; Sette and MacPhail, 1992). The next sections indicate the extent to which chemically induced changes can be interpreted as providing evidence of neurotoxicity.

## III. Hazard Characterization

## A. Neurotoxicological Studies: End Points and Their Interpretation

Identification and characterization of neurotoxic hazard can be based on either human or animal data (Anger, 1984; Reiter, 1987; U.S. EPA, 1993). Such data can result from accidental, inappropriate, or controlled experimental exposures. This section describes many of the general and some of the specific characteristics of human studies and reports of neurotoxicity. It then describes some features of animal studies of neuroanatomical, neurochemical, neurophysiological, and behavioral effects relevant to risk assessment. The process of characterizing the sufficiency or insufficiency of neurotoxic effects for risk assessment is described in section III.C. Additional sources of information relevant to hazard characterization, such as comparisons of molecular structure among compounds and in vitro screening methods, are also discussed.

- The hazard characterization should: a. Identify strengths and limitations of
- the database:
- —Epidemiological studies (case reports, cross-sectional, case-control, cohort, or human laboratory exposure studies);
- —Animal studies including (structural or neuropathological, neurochemical, neurophysiological, behavioral or neurological, or developmental end points).