b. Evaluate the validity of the database:

- —Content validity (effects result from exposure);
- Construct validity (effects are adverse or toxicologically significant);
- -Concurrent validity (correlative measures among behavioral, physiological, neurochemical, or morphological end points);
- —Predictive validity (effects are predictive of what will happen under various conditions).
- c. Identify and describe key toxicological studies.
- d. Describe the type of effects: —Structural (neuroanatomical
- alternations);
- Functional (neurochemical, neurophysiological, behavioral alterations).

e. Describe the nature of the effects (irreversible, reversible, transient, progressive, delayed, residual, or latent effects).

f. Describe how much is known about how (through what biological mechanism) the chemical produces adverse effects.

g. Discuss other health end points of concern.

h. Comment on any non-positive data in humans or animals.

i. Discuss the dose-response data (epidemiological or animal) available for further dose-response analysis.

j. Discuss the route, level, timing, and duration of exposure in studies demonstrating neurotoxicity as compared to expected human exposures.

k. Summarize the hazard characterization:

- -Confidence in conclusions;
- Alternative conclusions also supported by the data;
- -Significant data gaps; and
- -Highlight of major assumptions.

1. Human Studies

It is well established that information from the evaluation of human exposure can identify neurotoxic hazards (Anger and Johnson, 1985; Anger, 1990). Prominent among historical episodes of neurotoxicity in human populations are the outbreaks of methylmercury poisoning in Japan and Iraq and the neurotoxicity seen in miners of metals, including mercury, manganese, and lead (Carson et al., 1987; Silbergeld and Percival, 1987; OTA, 1990). In the last decade, lead poisoning in children has been a prominent issue of concern (Silbergeld and Percival, 1987). Neurotoxicity in humans has been studied and reviewed for many pesticides (Hayes, 1982; NRDC, 1989;

Ecobichon and Joy, 1982; Ecobichon et al., 1990). Organochlorines, organophosphates, carbamates, pyrethroids, certain fungicides, and some fumigants are all known neurotoxicants. They may pose occupational risks to manufacturing and formulation workers, pesticide applicators and farm workers, and consumers through home application or consumption of residues in foods. Families of workers may also be exposed by transport into the home from workers' clothing. Data on humans can come from a number of sources, including clinical evaluations, case reports, and epidemiologic studies. A more extensive description of issues concerning human neurotoxicology and risk assessment has been published elsewhere (U.S. EPA, 1993)

 a. Clinical Evaluations. Clinical methods are used extensively in neurology and neuropsychology to evaluate patients suspected of having neurotoxicity. An extensive array of examiner-administered and paper-andpencil tasks are used to assess sensory, motor, cognitive, and affective functions and personality states/traits. Neurobehavioral data are synthesized with information from neurophysiologic studies and medical history to derive a working diagnosis. Brain imaging techniques based on magnetic resonance imaging or emission tomography may also be useful in helping diagnose neurodegenerative disorders following chemical exposures in humans (Omerod et al., 1994; Callender et al., 1994). Clinical diagnostic approaches have provided a rich conceptual framework for understanding the functions (and malfunctions) of the central and peripheral nervous systems and have formed the basis for the development of methods for measuring the behavioral expression of nervous system disorders. Human neurobehavioral toxicology has borrowed heavily from neurology and neuropsychology for concepts of nervous system impairment and functional assessment methods. Neurobehavioral toxicology has adopted the neurologic/neuropsychologic model, using adverse changes in behavioral function to assist in identifying chemically or drug-induced changes in nervous system processes.

Neurologic and neuropsychologic methods have long been employed to identify the adverse health effects of environmental workplace exposures (Sterman and Schaumburg, 1980). Peripheral neuropathies (with sensory and motor disturbances), encephalopathies, organic brain syndromes, extrapyramidal syndromes, demyelination, autonomic changes, and dementia are well-characterized consequences of acute and chronic exposure to chemical agents. The range of exposure conditions that produce clinical signs of neurotoxicity also has been defined by these clinical methods. It is very important to make external/ internal dose measurements in humans to determine the actual dose(s) that can cause unwanted effects.

Aspects of the neurologic examination approach limit its usefulness for neurotoxicologic risk assessment. Information obtained from the neurologic exam is mostly qualitative and descriptive rather than quantitative. Estimates of the severity of functional impairment can be reliably placed into only three or four categories (for example, mild, moderate, severe). Much of the assessment depends on the subjective judgment of the examiner. For example, the magnitude and symmetry of muscle strength are often judged by having the patient push against the resistance of the examiner's hands. The end points are therefore the absolute and relative amount of muscle load sensed by the examiner in his or her arms.

Compared with other methods, the neurologic exam may be less sensitive in detecting early neurotoxicity in peripheral sensory and motor nerves. While clinicians' judgments are equal in sensitivity to quantitative methods in assessing the amplitude of tremor, tremor frequency is poorly quantified by clinicians. Thus, important aspects of the clinical neurologic exam may be insufficiently quantified and lack sufficient sensitivity for detecting early neurobehavioral toxicity produced by environmental or workplace exposure conditions. However, a neurologic evaluation of persons with documented neurobehavioral impairment would be helpful for identifying nonchemical causes of neurotoxicity, such as diabetes and cardiovascular insufficiency.

Administration of a neuropsychological battery also requires a trained technician, and interpretation requires a trained and experienced neuropsychologist. Depending on the capabilities of the patient, 2 to 4 hours may be needed to administer a full battery; 1 hour may be needed for the shorter screening versions. These practical considerations may limit the usefulness of neuropsychological assessment in large field studies of suspected neurotoxicity.

In addition to logistical problems in administration and interpretation, neuropsychological batteries and neurologic exams share two disadvantages with respect to neurotoxicity risk assessment. First,