studies, describes the kinds of effects that may be observed and some of the tests used to detect and quantify these effects, and provides guidance for interpreting data. Compared with human studies, animal studies are more often available for specific chemicals, provide more precise exposure information, and control environmental factors better (Anger, 1984). For these reasons, risk assessments tend to rely heavily on animal studies.

Many tests that can measure some aspect of neurotoxicity have been used in the field of neurobiology in the last 50 years. The Office of Prevention, Pesticides and Toxic Substances (OPPTS) has published animal testing guidelines that were developed in cooperation with the Office of Research and Development (U.S. EPA, 1991a). While the test end points included serve as a convenient focus for this section, there are many other end points for which there are no current EPA guidelines. The goal of this document is to provide a framework for interpreting data collected with tests frequently used by neurotoxicologists.

Five categories of end points will be described: Structural or neuropathological, neurophysiological, neurochemical, behavioral, and developmental end points. Table 1 lists a number of end points in each of these categories.

Table 1.-Examples of Possible Indicators of a Neurotoxic Effect

- I. Structural or Neuropathological End Points . Gross changes in morphology, including
 - brain weight
 - 2. Hemorrhage in nerve tissue
 - 3. Breakdown of neurons, glial cells
 - 4. Accumulation, proliferation, or
 - rearrangement of structural elements 5. Glial fibrillary acidic protein increases (in adults)
- II. Neurochemical End Points
- 1. Alterations in synthesis, release, uptake, degradation of neurotransmitters

- 2. Alterations in second messenger associated signal transduction
- 3. Alterations in membrane-bound enzymes regulating neuronal activity
- 4. Inhibition of neuropathy target enzyme (≥40%)
- III. Neurophysiological End Points 1. Change in velocity, amplitude, or
 - refractory period of nerve conduction 2. Change in latency or amplitude of
 - sensory-evoked potential 3. Change in electroencephalographic pattern
- IV. Behavioral and Neurological End Points
- 1. Increases or decreases in motor activity
- 2. Changes in touch, sight, sound, taste, or smell sensations
- 3. Changes in motor coordination, weakness, paralysis, abnormal movement or posture, tremor, ongoing performance
- Absence or decreased occurrence, magnitude, or latency of sensorimotor reflex
- 5. Altered magnitude of neurological measurement, including grip strength, hindlimb splay
- 6. Seizures
- 7. Changes in rate or temporal patterning of schedule-controlled behavior
- 8. Changes in learning, memory, intelligence, attention
- V. Developmental End Points
 - 1. Chemically induced changes in the time of appearance of behaviors during development
 - 2. Chemically induced changes in the growth or organization of structural or neurochemical elements.
 - a. Structural End Points of

Neurotoxicity. Structural end points are typically defined as neuropathological changes measured through gross observation or with the aid of a microscope. Gross changes in morphology can include discrete or widespread lesions in nerve tissue. Changes in brain size (weight, width, or length) are considered to be indicative of neurotoxic events. This is true regardless of changes in body weight, because brain size is generally protected during undernutrition or weight loss,

unlike many other organs or tissues. It is inappropriate to express brain weight changes as a ratio of body weight and thereby dismiss changes in absolute brain weight. The risk assessor should be aware that a unit of measurement that is biologically meaningful should be used for analysis. Brain length measurements, for example, expressed to 1 or 10 micron units is biologically meaningless. The same is true for brain width.

Neurons are composed of a neuronal body, axon, and dendritic processes. Various types of neuropathological lesions may be classified according to the site where they occur (WHO, 1986; Krinke, 1989; Griffin, 1990). Neurodegenerative lesions in the central or peripheral nervous system may be classified as a neuronopathy (changes in the neuronal cell body), axonopathy (changes in the axons), myelinopathy (changes in the myelin sheaths), or terminal degeneration. For axonopathies, a more precise location of the changes may also be described (i.e., proximal, central, or distal axonopathy). In the case of some developmental exposures, a neurotoxic chemical might delay or accelerate the differentiation or proliferation of cells or cell types. Alteration in the axonal termination site might also occur with exposure. In an aged population, exposure to some neurotoxicants might accelerate the normal loss of neurons associated with aging (Reuhl, 1991). In rare cases, neurotoxic agents have been reported to produce neuropathic conditions resembling neurodegenerative disorders in humans such as Parkinson's disease (WHO, 1986). Table 2 lists examples of such neurotoxic chemicals, their putative site of action, the type of neuropathology produced, and the disease or condition that each typifies.

TABLE 2.—NEUROTOXICANTS AND DISEASES WITH SPECIFIC NEURONAL TARGETS

Site of action	Neuropathology	Neurotoxicant	Corresponding neurodegenerative disease or condition
Neuron cell body	Neuronopathy	Methylmercury Quinolinic acid 3- Acetylpyridine.	Minamata disease, Huntington's disease, Cere- bellar ataxia.
Nerve terminal	Terminal destruction	1-Methyl-4-phenyl-1,2,3,6- tetrahydropyridine (dopaminergic).	Parkinson's disease.
Schwann cell Myelin	Myelinopathy	Hexachlorophene	Congenital hypomyelinogenesis.
Central-peripheral distal axon.	Distal axonopathy	Acrylamide Carbon disulfide n-Hexane	Peripheral neuropathy.
Central axons Proximal axon	Central axonopathy Proximal axonopathy	Clioquinol B,B'-iminodipropionitrile	Subacute myeloopticoneuropathy. Motor neuron disease.

Alterations in the structure of the nervous system (i.e., neuronopathy, axonopathy, myelinopathy, terminal

degeneration) are regarded as evidence of a neurotoxic effect. The risk assessor should note that pathological changes in many cases require time for the perturbation to become observable, especially with evaluation at the light