microscopic level. Neuropathological studies should control for potential differences in the area(s) and section(s) of the nervous system sampled, in the age, sex, and body weight of the subject, and in fixation artifacts (WHO, 1986). Concern for the structural integrity of nervous system tissues derives from its functional specialization and the lack of regenerative capacity in the central nervous system.

In general, chemical effects can lead to two types of structural alteration at the cellular level: the breakdown of cells, in whole or in part, or the accumulation, proliferation, or rearrangement of structural elements (e.g., intermediate filaments, microtubules) or organelles (e.g., mitochondria). Some changes may be associated with regenerative processes that reflect adaptive changes associated with exposure to a toxicant.

Chemically induced injury to the central nervous system may be associated with astrocytic hypertrophy. Such changes may be seen using immunocytochemical techniques visualized by light microscopy or quantified more precisely by radioimmunoassay (RIA) procedures. Assays of glial fibrillary acidic protein (GFAP), the major intermediate filament protein of astrocytes, have been proposed as a biomarker of this response (O'Callaghan, 1988). The interpretation of a chemical-induced change in GFAP is facilitated by corroborative data from the neuropathology or neuroanatomy

evaluation. A number of chemicals known to injure the central nervous system, including trimethyltin, methylmercury, cadmium, 3acetylpyridine, and methylphenyltetrahydropyridine (MPTP), have been shown to increase levels of GFAP. Measures of GFAP are now included in the Neurotoxicity Test Battery testing guidelines (U.S. EPA, 1991a).

Increases in GFAP above control levels may be seen at dosages below those necessary to produce damage seen by standard microscopic or histopathological techniques. Because increases in GFAP reflect an astrocyte response in adults, treatment-related increases in GFAP are considered to be evidence that a neurotoxic effect has occurred. Decreases in GFAP are not clearly interpretable as indicative of neurotoxicity. The absence of a change in GFAP following exposure does not necessarily mean that the chemical is devoid of neurotoxic potential. Known neurotoxicants such as cholinesteraseinhibiting pesticides, for example, would not be expected to increase brain levels of GFAP. Interpretation of GFAP changes prior to weaning is confounded by the possibility that chemically induced increases in GFAP may be masked by changes in the concentration of this protein associated with maturation of the central nervous system, and these data may be difficult to interpret.

b. Neurophysiological End Points of Neurotoxicity. Neurophysiological studies are those that measure the electrical activity of the nervous system. The term "neurophysiology" is often used synonymously with "electrophysiology" (Dyer, 1987). Neurophysiological techniques provide information on the integrity of defined portions of the nervous system. Several neurophysiological procedures are available for application to neurotoxicological studies. Examples of neurophysiological measures of neurotoxicity are listed in Table 3. They range in scale from procedures that employ microelectrodes to study the function of single nerve cells or restricted portions of them, to procedures that employ macroelectrodes to perform simultaneous recordings of the summed activity of many cells. Microelectrode procedures typically are used to study mechanisms of action and are frequently performed in vitro. Macroelectrode procedures are generally used in studies to detect or characterize the potential neurotoxic effects of agents of interest because of potential environmental exposure. The present discussion concentrates on macroelectrode neurophysiological procedures because it is more likely that they will be the focus of decisions regarding critical effects in risk assessment. All of the procedures described below for use in animals also have been used in humans to determine chemically induced alterations in neurophysiological function.

TABLE 3.—EXAMPLES OF NEUROPHYSIOLOGICAL MEASURES OF NEUROTOXICITY

System/function	Procedure	Representative agents
Retina	Electroretinography (ERG)	Developmental lead.
Visual pathway	Flash evoked potential (FEP)	Carbon disulfide.
Visual function	Pattern evoked potential (PEP) pattern size and contrast).	Carbon disulfide.
Auditory pathway	Brain stem auditory evoked potential (BAER) (clicks).	Aminoglycoside, Antibiotics, Toluene, styrene.
Auditory function	BAER (tones)	Aminoglycoside, Antibiotics, Toluene, styrene.
Somatosensory pathway	Somatosensory evoked potential (SEP) (shocks).	Acrylamide, n-Hexane.
Somatosensory function	SEP (tactile)	Acrylamide n-Hexane.
Spinocerebellar pathway	SEP recorded from cerebellum	Acrylamide n-Hexane.
Mixed nerve	Peripheral nerve compound action potential (PNAP).	Triethyltin.
Motor axons	PNAP isolate motor components	Triethyltin.
Sensory axons	PNAP isolate sensory components	Triethyltin.
Neuromuscular	Electromyography (EMG), H-reflex, M-re- sponse.	Dithiobiuret.
General central nervous system/level of arous- al.	Electroencephalography (EEG)	Anesthetics.

(1) Nerve conduction studies. Nerve conduction studies, generally performed on peripheral nerves, can be useful in investigations of possible peripheral neuropathy. Most peripheral nerves contain mixtures of individual sensory and motor nerve fibers, which may or may not be differentially sensitive to neurotoxicants. It is possible to distinguish sensory from motor effects in peripheral nerve studies by measuring activity in purely sensory