originate from seizure activity in the brain.

In addition to producing seizures directly, neurotoxicants also may alter the frequency, severity, duration, or threshold for eliciting seizures produced through other means. Such changes can occur after acute exposure or after repeated exposure to dose levels below the acute threshold and are considered to be neurotoxic effects. Examples of agents that produce convulsions include lindane, DDT (dichloro-diphenyltrichloroethane), pyrethroids, and trimethyltin.

(4) Electroencephalography (EEG). EEG analysis is used widely in clinical settings for the diagnosis of neurological disorders and less often for the detection of subtle toxicant-induced dysfunction (WHO, 1986; Eccles, 1988). The basis for using EEG in either setting is the relationship between specific patterns of EEG waveforms and specific behavioral states. Because states of alertness and stages of sleep are associated with distinct patterns of electrical activity in the brain, it is generally thought that arousal level can be evaluated by monitoring the EEG.

Dissociation of EEG activity and behavior can, however, occur after exposure to certain chemicals. Normal patterns of transition between sleep stages or between sleeping and waking states are known to remain disturbed for prolonged periods of time after exposure to some chemicals. Changes in the pattern of the EEG can be elicited by stimuli producing arousal (e.g., lights, sounds) and anesthetic drugs. In studies with toxicants, changes in EEG pattern can sometimes precede alterations in other objective signs of neurotoxicity (Dyer, 1987).

EEG studies must be done under highly controlled conditions, and the data must be considered on a case-bycase basis. Chemically induced seizure activity detected in the EEG pattern is evidence of a neurotoxic effect.

c. Neurochemical End Points of Neurotoxicity. Many different

neurochemical end points have been measured in neurotoxicological studies, and some have proven useful in advancing the understanding of mechanisms of action of neurotoxic chemicals (Bondy, 1986; Mailman, 1987; Morell and Mailman, 1987; Costa, 1988). Normal functioning of the nervous system depends on the synthesis and release of specific neurotransmitters and activation of their receptors at specific presynaptic and postsynaptic sites. Chemicals can interfere with the ionic balance of a neuron, act as a cytotoxicant after transport into a nerve terminal, block reuptake of neurotransmitters and their precursors, act as a metabolic poison, overstimulate receptors, block transmitter release, and inhibit transmitter synthetic or catabolic enzymes. Table 4 lists several chemicals that produce neurotoxic effects at the neurochemical level (Bondy, 1986; Mailman, 1987; Morell and Mailman, 1987; Costa, 1988).

TABLE 4.—EXAMPLES OF NEUROTOXICANTS WITH KNOWN NEUROCHEMICAL MECHANISMS

Site of action	Examples
1. Neurotoxicants Acting on Ionic Balance: A. Inhibit sodium entry B. Block closing of sodium channel C. Increase permeability to sodium D. Increase intracellular calcium 2. Cytotoxicants—Depend on uptake into nerve terminal 3. Uptake blockers 4. Metabolic poisons 5. Hyperactivation of receptors 6. Blocks transmitter release (Acetylcholine [ACh]) 7. Inhibition of transmitter degradation (ACh) 8. Blocks axonal transport	Tetrodotoxin. p,p'-DDT, pyrethroids. Batrachotoxin. Chlordecone. MPTP. Hemicholinium. Cyanide. Domoic acid. Botulinum toxin. Pesticides of the organophosphate and carbamate classes. Acrylamide.

As stated previously, any neurochemical change is potentially neurotoxic, but each determination requires professional judgment. Persistent or irreversible chemically induced neurochemical changes are indicative of neurotoxicity. Because the ultimate functional significance of some biochemical changes is not known at this time, neurochemical studies should be interpreted with reference to the presumed neurotoxic consequence(s) of the neurochemical changes. For example, many neuroactive agents can increase or decrease neurotransmitter levels, but such changes are not necessarily indicative of a neurotoxic effect. If, however, these neurochemical changes may be expected to have neurophysiological, neuropathological, or neurobehavioral correlates, then the neurochemical changes could be classified as neurotoxic effects.

Some neurotoxicants, such as the organophosphate and carbamate pesticides, are known to inhibit the activity of a specific enzyme, acetylcholinesterase (for a review see Costa, 1988), which hydrolyzes the neurotransmitter acetylcholine. Inhibition of the enzyme prolongs the action of the acetylcholine at the neuron's synaptic receptors and is responsible for the autonomic stimulation and death that these agents cause.

Within EPA and elsewhere, questions have arisen as to whether inhibition of cholinesterase activity constitutes an adverse effect for defining hazard potential and evaluating risk. There is agreement among scientists that statistically significant inhibition of cholinesterase activity in multiple organs and tissues accompanied by clinical effects constitutes a hazard. However, there is scientific uncertainty and related controversy about the risk assessment implications of data describing inhibition of cholinesterase enzyme activity in the absence of observable clinical effects. While there is agreement that such inhibition is a biomarker of exposure, there is continued disagreement over whether cholinesterase inhibition, especially in blood, constitutes an adverse effect.

At this point, it can be stated that there is general agreement among scientists that objective clinical measures of dysfunction/impairment can be overt manifestations of inhibition of cholinesterase in the nervous system. On the basis of clinical manifestations, e.g., muscle weakness, tremor, blurred vision, one should be able to evaluate dose-response and dose-effect relationships and define the presence and absence of given effects. A relationship between the effect and cholinesterase inhibition should be