nerves such as the sural nerve or by measuring the muscle response evoked by nerve stimulation to measure motor effects. While a number of end points can be recorded, the most critical variables are (1) nerve conduction velocity, (2) response amplitude, and (3) refractory period.

Nerve conduction measurements are influenced by a number of factors, the most important of which is temperature. An adequate nerve conduction study will either measure the temperature of the limb under study and mathematically adjust the results according to well-established temperature factors or control limb temperature within narrow limits. Studies that measure peripheral nerve function without regard for temperature are not adequate for risk assessment.

In well-controlled studies, statistically significant decreases in nerve conduction velocity are indicative of a neurotoxic effect. While a decrease in nerve conduction velocity is indicative of demyelination, it frequently occurs later in the course of axonal degradation because normal conduction velocity may be maintained for some time in the face of axonal degeneration. For this reason, a measurement of normal nerve conduction velocity does not rule out peripheral axonal degeneration if other signs of peripheral nerve dysfunction are present.

Decreases in response amplitude reflect a loss of active nerve fibers and may occur prior to decreases in conduction velocity in the course of peripheral neuropathy. Hence, changes in response amplitude may be more sensitive measurements of axonal degeneration than conduction velocity. Measurements of response amplitude, however, can be more variable and require careful application of experimental techniques, a larger sample size, and greater statistical power than measurements of velocity to detect changes. The refractory period refers to the time required after stimulation before a nerve can fire again and provides a measure reflecting the functional status of nerve membrane ion channels. Chemically induced changes in refractory periods in a wellcontrolled study indicate a neurotoxic effect.

In summary, alterations in peripheral nerve response amplitude and refractory period in studies that are well controlled for temperature are indicative of a neurotoxic effect. Alterations in peripheral nerve function are frequently associated with clinical signs such as numbness, tingling, or burning sensations or with motor impairments such as weakness. Examples of compounds that alter peripheral nerve function in humans or experimental animals include acrylamide, carbon disulfide, n-hexane, lead, and some organophosphates.

(2) Sensory, motor, and other evoked potentials. Evoked potential studies are electrophysiological procedures that measure the response elicited from a defined stimulus such as a tone, a light, or a brief electrical pulse. Evoked potentials reflect the function of the system under study, including visual, auditory, or somatosensory; motor involving motor nerves and innervated muscles; or other neural pathways in the central or peripheral nervous system (Rebert, 1983; Dyer, 1985; Mattsson and Albee, 1988; Mattsson et al., 1992; Boyes, 1992, 1993). Evoked potential studies should be interpreted with respect to the known or presumed neural generators of the responses, and their likely relationships with behavioral outcomes, when such information is available. Such correlative information strengthens the confidence in electrophysiological outcomes. In the absence of such supportive information, the extent to which evoked potential studies provide convincing evidence of neurotoxicity is a matter of professional judgment on a case-by-case basis. Judgments should consider the nature, magnitude, and duration of such effects, along with other factors discussed elsewhere in this document.

Data are in the form of a voltage record collected over time and can be quantified in several ways. Commonly, the latency (time from stimulus onset) and amplitude (voltage) of the positive and negative voltage peaks are identified and measured. Alternative measurement schemes may involve substitution of spectral phase or template shifts for peak latency and spectral power, spectral amplitude, rootmean-square, or integrated area under the curve for peak amplitude. Latency measurements are dependent on both the velocity of nerve conduction and the time of synaptic transmission. Both of these factors depend on temperature, as discussed in regard to nerve conduction, and similar caveats apply for sensory evoked potential studies. In studies that are well controlled for temperature, increases in latencies or related measures can reflect deficits in nerve conduction, including demyelination or delayed synaptic transmission, and are indicators of a neurotoxic effect.

Decreases in peak latencies, like increases in nerve conduction velocity, are unusual, but the neural systems under study in sensory evoked potentials are complex, and situations that might cause a peak measurement to occur earlier are conceivable. Two such situations are a reduced threshold for spatial or temporal summation of afferent neural transmission and a selective loss of cells responding late in the peak, thus making the measured peak occur earlier. Decreases in peak latency should not be dismissed outright as experimental or statistical error, but should be examined carefully and perhaps replicated to assess possible neurotoxicity. A decrease in latency is not conclusive evidence of a neurotoxic effect.

Changes in peak amplitudes or equivalent measures reflect changes in the magnitude of the neural population responsive to stimulation. Both increases and decreases in amplitude are possible following exposure to chemicals. Whether excitatory or inhibitory neural activity is translated into a positive or negative deflection in the sensory evoked potential is dependent on the physical orientation of the electrode with respect to the tissue generating the response, which is frequently unknown. Comparisons should be based on the absolute change in amplitude. Therefore, either increases or decreases in amplitude may be indicative of a neurotoxic effect.

Within any given sensory system, the neural circuits that generate various evoked potential peaks differ as a function of peak latency. In general, early latency peaks reflect the transmission of afferent sensory information. Changes in either the latency or amplitude of these peaks are considered convincing evidence of a neurotoxic effect that is likely to be reflected in deficits in sensory perception. The later-latency peaks, in general, reflect not only the sensory input but also the more nonspecific factors such as the behavioral state of the subject, including such factors as arousal level, habituation, or sensitization (Dyer, 1987). Thus, changes in later-latency evoked potential peaks must be interpreted in light of the behavioral status of the subject and would generally be considered evidence of a neurotoxic effect.

(3) Seizures/convulsions. Neurophysiological recordings of brain electrical activity that demonstrate seizure-like activity are indicative of a neurotoxic effect. Occasionally, behaviors resembling convulsions might follow actions outside the nervous system, such as direct effects on muscle. When convulsion-like behaviors are observed, as described in the behavioral section, neurophysiological recordings can determine if these behaviors