confirmed by biochemical measures of reduced cholinesterase activity.

In addition, a reduction in brain cholinesterase activity may or may not be accompanied by clinical manifestations. Most experts in the field acknowledge that when significant reductions in brain cholinesterase activity alone occur, reduced cholinesterase levels either are themselves toxic or would lead to a neurotoxic effect if exposure were to persist over time or increase in magnitude. Therefore, statistically significant decreases in brain cholinesterase could be considered to be a biologically significant effect.

A reduction in RBC and/or plasma cholinesterase activity also may or may not be accompanied by clinical manifestations. At this time, there is general agreement that the observation of inhibition of RBC and/or plasma cholinesterase contributes to the overall hazard identification of cholinesterase inhibiting agents by serving as biomarkers. As such, these enzyme parameters can provide information that will help scientists evaluate whether reported clinical effects are associated with cholinesterase inhibition. There remains, however, a lack of consensus as to whether RBC and/or plasma cholinesterase represent biologically significant events. Discussions on this topic are continuing within the Agency.

A subset of organophosphate agents also produces organophosphate-induced delayed neuropathy (OPIDN) after acute or repeated exposure. Prolonged inhibition (i.e., aging) of neurotoxic esterase (or neuropathy target enzyme) has been associated with agents that produce OPIDN (Johnson, 1990), a clear neurotoxic effect.

d. *Behavioral End Points of Neurotoxicity.* EPA's testing guidelines developed for the Toxic Substances Control Act and the Federal Insecticide, Fungicide and Rodenticide Act describe

the use of functional observational batteries (FOB), motor activity, and schedule-controlled behavior for assessing neurotoxic potential (U.S. EPA, 1991a). There are many other measures of behavior, including specialized tests of motor and sensory function and of learning and memory (Tilson, 1987; Anger, 1984). Examples of behavioral end points that have been used to detect neurotoxicity are included in Table 1. The risk assessor should know that the literature is clear that a number of other behaviors besides those listed in Tables 1 and 5 could be affected by chemical exposure. For example, alterations in food and water intake, reproduction, sleep, temperature regulation, and circadian rhythmicity are controlled by specific regions of the brain and chemical-induced alterations in these behaviors could be indicative of neurotoxicity. It is reasonable to assume that a NOAEL or LOAEL could be based on one or more of these end points.

TABLE 5.—SUMMARY OF MEASURES IN A REPRESENTATIVE FUNCTIONAL OBSERVATIONAL BATTERY, AND THE TYPE OF DATA PRODUCED BY EACH

Home cage and open field	Manipulative	Physiologic
Posture (D) Convulsions, tremors (D) Palpebral closure (R) Lacrimation (R) Piloerection (Q) Salivation (R) Vocalizations (Q) Rearing (C) Urination (C) Defecation (C) Gait (D, R) Arousal (R) Mobility (R). Stereotypy (D). Bizarre behavior (D)	Ease of removal (R) Handling reactivity (R) Palpebral closure (R). Approach response (R). Click response (R). Touch response (R). Tail pinch response (R). Righting reflex (R). Landing foot splay (I). Forelimb grip strength (I). Hindlimb grip strength (I). Pupil response (Q).	Body temperature (I). Body weight (I).

D-descriptive data; R-rank order data; Q-quantal data; I-interval data; C-count data.

Behavior is an indication of the overall well-being of the organism. Changes in behavior can arise from a direct effect of a toxicant on the nervous system or indirectly from its effects on other physiological systems. Understanding the interrelationship between systemic toxicity and behavioral changes is extremely important (e.g., the relationship between liver damage and motor activity). The presence of systemic toxicity may complicate, but does not necessarily preclude, interpretation of behavioral changes as evidence of neurotoxicity. In addition, a number of behaviors (e.g., schedule-controlled behavior) may require a motivational component for successful completion of the task. In such cases, experimental paradigms designed to assess the motivation of an

animal during behavior might be necessary to interpret the meaning of some chemical-induced changes in behavior.

The following sections describe in general behavioral tests and their uses and offer guidance on interpreting data.

(1) Functional observational battery. A functional observational battery is designed to detect and quantify major overt behavioral, physiological, and neurological signs (Gad, 1982; O'Donoghue, 1989; Moser, 1989). A number of batteries have been developed, each consisting of tests generally intended to evaluate various aspects of sensorimotor function (Tilson and Moser, 1992). Many FOB tests are essentially clinical neurological examinations that rate the presence or absence, and in many cases the severity, of specific neurological signs. Some FOBs in animals are similar to clinical neurological examinations used with human patients. Most FOBs have several components or tests. A typical FOB is summarized in Table 5 and evaluates several functional domains, including neuromuscular (i.e., weakness, incoordination, gait, and tremor), sensory (i.e., audition, vision, and somatosensory), and autonomic (i.e., pupil response and salivation) function. FOB data may be in the form of interval, ordinal, or continuous measurements.

The relevance of statistically significant test results from an FOB is judged according to the number of signs affected, the dose(s) at which effects are observed, and the nature, severity, and persistence of the effects and their