incidence in relation to control animals. If only a few unrelated measures in the FOB are affected, or the effects are unrelated to dose, the results are not considered evidence of a neurotoxic effect. If several neurological signs are affected but only at the high dose and in conjunction with other overt signs of toxicity, including systemic toxicity, large decreases in body weight, decreases in body temperature, or debilitation, there is no conclusive evidence of a direct neurotoxic effect. In cases where several related measures in a battery of tests are affected and the effects appear to be dose dependent, the data are considered to be evidence of a neurotoxic effect, especially in the absence of systemic toxicity. Recently, it was proposed that data from FOB studies be grouped into several neurobiological domains, including neuromuscular (i.e., weakness, incoordination, abnormal movements, gait), sensory (i.e, auditory, visual, somatosensory), and autonomic functions (Tilson and Moser, 1992). This statistical technique is useful when separating changes that occur on the basis of chance or in conjunction with systemic toxicity from those treatmentrelated changes indicative of neurotoxic effects. In the case of the developing organism, chemicals may alter the maturation or appearance of sensorimotor reflexes. Significant alterations in or delay of such reflexes is evidence of a neurotoxic effect.

Examples of chemicals that affect neuromuscular function are 3acetylpyridine, acrylamide, and triethyltin. Organophosphate and carbamate insecticides produce autonomic dysfunction, while organochlorine and pyrethroid insecticides increase sensorimotor sensitivity, produce tremors, and in some cases, cause seizures and convulsions (Spencer and Schaumberg, 1980).

(2) Motor activity. Motor activity represents a broad class of behaviors involving coordinated participation of sensory, motor, and integrative processes. Assessment of motor activity is noninvasive and has been used to evaluate the effects of acute and repeated exposure to neurotoxicants (MacPhail et al., 1989). An organism's level of activity can, however, be affected by many different types of environmental agents, including nonneurotoxic agents. Motor activity measurements also have been used in humans to evaluate disease states, including disorders of the nervous system (Goldstein and Stein, 1985).

Motor activity is usually quantified as the frequency of movements over a

period of time. The total counts generated during a test period will depend on the recording mechanism and size and configuration of the testing apparatus. Effects of agents on motor activity can be expressed as absolute activity counts or as a percentage of control values. In some cases, a transformation (e.g., square root) may be used to achieve a normal distribution of the data. The frequency of motor activity within a session usually decreases and is reported as the average number of counts occurring in each successive block of time. The EPA's Office of Prevention, Pesticides and Toxic Substances guidelines (U.S. EPA, 1991a), for example, call for test sessions of sufficient duration to allow motor activity to approach steady-state levels during the last 20 percent of the session for control animals. A sum of the counts in each epoch will add up to the total number of counts per session.

In the adult, neurotoxic agents generally decrease motor activity (MacPhail et al., 1989). Examples include many pesticides (e.g., carbamates, chlorinated hydrocarbons, organophosphates, and pyrethroids), heavy metals (lead, tin, and mercury), and other agents (3-acetylpyridine, acrylamide, and 2,4-dithiobiuret). Some neurotoxicants (e.g., toluene, xylene, triadimefon) produce transient increases in activity by presumably stimulating neurotransmitter release, while others (e.g., trimethyltin) produce persistent increases in motor activity by destroying specific regions of the brain (e.g., hippocampus).

Following developmental exposures, neurotoxic effects are often observed as a change in the developmental profile or maturation of motor activity patterns. Frequently, developmental exposure to neurotoxic agents will produce an increase in motor activity that persists into adulthood or that results in changes in other behaviors. This type of effect is evidence of a neurotoxic effect. Like other organ systems, the nervous system may be differentially sensitive to toxicants in groups such as the young. For example, toxicants introduced to the developing nervous system may kill stem cells and thus cause profound effects on adult structure and function. Moreover, toxicants may have greater access to the developing nervous system before the blood-brain barrier is completely formed or before metabolic detoxifying systems are functional.

Motor activity measurements are typically used with other tests (e.g., FOB) to help detect neurotoxic effects. Agent-induced changes in motor activity associated with other overt signs of toxicity (e.g., loss of body weight, systemic toxicity) or occurring in non-dose-related fashion are of less concern than changes that are dose dependent, related to structural or other functional changes in the nervous system, or occur in the absence of lifethreatening toxicity.

(3) Schedule-controlled operant behavior. Schedule-controlled operant behavior (SCOB) involves the maintenance of behavior (e.g., performance of a lever-press or key-peck response) by reinforcement. Different rates and patterns of responding are controlled by the relationship between response and subsequent reinforcement. SCOB provides a measure of performance of a learned behavior (e.g., lever press or key peck) and involves training and motivational variables that must be considered in evaluating the data. Agents may interact with sensory processing, motor output, motivational variables (i.e., related to reinforcement), training history, and baseline characteristics (Rice, 1988; Cory-Slechta, 1989). Rates and patterns of SCOB display remarkable species and experimental generality.

In laboratory animals, SCOB has been used to study a wide range of neurotoxicants, including methylmercury, many pesticides, carbon disulfide, organic and inorganic lead, and triethyl and trimethyltin (MacPhail, 1985; Tilson, 1987; Rice, 1988). The primary SCOB end points for evaluation are response rate and the temporal pattern of responding. These end points may vary as a function of the contingency between responding and reinforcement presentation (i.e., schedule of reinforcement). While most chemicals decrease the efficiency of responding at some dose, some agents may increase response efficiency on schedules requiring high response rates due to a stimulant effect or an increase in central nervous system excitability. Agent-induced changes in responding between reinforcements (i.e., the temporal pattern of responding) may occur independently of changes in the overall rate of responding. Chemicals may also affect the reaction time to respond following presentation of a stimulus. Agent-induced changes in response rate or temporal patterning associated with other overt signs of toxicity (e.g., body weight loss, systemic toxicity, or occurring in a non-doserelated fashion) are of less concern than changes that are dose dependent, related to structural or other functional changes in the nervous system, or occur in the absence of life-threatening toxicity.

(4) Convulsions. Observable convulsions in animals are indicative of an adverse effect. These events can