CHAPTER 11
Neurotoxicology

INTRODUCTION

There is continuing concern about environmental neurotoxicity and the potential effects of neurotoxic chemicals on human beings, caused in part by the dearth of information about the overall magnitude of the problem. Indeed, the number of people with neurotoxic disorders, and the extent of neurologic disease and dysfunction that results from exposure to toxic chemicals in the environment, are not known. Until a few years ago, for instance, only a few of the several thousand chemicals in commercial use in the United States had been tested for neurotoxicity, though it can be hoped the recent implementation of new federal guidelines for neurotoxicity and developmental neurotoxicity will lead these gaps in data to be filled.

Exposure to neurotoxic substances either in the workplace or through consumption of contaminated food has led to several outbreaks of neurotoxicity. Examples are the pesticides leptophos and kepone, triorthotolylphosphate, methylmercury, and domoic acid. Occupational and/or environmental exposure to a number of types of chemical such as solvents (e.g., toluene, styrene), metals (e.g., lead, organotins, manganese), and pesticides (e.g., organophosphates) are also associated with neurotoxic effects involving the central and/or peripheral nervous systems. Drugs of abuse, alcohol, and some pharmaceuticals may also cause neurotoxicity, particularly in developing organisms.

This chapter focuses on a variety of approaches that can be used in neurotoxicological research. Setting the stage for the chapter, UNIT 11.1 defines the principal issues in neurotoxicology. This is followed by three units on behavioral testing of rodents, which together provide an excellent tool to enable investigators to assess the neurotoxic potential of a chemical and its effect on cognitive functions. UNIT 11.2 describes what is known as the functional observational battery, a first-tier screening test for neurobehavioral effects that has become very important in the regulatory arena. UNITS 11.3 & 11.4 focus on tests of cognitive functions, which are often affected by neurotoxic chemicals. Tests of spatial memory (radial arm maze, Morris maze, and T maze), which are among the most widely used, are described in detail in UNIT 11.3, while advanced behavioral testing procedures for assessing cognition are described in UNIT 11.4.

UNIT 11.5 details testing protocols for organophosphate-induced delayed polyneuropathy, including behavioral and postmortem morphological assessment and enzyme assays. These tests are a regulatory requirement for all organophosphorus pesticides. A discussion of the issues dealing with risk assessment for neurotoxicity is presented in UNIT 11.6, while UNIT 11.7 provides a description of the behavioral tests (some computerized) available to detect neurotoxicity in humans.

UNITS 11.8 & 11.9 describe several models of global and focal ischemia in the mouse, which leads to neuronal degeneration.

A set of three units discuss electrophysiological approaches to neurotoxicology. UNIT 11.10 offers a general overview on how electrophysiology can be used in toxicological studies. UNIT 11.11 describes methods used for intracellular and extracellular recording in slices.
from different brain areas. **UNIT 11.12** focuses on whole-cell path-clamp electrophysiology in cultured cells for measuring voltage-sensitive calcium channels.

**UNIT 11.13** provides protocols for the assessment of sensory neuropathy in rats using thermal and mechanical stimuli. **UNIT 11.14** describes protocols to induce brain hyperthermia in rats.

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