- C. Neurotoxicity Risk Assessment
- D. Assumptions
- II. Definitions and Critical Concepts
- III. Hazard Characterization
- A. Neurotoxicological Studies: End Points and Their Interpretation
- 1. Human Studies
- a. Clinical Evaluations
- b. Case Reports
- c. Epidemiologic Studies
- (1) Cross-sectional studies
- (2) Case-control (retrospective) studies
- (3) Cohort (prospective, follow-up) studies
- d. Human Laboratory Exposure Studies
- 2. Animal Studies
- a. Structural End Points of Neurotoxicity
- b. Neurophysiological End Points of Neurotoxicity
- (1) Nerve conduction studies
- (2) Sensory, motor, and other evoked potentials
- (3) Seizures/convulsions
- (4) Electroencephalography (EEG)
- c. Neurochemical End Points of Neurotoxicity
- d. Behavioral End Points of Neurotoxicity
- (1) Functional observational battery
- (2) Motor activity
- (3) Schedule-controlled operant behavior
- (4) Convulsions
- (5) Specialized tests for neurotoxicity

- (a) Motor function
- (b) Sensory function
- (c) Cognitive function
- e. Developmental Neurotoxicity
- 3. Other Considerations
- Pharmacokinetics
- b. Comparisons of Molecular Structure
- c. Statistical Considerations
- d. In Vitro Data in Neurotoxicology
- B. Dose-Response Evaluation
- C. Characterization of the Health-Related Data Base
- IV. Dose-Response Analysis
 - A. LOAEL/NOAEL and Benchmark Dose (BMD) Determination
- B. Determination of the Reference Dose or Reference Concentration
- V. Exposure Assessment
- VI. Risk Characterization
 - A. Overview
 - B. Integration of Hazard Characterization, Dose-Response Analysis, and Exposure Assessment
 - C. Quality of the Data Base and Degree of Confidence in the Assessment
 - D. Descriptors of Neurotoxicity Risk
 - 1. Estimation of the Number of Individuals
 - 2. Presentation of Specific Scenarios
 - Risk Characterization for Highly **Exposed Individuals**
 - 4. Risk Characterization for Highly Sensitive or Susceptible Individuals
 - 5. Other Risk Descriptors
 - E. Communicating Results
- F. Summary and Research Needs
- VII. References

List of Tables

- Table 1. Examples of possible indicators of a neurotoxic effect
- Table 2. Neurotoxicants and diseases with specific neuronal targets
- Table 3. Examples of neurophysiological measures of neurotoxicity
- Table 4. Examples of neurotoxicants with known neurochemical mechanisms

- Table 5. Summary of measures in a representative functional observational battery, and the type of data produced by each
- Table 6. Examples of specialized behavioral tests to measure neurotoxicity
- Table 7. Examples of developmental neurotoxicants
- Table 8. Characterization of the Health-Related Database

I. Introduction

These proposed Guidelines describe the principles, concepts, and procedures that the U.S. Environmental Protection Agency (EPA; Agency) would follow in evaluating data on potential neurotoxicity associated with exposure to environmental toxicants. The Agency's authority to regulate substances that have the potential to interfere with human health is derived from a number of statutes that are implemented through multiple offices within the EPA. The procedures outlined here are intended to help develop a sound scientific basis for neurotoxicity risk assessment, promote consistency in the Agency's assessment of toxic effects on the nervous system, and inform others of the approaches used by the Agency in those assessments.

A. Organization of These Guidelines

This Introduction (section I) summarizes the purpose of these proposed Guidelines within the overall framework of risk assessment at the EPA. It also outlines the organization of the guidance and describes several default assumptions to be used in the risk assessment process as discussed in the recent National Research Council report "Science and Judgment in Risk Assessment (NRC, 1994).

Section II sets forth definitions of particular terms widely used in the field of neurotoxicology. These include "neurotoxicity" and "behavioral alterations." Also included in this section are discussions concerning reversible and irreversible effects and direct versus indirect effects.

Risk assessment is the process by which scientific judgments are made concerning the potential for toxicity to occur in humans. The National Research Council (NRC, 1983) has defined risk assessment as including some or all of the following components (paradigm): hazard identification, dose-response assessment, exposure assessment, and risk characterization. In its 1994 report Science and Judgment in Risk Assessment" the NRC extended its view of the paradigm to include characterization of each component (NRC, 1994). In addition, it noted the importance of an approach that is less

fragmented and more holistic, less linear and more interactive, and one that deals with recurring conceptual issues that cut across all stages of risk assessment. These Guidelines propose a more interactive approach by organizing the process around components that focus on evaluation of the toxicity data (hazard characterization), the quantitative dose-response analysis, the exposure assessment, and the risk characterization. This is done because, in practice, hazard identification for neurotoxicity and other noncancer health effects is usually done in conjunction with an evaluation of doseresponse relationships in the studies used to identify the hazard. Determining a hazard often depends on whether a dose-response relationship is present (Kimmel et al., 1990). Thus, the hazard characterization provides an evaluation of a hazard within the context of the dose, route, duration, and timing of exposure. This approach combines the information important in comparing the toxicity of a chemical to potential human exposure scenarios (Section V). Secondly, it avoids the potential for labeling chemicals as "neurotoxicants" on a purely qualitative basis. This organization of the risk assessment process is similar to that discussed in the Guidelines for Developmental Toxicity Risk Assessment (56 FR 63798), the main difference being that the quantitative dose-response analysis is discussed under a separate section in these guidelines.

Hazard characterization involves examining all available experimental animal and human data and the associated doses, routes, timing, and durations of exposure to determine if an agent causes neurotoxicity in that species and under what conditions. From the hazard characterization and criteria provided in these Guidelines, the health-related data base can be characterized as sufficient or insufficient for use in risk assessment (section III.C). Combining hazard identification and some aspects of doseresponse evaluation into hazard characterization does not preclude the evaluation and use of data when quantitative information for setting reference doses (RfDs) and reference concentrations (RfCs) are not available.

The next step, the dose-response analysis (section IV) is the quantitative analysis, and includes determining the no-observed-adverse-effect-level (NOAEL) and/or the lowest-observedadverse-effect-level (LOAEL) for each study and type of effect. Because of the limitations associated with the use of the NOAEL, the Agency is beginning to use an additional approach, i.e., the