benchmark dose approach (Crump, 1984; U.S. EPA, 1995a), for more quantitative dose-response evaluation when sufficient data are available. The benchmark dose approach takes into account the variability in the data and the slope of the dose-response curve, and provides a more consistent basis for calculation of the RfD or RfC. If data are considered sufficient for risk assessment, and if neurotoxicity is the effect occurring at the lowest dose level (i.e., the critical effect), an oral or dermal RfD or an inhalation RfC, based on neurotoxic effects, is then derived. This RfD or RfC is derived using the NOAEL or benchmark dose divided by uncertainty factors to account for interspecies differences in response, intraspecies variability and other factors of study design or the data base. A statement of the potential for human risk and the consequences of exposure can come only from integrating the hazard characterization and doseresponse analysis with the human exposure estimates in the final risk characterization.

The section on exposure assessment (section V) identifies human populations exposed or potentially exposed to an agent, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the agent. The exposure assessment provides an estimate of human exposure levels for particular populations from all potential sources.

In risk characterization (section VI), the hazard characterization, doseresponse analysis, and the exposure assessment for given populations are combined to estimate some measure of the risk for neurotoxicity. As part of risk characterization, a summary of the strengths and weaknesses of each component of the risk assessment is given along with major assumptions, scientific judgments, and, to the extent possible, qualitative and quantitative estimates of the uncertainties. This characterization of the health-related data base is always presented in conjunction with information on the dose, route, duration and timing of exposure as well as the dose-response analysis including the RfD or RfC. If human exposure estimates are available, the exposure basis used for the risk assessment is clearly described, e.g., highly exposed individuals or highly sensitive or susceptible individuals. The NOAEL may be compared to the various estimates of human exposure to calculate the margin(s) of exposure (MOE). The considerations for judging the acceptability of the MOE are similar to those for determining the appropriate

size of the uncertainty factor for calculating the RfD or RfC.

The Agency recently issued a policy statement and associated guidance for risk characterization (U.S. EPA, 1995b, 1995c), which is currently being implemented throughout EPA. This policy statement is designed to ensure that critical information from each stage of a risk assessment is used in forming conclusions about risk and that this information is communicated from risk assessors to risk managers (policy makers), from middle to upper management, and from the Agency to the public. Additionally, the policy provides a basis for greater clarity, transparency, reasonableness, and consistency in risk assessments across Agency programs. Final neurotoxicity risk assessment guidelines may reflect additional changes in risk characterization practices resulting from implementation activities.

Risk assessment is just one component of the regulatory process and defines the potential adverse health consequences of exposure to a toxic agent. The other component, risk management, combines risk assessment with statutory directives regarding socioeconomic, technical, political, and other considerations, to decide whether to control future exposure to the suspected toxic agent and, if so, the nature and level of control. One major objective of these risk assessment Guidelines is to help the risk assessor determine whether the experimental animal or human data indicate the potential for a neurotoxic effect. Such information can then be used subsequently to categorize evidence to identify and characterize neurotoxic hazards as described in section III.3.C. Characterization of the Health-Related Data Base, and Table 8 of these Guidelines. Risk management is not dealt with directly in these Guidelines because the basis for decision making goes beyond scientific considerations alone, but the use of scientific information in this process is discussed. For example, the acceptability of the MOE is a risk management decision, but the scientific bases for establishing this value are discussed here.

B. The Role of Environmental Agents in Neurotoxicity

Chemicals are an integral part of life, with the capacity to improve as well as endanger health. The general population is exposed to chemicals with neurotoxic properties in air, water, foods, cosmetics, household products, and drugs used therapeutically or illicitly. Naturally occurring neurotoxins, such as animal and plant toxins, present additional hazards. During daily life, a person experiences a multitude of exposures, both voluntary and unintentional, to neuroactive substances, singly and in combination. Levels of exposure vary and may or may not pose a hazard depending on dose, route, and duration of exposure.

A link between human exposure to some chemical substances and neurotoxicity has been firmly established (Anger, 1986; OTA, 1990). Because many natural and synthetic chemicals are present in today's environment, there is growing scientific and regulatory interest in the potential for risks to humans from exposure to neurotoxic agents. If sufficient exposure occurs, the effects resulting from such exposures can have a significant adverse impact on human health. It is not known how many chemicals may be neurotoxic in humans (Reiter, 1987). The EPA's inventory of toxic chemicals is greater than 65,000 and increasing yearly. An overwhelming majority of the materials in commercial use have not been tested for their neurotoxic potential (NRC, 1984). Estimates of the number of chemicals with neurotoxic properties have been made for subsets of substances. For instance, a large percentage of the more than 500 registered active pesticide ingredients are neurotoxic to varying degrees. Of 588 chemicals listed by the American **Conference of Governmental Industrial** Hygienists, 167 affected the nervous system or behavior at some exposure level (Anger, 1984). Anger (1990) estimated that of the approximately 200 chemicals to which one million or more American workers are exposed, more than one-third may have adverse effects on the nervous system, if sufficient exposure occurs. Anger (1984) also recognized neurotoxic effects as one of the 10 leading workplace disorders. A number of therapeutic substances, including some anticancer and antiviral agents and abused drugs, can cause adverse or neurotoxicological side effects at therapeutic levels (OTA, 1990). Thus, estimating the risks of exposure to chemicals with neurotoxic potential is of concern with regard to the overall impact of these exposures on human health.

C. Neurotoxicity Risk Assessment

In addition to its primary role in cognitive functions, the nervous system controls most, if not all, other bodily processes. It is sensitive to perturbation from various sources and has limited ability to regenerate. There is evidence that even small anatomical, biochemical, or physiological insults to the nervous system may result in