demonstrated over a range of stimulus and response conditions and testing conditions. In developmental exposures, it should be shown that the animals have matured enough to perform the specified task. Developmental neurotoxicants can accelerate or delay the ability to learn a response or interfere with cognitive function at the time of testing. Older animals frequently perform poorly on some types of tests, and it must be demonstrated that control animals in this population are capable of performing the procedure. Neurotoxicants might accelerate agerelated dysfunction or alter motivational variables that are important for learning to occur. Further, it is not necessarily the case that a decrease in responding on a learning task is adverse while an increase in performance on a learning task is not. It is well known that lesions in certain regions of the brain can facilitate the acquisition of certain types of behaviors by removing preexisting response tendencies (e.g., inhibitory responses due to stress) that moderate the rate of learning under normal circumstances. Examples of learning and memory procedures include simple habituation, classical conditioning, and operant (or instrumental) conditioning, including tests for spatial learning and memory.

e. Developmental Neurotoxicity. Although the previous discussion of various neurotoxicity end points and tests applies to studies in which developmental exposures are used, there are particular issues of importance in the evaluation of developmental neurotoxicity studies. Exposure to chemicals during development can result in a spectrum of effects, including death, structural abnormalities, altered growth, and functional deficits (U.S. EPA, 1991b). Children are often differentially sensitive to chemical exposure. A number of agents have been shown to cause developmental neurotoxicity when exposure occurred during the period between conception and sexual maturity (e.g., Riley and Vorhees, 1986; Vorhees, 1987). Table 7 lists several examples of agents known to produce developmental neurotoxicity in experimental animals. Animal models of developmental neurotoxicity have been shown to be sensitive to several environmental agents known to produce developmental neurotoxicity in humans, including lead, ethanol, xirradiation, methylmercury, and polychlorinated biphenyls (PCBs) (Kimmel et al., 1990; Needleman, 1990; Jacobson et al., 1985; Needleman, 1986). In many of these cases, functional deficits are observed at dose levels

below those at which other indicators of developmental toxicity are evident or at minimally toxic doses in adults. Such effects may be transient, but generally are considered to be adverse effects.

TABLE 7.—EXAMPLES OF DEVELOPMENTAL NEUROTOXICANTS

Methanol, ethanol.
X-radiation,
azacytidine.
DDT, kepone.
Lead, methylmercury,
cadmium.
PCBs, PBBs.
Carbon disulfide, tolu- ene.

Testing for developmental neurotoxicity has not been required routinely by regulatory agencies in the United States, but is required by the EPA when other information indicates the potential for developmental neurotoxicity (U.S. EPA, 1986, 1988a, 1988b, 1989, 1991a, 1991b). Useful data for decision making may be derived from well-conducted adult neurotoxicity studies, standard developmental toxicity studies, and multigeneration studies, although the dose levels used in the latter may be lower than that in studies with shorter term exposure.

Important design issues to be evaluated for developmental neurotoxicity studies are similar to those for standard developmental toxicity studies (e.g., a dose-response approach with the highest dose producing minimal overt maternal or perinatal toxicity, number of litters large enough for adequate statistical power, randomization of animals to dose groups and test groups, litter generally considered as the statistical unit). In addition, the use of a replicate study design provides added confidence in the interpretation of data. A pharmacological/physiological challenge may also be valuable in evaluating neurologic function and "unmasking" effects not otherwise detectable. For example, a challenge with a psychomotor stimulant such as d-amphetamine may unmask latent developmental neurotoxicity (Hughes and Sparber, 1978; Adams and Buelke-Sam, 1981; Buelke-Sam et al., 1985).

Direct extrapolation of developmental neurotoxicity to humans is limited in the same way as for other end points of toxicity, i.e., by the lack of knowledge about underlying toxicological mechanisms and their significance (U.S. EPA, 1991b). However, comparisons of human and animal data for several agents known to cause developmental neurotoxicity in humans showed many similarities in effects (Kimmel et al., 1990). Comparisons at the level of functional category (sensory, motivational, cognitive, and motor function and social behavior) showed close agreement across species for the agents evaluated, even though the specific end points used to assess these functions varied considerably across species (Stanton and Spear, 1990). Thus, it can be assumed that developmental neurotoxicity effects in animal studies indicate the potential for altered neurobehavioral development in humans, although the specific types of developmental effects seen in experimental animal studies will not necessarily be the same as those that may be produced in humans. Therefore, when data suggesting adverse effects in developmental neurotoxicity studies are encountered for particular agents, they should be considered in the risk assessment process.

Functional tests with a moderate degree of background variability (e.g., a coefficient of variability of 20 percent or less) may be more sensitive to the effects of an agent on behavioral end points than are tests with low variability that may be impossible to disrupt without using life-threatening doses. A battery of functional tests, in contrast to a single test, is usually needed to evaluate the full complement of nervous system functions in an animal. Likewise, a series of tests conducted in animals in several age groups may provide more information about maturational changes and their persistence than tests conducted at a single age.

It is a well-established principle that there are critical developmental periods for the disruption of functional competence, which include both the prenatal and postnatal periods to the time of sexual maturation, and the effect of a toxicant is likely to vary depending on the time and degree of exposure (Rodier, 1978, 1990). It is also important to consider the data from studies in which postnatal exposure is included, as there may be an interaction of the agent with maternal behavior, milk composition, pup suckling behavior, as well as possible direct exposure of pups via dosed food or water (Kimmel et al., 1992)

Agents that produce developmental neurotoxicity at a dose that is not toxic to the maternal animal are of special concern. However, adverse developmental effects are often produced at doses that cause maternal toxicity (e.g., <20 percent reduction in weight gain during gestation and lactation). In these cases, the