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developmental effects are still considered to represent neurotoxicity and should not be discounted as being secondary to maternal toxicity. At doses causing moderate maternal toxicity (i.e., ≥20 percent reduction in weight gain during gestation and lactation), interpretation of developmental effects may be confounded. Current information is inadequate to assume that developmental effects at doses causing minimal maternal toxicity result only from maternal toxicity; rather, it may be that the mother and developing organism are equally sensitive to that dose level. Moreover, whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while the effects on the offspring may be permanent. These are important considerations for agents to which humans may be exposed at minimally toxic levels either voluntarily or involuntarily, because several agents are known to produce adverse developmental effects at minimally toxic doses in adult humans (e.g., alcohol) (Coles et al., 1991).

Although interpretation of developmental neurotoxicity data may be limited, it is clear that functional effects must be evaluated in light of other toxicity data, including other forms of developmental toxicity (e.g., structural abnormalities, perinatal death, and growth retardation). For example, alterations in motor performance may be due to a skeletal malformation rather than nervous system change. Changes in learning tasks that require a visual cue might be influenced by structural abnormalities in the eye. The level of confidence that an agent produces an adverse effect may be as important as the type of change seen, and confidence may be increased by such factors as reproducibility of the effect either in another study of the same function or by convergence of data from tests that purport to measure similar functions. A dose-response relationship is an extremely important measure of a chemical's effect; in the case of developmental neurotoxicity both monotonic and biphasic doseresponse curves are likely, depending on the function being tested. The EPA Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b) may be consulted for more information on interpreting developmental toxicity studies. The endpoints frequently used to assess developmental neurotoxicity in exposed children was recently reviewed by Winneke (1995).

3. Other Considerations

a. Pharmacokinetics. Extrapolation of test results between species can be aided considerably by data on the pharmacokinetics of a particular agent in the species tested and, if possible, in humans. Information on a toxicant's half-life, metabolism, absorption, excretion, and distribution to the peripheral and central nervous system may be useful in predicting risk. Of particular importance for the pharmacokinetics of neurotoxicants is the blood-brain barrier, which ordinarily excludes ionic and nonlipid soluble chemicals from the central nervous system. The brain contains circumventricular organs whose purpose seems to be to sense the chemical composition of the peripheral circulation and activate mechanisms to bring the composition of the blood back to equilibrium if disturbed. These areas are technically inside the brain, but they lie outside of the blood-brain-barrier. Therefore, chemicals from the periphery can pass directly into the brain at these sites. The majority of these structures are located within or near the hypothalamus, an area that is crucial for maintenance of neuroendocrine function. Pharmacokinetic data may be helpful in defining the dose-response curve, developing a more accurate basis for comparing species sensitivity (including that of humans), determining dosimetry at target sites, and comparing pharmacokinetic profiles for various dosing regimens or routes of administration. The correlation of pharmacokinetic parameters and neurotoxicity data may be useful in determining the contribution of specific pharmacokinetic processes to the effects observed.

b. Comparisons of Molecular Structure. Comparisons of the chemical or physical properties of an agent with those of known neurotoxicants may provide some indication of the potential for neurotoxicity. Such information may be helpful for evaluating potential toxicity when only minimal data are available. The structure-activity relationships (SAR) of some chemical classes have been studied, including hexacarbons, organophosphates, carbamates, and pyrethroids. Therefore, class relationships or SAR may help predict neurotoxicity or interpret data from neurotoxicological studies. Under certain circumstances (e.g., in the case of new chemicals), this procedure is one of the primary methods used to evaluate the potential for toxicity when little or no empirical toxicity data are available. It should be recognized, however, that effects of chemicals in the same class

can vary widely. Moser (1994), for example, reported that the behavioral effects of prototypic cholinesteraseinhibiting pesticides differed qualitatively in a battery of behavioral tests.

c. Statistical Considerations. Properly designed studies on the neurotoxic effects of compounds will include appropriate statistical tests of significance. In general, the likelihood of obtaining a significant effect will depend jointly on the magnitude of the effect and the variability obtained in control and treated groups. A number of texts are available on standard statistical tests (e.g., Siegel, 1956; Winer, 1971; Sokal and Rohlf, 1969; Salsburg, 1986; Gad and Weil, 1988).

Neurotoxicity data present some unique features that must be considered in selecting statistical tests for analysis. Data may involve several different measurement scales, including categorical (affected or not), rank (more or less affected), and interval and ratio scales of measurement (affected by some percentage). For example, convulsions are usually recorded as being present or absent (categorical), whereas neuropathological changes are frequently described in terms of the degree of damage (rank). Many tests of neurotoxicity involve interval or ratio measurements (e.g., frequency of photocell interruptions or amplitude of an evoked potential), which are the most powerful and sensitive scales of measurement. In addition, measurements are frequently made repeatedly in control and treated subjects, especially in the case of behavioral and neurophysiological end points. For example, OPPTS guidelines for FOB assessment call for evaluations before exposure and at several times during exposure in a subchronic study (U.S. EPA, 1991a).

Descriptive data (categorical) and rank order data can be analyzed using standard nonparametric techniques (Siegel, 1956). In some cases, if it is determined that the data fit the linear model, the categorical modeling procedure can be used for weighted least-squares estimation of parameters for a wide range of general linear models, including repeated-measures analyses. The weighted least-squares approach to categorical and rank data allows computation of statistics for testing the significance of sources of variation as reflected by the model. In the case of studies assessing effects in the same animals at several time points, univariate analyses can be carried out at each time point when the overall dose effect or the dose-by-time interaction is significant.