

ignores both the slope of the dose-response function and baseline variability in the end point of concern. Because the baseline variability is not taken into account, the NOAEL from a study using small group sizes may be higher than the NOAEL from a similar study in the same species that uses larger group sizes. The NOAEL is also directly dependent on the dose spacing used in the study. Finally, and perhaps most importantly, use of the NOAEL does not allow estimates of risk or extrapolation of risk to lower dose levels.

Because of these and other limitations in the NOAEL approach, mathematical curve-fitting techniques (Crump, 1984; Gaylor and Slikker, 1990; Glowa, 1991; U.S. EPA, 1995a) are beginning to be used with, or as an alternative to, the NOAEL in calculating the RfD or RfC. The Agency is in the process of implementing these newer techniques and strongly encourages the calculation of BMDs for neurotoxicity and other health effect end points. These techniques typically apply a mathematical function that describes the dose-response relationship and then interpolate to a level of exposure associated with a small increase in effect over that occurring in the control group or under baseline conditions. The BMD has been defined as a lower confidence limit on the effective dose associated with some defined level of effect, e.g., a 5 percent or 10 percent increase in response (i.e., a BMD₀₅ or BMD₁₀ for a particular effect). Because the model is only used to interpolate within the dose range of the study, no assumptions about the existence (or nonexistence) of a threshold are needed. Thus, any model that fits the data well is likely to provide a reasonable estimate of the BMD.

Many neurotoxic end points provide continuous measures of response, such as response speed, nerve conduction velocity, IQ score, degree of enzyme inhibition, or the accuracy of task performance. Although it is possible to impose a dichotomy on a continuous effects distribution and to classify some level of response as "affected" and the remainder as "unaffected," it may be very difficult and inappropriate to establish such clear distinctions, because such a dichotomy would misrepresent the true nature of the neurotoxic response. Alternatively, quantitative models designed to analyze continuous effect variables may be preferable. Other techniques that allow this approach, with transformation of the information into estimates of the incidence or frequency of affected individuals in a population, have been

proposed (Crump, 1984; Gaylor and Slikker, 1990). Categorical regression analysis has been proposed since it can evaluate different types of data and derive estimates for short-term exposures (Rees and Hattis, 1994). Decisions about the most appropriate approach require professional judgment, taking into account the biological nature of the continuous effect variable and its distribution in the population under study.

Although dose-response functions in neurotoxicology are generally linear or monotonic, curvilinear functions, especially U-shaped or inverted U-shaped curves, have been reported as noted earlier (Section III B). Dose-response analyses should consider the uncertainty that U-shaped dose-response functions might contribute to the estimate of the NOAEL/LOAEL or BMD. Typically, estimates of the NOAEL/LOAEL are taken from the lowest part of the dose-response curve associated with impaired function or adverse effect.

B. Determination of the Reference Dose or Reference Concentration

Since the availability of dose-response data in humans is limited, extrapolation of data from animals to humans usually involves the application of uncertainty factors to the NOAEL/LOAEL or BMD. The NOAEL or BMD/uncertainty factor approach results in a RfD or RfC, which is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The oral RfD and inhalation RfC are applicable to chronic exposure situations and are based on an evaluation of all the noncancer health effects, including neurotoxicity data. RfDs and RfCs in the Integrated Risk Information System (IRIS-2) data base for several agents are based on neurotoxicity end points and include a few cases in which the RfD or RfC is calculated using the BMD approach (e.g., methylmercury, carbon disulfide). The size of the final uncertainty factor used will vary from agent to agent and will require the exercise of scientific judgment, taking into account interspecies differences, the shape of the dose-response curve, and the neurotoxicity end points observed. Default uncertainty factors are typically multiples of 10 and are used to compensate for human variability in sensitivity, the need to extrapolate from animals to humans, and the need to extrapolate from less than lifetime (e.g., subchronic) to lifetime exposures. An

additional factor of up to 10 may be included when only a LOAEL (and not a NOAEL) is available from a study, or depending on the completeness of the data base, a modifying factor of up to 10 may be applied, depending on the confidence one has in the data base. Barnes and Dourson (1988) provide a more complete description of the calculation, use, and significance of RfDs in setting exposure limits to toxic agents by the oral route. Jarabek et al. (1990) provide a more complete description of the calculation, use, and significance of RfCs in setting exposure limits to toxic agents in air. Neurotoxicity can result from acute, shorter term exposures, and it may be appropriate in some cases, e.g., for air pollutants or water contaminants, to set shorter term exposure limits for neurotoxicity as well as for other noncancer health effects.

V. Exposure Assessment

Exposure assessment describes the magnitude, duration, frequency, and routes of exposure to the agent of interest. This information may come from hypothetical values, models, or actual experimental values, including ambient environmental sampling results. Guidelines for exposure assessment have been published separately (U.S. EPA, 1992) and will, therefore, be discussed only briefly here.

The exposure assessment should include an exposure characterization that:

- a. Provides a statement of the purpose, scope, level of detail, and approach used in the exposure assessment;
- b. Presents the estimates of exposure and dose by pathway and route for individuals, population segments, and populations in a manner appropriate for the intended risk characterization;
- c. Provides an evaluation of the overall level of confidence in the estimate of exposure and dose and the conclusions drawn; and
- d. Communicates the results of the exposure assessment to the risk assessor, who can then use the exposure characterization, along with the characterization of the other risk assessment elements, to develop a risk characterization.

A number of considerations are relevant to exposure assessment for neurotoxicants. An appropriate evaluation of exposure should consider the potential for exposure via ingestion, inhalation, and dermal penetration from relevant sources of exposures, including multiple avenues of intake from the same source. On-going Agency activities that support neurotoxicity exposure