

application of safety factors to estimates of the lower confidence limit of a concentration producing an effect of defined size less than the mean, this lower limit has been called a "benchmark" concentration. Both of these approaches have appeal in contrast to the use of no-effect level (NOEL) experiments because poor NOEL experiments recommend high exposure levels, both require the precise detection of small effects, and reward the reduction of experimental variance by using the lower confidence bound as the starting point for recommending exposure limit values. Acute behavioral effects of solvents are frequently the ultimate basis for short-term exposure limit values. Studies of toluene's acute effects on learned animal behavior during exposure have not been strikingly sensitive, increasing the number of observations at low concentrations and the number of animals studied is a reasonable approach to refining sensitivity. Human performance impairment has been reported to occur following toluene exposure at concentrations as low as 100 ppm (Dick *et al.*, 1984, Baelum *et al.*, 1985). Robust concentration-related effects occurred following brief human exposures to 300 ppm (Gamberale and Hultengren, 1972). By refining the techniques of behavioral pharmacology, we found robust effects in rats at concentrations equivalent to the lowest concentrations at which signs of impairment are reported during experimental human exposures. The short-term exposure limit value for toluene is 150 ppm, the time-weighted average threshold limit value is 100 ppm. The present experiment produced benchmark estimates near or below the current short-term exposure limit value before the application of any safety factors. When scaling from rat to man, it is generally presumed (perhaps erroneously) that the rat is a less sensitive species, this suggests that such preparations might be used for direct safety evaluation, on the premise that if the effect could not be detected in rats, it probably could not be detected in humans. Perhaps more reasonably, current approaches to human experimental work may be too insensitive to provide adequate protection against acute central nervous system impairment. Although difficult and costly to perform, experiments in humans using the experimental design considerations employed here might improve the sensitivity of human studies, i.e. the use of subjects as their own control, and the routine use of multiple replications at several low doses.

ASSESSING METHODS FOR RISK ASSESSMENT John R. Glowa, Biological Psychiatry Branch, NIMH

Risk assessment attempts to characterize the likelihood of obtaining adverse effects from chemical exposures. Traditionally levels of agents which are presumed to be safe have been established either by determining no-effect-levels (NOEL) and applying safety factors to produce acceptable daily intakes (ADI-SF) or by estimating the effects of very low levels using low-dose extrapolation models. For non-cancerous endpoints, there are several reasons why such approaches are unsuitable. First, the estimate of a NOEL is difficult to obtain because it necessarily involves either the determination of a maximal dose with no observable effects, or the use of a sufficiently large "n" to obtain statistically significant results. Some endpoints have variable background levels complicating the separation of the signal from the noise. Secondly, the most important indication of the change in effect over doses, the slope of the dose-effect function, does not enter into the analysis. Low-dose extrapo-

lation models take threshold and slope into account, fitting curves to measurable dose-effect data in an attempt to model the effects of low doses which have not been directly measured. In terms of the precision of the estimate, this method may be less appealing than the ADI-SF approach. A promising new method is presented which employs the "tolerance" of measurable effects to predict doses with a minimally detectable effect (10%) in acceptably small proportions of the population. It avoids extrapolation beyond the limits of the experimental data. The method is illustrated using a small and large data set. The effect is the decrement in normal behavioral functioning, a critical endpoint for neurotoxicity, produced by inhalational exposure to toluene. The method is compared with traditional approaches and its applicability for use with other endpoints is discussed. It appears superior on the basis of producing consistent figures that are not overly conservative, and thus, should be considered by both policy makers and toxicologists.

ESTIMATING PROBABILITIES OF POPULATION RESPONSE RATES FROM DATA AND JUDGMENTS

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One approach to risk assessment for adverse effects due to toxic substances involves (1) defining the population at risk (e.g., children under the age of 7), (2) defining critical levels of the adverse effect in question (e.g., a hearing deficit of at least a certain amount, or at least a 50 msec loss in reaction time), and then (3) estimating probability distributions over the proportion of the population showing each critical effect under well defined exposure conditions. An advantage of this approach is that one can compare risks associated with toxics under alternative exposure conditions (e.g., an "as is" condition versus conditions that might obtain given specific regulatory actions). This approach can be implemented with straightforward statistical techniques when appropriate data are available for the population and conditions in question. However, when extrapolation beyond the data is required (as from effects in rats to those in humans, or from adults to children), then statistics alone is insufficient. Expert judgment, expressed as probabilities, may be helpful in such instances. Further, if these judgments are not combined into a single distribution, but rather are propagated independently through the analysis, the final result can display usefully the degree of consensus over experts. The techniques advocated above will be illustrated by means of a risk assessment concerning the effects of lead on hemoglobin decrement and on IQ decrement.

MATHEMATICAL APPROACHES TO SYSTEMIC TOXICANT RISK ASSESSMENT L. S. Erdreich, R. C. Hertzberg and M. L. Dourson, U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati

The current approach to non-cancer risk assessment is based on estimation of the population threshold for toxicity, rather than on extrapolation from all response data. In this approach a presumed safe 'Reference Dose' is derived by scaling a no-observed-adverse-effect level (NOAEL) with adjustments for interindividual variability, interspecies differences and exposure duration. The NOAEL is generally