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 observeable 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 extrapolation 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 measureable 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 Thomas S Wallsten Department of Psychology, University of North Carolina at Chapel Hill

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 variabilty, interspecies differences and exposure duration The NOAEL is generally

selected from animal data because of the limitations on using human data, mainly the difficulty of identifying sensitive endpoints with noninvasive techniques With optimal data—chronic duration, human subjects, sensitive endpoints—there will be much less uncertainty in the estimates Mathematical approaches focus either on refinements to the existing approach or modeling of the dose-response relationship Refinements under study include statistical estimation of the expected value and variability of the NOAEL, and modeling the probability distribution of the standard scaling factors Other approaches under investigation include dose-incidence and dose-severity models The selection of biologically valid dose-response models is complicated by the multiplicity of endpoints, the varying degrees of severity and the shift of toxic endpoint with dose The presentation will discuss mathematical and biologic considerations in developing models for animal data and extrapolating to humans, limitations of existing models, and utilizing human data in the models

SYMPOSIUM

Severity Issues in Substance Use Disorders
Sunday August 30, 1987 • 1 00 p m –2 50 p m
Marriott Marquis Hotel • Julliard/Imperial Room
Chair *Dace Svikis,* Johns Hopkins University

SEVERITY INDICATORS AS PREDICTORS OF NATURAL HISTORY IN TREATED ALCOHOLICS Thomas E Babor, Ph D University of Connecticut Health Center

This paper begins with a review of treatment evaluation studies with alcoholic patients The literature reveals a remarkable lack of consistency across studies in the significance of various severity indicators in predicting treatment response and natural history of alcoholism The methodological limitations of this research are discussed in terms of sampling bias, statistical artifact and failure to measure relevant variables Data from a prospective, longitudinal study of 321 alcoholics are used to illustrate the relative contributions of different types of variables to the prediction of course over a three-year period Included in an extensive battery of predictor variables are measures of familial alcoholism, psychopathology, life stress, cognitive function, psychiatric diagnoses, lifetime alcohol consumption, recent alcohol and drug use, severity of dependence, blood chemistry abnormalities, and history of institutional treatment for alcohol problems The results indicate that a variety of biological, behavioral and psychosocial indicators contribute to prediction of various outcome measures three years later Although a number of severity indicators predict outcome status, no one domain predominates The methodological and theoretical implications of these findings for alcoholism treatment research are discussed

PSYCHOPATHOLOGY AS A MEASURE OF SEVERITY Thomas McLellan, Ph D VA Medical Center, Philadelphia

This paper discusses the concept of severity and presents the available data relating drug use severity to treatment outcome in one or more forms of treatments and among different classes of drug abusers The case is presented that much of the relationship that has been demonstrated between this variable and outcome depends upon the specific definition of severity, and its relation to the particular outcome criteria measures Part of the difficulty involved in evaluating the relationship between the severity of the drug use disorder and treatment outcome is that there have been several reasonable yet different definitions of severity each involving different degrees of emphasis upon factors such as number and types of drugs used, physical dependence (i e , tolerance-withdrawal), social problems resulting from drug use, loss of control over the use, etc

INHERITANCE OF SEVERITY OF ALCOHOLISM Roy W Pickens, Ph D and Dace S Svikis National Institute on Drug Abuse and Johns Hopkins University

Previously we have shown that genetic factors are involved in the etiology of alcoholism and drug dependence Monozygotic (MZ) twins were found to be about 1 4 times more likely to be concordant for DSM-III diagnosis of Alcohol Abuse/Dependence than were dizygotic (DZ) twins In the present paper we examine the role of genetic factors as determinants of severity of alcoholism The present data were drawn from a twin study of alcoholism currently being conducted at the University of Minnesota Patients entering alcoholism treatment programs are screened to determine twin status Questionnaire and structured personal interview data are being collected on probands and cotwins to determine history of personal and family alcohol use and psychopathological symptomatology Zygosity is being determined by questionnaire items concerning pair similarity (95% accuracy), supplemented when necessary by results from blood group analyses The present report is based on preliminary analyses of questionnaire data from 132 same-sex twin pairs, where at least one member of each pair met DSM-III criteria for Alcohol Abuse/Dependence There was no significant difference in mean age and sex ratio for the 59 MZ and 73 DZ pairs In determining alcoholism severity in probands and cotwins, several measures were used The primary measure was number of pathological use indicators reported by each subject Pathological use indicators were 12 items taken from the DSM-III criteria that included loss of control over alcohol use, drinking of nonbeverage alcohol, etc Other severity measures included reported frequency and quantity of use and admission of previous "heavy" use While MZ and DZ probands reported a similar number of pathological use symptoms (mean 7 6 and 7 5, respectively), concordance rates for greater than 9 symptoms was 40 0 for MZ and 6 2 for DZ, approximately a six-fold difference Concordance rates for quantity of use (drinking at least a pint of alcohol on each drinking occasion) was 14 3 for MZ and 4 8 for DZ, approximately a three-fold difference Concordance rates for admission of previous "heavy" use was 56 0 for MZ and 24 3 for DZ, approximately a two-fold difference Only for frequency of drinking (drinking at least daily) were concordance rates comparable for MZ and DZ twins (41 2 and 44 2, respectively) These results suggest a role for genetic factors in determination of severity of alcoholism, as well as in determination of the transmission of the clinical disorder

DRUG SELF-ADMINISTRATION AS AN INDICATOR OF SEVERITY POTENTIAL Martin Iguchi, Ph D and Roland Griffiths, Ph D Johns Hopkins University, Francis Scott Key Medical Center

While considerable attention has focused upon organis-