HYPERSENSITIVITY TO D-AMPHETAMINE YEARS AFTER EARLY SOCIAL ISOLATION William T McKinney, M D Professor of Psychiatry, University of Wisconsin School of Medicine, Clinical Sciences Center, 600 Highland Avenue, Madison, WI 53792, and Gary W Kraemer, Ph D Associate Scientist, Primate Laboratory, 22 North Charter Street, Madison, WI 53715

Following removal from a one month period of isolation during the second six months of life, rhesus monkeys exhibited a range of abnormal behaviors They were subsequently rehabilitated, using behavioral methods, and showed age appropriate social behaviors under baseline conditions However, the administration of low doses of d-amphetamine at 30–36 months of age precipitated bouts of severe aggression some of which could be terminated only by separating them into individual cages They also showed other behavioral effects plus a much higher elevation of cerebrospinal fluid norepinephrine in response to the amphetamine than control animals with no history of early isolation

THE BENZODIAZEPINE-GABA RECEPTOR SYSTEM AND SOCIAL ATTACHMENT Thomas R Insel Laboratory of Clinical Science, NIMH, Poolesville, MD 20837

Maternal-infant attachment in rodents provides a potentially useful model for testing hypotheses about human developmental psychobiology Recently, clinical researchers have linked childhood separation anxiety to adult anxiety disorders (Gittleman, 1985) To investigate one aspect of this link, we studied the role of the benzodiazepine-GABA receptor system in a rodent model of separation distress Infant rats, when isolated, emit ultasonic distress vocalizations These ultrasonic cries, inaudible to human observers, are a potent stimulus for eliciting maternal retrieval Diazepam, an anxiolytic benzodiazepine, was found to decrease, while pentylenetetrazol, a potent anxiogenic, was found to increase the number of these ultrasonic distress calls during a 2-minute isolation test The benzodiazepine receptor antagonist, RO-15-1788, which generally lacks intrinsic effects, also decreases the number of ultrasonic distress calls at relatively low doses (5 0 mg/kg) suggesting that the benzodiazepine receptor system may be involved in the physiologic mediation of these calls To further investigate this possibility, benzodiazepine receptors were labeled *in vivo* with ^{3}H-RO-15-1788 injected either during a quiet period with littermates or during a period of social isolation Results from autoradiographic studies of labeled brain sections suggest that certain subgroups of benzodiazepine receptors may be involved in the neural response to social separation

ALCOHOL AND AGGRESSION INTERACTIONS WITH GONADAL HORMONES AND BENZODIAZEPINES Klaus A Miczek Department of Psychology, Tufts University, Medford, MA 02155

Alcohol and benzodiazepines share a similar behavioral profile in preclinical tests For example, the effects of these drugs on attack and threat behavior as compared to those on defensive behavior are characterized by biphasic dose-effect curves, i e , low doses increase attacks and threats, whereas higher doses decrease these behaviors Tolerance develops to the aggression-suppressant effects of these drugs, and increases in aggression are seen during withdrawal from chronic exposure to these drugs That these drugs share common mechanisms of action for their behavioral effects, particularly those on aggression, is likely, since they potentiate each others pro- and anti-aggressive effects One current strategy focuses on the GABA-benzodiazepine receptor-chloride ion channel complex The benzodiazepine receptor antagonist Ro15-1788 blocks the increasing as well as decreasing effects of diazepam on aggression, but fails to show similar effects on alcohol's aggression-modulating effects The partial benzodiazepine antagonist Ro15-4513 blocks the sedative and motor impairing effects of ethanol to some extent, but does not block the aggression-decreasing effects of ethanol, Ro15-4513, similar to partial or full inverse agonists, has aggression-suppressing effects in itself, and leads to seizures in squirrel monkeys Another strategy examines gonadal steroids and their releasing hormones as potential mediators of the aggression-modulating effects of alcohol In mice, rats and squirrel monkeys that have high blood titers of testosterone, low doses of alcohol increase aggressive behavior toward intruders or toward members of the social group The aggression-heightening effect of alcohol is seen only when the dominant males in a social group are in the mating season, i e , when testosterone is elevated to more than 200 mg/dl in blood When subordinate monkeys receive SC testosterone injections to produce blood levels in exess of those seen in dominant monkeys, similar aggression-heightening effects of alcohol can be seen Castrated mice that are implanted SC with large testosterone pellets or receive testosterone implants into discrete subcortical structures show aggression-heightening effects of low to intermediate doses of alcohol and require twice as high alcohol doses to suppress aggressive behavior than intact mice The interaction of alcohol with androgen-sensitive sites in the CNS and with benzodiazepine receptors as potential mechanisms for the alcohol-aggression effects promises to provide clues for the neurobiological basis for these highly significant actions of alcohol

SYMPOSIUM

Risk Assessment Techniques in Behavioral Toxicology
Sunday August 30, 1987 • 11 00 a m –12 50 p m
Marriott Marquis Hotel • Gotham Room
Chair *Michael Gage,* U S Environment Protection Agency, Research Triangle Park, NC

PROVIDING DATA FOR RISK ASSESSMENT ACUTE BEHAVIORAL TOXICITY OF SOLVENTS Ronald W Wood, Ph D Research Associate Professor of Environmental Medicine, New York University Medical Center, New York, NY 10016

Reflecting upon the problems of risk extrapolation below the doses used experimentally, Dews called for a new approach to small risk estimation, namely the determination of an ED 10 for each replicate, the variation in this estimate, and the subsequent assumption of a normal distribution to estimate the dose which produces a 10^{-5} or 10^{-6} effect (Dews, 1980) Dews (1986) expanded upon this notion, and offered an example drawn from the work of his collaborators (Glowa *et al* , 1983) In proposing a similar method to generate allowable daily intakes, Crump (1984) advocated the

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