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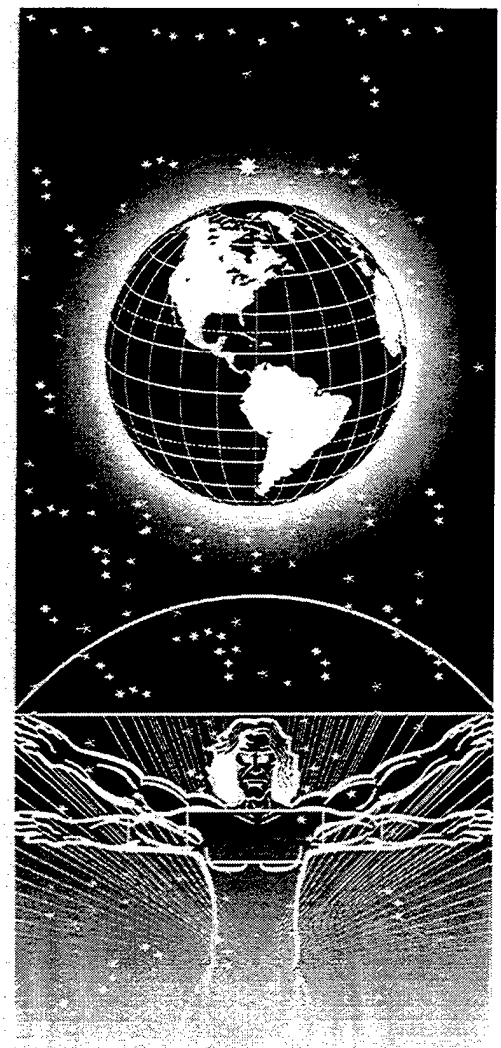

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NON-HUMAN PRIMATE MODEL FOR PERFORMANCE EFFECTS OF ETHANOL

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This report has been reviewed and is approved for publication.

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the In-stitute of Laboratory Animal Resources, National Research Council, under a protocol (#90-12) approved by the Institutional Animal Care and Use Committee.

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13. ABSTRACT *(Maximum 200 words)*

Twenty adult male (4.8-7.5 kg) rhesus monkeys (M. mulatta) ingested various doses of ethanol mixed in orange-flavored drink (10 to 20% ethanol by volume). After each dose, 4-5 blood samples were analyzed to determine peak blood alcohol level (BAL), so as to estimate a dose-response function for each animal. Then, in different (but balanced) random orders, the animals received ethanol doses estimated to produce BALs of 0.00, 0.08, 0.12, 0.16, and 0.20%. Performance of a well-trained compensatory tracking task, the Primate Equilibrium Platform (PEP) task, was tested for 2 hr, commencing 30 min after the beginning of ethanol ingestion (which was completed in <15 min). BAL was determined at 30 min intervals before, during, and after PEP testing. The significant and dose-related performance decrements induced by ethanol varied in severity from nearly undetectable at the lowest dose to periods of incapacitation in many subjects at the highest dose.

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INTRODUCTION

Behavioral pharmacology and behavior toxicology examine the changes in performance induced by exposure to pharmacological agents and toxicants. Agents and toxicants of interest may occur naturally or they may be manufactured for use in industry, agriculture, or warfare. Other stressors of interest include electromagnetic radiations that may interfere with normal sensory or neural function. Many of the stressors/toxicants/agents of interest cannot be tested experimentally in human subjects, at least not over the full dosage range of interest. Therefore, testing in animal models is required to ascertain the modes and mechanisms of actions of agents of interest, as well as the performance decrements they may produce.

Using an animal model to assess the risks of significant exposure-induced performance decrements in humans requires not only good experimental data from animal studies, but also a set of validated algorithms for extrapolating from such animal performance data to the human case. We have embarked on a program to develop and validate such algorithms. Our approach is to measure human and animal performance of essentially identical tasks under the influence of agents that can be tested in both humans and animals. We have selected tasks that sample several levels of neural integration. One of these tasks, the Primate Equilibrium Platform (PEP) task, is sensitive to changes in central nervous system (CNS) sensorimotor integration, but does not necessarily involve complex cognitive functions. The PEP task is a non-human primate model that the Air Force has used for more than 20 years to measure the effects of hazardous environments on performance. Among the environmental hazards that have been studied are ionizing (2,34,49) and nonionizing (41) radiation, chemical warfare agents (4,5,7,8), and chemical warfare defense pretreatments and/or therapies (6,15,30,33,48).

The experiment presented here is the first of a planned series in which the effects of ethanol on human and animal performance will be assessed using the PEP task, as well as two other tasks. This experiment on rhesus monkeys will next be partially replicated in humans performing on a Human Equilibrium Platform (HEP), which is a scaled-up version of the PEP. Ethanol is of interest not only because it is a widely used and abused substance with well recognized detrimental effects on highway (9,27,29) and air (1,3,10,14,19,28,31,39,40) traffic safety, but also because it is a well-studied reference substance (25,26) for use in behavioral pharmacology/toxicology experiments and model building. For example, Klein (25) proposed that the detrimental effects of other drugs and toxicants on pilot performance and flight safety could be scaled in terms of the relatively well known effects of alcohol. Dellinger et al. (11) quantified the performance-degrading effects of atropine by estimating the median effective dose (ED50) of atropine likely to produce the same flight simulator performance decrements as the legal driving limit (0.08%) blood alcohol level. Thapar et al. (43) have recently proposed that alcohol be used as a standard for quantifying the effects of sedatives and analgesics used in ambulatory surgery. Kennedy et al. (23,24) have further developed the concept of alcohol as reference substance,

suggesting methods for scaling the effects of other intoxicants in terms of equivalent dosages of alcohol.

When using ethanol as a reference substance, it is important to choose dose levels that span the range of practical significance. While most of the states recognize that blood level of 100 mg/dl (0.10%) represents a level of intoxication that prevents safe operation of a motor vehicle, a few states allow levels up to 150 mg/dl (0.15%). Most Western European countries, Canada, and most of Australia use 80 mg/dl as the critical value (36,42), and a growing number of U.S. states have adopted this more stringent standard. The FAA has set the maximum legal blood alcohol level for flight crews to (0.04% or 40 mg/dl (37,38), in addition to its 8-hour rule and general rules against flying under less than safe conditions (F.A.R. Sec. 91.17). Therefore, if ethanol is to be used as a reference substance, then development of dose response curves based on 0.04, 0.08, 0.12, and 0.16% blood ethanol levels [plus a 0-dose (vehicle-only) control] should encompass the range of interest.

METHOD

SUBJECTS

The subjects were 20 adult male rhesus macaques (4.8-7.5 kg) previously trained to perform the Primate Equilibrium Platform (PEP) task to a stable level of performance. Each monkey was housed individually in a standard stainless steel monkey cage. The room temperature was maintained at 24 (2(C with a 12:12 hour light: dark cycle. The diet consisted of monkey chow supplemented with fresh fruit, with water available ad libitum except during brief ((16 h) periods of water deprivation prior to ethanol presentations.

PEP TRAINING AND TESTING

The PEP task was developed at the USAF Armstrong Laboratory and has recently been used to assess the effects of nerve agents, prophylactics, antidotes and their combinations (4-8,15,33,48). The PEP is a continuous compensatory tracking task that should be sensitive to the effects of low to moderate levels of ethanol. The monkey is seated in a restraint chair that rotates on the pitch axis about his center of gravity. Random and unpredictable oscillations in pitch are generated by a computer. If a monkey is not present, large variations in platform position occur, with a standard deviation of position of 12-15(. The monkey's task is to manipulate a joystick control to compensate for these random oscillations. When the platform position deviates from the horizontal by more than 15(, the monkey receives a mild electric shock (2 mA. maximum current, 200 msec duration) delivered to the tail. A well-trained subject can reduce the variation to 2-4(and receive no shocks. The performance measure is the variability (standard deviation, or () of platform position on the pitch axis. This measure (() is calculated for each 5-minute epoch, based on a sample of platform positions gathered at a sampling rate of 10 Hz.

PROCEDURES

The monkeys were trained to drink the ethanol solution by the method of successive approximations. Initially, each monkey was deprived of water for 16 hours and presented with a sample of a flavored fluid (orange drink). All animals readily accepted this vehicle. On succeeding training days (maximum 2 days/week, for up to 4 weeks) the monkeys were water-deprived and presented with the orange drink with increasing concentrations of ethanol (5%, 10%, 15%, and 20%) until they drank the 20% ethanol solution in the required volume. Vehicle and ethanol were presented to the animals in water bottles attached to their home cages. A basin was placed below the cage to catch spillage, so that dosage could be accurately determined. For most monkeys, spillage was negligible. A few animals were "sloppy drinkers," but these monkeys tended to spill a relatively constant proportion of the presented fluid. Thus dosages could be appropriately adjusted and verified by measuring the spillage. We replaced 3 subjects who consistently failed to consume sufficient volumes of 15 or 20% ethanol within 15 min after presentation. Most subjects consumed the required volumes within 3-6 minutes. During the performance testing phase of the experiment, monkeys that failed to consume the allocated dose within 15 min were immediately chaired; the remainder of the dose was then administered by nasogastric intubation. During initial dose-response determinations, blood samples (1.0-2.0 ml) were drawn from a convenient leg vein at 30 min intervals from 30 to 210 min after ingestion was completed. During the PEP testing phase, the samples were drawn at 30 min intervals from 30 to 150 min after the start of ingestion. This interval was chosen to minimize the disruption of the performance task. Variability in the time to peak BAL after ingestion has been shown to be very large in humans. Dubowski (16) reported that after a large dose (1 g/kg) the time to peak BAL was 52 ± 34.6 min (mean ± S.D.); the longest time to peak BAL was as much at 14 times the shortest. Since the decline in BAL after the peak is only about 0.0045% per 15 minutes (16), this sampling interval was considered to provide a sufficiently precise estimate of peak BAL, given the inherent variability of the measurement. Time to peak BAL was not recorded.

Performance testing began immediately after the first blood sample was drawn, and continued for 120 min, with only brief (1-3 min) interruptions at 30 min intervals for blood sampling. Animals that were unable to perform under the influence of alcohol had their chairs locked in the upright position until the beginning of the next 5 min test epoch, at which time an attempt was made to restart testing. For each epoch during which the chair was locked, a score of 15(was assigned. This is the approximate score that results from the random noise input when stick input is disabled. BALs were determined in the U.S. Air Force Drug Testing Laboratory by headspace gas chromatography (22).

Prior to any performance testing under the influence of alcohol, a dose-response function relating ingested alcohol to peak blood alcohol level (BAL) was determined for each monkey. Then each monkey was tested after ingesting a control dosage (vehicle only) plus 4 additional dosages estimated from that

individual monkey's dose-response curve to produce BALs of 0.08, 0.12, 0.16, & 0.20%. The order of dosages was balanced across subjects. The initial experimental plan called for dosages that would produce 0.04 to 0.16% BALs, but preliminary studies showed that the lowest dose had little or no effect on PEP performance, while the highest dose (0.16% target BAL) produced at most moderate performance decrements in some monkeys. We therefore decided to delete the 0.04% dose and add a 0.20% dose so as to be certain to sample the full range of performance effects in our monkeys.

DATA ANALYSIS

After each of the preliminary exposures, the dosage and the largest measured value of BAL were entered into a dataset for each monkey. After a range of doses that produced peak BALs ranging from about 0.05% to about 0.20% had been sampled for each monkey, a dose-response function was generated by fitting a nonlinear (2nd order) regression line to the data, with the restriction that the regression line pass through the origin (i.e., zero-dose, 0% BAL point). The fitted regression line was used to generate the dosages used in the performance phase of the experiment.

The performance data were analyzed by repeated-measures analysis of variance (ANOVA), with target BAL (0, .08, .12, .16, & .20%) and time after ingestion (24 5-min epochs) as within-subjects variables. Since a substantial number of the data points at the highest dosage were artificial (15(values entered when subjects were unable to perform the task), the analysis was repeated with the highest dose excluded. The BAL data from the performance phase of the experiment were also analyzed by repeated measures ANOVA. Where significant effects were found, post hoc tests (Duncan's Multiple Range and Tukey's Studentized Range) were used to determine which levels of the variables produced effects significantly different from the other levels. Since we anticipated that the targeted dosages would produce time-dependent changes in both BAL and the alcohol-induced performance decrements, the BAL values and the performance scores (for the epochs closest in time to collection of the blood samples) were entered into a multivariate analysis of variance to examine these interactions more closely.

RESULTS

The dose-response functions relating peak BAL to ethanol dose varied considerably from subject to subject. Figure 1 shows second-order nonlinear regressions of peak %BAL on ethanol dose for 10 randomly selected monkeys, along with a best-fit regression line for all the points shown. While these individual dose-response functions are clustered closely around the group average, there is enough variation at low doses to make the predicted dose for a BAL of 0.08% in each monkey vary from 0.82 to 1.22 mg/kg. At higher levels of dose and BAL, the larger scatter of dose-response functions produce predicted doses for a BAL of 0.20% ranging from 2.08 to 2.82 mg/kg in this group of monkeys.

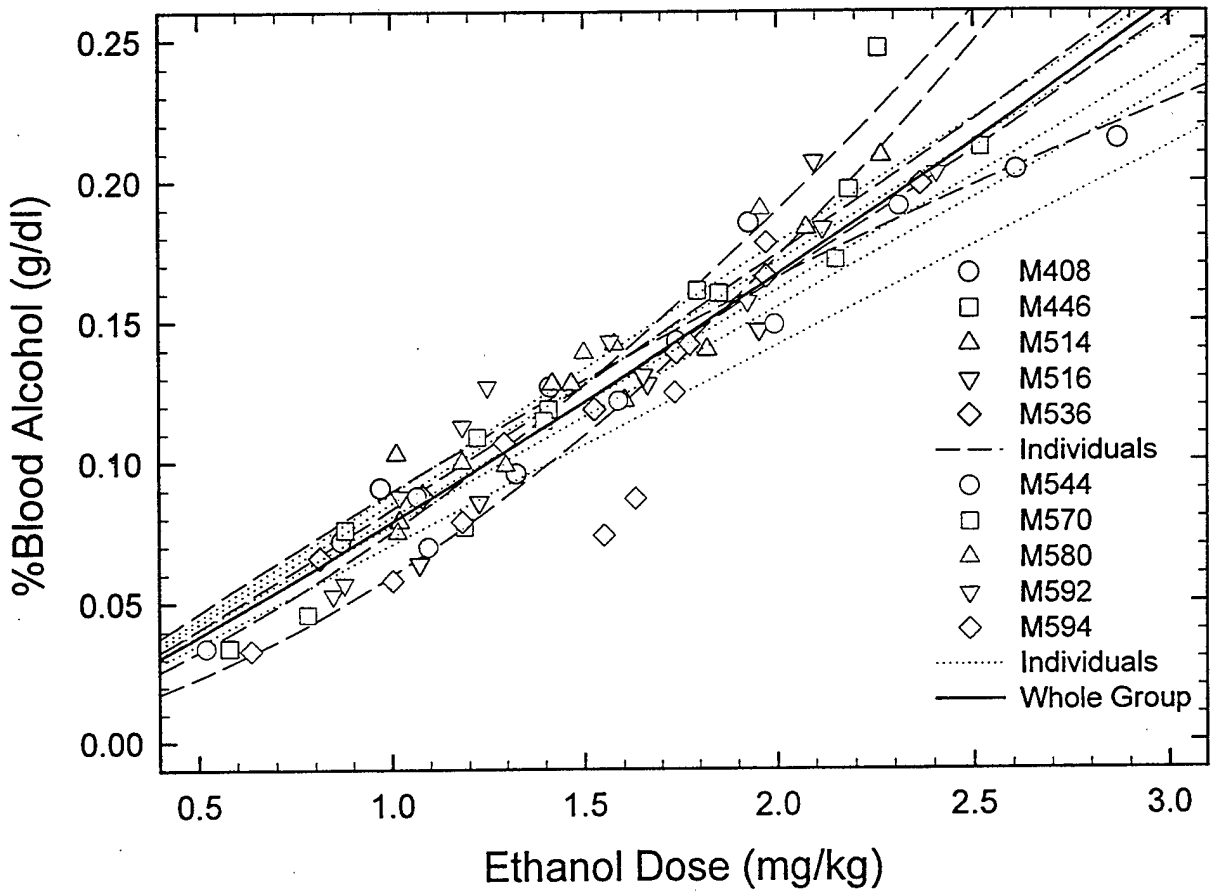

Figure 1. Dose-response relationships between ethanol dose and blood alcohol level for a randomly selected half of the monkeys used in this experiment. The 2nd order nonlinear regression lines for all subjects intersect the origin. Five monkeys are shown with open symbols and dashed lines; the other 5 with filled symbols and dotted lines. The solid line is the regression of BAL on dose for all points shown.

Figure 2 shows the average time-course of PEP performance changes after the ingestion of alcohol doses selected to produce the targeted changes in peak BAL. The ANOVA for all 5 dosage levels showed significant ($p<.001$) effects of dose and time, and a significant ($p<0.05$) dose by time interaction. Post hoc tests showed that the effect of the highest dose differed significantly from all others. The ANOVA for the 4 lowest doses showed significant dose

($p<0.01$) and time ($p<0.05$) effects, but the interaction between dose and time was not significant. The post hoc tests showed that the control condition differed from all other ethanol doses, as did the 0.16% dose. The 0.08 and 0.12% doses did not differ significantly from each other in their performance effects, although the magnitudes of the effects were monotonic with dosage. The variation from subject to subject in the form of the dosage effect was large. PEP performance data from a selection of individual subjects are shown in Figure 3 to illustrate this variation.

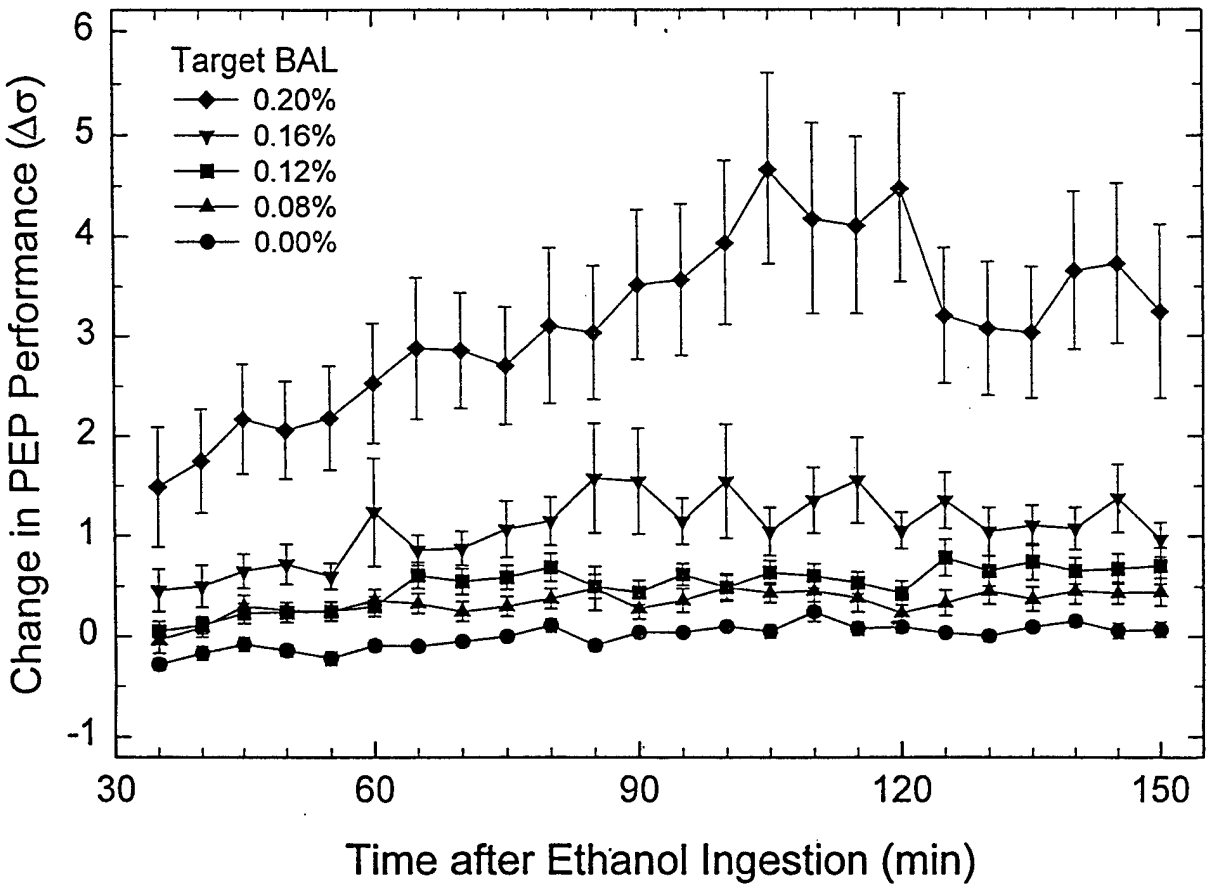

Figure 2. Mean (±s.e.m) change in PEP performance after doses targeted to produce 0.00 (vehicle only), 0.08, 0.12, 0.16, and 0.20% peak BAL. Changes were measured from the average of 3 baseline runs collected during the week preceding each ethanol exposure. Ethanol exposures were separated by at least 7 days. Dosage order was balanced across the 20 subjects so that each dosage occurred an equal number of times in each serial position and each dosage followed every other dosage an equal number of times.

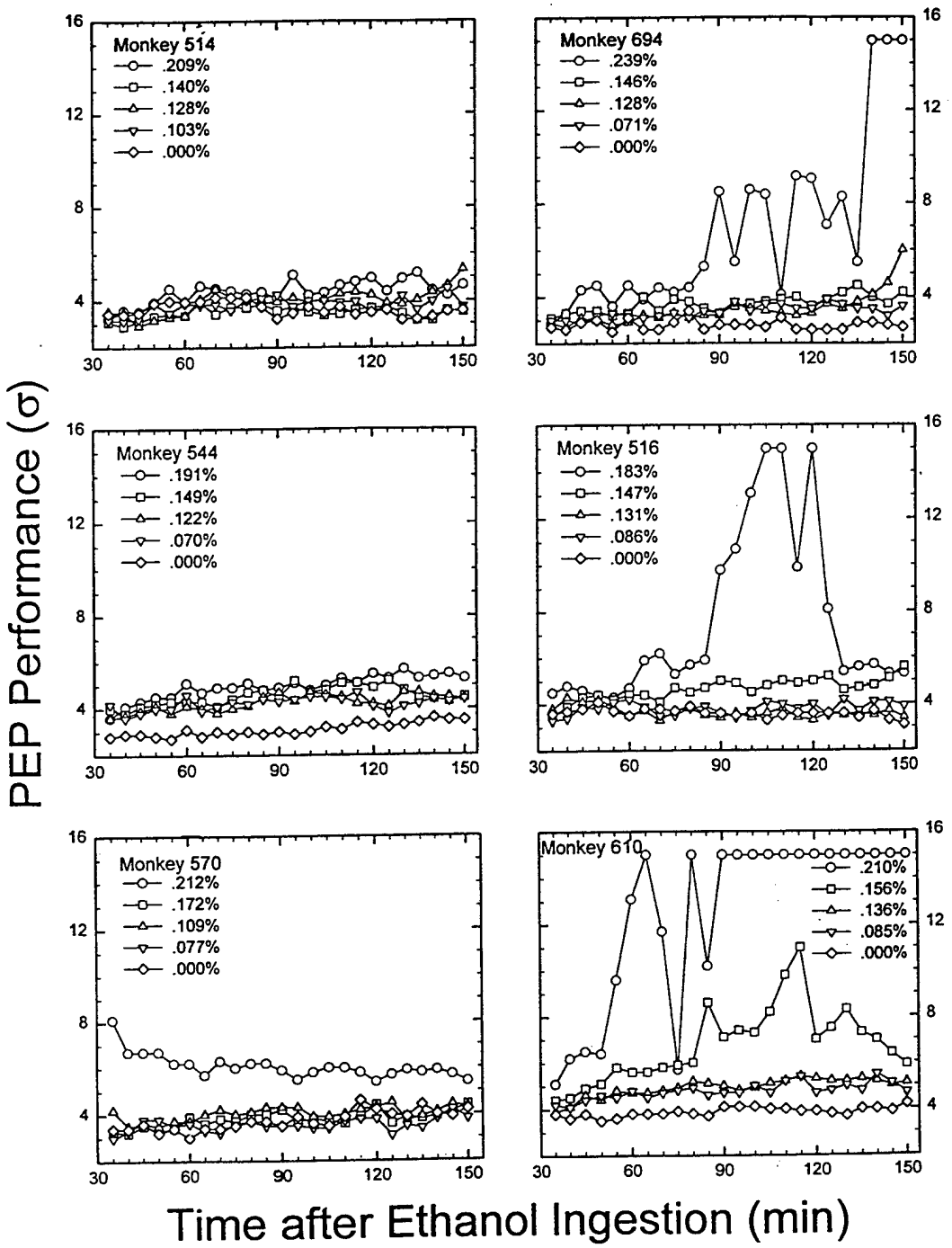

Figure 3. Individual animal performance data illustrates the large variation from subject to subject in both the magnitude and the form of the effect of ethanol dose on PEP performance.

The ANOVA for changes in BAL following the ingestion of vehicle only or the 4 targeted ethanol dosages showed the expected significant effects of dosage and time, plus a significant dosage by time interaction. Figure 4 (filled symbols with error bars) shows the average time course of %BAL after the non-

zero dosages. The time courses of average changes in PEP Performance (open symbols, scale on right ordinate) are plotted on the same graph for comparison. The nonlinear relationship between BAL and the associated performance decrements is shown in the inset graph at the upper left.

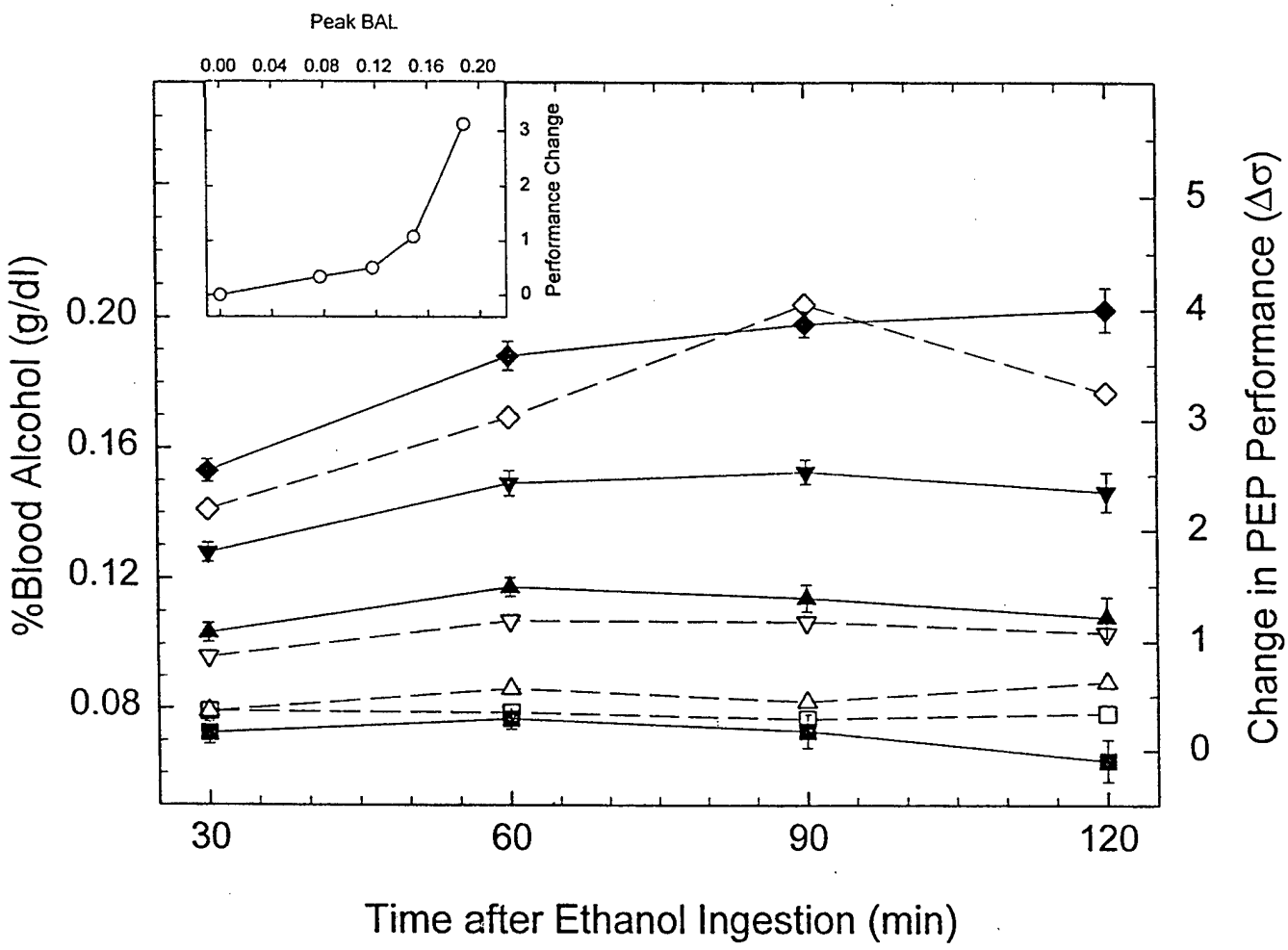

Figure 4. Time course of changes in BAL (filled symbols with error bars, left ordinate) and PEP performance (open symbols, right ordinate) after ingestion of dosages targeted to produce 4 different peak BALs. Performance points are the means for 20 monkeys of the 6 5-min epochs that followed each blood sample. The inset graph shows the relationship between mean peak BAL and mean PEP performance change.

The relationship among targeted dosages, BAL and PEP performance decrements is complex. At the highest alcohol dosage (target BAL 0.20%), performance begins to recover while BAL is still increasing (see fig. 4). At the 0.16% dosage, BAL and performance changes are much more parallel. The nature of the interactions between time and dose in the BAL measures and the PEP performance measures was examined via a multivariate ANOVA, with the hope of determining whether the variation in performance over time depends both on the change in BAL over time and on the initial dosage. The partial correlation between measured BAL and PEP performance from the error sum of squares and cross products matrix was near zero (-0.09, $p=.24$), while all tests of the time by target dosage interaction were significant (Wilks' Lambda = .7520, $f = 2.89$, $df = 18$, $p<.0001$). Thus, it appears that performance does vary over time in a manner that depends on the target dose even for the 4 lowest doses; this interaction is preserved when data from the highest dose are excluded. Time dependencies in both BAL and performance merit further study, as differences in recovery rates between monkeys and humans would require inclusion in extrapolation models.

DISCUSSION

A purpose of the current study was to use alcohol as a reference substance (26) to further validate a non-human primate model that the Air Force has used for more than 25 years to measure the effects of hazardous environments on performance. Among the environmental hazards that have been studied are ionizing (2,34,49) and nonionizing (41) radiation, chemical warfare agents (4,5,7,8), and chemical warfare defense pretreatments and/or therapies (6,15,30,33,48). The work reported here is part of an effort to increase the accuracy of extrapolations of performance effects from animal models to human conditions.

Alcohol research using human subjects is generally considered safe and ethical. However, there may be instances in which the effects of interest are those of alcohol at doses too high for use in routine experiments with human subjects. Also, alcohol is often used or abused in combination with other drugs, both medicinal and recreational. Alcohol consumption may also inadvertently be combined with other stressors or hazardous environments, including those encountered by military members. Studies of interactions between alcohol and other drugs or stressors may not be as safe as studies of the effects of alcohol alone. Furthermore, the interacting drug or stressor might not be approved for human use, or it could have unknown or unpredictable (44), and possibly dangerous, interactions with alcohol. Therefore, the animal model developed here may be valuable for such interaction studies in which the use of human subjects may be impracticable, e.g., studies of the interactions between valium (a commonly used and abused benzodiazepine) and alcohol (45) or other stressors (33).

The results have shown that the PEP performance task is a sensitive

indicator of disruptions in psychomotor performance induced by alcohol; it demonstrated significant and dose-related decrements in performance, even at the lowest dose tested. However, the magnitude of the decrements induced by ethanol at low dosages appear small in comparison the deficits in complex human performance tasks that have been demonstrated by others (21,32). This may be due to the fact that the task does not place heavy cognitive demands on the subject and is less sensitive to ethanol effects than other tasks, or it may be because monkeys are less sensitive to the deleterious effects of ethanol than are humans, or both. A number of reports have indicated that task difficulty is an important variable. For example, Aksnes (1) reported large individual differences in alcohol effects on Link trainer performance; effects seen at BAL as low as 0.05% seemed "less noticeable in the steadiest flyers" (p. 688). Billings et al. (3) also noted that, in actual flight tests, alcohol-induced tracking errors were more pronounced in less experienced pilots. Holloway (21), in his review of the recent literature, concluded that the kind of task and the skills or abilities the task requires have important implications for alcohol effects on task performance, especially at low doses. Holloway found that "controlled performance tasks," such as difficult tracking or digit-symbol substitution, which require attention to multiple tasks or task features, are most susceptible to low-dose effects. "Automatic performance" tasks like reaction time or simple tracking have higher threshold BALs for significant performance decrements. In an earlier review, Moskowitz and Robinson (32) also concluded that divided attention tasks were most sensitive at low doses, followed by tracking tasks, with median BAL values to produce reliable performance decrements of 0.050 and 0.055%, respectively. Thus the low level of cognitive demand involved in our relatively simple tracking task may make it less sensitive to low-dose effects than the more complex human tasks commonly used in human studies. The findings of Fagan et al. (17) of relatively minor effects on a psychomotor test battery at the British legal BAL limit (0.08%), even though this battery is sensitive to effects of other drugs (benzodiazepines, etc.), are consistent with this interpretation.

Differences in alcohol metabolism and distribution between monkeys and humans may also account for differences in observed performance effects. Zorzano (50) found that macaques eliminate ethanol substantially faster than men, even though liver metabolic pathways do not appear dissimilar enough to account for the differences. Winneke (18,47) has pointed out the importance of knowing blood levels (or even better, target organ levels) of a toxicant, because, for example, the toxic effects of lead are quite consistent across several species (rat, monkey, and man) when compared by blood levels; they are very inconsistent when dosages (mg/kg/day) are the basis of comparison. In the present study, dosages were chosen to produce specific blood alcohol levels, so a greater rate of metabolism should only produce more rapid dissipation of behavioral effects, unless the distribution of alcohol from the blood to target locations in the nervous system are quite different between old-world primate species (rhesus monkeys and humans), which seems unlikely.

The fact that laboratory primates are good models of general ethanol effects in humans has been well documented. Deneu et al. (12), used self-

administration via indwelling IV cannulas to demonstrate that alcohol has abuse potential in monkeys, as it clearly does in man. Abuse potential was demonstrated by the fact that monkeys will self-administer doses that cause both performance decrements and withdrawal symptoms on sudden discontinuance. Pieper & Skeen (35) demonstrated that monkeys develop both dependence and metabolic tolerance for ethanol. DeNoble & Begleiter (13) exposed macaques to 5 repeats of high-dose ethanol (5 g/kg IV at 3-day intervals). Both peak BAL and behavioral deficits were reduced by tolerance development (behavioral tolerance in addition to physiologic). Higley et al. (20) compared responses to alcohol in peer-reared monkeys to those that grew up with normal access to adults. The peer-reared monkeys tended to be fearful, and to consume more alcohol, given free access to alcohol solutions and water. Mother-reared animals tended to consume much less alcohol in normal situations, but responded to stress by increasing their ethanol intake to levels like those consumed by the peer-reared animals without added stress. The large individual differences in baseline alcohol consumption levels observed by Higley et al. were stable over time.

The large individual differences we observed in our monkeys may well be echoed in human subjects performing essentially the same task. In humans, Wison & Plomin (46) found large individual differences in responses to alcohol. Differences in the development of acute tolerance were also large, and seemed more strongly related to genetic constitution than to variables like age, size, gender, or history of exposure. Thus, we may find that human subjects, when performing the same task as our monkeys, show a similarly wide range of variability in the performance effects of alcohol.

REFERENCES

1. Aksnes, E. G. Effects of small doses of alcohol upon performance in a Link trainer. J. Aviat. Med. 25:680-693; 1954.
2. Barnes, D. J.; Brown, G. C.; Fractor, B. S. Differential effects of multiple and single irradiations upon the primate equilibrium function. USAF School of Aerospace Medicine, SAM-TR-71-1:1971.
3. Billings, C. E.; Wick, R. L.,Jr.; Gerke, R. J.; Chase, R. C. Effects of ethyl alcohol on pilot performance. Aerosp. Med. 44:379-382; 1973.
4. Blick, D. W.; Kerenyi, S. Z.; Miller, S. A.; Murphy, M. R.; Brown, G. C.; Hartgraves, S. L. Behavioral toxicity of anticholinesterases in primates: Chronic pyridostigmine and soman interactions. Pharmacol. Biochem. Behav. 38:527-532; 1991.
5. Blick, D. W.; Miller, S. A.; Brown, G. C.; Murphy, M. R. Behavioral toxicity of anticholinesterases in primates: Chronic physostigmine and soman interactions. Pharmacol. Biochem. Behav. 45:677-683; 1993.
6. Blick, D. W.; Murphy, M. R.; Brown, G. C.; Hartgraves, S. L. Primate performance decrements following acute soman exposure: Failure of chemical countermeasures. Pharmacol. Biochem. Behav. 49:503-510; 1994.

7. Blick, D. W.; Murphy, M. R.; Brown, G. C.; Yochmowitz, M. G.; Fanton, J. W.; Hartgraves, S. L. Acute behavioral toxicity of pyridostigmine or soman in primates. Toxicol. Appl. Pharmacol. 126:311-318; 1994.

8. Blick, D. W.; Weathersby, F. R.,Jr.; Brown, G. C.; Murphy, M. R. Behavioral toxicity of anticholinesterases in primates: Effects of daily repeated soman exposure. Pharmacol. Biochem. Behav. 48:643-649; 1994.

9. Brewer, N.; Sandow, B. Alcohol effects on driver performance under conditions of divided attention. Ergonomics 23:185-190; 1980.

10. Collins, W. E.; Mertens, H. W. Age, alcohol, and simulated altitude: effects on performance and breathalyzer scores. Aviat. Space Environ. Med. 59:1026-1033; 1988.

11. Dellinger, J. A.; Taylor, H. L.; Richardson, B. C. Comparison of the effectrs of atropine sulfate and ethanol on performance. Aviat. Space Environ. Med. 57:1185-1188; 1986.

12. Deneau, G.; Yanagita, T.; Seevers, M. H. Self-administration of psychoactive substances by the monkey. Psychopharmacologia (Berlin) 16:30-48; 1969.

13. DeNoble, V.; Begleiter, H. Changes in fixed-ratio performance and blood alcohol levels in monkeys. Psychopharmacology 55:213-216; 1977.

14. Dille, J. R.; Morris, E. W. Human factors in general aviation accidents. Aerosp. Med. 38:1063-1066; 1967.

15. Doctor, B. P.; Blick, D. W.; Caranto, G.; Castro, C. A.; Gentry, M. K.; Larrison, R.; Maxwell, D. M.; Murphy, M. R.; Schutz, M.; Waibel, K.; Wolfe, A. D. Cholinesterases as scavengers for organophosphorus compounds: Protection of primate performance against soman toxicity. Chemico-Biological Interactions 87:285-293; 1993.

16. Dubowski, K. M. Absorption, distribution and elimination of alcohol: highway safety aspects. J. Stud. Alcohol Suppl. 10:98-108; 1985.

17. Fagan, D.; Tiplady, B.; Scott, D. B. Effects of ethanol on psychomotor performance. British J. Anaesth. 59:961-965; 1987.

18. Fairweather, D.; Hindmarch, I. The behavioral toxicity of reversible inhibitors of monoamine oxidase A:Laboratory and clinical investigations. J. Clin. Psychopharmacol. 15(suppl 2):68S-75S; 1995.

19. Henry, P. H.; Davis, T. Q.; Engelken, E. J.; Triebwasser, J. H.; Lancaster, M. C. Alcohol-induced performance decrements assessed by two Link trainer tasks using experienced pilots. Aerosp. Med. 45:1180-1189; 1974.

20. Higley, J. D.; Hasert, M. F.; Suomi, S. J.; Linnoila, M. Nonhuman primate model of alcohol abuse: effects of early experience, personality, and stress on alcohol consumption. Proc. Natl. Acad. Sci. U. S. A. 88:7261-7265; 1991.

21. Holloway, F. A. Low-Dose Alcohol Effects on Human Behavior and Performance: A Review of Post-1984 Research. Washington, D.C.: Office of Aviation Medicine, DOT/FAA/AM-94/24:1-47; 1994.

22. Jones, A. W.; Jonsson, K. A.; Jorfeldt, L. Differences between capillary and venous blood-alcohol concentrations as a function of time after drinking, with emphasis on sampling variations in left vs right arm. Clin. Chem. 35:400-404; 1989.

23. Kennedy, R. S.; Turnage, J. J.; Dunlap, W. P. The use of dose equivalency as a risk assessment index in behavioral neurotoxicology. Neurotoxicol. Teratol. 14:167-175; 1992.

24. Kennedy, R. S.; Turnage, J. J.; Rugotzke, G. G.; Dunlap, W. P. Indexing cognitive tests to alcohol dosage and comparison to standardized field sobriety tests. J. Stud. Alcohol 55:615-628; 1994.

25. Klein, K. E. Prediction of flight safety hazards from drug induced performance decrements with alcohol as a reference substance. Aerosp. Med. 43:1207-1214; 1972.

26. Laties, V. G. On the use of reference substances in behavioral toxicology. In: Horvath, M. ed. Adverse effects of environmental chemicals and psychotropic drugs: Quantitative interpretation of functional tests. New York: Elsevier; 1973:83-88.

27. Laurell, H. Effects of Small Doses of Alcohol on Driver Performance in Emergency Traffic Situations. VTI-68-A:1-27; 1975.

28. Li, G. Pilot-related factors in aircraft crashes: a review of epidemiologic studies. Aviat. Space Environ. Med. 65:944-952; 1995.

29. Mattila, M. J.; Kuitunen, T.; Veilahti, J. Related coordinative, reactive and cognitive performances as impaired by drugs and alcohol: Comparison with clinical test for driving fitness. J. Traffic Med. (Sweden) 21:101-114; 1993.

30. Miller, S. A.; Blick, D. W.; Kerenyi, S. Z.; Murphy, M. R. Efficacy of physostigmine as a pretreatment for organophosphate poisoning. Pharmacol. Biochem. Behav. 44:343-347; 1993.

31. Morrow, D.; Leirer, V.; Yesavage, J.; Tinklenberg, J. Alcohol, age, and piloting: Judgment, mood, and actual performance. Int. J. Addict. 26:669-683; 1991.

32. Moskowitz, H.; Robinson, C. Effects of low doses of alcohol on driving-related skills: A review of the evidence. Washington, D.C.: U.S. Dept. of Transportation, 1988.

33. Murphy, M. R.; Blick, D. W.; Dunn, M.; Fanton, J. W.; Hartgraves, S. L. Diazepam as a treatment for nerve agent poisoning. Aerosp. Med. 64:110-115; 1993.

34. Patrick, R. P.; Rahe, A. J.; Lof, N. E.; Hardy, K. A.; Cordts, R. E. Nuclear survivability/vulnerability of aircrews: an experimental approach. USAF School of Aerospace Medicine, SAM-TR-81-1:1981.

35. Pieper, W. A.; Skeen, M. J. Induction of physical dependence on ethanol in rhesus monkeys using an oral acceptance technique. Life Sci. 11:989-997; 1972.

36. Reed, T. F. One man's tipple is another man's poison. New Scientist 746-751; 1983.

37. Ross, L. E.; Munt, J. C. Effects of a low blood alcohol on pilot performance. Proc. Hum. Fact. Soc: 1182-1186; 1986.

38. Ross, S. M.; Ross, L. E. Pilots' knowledge of blood alcohol levels and the 0.04% blood alcohol concentration rule. Aviat. Space Environ. Med. 61:412-417; 1990.

39. Ryan, L. C.; Mohler, S. R. Current role of alcohol as a factor in civil aircraft accidents. Aviat. Space Environ. Med. 50:275-279; 1979.

40. Schroeder, D. J.; Gilson, R. D.; Guedry, F. E.; Collins, W. E. Alcohol and Disorientation-Related Responses. VI. Effects of Alcohol on Eye Movements and Tracking Performance During Laboratory Angular Accelerations about the Yaw and Pitch Axes. Washington, D.C.: U.S. Dept. of Transportation, FAA-AM-72-34:1-16; 1972.

41. Sherry, C. J.; Blick, D. W.; Walters, T. J.; Brown, G. C.; Murphy, M. R. Lack of behavioral effects in non-human primates following exposure to ultrawide band electromagnetic radiation in the microwave frequency range. Radiat. Res. 143:93-97, 1995.

42. Simpson, G. Medicolegal alcohol determination: Comparison and consequences of breath and blood analysis. J. Anal. Toxicol. 13:361-366; 1989.

43. Thapar, P.; Zacny, J. P.; Thompson, W.; Apfelbaum, J. L. Using alcohol as a standard to assess the degree of impairment induced by sedative and analgesic drugs used in ambulatory surgery. Anesthesiology 82:53-59; 1995.

44. Van Steveninck, A. L.; Gieschke, R.; Schoemaker, H. C.; Pieters, M. S. M.; Kroon, J. M.; Breimer, D. D.; Cohen, A. F. Pharmacodynamic interactions of diazepam and intravenous alcohol at pseudo steady state. Psychopharmacology 110:471-478; 1993.

45. Wayner, M. J.; Dalterio, S. L.; Geller, I.; Hartmann, R. J. Ethanol-diazepam interactions on delayed match-to-sample performance in baboons. Brain Res. Bull. 23:333-338; 1989.

46. Wilson, J. R.; Plomin, R. Individual differences in sensitivity and tolerance to alcohol. Soc. Biol. 32:162-184; 1985.

47. Winneke, G.; Lilienthal, H. Extrapolation from animals to humans: Scientific and regulatory aspects. Toxicol. Lett. 64-65:239-246; 1992.

48. Wolfe, A. D.; Blick, D. W.; Murphy, M. R.; Miller, S. A.; Gentry, M. K.; Hartgraves, S. L.; Doctor, B. P. Use of cholinesterases as pretreatment drugs for the protection of rhesus monkeys against soman toxicity. Toxicol. Appl. Pharmacol. 117:189-193; 1992.

49. Yochmowitz, M. G.; Patrick, R. P.; Jaeger, R.; Barnes, D. J. Protracted radiation-stressed primate performance. Aviat. Space Environ. Med. 48:598-606; 1977.

50. Zorzano, A.; Herrera, E. In vivo ethanol elimination in man, monkey and rat: a lack of relationship between the ethanol metabolism ant the hepatic activities of alcohol and aldehyde dehydrogenases. Life Sci. 46:223-230; 1990.