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EXECUTIVE SUMMARY

This report concerns the effects of marijuana smoking on actual driving performance. It presents the results of one pilot and three actual driving studies which were conducted between april 1990 and march 1992. The program was funded by the U.S. National Highway Traffic Safety Administration (NHTSA), with the exception of the alcohol part of the city driving study which was sponsored by the Dutch Road Safety Directorate of the Dutch Ministry of Transport and Public Works. The project was conducted by the Institute for Drugs, Safety and Behavior of the University of Limburg, Maastricht, The Netherlands. The major objectives of the program were to determine the dose-response relationship between Δ^9-tetrahydrocannabinol (THC), marijuana's main constituent, and objectively and subjectively measured aspects of real-world driving; and, to determine whether it is possible to correlate driving performance impairment with plasma concentrations of the drug or a metabolite. A variety of driving tests were employed, including: maintenance of a constant speed and lateral position during uninterrupted highway travel, following a leading car with varying speed on a highway, and city driving. The purpose of applying different tests was to determine whether similar changes in performance under the influence of THC occur in all, thereby indicating a general drug effect on driving ability.

Chapter One provides background information about the drug, its pharmacological properties, the prevalence of its use, and a review of marijuana smoking and traffic safety. THC's effects on the ability of drivers to operate safely in traffic situations have traditionally been determined in two ways: from epidemiological surveys of users' involvement in traffic accidents and from empirical studies to measure the drug's influence on skills related to driving, or driving itself. Epidemiology shows that people drive after marijuana use and that drivers involved in accidents often show the drug's presence. The results are, however, inconclusive because of the high proportion of cases which also involve alcohol use and the lack of proper control groups. Therefore, the extent marijuana contributes to traffic accident causality remains obscure. Results from driving simulator and closed-course tests show that THC in single inhaled doses up to about 250 $\mu g/kg$ has relatively minor effects on driving performance, certainly less than blood alcohol concentrations (BACs) in the range of 0.08-0.10 g%.

Chapter Two describes the studies of the program and certain procedures that were common to all. These were subject recruiting, compliance with ethical and legal standards, screening for the presence of other illicit drugs and alcohol, blood sampling procedures and quantitative analyses. Subjects in all studies were recreational users of cannabis, i.e. smoking marijuana or hashish more than once a month but not daily. They were all healthy, between 21 and 40 years of age, had normal weight and binocular acuity, and were licensed to drive an automobile. Subjects were accompanied in every driving test by an licensed driving instructor, experienced in supervising subjects who operated under the influence of medicinal drugs in previous studies. Redundant control system in the test vehicle was available for controlling the car if emergency situations should arise. Marijuana and placebo marijuana cigarettes were supplied by the U.S. National Institute on Drug Abuse (NIDA).

Chapter Three presents the results of the pilot study. It was conducted in a hospital under strict medical supervision to identify THC doses that recreational marijuana users were likely to consume before driving. Twenty-four subjects, twelve males and twelve females, participated.

They were allowed to smoke part or all of the THC content in three cigarettes until achieving the desired psychological effect. Cigarettes were smoked through a plastic holder in a manner determined by the subjects. The only requirement was to smoke continuously for a period not exceeding 15 minutes. When subjects voluntarily stopped smoking, cigarettes were carefully extinguished and retained for subsequent gravimetric estimation of THC consumed. Six subjects consumed one cigarette, thirteen smoked two and four smoked three. The average amount of THC consumed was 20.8 mg, after adjustment for body weight, 308 μg/kg. There was no significant difference between males and females with respect to the weight adjusted preferred dose. It was decided that the maximum dose for subsequent driving studies would be 300 μg/kg. This is considerably higher than doses that have usually been administered to subjects in experimental studies (typically, 100-200 μg/kg THC).

The study provided the opportunity for obtaining valuable information about THC's pharmacokinetics and its pharmacodynamic effects after marijuana smoking. Blood samples were repeatedly taken for measuring plasma concentrations of THC and its major inactive metabolite, THC-COOH. The subjects repeatedly performed certain simple laboratory tests, estimated their levels of intoxication and indicated their willingness to drive under several specified conditions of urgency. Heart rate was measured at these times. The secondary purpose of the pilot study was that of specifying relationships between [THC] and [THC-COOH] with changes in the other physiological, performance or subjective variables. Other results from the pilot study showed that perceived "high" and heart rate are very sensitive measures of marijuana intoxication which confirms prior findings. Impairments in laboratory tests performance were found at the time of peak subjective feelings but generally, objective impairment dissipated more rapidly than the feelings themselves.

The first driving study, described in <u>***Chapter Four***</u>, was conducted on a highway closed to other traffic. One objective of the study was to determine whether it would be safe to repeat the study on a normal highway in the presence of other traffic. The second objective was to define the dose-effect relationship between inhaled THC dose and driving performance. The same twelve men and twelve women who participated in the pilot study served again as the subjects. They were treated on separate occasions with THC doses of 0, 100, 200, 300 μg/kg. Treatments were administered double-blind and in a counterbalanced order. On each occasion, subjects performed a road tracking test beginning 40 minutes after initiation of smoking and repeated one hour later. The test, developed and standardized by O'Hanlon *et al.* (1982, 1986), involved maintaining a constant speed at 90 km/h (56 mph) and a steady lateral position between the delineated boundaries of the traffic lane. Subjects drove 22 km (13.6 mi) on a primary highway and were accompanied by a licensed driving instructor. The latter was charged with responsibility for ensuring safety at all times and was able to intervene, if necessary, using redundant vehicular controls. The primary dependent variable was the standard deviation of lateral position (SDLP), which has been shown to be both highly reliable and very sensitive to the influence of sedative drugs and alcohol. Other dependent variables were mean speed, and standard deviation of speed and steering wheel angle. Blood samples were taken prior to each driving test; and, performance in critical tracking and hand steadiness tests, heart rate, and blood pressure were measured after its termination. Questionnaires were repeatedly administered to estimate the "high" and other subjective feelings.

All subjects were willing and able to finish the driving tests without great difficulty. The study demonstrated that marijuana impairs driving performance as measured by an increase in SDLP; all three THC doses significantly affected SDLP relative to placebo. The driving performance decrement after smoking marijuana persisted almost undiminished for two hours after smoking while drug plasma concentrations, perceived "high" and heart rate elevation had decreased. Marijuana's effects on SDLP were compared to those of alcohol obtained in a very similar study by Louwerens *et al.* (1985, 1987). It appeared that THC's effects on SDLP were equivalent to those associated with BACs in the range of 0.03-0.07 g%. Other driving performance measures were not significantly affected by THC. Intersubject correlations between plasma concentrations of the drug and driving performance after every dose were essentially nil. Thus, driving impairment cannot be predicted by prevailing plasma concentrations of THC or THC-COOH. Driving impairment was also not related to performance in the laboratory tests. Both the observed degree of driving impairment, and what subjects said and did, indicated that normal safeguards would be sufficient for ensuring safety in further testing. Hence, the final conclusion was to repeat this study on a normal highway in the presence of other traffic.

The second driving study, described in *Chapter Five*, was conducted to come a step closer to driving reality than its predecessor. Driving tests were now conducted on a highway in the presence of other traffic. The major objective of this study was to confirm the relationship between inhaled THC dose and lateral position variability in the context of a standard road tracking test. A secondary objective was to measure performance in another actual driving test, i.e. car following. The third objective was to continue efforts to correlate plasma concentrations of THC and THC-COOH with driving performance impairment as measured in both tests.

A new group of sixteen subjects, equally comprised of men and women, participated in this study. A conservative approach was chosen in designing the present study in order to satisfy the strictest safety requirements. That is, the study was conducted according to an ascending dose series design where both active drug and placebo conditions were administered, double-blind, at each of three THC dose levels. THC doses were the same as those used in the previous study, namely 100, 200, and 300 μg/kg. Cigarettes appeared identical at each level of treatment conditions and were smoked through a plastic holder in a fashion determined by the subject within a time limit of 10 minutes. If any subject would have reacted in an unacceptable manner to a lower dose, he/she would not have been permitted to receive a higher dose.

Two subjects at a time commenced smoking. Thirty minutes after onset of smoking the subjects performed a battery of laboratory tests (tracking, hand steadiness and body sway), yielded a blood sample, and rated their "high" and other subjective feelings. They were then transported to a primary highway were the driving tests were performed. Two instrumented vehicles were employed. The subjects performed the car following test on a 16 km (9.9 mi) segment of the highway for about twelve minutes. After conclusion of the car following test, both subjects then commenced the road tracking test in separate instrumented vehicles. The highway was the same as for the car following test. Subjects drove 64 km (40 mi) without stopping in about 50 minutes. At the conclusion of this test, both subjects participated again in the car following test. Subjects were then transported back to the laboratory where they rated subjective feelings, yielded a blood sample, and repeated the test battery. The subjects' heart rate was registered continuously during both driving tests.

The road tracking test was the same as in the previous study except for its duration and the presence of other traffic. Subjects were instructed to maintain a constant speed of 95 km/h (59 mph) and a steady lateral position between lane boundaries in the right traffic lane. They were allowed to deviate from this only if it would become necessary to pass a slower vehicle in the same lane. Data from the standard test were analyzed to yield the same performance measures as in the previous study; i.e. SDLP, mean and standard deviation of speed, and standard deviation of steering wheel angle. The car following test measures drivers' ability to perceive changes in a preceding vehicle's speed and to react in a manner maintaining a constant headway. It began as the preceding and the following vehicle, respectively driven by one of the driving instructors and the subject, operated in tandem on the slower traffic lane while travelling at a speed of 100 km/h (62 mph). The subject was instructed to maintain a 50 m (164 ft) headway however the preceding vehicle's speed might vary. After driving in this manner for about one minute, the operator of the preceding vehicle released the accelerator pedal allowing its speed to fall to 80 km/h (50 mph). Immediately thereafter, the operator of the preceding vehicle accelerated to 100 km/h (62 mph). The duration of one deceleration and acceleration maneuver was approximately 50 seconds and six to eight, depending upon traffic density, were executed during one test. The subject's average reaction time to the movements of the leading vehicle, mean headway and coefficient of variation of headway during maneuvers were taken as the dependent variables from this.

All subjects were able to complete the series without suffering any untoward reaction while driving. Road tracking performance in the standard test was impaired in a dose-related manner by THC and confirmed the results obtained in the previous closed highway study. The 100 μg/kg dose produced a slight elevation in mean SDLP, albeit nearly significant. The 200 μg/kg dose produced a significant elevation, of dubious practical relevance. The 300 μg/kg dose produced a highly significant elevation which may be viewed as practically relevant but unexceptional in comparison with similarly measured effects of many medicinal drugs. Following marijuana smoking subjects drove with an average speed that was only slightly lower than after placebo and very close to the prescribed level.

In the car following test subjects maintained a headway of 45-50 m (148-164 ft) while driving in the successive placebo conditions. They lengthened mean headway by 8, 6 and 2 m (26.2, 19.7 and 6.6 ft) in the corresponding THC conditions after 100, 200 and 300 μg/kg, respectively. The initially large drug-placebo difference and its subsequent decline is a surprising result. Our explanation for this observation is that the subjects' caution was greatest the first time they undertook the test under the influence of THC and progressively less thereafter. Reaction time to changes in the preceding vehicle's speed increased following THC treatment, relative to placebo. The administered THC dose was inversely related to the change in reaction time, as it was to headway. However, increased reaction times were partly due to longer headway. Statistical adjustment for this confounding resulted in smaller and non-significant increases in reaction time following marijuana treatment, the greatest impairment (0.32 s) being observed in the first test following the lowest THC dose. Headway variability followed a similar pattern as mean headway and reaction time; the greatest impairment was found following the lowest dose.

An important practical objective of this study was to determine whether degrees of driving impairment can be accurately predicted from either measured concentrations of THC in plasma or performance measured in potential roadside "sobriety" tests of tracking ability or hand and posture stability. The results, like many reported before, indicate that none of these measures accurately predicts changes in actual driving performance under the influence of THC.

The program then proceeded into the third driving study, presented in ***Chapter Six***, which involved tests conducted in high-density urban traffic. There were logical and safety reasons for restricting the THC dose to 100 μg/kg. It was given to a group of regular cannabis users, along with placebo. For comparative purposes another group of regular alcohol users were treated with a modest dose of their preferred recreational drug, and again placebo, before undertaking the same city driving test. Two groups of sixteen new subjects apiece, equally comprised of men and women, participated. Subjects in the alcohol group were regular users of alcohol but not marijuana. Both groups were treated on separate occasions with active drug and placebo. Active marijuana was administered to deliver 100 μg/kg THC. The driving test commenced 30 minutes after smoking. The alcohol dose was chosen to yield a BAC approaching 0.05 g% when the driving test commenced 45 minutes after onset of drinking. Active drug and placebo conditions were administered double-blind and in a counterbalanced order in each group.

Driving tests were conducted in daylight over a constant 17.5 km (10.9 mi) route within the city limits of Maastricht. Subjects drove their placebo and active drug rides through heavy, medium and low density traffic on the same day of the week, and at the same time of day. Two scoring methods were employed in the present study. The first, "molar" approach, required the driving instructor acting as the safety controller during the tests to retrospectively rate the driver's performance using a standard scale. The second, a more "molecular" approach, involved the employment of a specially trained observer who applied simple and strict criteria for recording when the driver made or failed to make each in a series of observable responses at predetermined points along a chosen route. Immediately prior to and following the driving tests subjects performed hand steadiness and time perception tests, yielded a blood sample, and were administered the same subjective questionnaires used in the previous studies.

The study showed that a modest dose of alcohol (BAC=0.04 g%) produced a significant impairment in city driving as measured by the molar approach, relative to placebo. More specifically, alcohol impaired vehicle handling and traffic maneuvers. Marijuana, administered in a dose of 100 μg/kg THC, on the other hand, did not significantly change mean driving performance as measured by this approach. Neither alcohol nor marijuana significantly affected driving performance measures obtained by the molecular approach indicating that it may be relatively insensitive to drug-induced changes.

Driving quality as rated by the subjects contrasted with observer ratings. Alcohol impaired driving performance according to the driving instructor but subjects did not perceive it; marijuana did not impair driving performance but the subjects themselves perceived their driving performance as such. Both groups reported about the same amount of effort in accomplishing the driving test following placebo. Yet only subjects in the marijuana group reported significantly higher levels of invested effort following the active drug. Thus, there was evidence that subjects in the marijuana group were not only aware of their intoxicated condition but were also attempting to compensate for it. These seem to be important findings. They support both the common belief that drivers become overconfident after drinking alcohol and investigators' suspicions that they become more cautious and self-critical after consuming low THC doses by smoking marijuana.

The laboratory performance tests also discriminated between the drugs' effects. Hand steadiness was impaired following THC and improved following alcohol, relative to placebo. The difference between the drugs' effects was significant, both before and after the driving test. Impairment after THC was about as much as that produced by the same dose in the previous study, indicating equivalent sensitivities of the present and previous groups. Production of time intervals was not affected by alcohol, but THC significantly shortened interval production, relative to placebo.

Drug plasma concentrations were neither related to absolute driving performance scores nor to the changes that occurred from placebo to drug conditions. With respect to THC, these results confirm the findings in previous studies. They are somewhat surprising for alcohol but may be due to the restricted range of ethanol concentrations in the plasma of different subjects.

Chapter Seven concludes the report with a general discussion of the results of the program and ends with a list of conclusions and recommendations. It starts with a discussion of the THC dose which marijuana users actually prefer for achieving their desired "high". Several questions are raised and discussed, such as: how do people regulate their THC consumption, what role plays familiarization with the drug, and what would the preferred dose have been if marijuana of much higher potency were smoked. The discussion then continues with a description of the differences between the driving tests in terms of the type of information processing each requires, automatic *vs* controlled, and the relevance of each to traffic safety.

Attention is further focussed on the effects of THC on driving performance. The results of the studies corroborate those of previous driving simulator and closed-course tests by indicating that THC in single inhaled doses up to 300 μg/kg has significant, yet not dramatic, dose-related impairing effects on driving performance. Standard deviation of lateral position in the road tracking test was the most sensitive measure for revealing THC's adverse effects. This is because road tracking is primarily controlled by an automatic information processing system which operates outside of conscious control. The process is relatively impervious to environmental changes but highly vulnerable to internal factors that retard the flow of information through the system. THC and many other drugs are among these factors. When they interfere with the process that restricts SDLP, there is little the afflicted individual can do by way of compensation to restore the situation. Car following and, to a greater extent, city driving performance depend more on controlled information processing and are therefore more accessible for compensatory mechanisms that reduce the decrements or abolish them entirely.

It appears that performance is more affected by THC in laboratory than actual driving tests. Several reasons that may account for the apparent discrepancy are discussed. First, laboratory tests are experimentally controlled by drastic simplification which may affect a subject's motivation to perform the test by making it appear "unreal". Secondly, the restriction of response options in laboratory performance tests leave fewer possibilities for compensation. In real life, drivers always apply numerous skills in parallel and series. Should one become deficient, they are often able to compensate in a number of ways to achieve a satisfactory level of proficiency. Finally, after learning to drive, subjects possess such skills in abundance and one can only demonstrate how they vary with drug effects in the real task or a very close approximation thereof. Profound drug impairment constituting an obvious traffic safety hazard could as easily be demonstrated in a laboratory performance test as anywhere else. But THC is not a profoundly impairing drug. It does affect automatic information processing, even after low doses, but not to any great extent after high doses. It apparently affects controlled information processing in a variety of laboratory tests, but not to the extent which is beyond the individual's ability to control when he is motivated and permitted to do so in real driving.

Marijuana's effects on driving performance were compared to those of many other drugs. It was concluded that THC's effects after doses up to 300 μg/kg never exceed alcohol's at BACs of 0.08 g%; and, were in no way unusual compared to many medicinal drugs'. Yet THC's effects differ qualitatively from many other drugs, especially alcohol. Evidence from the present and previous studies strongly suggests that alcohol encourages risky driving whereas THC encourages greater caution, at least in experiments. Another way THC seems to differ qualitatively from many other drugs is that the former's users seem better able to compensate for its adverse effects while driving under the influence. Still one can easily imagine situations where the influence of marijuana smoking might have an exceedingly dangerous effect; i.e., emergency situations which put high demands on the driver's information processing capacity, prolonged monotonous driving, and after THC has been taken with other drugs, especially alcohol.

Finally, the relation between driving impairment following marijuana smoking and plasma concentrations of THC and THC-COOH is discussed. It appears not possible to conclude anything about a driver's impairment on the basis of his/her plasma concentrations of THC and THC-COOH determined in a single sample.

CHAPTER 1 - MARIJUANA AND DRIVING: A REVIEW

Marijuana's effects on the ability of drivers to operate safely in traffic situations have traditionally been determined in two ways: from epidemiological surveys of users' involvement in traffic accidents and from empirical studies to measure the drug's influence on skills related to driving and driving itself. A review of results obtained from both approaches, partly relying upon previously published reviews, is provided. Its purpose is providing the reader a broader context in which the present report should be viewed. First, however, the drug and its pharmacological properties, and the prevalence of its use, will be discussed.

THE DRUG AND ITS PHARMACOLOGICAL PROPERTIES

Marijuana is the common name for any part of the hemp plant, cannabis sativa, or extracts which possess characteristic psychoactive properties in man. The plant contains more than 400 compounds. More than 60, the cannabinoids, are specific to that plant. The majority of the cannabinoid products are pharmacologically inactive. The major active product and that primarily responsible for the physiological and psychological effects of marijuana smoking is Δ^9-tetrahydrocannabinol (THC).

Besides being used as an intoxicant to produce a psychological "high" or euphoria, marijuana has been used as a sedative and analgesic (Maykut, 1985) but also, in Eastern countries, for relieving fatigue and stimulating appetite (Murray, 1985). It reliably produces both tachycardia and marked conjunctivitis. The mechanisms by which THC produces these physiological effects or the psychological effects sought by its users are still poorly understood (Jaffe, 1990). As a therapeutic agent, marijuana has been successfully applied in some cases of glaucoma (Relman, 1982) and anorexia nervosa (Zinberg, 1979). The most promising potential clinical use of marijuana is in the treatment of nausea and vomiting caused by cancer chemotherapy (Relman, 1982; Vinciguerra *et al.*, 1988; Randall, 1990). Synthetically formulated THC was approved in 1985 by the U.S. Food and Drug Administration (FDA) for use in the treatment of emesis, and is now marketed under the trade name Marinol (Unimed, Somerville, NJ). Patients suffering from AIDS may also benefit from marijuana because of its antiemetic and appetite stimulating effects. Yet there are also reports of adverse health effects of marijuana smoking on fetal growth, sperm cell motility, female reproductive hormone function, immunological system, cardiopulmonary system and central nervous system (Jaffe, 1990; Mendelson, 1987; Maykut, 1985).

The THC content in marijuana cigarettes varies in the United States from about 0.5% to 11% (Jaffe, 1990). In The Netherlands, seized hemp material usually contains about 10% THC, though it may range from 5 to 15% and, in exceptional cases, to 25% (Dutch Forensic Laboratory, personal communication). The inhaled dose in marijuana smoke varies also widely, depending upon the smoking technique and the amount altered by pyrolysis. In general it is thought that no more than about 25% of the available THC enters the circulation when marijuana is smoked in the usual manner (Davis *et al.*, 1984; Ohlsson *et al.*, 1980; Agurell and Leander, 1971), though if it were possible to continuously inhale smoke from an entire cigarette, up to 70% would become available (Agurell and Hollister, 1986).

The metabolism of THC is exceedingly complex and more than 80 metabolites are known to be formed in man. After marijuana smoking or THC injection, the first metabolite, 11-hydroxy-THC (11-OH-THC) is formed in the lungs and liver. Its peak concentration in relation to the parent compound's is about 1:10-20 (Wall *et al.*, 1983). After oral THC the ratio is about 1:1-2. Because this metabolite's psychological activity is equipotent to the parent's, it contributes to the total marijuana effect, particularly when the drug is ingested. 11-OH-THC is converted by the liver into a number of inactive metabolites. The primary pathway leads to the formulation of 11-nor-THC-9-carboxylic acid (THC-COOH), the most abundant inactive metabolite in plasma, and in urine where it is partially conjugated.

Plasma concentrations of THC peak during the smoking process and decline in sequential exponential phases; a redistribution (α) phase wherein the drug passes rapidly out of the plasma and into fatty tissues including the brain, followed by a much more prolonged elimination (β) phase wherein it is metabolized and excreted in urine and feces. The α-phase half life ($t_{\frac{1}{2}\alpha}$) is only about 30 minutes, whereas that of the β-phase ($t_{\frac{1}{2}\beta}$) varies between 18 and 36 hours depending upon the individual (Wall *et al.*, 1983; Chiang and Barnett, 1984; Agurell *et al.*, 1986).

The peak plasma concentration of 11-OH-THC is achieved within 15-30 minutes and from there declines according to essentially the same pharmacokinetic profile as its parent. The rise in THC-COOH's plasma concentration is relatively slow, reaching an ill defined peak in different individuals within 1-2 hours. Its elimination follows a monoexponential profile with various individuals showing $t_{\frac{1}{2}\beta}$'s from less then 24 to more than 72 hours. It is interesting to note that the inactive metabolite's mean plasma concentration exceeds that of THC from about the first hour onward.

Though peak concentrations of THC are achieved during smoking, the maximum psychological effect (the "high") occurs 15-30 minutes after its cessation, suggesting that brain concentrations increase as plasma concentrations decrease. Both peak concentrations and maximum "high" are roughly proportional to the inhaled THC dose, but correlations between these parameters measured simultaneously at times 3-240 min after the cessation of smoking are, albeit significant, not especially strong. For example, Ohlsson *et al.* (1980) found the overall correlation for repeated measurements obtained from 11 experienced smokers to be $r=0.53$. After four hours the psychological "high" had vanished and plasma THC levels were very low. Great interindividual variation exists in plasma levels of THC after smoking and this variation cannot be attributed to the regularity of marijuana use (Lindgren *et al.*, 1981; Agurell and Hollister, 1986).

Available evidence leads to the conclusion that it is usually impossible to predict the psychological effects of THC from its determination in a single plasma sample. But this is not the same as saying that no biological index of marijuana intoxication will ever be found. One possible candidate is THC's inactive metabolite THC-COOH. The relationship between this metabolite's plasma concentration and the perceived "high" after marijuana smoking has never been defined, although both parameters were measured in the study by Perez-Reyes *et al.* (1982). Peak and time integrated THC-COOH concentrations were proportional to the administered THC doses. Interestingly, the occurrence of the peak THC-COOH concentration coincided in time with the subjects' report of maximum "high". The authors failed, however, to measure, or at least report, the correlation between plasma THC-COOH concentration and subjective feelings because of the metabolite's pharmacological inactivity. Yet this coincidence might signify a useful epiphenomenal correlation. This possibility was repeatedly explored in this program.

PREVALENCE OF MARIJUANA USE

Marijuana usage prevalence peaked in the late 1970s and has been declining ever since. Still, marijuana is by far the most commonly used illicit drug in the United States (Jessor *et al.*, 1986; Johnston *et al.*, 1992). The most recent data about marijuana usage prevalence are available from the 17th National Survey of American High School Seniors, and the 12th National Survey of American College Students (Johnston *et al.*, 1992). Life time prevalence among high school seniors declined from 60% in 1980 to 37% in 1991; and, among college students, from 65% in 1980 to 46% in 1991. Thirty-day prevalence declined in both groups from 34% in 1980 to 14% in 1991. About 9% of high school seniors and 7% of college students admitted daily use of marijuana in 1980. Only 2% of both groups did in 1991.

A 1988/1989 survey of cannabis use among Dutch students, 10-20 years old, provided different results (Plomp *et al.*, 1990). Considering only those in an age bracket comparable to American high school seniors and recent graduates (17-20 yrs; N=1806), the lifetime use prevalence of cannabis was 21% and 13% among males and females, respectively. Those who smoked at least once during the last month comprised 5.8% and 3.0% of the respective samples. Compared to results obtained from a similar survey executed in 1984 (Van der Wal, 1985) the lifetime and current prevalence of use have risen in The Netherlands by factors of 1.7 and 1.5, respectively.

In short, relatively more young Americans formerly used and still use cannabis than their Dutch counterparts, but the disparities between lifetime and current use prevalences are narrowing due to opposite trends in the two countries.

It is perhaps important to note in this context that possession of cannabis is prohibited by law in The Netherlands, as in the United States. The seriousness of the offense is, however, determined by the amount found in the Dutch user's possession and prosecution is unlikely to occur when that is less than 30 g (1 oz).

MARIJUANA AND TRAFFIC SAFETY

Epidemiological Research

Simpson (1986) has reviewed recent epidemiological evidence regarding marijuana's role in traffic accident causality. His first concern was to determine the frequency of driving after marijuana use in order to identify the proportion of the total driving population who may be considered "at risk" of causing an accident for that reason. His information was derived from two sources: questionnaire surveys of adolescents (16-19 years), who were licensed to drive, and roadside surveys of recent usage among passing motorists.

He mentioned the reasonably consistent results of four questionnaire surveys conducted in the United States or Canada between 1979 and 1982. About one in six teenage drivers admitted driving while smoking or shortly afterward, and about 10% said they had done so between one and five times during the preceding month. Taken at face value, these results indicate that most users do not drive during or shortly after marijuana smoking which implies they do perceive risks associated with marijuana use and driving. Unfortunately it is not easy to generalize these results to older drivers in North America, nor to Europeans who are generally not licensed to drive until older than 18 years of age.

Only two surveys of recent marijuana use among drivers stopped at roadside check points have apparently been reported. These were widely separated in place and time. The first was completed in Canada in 1974 (Smith *et al.*, 1975), the second in Italy in 1982 (Ferrara and Rozza, 1985). Moreover, the former relied upon the drivers' admission of use and the latter upon detection of cannabinoids in urine samples. Nonetheless, the indications of recent marijuana use given by the two sets of results were not grossly different; 4% by the first and 1.2% by the second.

The incidence of drivers whose recent use of marijuana resulted in their injury or death in motor vehicle accidents can only be estimated from the detection of THC in plasma samples obtained shortly after the occurrence of the event. Hemolyzed blood samples obtained from dead victims provide unreliable estimates and analyses of urine samples to determine metabolite concentrations yield no indication of whether the drug was active at the time of the accident.

Terhune (1982) tested 497 injured drivers for the presence of a wide range of drugs during treatment at the Rochester General Hospital in New York. THC in blood was detected in 9.5% of the drivers, but more than half of them also tested positively for alcohol. Chesher and Starmer (1983) found THC in 6.7% of 104 injured drivers in New South Wales, Australia, but again about half of them showed alcohol as well. Daldrup *et al.* (1987) examined 597 blood samples from injured drivers in the region around the German city Düsseldorf for the presence of alcohol. Blood samples having alcohol concentrations (BAC) below 0.13 g% were additionally analyzed for the presence of cannabinoids; twenty-five of the 220 blood samples (10%) were positive. More recently, Soderstrom *et al.* (1988) determined prior marijuana and alcohol use in 1023 patients who were injured as the result of vehicular and nonvehicular accidents and treated in the Shock Trauma Center in Baltimore, Maryland. THC was found in blood by radioimmunoassay in 34.7% of the patients, alcohol in 33.5%. Among automobile drivers, the numbers were 31.7% and 34.6%, respectively. Again, in about 50% of the marijuana positive cases alcohol was also found. It is not clear why these results contrast with those of previous studies. The most plausible explanation is that residents of the Baltimore area tend, in general, to use THC more often than those in the other regions surveyed.

Canadian and American surveys of fatally injured drivers have generally found the incidence of those showing THC in plasma to be between 3% and 11% and in all cases the coincidence of this drug and alcohol was above 70% (Cimbura *et al.*, 1980, 1982, 1990; Donelson *et al.*, 1985; Owens, 1981; Mason and McBay, 1984). Disparate results were obtained by Williams *et al.* (1985) who found THC in plasma from 37% of 440 dead drivers in California (80% in combination with alcohol). The reason for this disparity could be due to the greater prevalence of marijuana use in California but it was more probably related to these investigators' selection criteria: they only included male drivers younger than 35 years of age in their sample. Simpson estimated that if female and older male fatalities had been included in this survey, the overall percentage showing THC would have been about 20%. This figure is still double the estimates from other studies, which reinforces suspicions about the prevalence of marijuana use in California. However neither this nor any other survey allowed for the local and contemporary comparison of the fatally injured percentage of drivers showing THC plasma levels with that of the driving population in general.

If it is true that the population at risk from driving after marijuana smoking is 4%, or less, then the higher percentages of drivers injured or killed in traffic accidents while showing plasma THC concentrations seem to be an over-representation. However, there are obvious reasons to doubt whether valid estimates of the population at risk in urban North America can be derived from data that are more than 14 years old or were obtained at two locations in Northern Italy. Even if the population at risk is as small as estimated, the surveys of THC incidence in injured or killed drivers have not provided evidence for a causal role of the drug per se in accidents. Alcohol was present in the vast majority of victims showing plasma concentrations of THC. The fact that the two drugs in combination possess a greater risk potential than either alone, is most likely. But the independent contribution of THC to traffic accident causality, particularly in concentrations which are likely to be found in most users who drive, is still questionable.

One major problem in epidemiological research on the relationship between marijuana and traffic accidents is the lack of sound control groups as have been used in studies of alcohol involvement in accidents (e.g. Borkenstein *et al.*, 1964). In those studies BACs derived from breath samples of drivers involved in accidents were compared with those of randomly selected drivers passing the accident site in the same direction at the same time of day and day of week. As Moskowitz (1985) noted, these kind of studies rely on two assumptions that do not hold well for investigations on marijuana. The first is that nearly all drivers will cooperate, which holds for alcohol studies in which typically 97% are willing to supply a breath sample, but does not hold for marijuana studies in which only 50-75% are willing to cooperate due to the necessity of sampling blood rather than breath. A second assumption is that drug concentrations found are well correlated with performance impairment, which holds for alcohol but seems not to for marijuana.

One way to circumvent this problem is the use of a culpability index, which reflects the percentage of drivers with detectable drug levels and deemed culpable compared to drug free drivers from the same sample who were also responsible for causing an accident. Warren *et al.* (1981) reanalyzed the data from Cimbura *et al.* (1980) and reported that 52% of the drug free fatally injured drivers were deemed culpable compared to 90% of those with evidence of marijuana use resulting in a culpability index of 1.7, a level also found for alcohol. Results of two other studies (Terhune, 1982; Donelson *et al.*, 1985) are consistent with these findings, whereas Mason and McBay (1984) found no evidence of marijuana as a risk factor. In contrast to these studies, Williams *et al.* (1985) found that drivers in whom only marijuana was detected were less likely to be culpable (53% *vs* 71%). In contrast, dead drivers showing only alcohol were judged responsible in 92% of all cases. Those showing both THC and alcohol were slightly more often responsible for causing the accident than those in whom only alcohol was found. It should be noted, however, that the frequencies of injured drivers showing THC alone are commonly very low and prohibit any definite conclusion.

In summary, epidemiological literature shows that people do drive after marijuana use and that drivers involved in accidents often show the drug's presence, but results are inconclusive especially because of the high proportion of cases that also involve alcohol use. Therefore, the extent marijuana contributes to traffic accident causality remains obscure.

Marijuana's Effects upon Driving Simulator Performance

Early studies by Crancer *et al.* (1969), Rafaelsen *et al.* (1973), Ellingstad *et al.* (1973) and Moskowitz *et al.* (1976) utilized the filmed ride approach where subjects had little or no control over the presented imagery Dott (1972) used a different approach for measuring subjects' decisions to pass a preceding car, or not, in the presence of an opposing vehicle portrayed as models on a continuous belt. Doses of inhaled THC varied from about 3 to 22.5 mg (43-321 μg/kg for 70 kg, or 154 lb, persons). Smiley (1986) reviewed these early studies to conclude that THC had (1) not affected vehicle control, (2) increased decision latency before starting, stopping or overtaking, (3) reduced the willingness to accept a risk during passing maneuvers, and (4) impaired speedometer monitoring. Except in the case of one individual who, after inhaling 12 mg THC, repeatedly drove through stop lights during a filmed ride, no particular sign of dangerous driving behavior was observed.

Smiley *et al.* (1981) conducted the first study using an interactive simulator with accurate visual imagery, though not moving base dynamics. The simulated tasks contained in a 45-minute scenario included curve following, reacting to wind gusts, car following, route selection from signs, avoiding an obstacle which appeared in front of the simulated vehicle and passing. A visual choice reaction time was also superimposed on driving. Three groups of marijuana users smoked cigarettes containing 0, 100 and 200 μg/kg THC on two occasions per dose, once with and once without alcohol. The quantity of alcohol consumed varied between groups to reach intended blood concentrations of 0.00, 0.05 and 0.08 g%, respectively. To ensure high motivation, good driving was rewarded and blatant errors, such as crashes, were penalized financially. The test began 15 minutes after the cessation of smoking. Both THC doses increased lateral position variability and the highest dose increased speed variability during curve following. Both increased headway variability, and the highest, lateral position variability during car following. Both doses caused the subjects to miss more signs indicating the need to follow another route. The high dose caused the subjects to hit the roadway obstacle more often than placebo, and also, to react slower to the subsidiary task. Yet both THC doses caused the subjects to drive in a more conservative manner. They maintained a longer headway while car following, refused more opportunities to pass, and when they did, began this maneuver at a greater distance from the approaching vehicle. Alcohol's effects in this study were generally less than THC's. Chesher (1986) was puzzled by this, calling the alcohol effect "surprisingly small" and its interactive effect with THC, "unclear". Certainly it is so that BACs of 0.08 g% and below have been enough to substantially degrade drivers' control of vehicular lateral position in real driving tests (Louwerens *et al.*, 1987; Ramaekers *et al.*, 1992a).

Stein *et al.* (1983) conducted two studies of alcohol and marijuana effects using a driving simulator and a 15-minute test scenario that were very similar to those employed by Smiley *et al.* (1981). The former administered the two drugs in complete crossover designs. THC doses of 0, 50 and 100 μg/kg THC were combined with BACs of 0.00 and 0.10 g% in the first study. The same BACs were combined with 100 and 200 μg/kg in the second. This time alcohol had the expected adverse effect on practically every performance parameter, THC had little effect in the first study and little in the second in spite of the higher dose. The latter did cause the subjects to operate at generally lower speeds, however. The combination of drugs produced widely different individual reactions. After the highest THC dose, the combination produced more adverse reactions than alcohol alone.

Marijuana's Effects upon Actual Driving Performance

A number of studies on marijuana's effects upon actual car driving have been reported since 1974. All studies but one were carried out on courses closed to other traffic. Klonoff (1974) conducted the exceptional study wherein 64 subjects drove on a closed course and 38 also participated in a city driving test. In his first study subjects were assigned to one of three groups that were treated with (1) placebo, (2) 4.9 mg THC, and (3) 8.4 mg THC. They undertook eight tests: a slalom, two tunnel tests, a funnel test, a backing up, turning in a corner, a risk judgment test and an emergency braking test. Except for the latter two, the performance measure was number of cones hit. Subjects performed 20 trials in four blocks of five. Treatments were administered between the third and fourth block and each subject's performance was related to his/her performance predicted by means of regression analysis over the first three blocks. Performance after placebo was as predicted, but after marijuana, significantly worse, though not much. The low dose impaired performance in two tests (tunnel and corner) and the high dose in five (slalom, both tunnel tests, funnel and risk judgment).

Subjects in the city driving test were divided among four groups who were treated with placebo and marijuana, on separate occasions a week apart. The respective groups' treatments were (1) placebo followed by 4.9 mg THC, (2) the same in reverse order, (3) placebo followed by 8.4 mg THC, and (4) the same in reverse order. After smoking a placebo or marijuana cigarette, the subjects drove for 45 minutes over a 16.8 mi (27.0 km) route on city streets while aspects of their performance were rated by a professional examiner using an abbreviated version of the British Columbia Department of Motor Vehicles' standard driver's licensing test. All subjects were allowed to complete the test which indicates that their performance never became dangerously unsafe under the drug's influence. Nonetheless, the examiner rated the subjects' performance as significantly worse on scales of judgement and concentration following the highest but not the lowest dose. The majority showed some impairment, but 32% after the low dose and 16% after the high dose performed significantly better than they had following placebo suggesting qualitative differences between the drug's effects in different subjects.

Hansteen *et al.* (1976) tested sixteen subjects in four conditions, (1) placebo alcohol + placebo marijuana, (2) placebo alcohol + marijuana (THC dose of 21 μg/kg), (3) placebo alcohol + marijuana (THC dose of 88 μg/kg), and (4) alcohol (BAC 0.07 g%) + placebo marijuana. Subjects were instructed to drive through a 1.1 mi (0.7 km) course delineated by traffic cones as quickly as possible but without exceeding 30 mph (19 km/h). Performance was measured shortly after smoking and three hours later. Number of cones hit, "rough handling" (superfluous and/or awkward movements as observed by an accompanying investigator), and driving time were scored. More cones were hit and more time was taken to complete each lap after consuming the higher THC dose, but no increase in rough handling was observed. Alcohol, on the other hand, adversely affected both performance measures and diminished the time taken to complete each lap. The authors concluded that the drug effects on performance were not dramatic since no major differences were found between conditions with respect to observer ratings.

Casswell (1979) was the first who included a subsidiary task to simulate the demands for monitoring the environment. Thirteen males were tested in three treatment sessions receiving alcohol and marijuana treatments twice in each session and drove for 35 minutes after each treatment. Treatments included (1a) alcohol (0.10 g% BAC) + placebo marijuana, (1b) placebo alcohol + marijuana (6.25 mg THC), (2a) double placebo, (2b) placebo alcohol + marijuana (6.25 mg THC), (3a) alcohol (0.05 g% BAC) + marijuana (3.12 mg THC), and (3b) alcohol (0.05 g% BAC) + marijuana (3.12 mg THC). Subjects' tasks included overtaking, driving on straight sections, through a hairpin bend, and through narrow gaps, while responding to road signals, traffic signals, and auditory signals in the subsidiary task. Alcohol alone and in combination with marijuana produced more coarse steering corrections, higher speed and increased lateral position variability. Marijuana alone was associated with lower driving speed and prolonged reaction times in the subsidiary task. Reaction times were also prolonged by the combination of marijuana and alcohol. The authors said that drivers under the influence of marijuana appeared to compensate for what they felt were the adverse effects of the drug by maintaining control effort, and decreasing speed to reduce the required rate of information processing. Alcohol, in contrast, appeared to produce more risky behavior.

Attwood *et al.* (1981) also employed normal driving tasks on a closed course. Eight males participated in a within-subjects design, receiving (1) double placebo, (2) alcohol (0.08 g% BAC) + placebo marijuana, (3) placebo alcohol + marijuana (150 μg/kg THC), and (4) alcohol (0.04 g% BAC) + marijuana (75 μg/kg THC). The driving tasks were performed on an airfield runway and included: maintenance of a constant lateral position and velocity, maintenance of a constant headway while following a lead car that varied in speed, bringing the car to a smooth stop at a traffic signal, and deciding whether or not to overtake a preceding vehicle in the presence of an approaching car. The latter maneuver was, however, not actually undertaken. Various measures, as speed, lateral position, acceleration and headway, were taken but the number of significant comparisons were no more than expected by chance. All measures were then subjected to a discriminant analysis that separated overall treatment effects. Overall driving performances after all drug treatments were significantly worse than following placebo when tested in this multivariate analysis. Smiley (1986) suspected that the lack of univariate effects was attributable to the low number of subjects and the lack of a subsidiary task.

Peck *et al.* (1986) assigned 84 subjects in equal proportions to four treatment conditions: (1) double placebo, (2) alcohol (0.08 g% BAC) + marijuana placebo, (3) marijuana (19 mg THC) + alcohol placebo, and (4) both drugs combined. If these subjects could have inhaled all of the drug available in the cigarette, one weighing 70 kg (154 lb; population average) would have received a dose of about 270 μg/kg. Because of the remaining butt, the actual THC dose probably never exceeded 250 μg/kg. The subjects were tested four times in complete replications of a driving test battery beginning shortly after drug administration and continuing at hourly intervals thereafter. Ratings of the subjects' driving proficiency were obtained from driving licence examiners who rode with the subjects or observed them from static positions at points along the course; and, by California Highway Patrol officers who followed the subjects' vehicle in a police car. A computerized system within the subjects' vehicle recorded their use of controls, speed and lateral position relative to course delineation. A risk acceptance test was included to measure the subjects' willingness and ability to drive through gaps wider and narrower than the vehicle. Other tasks involved stopping in response to signals, making a forced lane change and driving through pylons in a chicane. Finally, a standard police field sobriety examination and two standard laboratory tests (tracking and time estimation) were administered to the subjects outside of the vehicle. Several hundred measures of performance were obtained. No dramatic performance failures were reported as an effect of either drug or their combination. In general, the number of significant drug effects on particular measures were about what one might expect given the total number of statistical tests.

The investigators resorted, like Attwood *et al.*, to multivariate statistical analysis of their data. Twelve performance measures were combined in discriminant analysis, which significantly separated the effects of each drug or their combination from placebo's. The THC effect was significant over all four replications of the tests, being greatest in the first trial. Alcohol's effect was greatest in the second trial and slightly greater than THC in every one. The combination of THC and alcohol produced significantly more impairment then did either drug alone in the first and third trials. Field sobriety checks by the police and ratings of the subjects' driving proficiency by experts failed to show any effect of THC, though these did reveal the effects of that drug in combination with alcohol. Practically the only indication of a serious effect of THC was provided by the officers following the subject's vehicle in a police car. They reported that they would have stopped the subject for suspicion of being intoxicated on 32% of all THC trials (alcohol 50%, both drugs 60%). But they also said they would have stopped 15% of the placebo treated subjects. This either indicates that the subjects were exceptionally poor drivers, or were made to appear so under conditions of the test, or that the officers were responding to cues that they ordinarily would have ignored in real driving conditions.

Smiley *et al.* (1987) tested the effects of marijuana (0, 100 and 200 μg/kg THC) in combination with alcohol (0.00 and 0.05 g% BAC) and alcohol alone (0.08 g% BAC) on driving in a closed-course study. Treatments were administered to groups of nine males over a three hour period in a party-like atmosphere in the evening. Subjects drove shortly after smoking as well as on the following morning. Driving tasks included maintenance of a constant lateral position at 80 km/h (50 mph), curve following, car following, route navigation, obstacle avoidance, and emergency decision making. Additionally, subjects had to perform a subsidiary task requiring visual monitoring. The high THC dose resulted in increased headway and headway variability. Alcohol alone at the 0.05 g% BAC level produced increased speed. Number of subsidiary task detections decreased at 0.05 g% BAC but increased at 0.08 g% BAC. Smiley's (1986) conclusion from her own and previous studies was as follows:

> "...., marijuana does appear to impair driving behaviour. However, this impairment is mediated in that subjects under marijuana treatment appear to perceive that they are indeed impaired. Where they can compensate, they do, for example, by not overtaking, by slowing down and by focusing their attention when they know a response will be required. Unfortunately, such compensation is not possible where events are unexpected or where continuous attention is required. Effects on driving behaviour are present shortly after smoking but do not continue for extended periods." (p. 133).

General Conclusion

The foremost impression one gains from reviewing the literature is that no clear relationship has ever been demonstrated between marijuana smoking and either seriously impaired driving performance or the risk of accident involvement. The epidemiological evidence, as limited as it is, shows that the combination of THC and alcohol is over-represented in injured and dead drivers and more so in those who actually caused the accidents to occur. Yet there is little if any evidence to indicate that drivers who have used marijuana alone are any more likely to cause serious accidents than drug free drivers. To a large extent, the results from driving simulator and closed-course tests corroborate the epidemiological findings by indicating that THC in single inhaled doses up to 250 μg/kg has relatively minor effects on driving performance, certainly less than BACs in the range 0.08-0.10 g%.

CHAPTER 2 - GENERAL METHODS

Before presenting the designs and results of the individual studies in separate chapters, it seems appropriate to describe the studies of the program and certain procedures that were common to all. These were subject recruiting, compliance with ethical and legal standards, screening for the presence of other illicit drugs and alcohol, and blood sampling procedures and quantitative analyses.

DESCRIPTION OF A 4-STUDY PROGRAM

The present relationship between drivers' use of marijuana and other substances containing the psychoactive drug (THC) and their involvement in traffic accidents is exceedingly obscure. For a variety of practical reasons, epidemiological research has failed to define that relationship in a manner approximating the demonstration of alcohol's effects on traffic safety (Terhune, 1986). The classical approach of first showing that a drug is actually causing traffic accidents before determining how has simply failed for THC.

Yet abundant experimental evidence exists to show that some doses of THC can impair skills deemed important for safe driving. Unfortunately, most of it is of dubious relevance to the actual driving situation: nearly all of the studies on THC's behavioral effects were accomplished using laboratory tests that are not directly related to actual car driving. If previous experience is any guide, little of crucial importance will emerge from experimental research until it is conducted in a more "real world".

Closed-course driving studies have shown that marijuana can impair driving performance but it is unknown to what extent these effects translate into driving performance in the real world. Only one study has been conducted in real world (city driving; Klonoff, 1974). This study demonstrated that subjects perform less competently when under the influence of marijuana, but the scoring method was questioned by others as regards its relationship to safe driving performance.

Bearing these limitations of previous studies in mind a program was set up to determine the dose-response relationship between marijuana and objectively and subjectively measured aspects of real world driving; and, to determine whether it is possible to correlate driving performance impairment with plasma concentrations of the drug or a metabolite. These goals are the same as those of many unsuccessful investigations in the past. Yet none before has gone so far in seeking to achieve them in the environment where the "drugs and driving" problem actually exists. In the present studies, a variety of driving tasks were employed, including: maintenance of a constant speed and lateral position during uninterrupted highway travel, following a leading car with varying speed on a highway, and city driving. The purpose of applying different tests was to determine whether similar changes in performance under the influence of THC occurs in all thereby indicating a general drug effect on driving safety.

The program consisted of one minor and three major studies; a series of separate but interdependent experiments that successively approached driving reality. This approach was necessary to ensure subject safety throughout the program. The program started with a pilot study (Chapter 3), conducted in a hospital under strict medical supervision, to identify THC doses that recreational marijuana users were likely to consume before driving.

The first driving study (Chapter 4) was executed on a closed section of a public highway. The major goal was to determine the dose-response and dose-response-time relationship between marijuana (three different THC doses, and placebo) and road tracking precision as measured by the "weaving" motion of the subject's vehicle during uninterrupted highway travel. Results of this are compared to those from a previous study undertaken by the investigators to measure the effects of different blood alcohol concentrations on driving performance in essentially the same test situation (Louwerens *et al.*, 1987). A practical purpose was to determine whether the drug's effects as measured in a standard driving test were of a magnitude that would safely allow application of the same test and others on public roads in traffic.

Upon completion of this study with the demonstration that THC's effects could be safely controlled, a second driving study (Chapter 5) was conducted to come a step closer to driving reality than its predecessor. The methods applied were, with the addition of a car following test, the same as those used in the first driving study. However, driving tests were now conducted on a highway in the presence of other traffic. The greatest discretion was employed in designing this study to reach limited objectives. We choose a conservative approach which closely follows that used to determine the tolerability of medicinal drugs in human pharmacological research. It is to test THC's effects on actual driving performance in an ascending dose series. The ultimate goal was to define the THC dose (or plasma concentration) limit which separates low and high risk driving performance impairment by approaching it from the bottom up.

Yet normal driving is far more complex and varied than simply to maintain a safe lateral position and headway during uninterrupted travel on a highway. A THC dose having no effect on these parameters might still impair driving performance in more complex urban driving situations. For this reason the program then proceeded into the third and final driving study (Chapter 6) which involved tests conducted in high density urban traffic. The highest dose which had no significant effect on highway driving in the previous study was given to subjects who would now operate in an urban driving test. This provided an opportunity to measure a far broader range of driving performance. If no effect were again observed, the generality of the dose-effect relationship would be strengthened. But if a new kind of impairment were observed, the conclusion would have to be that the dose effect relationship can not be validly used to define the effects of THC on driving performance, in general. The nature of the new impairment would provide insight into the kinds of traffic safety problems that may be first to appear as a consequence of the drug's effects. A second group also participated in this study and undertook the same driving test, but then after drinking alcohol (reaching an average BAC of 0.04 g%), and a placebo. This was done for two reasons; first, the alcohol condition served as a control whether the employed tools to assess driving performance were sensitive; and, secondly, it made a comparison possible between low doses of alcohol and THC.

SUBJECTS

The ideal subjects would be male and female marijuana users whose consumption of the drug represents that of the majority in that particular population. Van der Wal's (1985) data for the oldest group (17-18 years) in his sample of present Dutch cannabis users indicate that about 56%

of the males and females have a usage frequency of more than once per month and less than daily. This usage frequency was considered as the first selection criterion.

The second criterion was that the users should also be experienced drivers in possession of a driver's licence. Subjects must have driven at least 5,000 km (3,108 mi) per year over the previous three years. This criterion was, however, not always met because of the difficulties in recruiting subjects.

As the third criterion the users should have indicated on a questionnaire that they had driven within one hour after smoking cannabis at least once within the preceding year. These users not only possess the requisite driving experience under the influence of marijuana, they also constitute the "drivers at risk". In addition, the application of this criterion avoided the ethical dilemma of requiring subjects to accept a risk which they would otherwise avoid.

As a fourth criterion, the subjects should agree to refrain from their normal marijuana use for at least five days prior to their participation in any test.

Other inclusion criteria were as follows: age 21-40 years; normal (corrected or uncorrected) binocular acuity (i.e. 20/25 Snellen acuity, or better); body weight within the 85^{th} - 115^{th} percentile range according to the 1983 table from the Metropolitan Life Insurance Company; and, Dutch nationality. The latter criterion was a condition set by the Dutch Ministry of Health which has no authority to permit the use of an illicit drug by foreign nationals.

Exclusion criteria included the following:

1. No history of treatment for drug or alcohol abuse or addiction and no reasonable possibility of dependence occurring as the result of participation in the investigation.
2. No record of arrests or conviction for drug trafficking.
3. No history of psychiatric or organic brain disorders.
4. No overt signs of cardiovascular, respiratory, renal, hepatic, metabolic or neuromuscular disorders and no history of serious disorders of this type.
5. No current use of any psychoactive medication (tranquilizers, antidepressants etc.)
6. For females, no pregnancy or any reasonable probability that pregnancy might occur during participation in the investigation.

Some subjects volunteered spontaneously after reading about the planned study in newspapers. Other volunteers for the first two studies were primarily obtained from among the local population of marijuana users by means of advertisements. Both the second and the third driving study required new samples of subjects. In these cases it was more difficult to recruit subjects since advertisements could not be placed where they might attract the attention of news media. The desire to avoid attention was fostered by a need to ensure subjects' anonymity and avoid the media's interference with data collection involving driving in traffic on public highways and city streets. Subjects were therefore recruited in the last two studies mainly by contacts obtained from subjects from the preceding ones. Admittedly this procedure is not the best to acquire independent samples but was necessary for practical reasons.

Volunteers were screened in two stages; first from their responses to a combined cannabis use, driving experience and medical history questionnaire; and secondly, on the basis of an interview and physical examination. Furthermore law enforcement authorities were contacted, with the volunteers' consent, to verify that they had no previous arrests or convictions for drug trafficking.

Subjects were instructed to sleep normally on the nights before test days. Alcohol consumption was prohibited for 24 hours before tests, and consumption of beverages containing caffeine, for 2 hours beforehand. Those who smoked tobacco were advised that this would also be prohibited for one hour before testing until its completion.

COMPLIANCE WITH ETHICAL AND LEGAL STANDARDS

All studies described in this report complied with the code of ethics on human experimentation established by the *Declaration of Helsinki* (1964) as amended in Tokyo (1975), Venice (1983), and Hong Kong (1989). This implies that the volunteer subjects were fully informed of all procedures, possible adverse reactions to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without penalty or censure. All subjects gave their informed consent, in writing. Their anonymity was and will be maintained in all communications from the project. The investigators provided for continuous medical supervision and emergency medical treatment during the studies. Approvals for individual studies were separately obtained from the University's Medical Ethics Committee.

Before the program started an Independent Advisory Committee was formed whose function was to ensure that the program proceeded in accordance with all medical and legal standards. This committee comprised the Assistant District Attorney, the Municipal Traffic Attorney for the City of Maastricht, a member of the University's Medical Ethical Committee, and the Dutch Regional Inspector for Public Health (Drugs). A permit for obtaining, storing and administering marijuana was obtained from the Dutch Drug Enforcement Administration.

Subjects were accompanied on every driving test by a licensed driving instructor experienced in supervising subjects who operated under the influence of medicinal drugs in previous studies. The instructor's sole task was that of monitoring ride safety. Redundant control system in the test vehicle was available for controlling the car if emergency situations should arise. However, the primary guarantor of the subject's safety was the subject himself/herself. The subject, like any licensed Dutch driver, had the legal responsibility to stop driving when feeling "under the influence" to the point where he/she could no longer be sure of his/her ability for safely controlling the vehicle. Subjects in this investigation were reminded of their responsibility and urged not to undertake any test, or to stop driving during a test in progress, if they felt incapable of driving safely. Subjects were always transported to and from their appointments and were strictly instructed not to operate their own vehicles for a period of 12 hours after having received the experimental treatment.

SCREENING FOR THE PRESENCE OF OTHER ILLICIT DRUGS AND ALCOHOL

Though it seemed unlikely that subjects would regularly resort to using other illicit drugs or alcohol prior to controlled marijuana smoking and testing, the possibility could not be definitely excluded without testing the subjects for the presence of these drugs. Therefore they were informed beforehand of the intention to obtain urine and breath samples which would be analyzed for the presence of prohibited agents.

Each subject was required to submit a urine sample immediately upon arrival at the test site. Samples were later assayed qualitatively for the following drugs (or metabolites): cannabinoids, benzodiazepines, opiates, cocaine, amphetamines and barbiturates. In addition a breath sample was analyzed on the spot for the presence of alcohol using a Lion S-D3 Breath-Alcohol

Analyzer. The urine and breath sample screening procedures were employed in all studies in the program.

Drugs other than cannabinoids were found in urine of four subjects. In the pilot study, the urine of two subjects was positive for benzodiazepines; and, of one subject for barbiturates. Analyses of six urine samples obtained from these subjects during the successive driving study failed to show the presence of these drugs. Since all urine samples from both the pilot and first driving study were analyzed after completion of the latter, the failure to detect the drugs in samples obtained during the driving study indicates that they did not abuse these drugs. Upon questioning, all three subjects denied that they had taken these drugs. Since no urine or plasma was left from these subjects, it was, however, not possible to check whether the results were false positives. Data obtained from these subjects in the pilot study were not excluded from the statistical analyses. One subject's urine, obtained prior to smoking in the 200 μg/kg condition in the first driving study, was positive for cocaine. Upon questioning, the subject replied that some friends had surreptitiously administered him cannabis cake and cocaine the day before. Assuming that the drugs' effects had dissipated the next day, these subject's data were also not excluded from statistical analyses.

BLOOD SAMPLING AND QUANTITATIVE ANALYSES

Blood samples were taken by venepuncture. Two 10 ml aliquots were obtained in every case. These were heparinized and centrifuged within 30 minutes. Plasma was placed in frozen (-20°C) storage prior to analysis. The quantitative chemical analysis of THC and THC-COOH in plasma was performed by gas chromatography/mass spectrometry (GC/MS) using deuterated cannabinoids as internal standards (Möller *et al.*, 1992). Of the many analytic techniques available at present, GC/MS is the reference method of choice (Cook, 1986). Applying this method, the detection limits for THC and THC-COOH were about 0.3 and 3.0 ng/ml, respectively. THC and THC-COOH concentrations in plasma will further be abbreviated to [THC] and [THC-COOH].

If the urine analysis (above) was positive for cannabinoids, plasma taken before smoking was also analyzed to quantitatively determine [THC] and [THC-COOH]. Subjects with detectable THC in pre-smoking plasma are shown in Table 2.1. In the pilot and first driving study, THC was detected in each pre-smoking plasma sample from two subjects and in one sample from another subject, namely prior to smoking in the 200 μg/kg condition. In the second driving study, THC was detected in one sample from one male and in five out of six samples from another male. In the city driving study, THC was not detected in any pre-smoking sample.

It seems obvious that those subjects, who had detectable [THC] before smoking, did not comply with the instruction to abstain from cannabis consumption for at least five days prior to the trial. They all had long histories (at least 7 years) of cannabis experience and were frequent (at least twice a week) users. Gieringer (1988) reports that THC may persist in the blood of chronic smokers at levels up to 4.0 ng/ml after 48 hours. It therefore remains an open question when their latest consumption was or whether they were impaired upon arrival at the laboratory.

The same pattern of pre- to post-smoking values as shown in Table 2.1 was observed in the other subjects, i.e. [THC] and [THC-COOH] increased considerably after smoking the administered marijuana cigarettes and not following placebo. Therefore, these subjects' data were not excluded from the statistical analyses.

Table 2.1 Pre-smoking and post-smoking [THC] in subjects with detectable THC in pre-smoking plasma samples.

Study	Subject no.	Condition	[THC] before Smoking (ng/ml)	[THC] after Smoking†† (ng/ml)
Pilot study	1513	†	3.0	35.5
	1525	†	1.2	13.3
1st driving study	1507	200 µg/kg	1.9	39.3
	1513	placebo	2.0	1.8
		100 µg/kg	2.4	9.2
		200 µg/kg	2.7	34.7
		300 µg/kg	4.2	26.8
	1525	placebo	1.1	1.1
		100 µg/kg	1.5	19.5
		200 µg/kg	1.1	6.9
		300 µg/kg	2.7	13.9
2nd driving study	1536	1st placebo	0.5	0.6
		100 µg/kg	0.6	10.7
		2nd placebo	0.7	0.6
		3rd placebo	1.2	1.3
		300 µg/kg	1.3	30.9
	1537	1st placebo	0.6	0.5

† only one condition (smoking until the desired effect was achieved).
†† sampling time was 40, 30 and 35 minutes after initiation of smoking in the pilot, first and second driving study, respectively.

Fifty percent of the pre-smoking plasma samples obtained from subjects in the pilot and first driving study, whose urine tests were negative for cannabinoids, were also analyzed. These analyses were performed to examine whether any false negative urine analyses had occurred. Results showed that none of these samples contained detectable [THC] or [THC-COOH]. From these results it was inferred that in subsequent studies pre-smoking blood samples need only be taken if the urine test for cannabinoids were positive.

CHAPTER 3 - PILOT STUDY TO SELECT THC DOSES

INTRODUCTION

Doses used in all previous studies of inhaled THC have been selected without consulting the subjects beforehand to determine whether these realistically approximated doses they commonly use. In the opinion of several experts (Moskowitz, 1985; Chesher, 1986; Peck *et al.*, 1986) this has resulted in the selection of maximum doses for experimental purposes that are considerably less than those used for recreational pursuits. One could arbitrarily select higher doses but with the risk of erring in the opposite direction. A dose of, say 300 μg/kg, might be higher than any taken at one time by street users or, at any rate, higher than one they might take and then drive. If we were to select unrealistically high doses these could result in bizarre and potentially dangerous reactions in even the most controlled driving test. To avoid arbitrarily selecting the wrong maximum dose, it seemed necessary to consult the subjects in the context of a "clinical" pilot study.

The pilot study's major purpose was therefore to establish the maximum dose for subsequent driving studies. Yet it provided several opportunities for obtaining valuable information about THC's pharmacokinetics and its pharmacodynamic effects after marijuana smoking. Blood samples were repeatedly taken for measuring [THC] and [THC-COOH]. The subjects repeatedly performed certain simple laboratory tests, estimated their levels of intoxication and indicated their willingness to drive under several specified conditions of urgency. In addition, heart rate was measured at these times. The secondary purpose was that of specifying relationships between [THC] and [THC-COOH] with changes in the other physiological, performance or subjective variables.

METHODS

Subjects

Twenty-four healthy volunteers, 12 males and 12 females, volunteered to participate in this study. They were screened as described in Chapter 2. Groups of six were treated and tested per night. Sessions were conducted in the evening between 19.00 and 24.00 hours and subjects smoked and were tested at staggered intervals of 10 minutes. GC/MS analysis of plasma obtained from one male revealed trivial amounts of values THC in the first and second samples after smoking but none thereafter, and no THC-COOH in any sample. It was concluded that this subject had not inhaled smoke so his data were excluded from further analyses. Characteristics of the remaining 23 subjects are given in Table 3.1. T-tests for independent samples showed that males were more experienced smokers than females ($p < .044$). Males' driving experience was nearly significantly greater than females' ($p < .056$ & .089 for number of years and km (mi), respectively).

Table 3.1 Mean±SD (range) of subjects' characteristics.

	Males (N=11)	Females (N=12)
Age (yrs)	27.0±4.6 (22-38)	24.6±2.9 (21-31)
Weight (kg)	69.8±10.3 (56.5-87.0)	66.6±9.1 (52.0-79.0)
Weight (lb)	154±23 (125-192)	147±20 (115-174)
Smoking Experience (yrs)	9.2±5.8 (1-23)	5.0±3.3 (2-14)
# Joints/Month	5.9±3.7 (1-14)	5.8±5.4 (1-20)
Driving Experience (yrs)	8.5±5.7 (3-23)	4.8±2.7 (1-12)
Driving Experience (km x 1000)	121±118 (15-360)	54±54 (5-175)
Driving Experience (mi x 1000)	75±73 (9-224)	34±34 (3-109)
# of Subjects Having Driven within 1 Hour following Cannabis Consumption:		
less than 5 times	1	9
5 times or more	10	3

Smoking Procedures

Marijuana cigarettes were supplied by the U.S. National Institute on Drug Abuse (NIDA). The cigarettes had an average weight of 767 mg and contained 2.57% or about 20 mg THC. Cigarettes were humidified by placing them at room temperature overnight in a desiccator containing a small quantity of saturated sodium chloride solution. This procedure raised the moisture content of the cigarettes from 10% to 15%, on the average. The subjects were allowed to smoke part or all of the THC content in three cigarettes until achieving the desired psychological effect. Cigarettes were smoked through a plastic holder, in a fashion determined by the subject. The only requirement was to smoke continuously for a period not exceeding 15 minutes. When subjects voluntarily stopped smoking, cigarettes were carefully extinguished and retained for subsequent gravimetric estimation of THC consumed (2.57% of the difference between the weight of the original cigarette and the remaining unsmoked portion). This method of estimating THC amounts consumed is based upon the assumption that THC is equally distributed over the entire cigarette. Perez-Reyes *et al.* (1982) analyzed THC concentrations in the unsmoked portions of marijuana cigarettes of three different potencies and indeed found that they were identical to those in the unlit cigarette.

Measurements

A test battery which lasted 20 minutes took place before smoking and was repeatedly administered at 30, 90, 150 and 210 minutes after initiation of smoking. The battery consisted of:

1. The Critical Tracking Test (CTT). This test, described in detail by Jex *et al.* (1966), was implemented on a IBM-compatible MS-DOS computer and measures the subject's ability to control a displayed error signal in a 1st-order compensatory tracking task. Error appears as horizontal deviation of a cursor from midpoint on a horizontal, linear scale. Compensatory joy-stick movements null the error by returning the cursor to the midpoint. The frequency

of cursor deviations, and therefore its velocity, increase as a stochastic, linear function of time. The frequency at which the subject loses control is called the critical frequency (λ_c, expressed in rad/s). Theoretically, λ_c is the reciprocal of the operating delay lag in human closed-loop manual control. The test included 5 trials of which the lowest and highest score were removed; the average of the remaining scores was taken as the final test score. Total test time duration was approximately 5 minutes.

2. Questionnaires. Subjects were required to rate their feeling of "high" as a percentage of the maximum ever experienced, and to indicate certain feelings of present cognitive and emotional state using the 16-item visual-analog scale developed and standardized for drug research by Bond and Lader (1974). Scores on the latter scales were grouped to form three cluster scores for measuring the corresponding factors: alertness, contentedness and calmness which will be expressed as percentage of the maximum. In addition, the subjects' willingness to operate a motor vehicle was assessed by asking them to declare whether they would attempt to drive for a set distance if the reasons were: *A.* unimportant though gratifying, such as for transporting a friend to another party; *B.* important but avoidable, such as for transporting a mildly sick friend home when he would otherwise have to call a taxi; and *C.* urgent, such as transporting a severely sick infant to the hospital. These ratings were made by subjects immediately after termination of smoking and after conclusion of the CTT. All questionnaires are enclosed in Appendix A.
3. Heart Rate. Heart rate was measured by counting the number of beats per minute immediately after completion of the questionnaires.
4. Hand Steadiness Test. Thereafter, hand steadiness was measured from the number of side contacts occurring as the subject attempted to hold a 1 mm (0.04 in) stylus for 15 seconds within each of five circular holes with successively diminishing diameters (3.90, 3.05, 2.70, 2.20 and 1.85 mm, respectively; or, 0.15, 0.12, 0.11, 0.09 and 0.07 in). Subjects were allowed to rest their hand on the table. The test score was defined as the total number of contacts of the stylus with any side. Since the distribution of subjects' scores were skewed, a square root transformation was applied to normalize data. The test lasted about 3 minutes.
5. Blood Sampling. A blood sample was taken by means of a venepuncture ten minutes after the beginning of the test battery. The sample (2 aliquots containing 10 ml blood apiece) was heparinized and centrifuged, and plasma was placed in frozen (-20°C) storage prior to analysis for THC and its major metabolite THC-COOH. Blood samples were taken before and at 40, 100, 160 and 220 minutes after initiation smoking.

Subjects were familiarized with the questionnaires and practiced the CTT and hand steadiness test on three separate occasions during the weeks prior to the test night until they reached a steady performance level.

Data Analysis

Parametric data were analyzed as follows. All data including baseline values entered a repeated measures multivariate analysis of variance (MANOVA) with *Sex* as a between-groups and *Time* as a within-subjects factor and the criterion for significance set at .05. If a significant *Time* effect was found, a repeated measures univariate analysis of variance (ANOVA) was performed to separately compare each post-smoking measurement with baseline. *Sex* was not a factor in these ANOVA's unless MANOVA had revealed a significant *Sex by Time* interaction. Individual comparisons with baseline were not possible for perceived "high" ratings and plasma levels of the drug since baseline values were zero in most cases. Instead, if MANOVA revealed a significant *Time* effect, the data were further analyzed in an ANOVA trends analysis to determine the significance of linear, quadratic and cubic components. In the figures, the mean of the variable is depicted by a point and its standard error (SE) by the height of the vertical line above the point.

The subjects' expressions of willingness to drive were made on the basis of a dichotomous decision and could not for that reason be analyzed in the same manner as other variables. These data were therefore analyzed using Cochran's Q-statistic to determine if the proportion of subjects willing to drive changed over time. If they did significantly, separate changes from baseline were tested by McNemar's sign-test.

Criterion for statistical significance in individual comparisons was adjusted by means of the "Sequential Bonferroni" correction (Overall and Rhoades, 1987) to retain a constant type I error probability of .05 across the entire set of comparisons. This means that for the largest of four differences tested at once, p had to be less than $.05/4 = .013$ to be judged significant. For the second, it had to be $< .05/3 = .017$; for the third, $< .05/2 = .025$; and for the smallest difference, $p < .05$.

Significant *Sex* effects were generally absent. Results pertaining to differences between the sexes are therefore only reported for the exceptional cases where the differences were significant.

Two types of correlations were calculated to determine the linear relationship between two variables; i.e., the inter-subject and intra-subject correlation. The first is the most commonly used; it is obtained from pairs of variables measured in a group of subjects. In this study, for example, the correlation between [THC] and λ_c, the tracking performance score, was calculated for all subjects at each sampling time separately. This resulted in four correlations (one at $t=40$, 100, 160 and 220 min) obtained from 23 subjects (N=23). These correlations were tested for significant departures from zero by t-test.

The intra-subject correlation, on the other hand, is the correlation between pairs of variables within one subject. In the present study, for example, the correlation between [THC] and λ_c was also calculated for each subject, across all sampling times, separately. This resulted in 23 correlations (one from each subject) obtained from four repeated measurements (N=4; baseline values were excluded). These were transformed into Fisher's z-scores and then averaged across subjects yielding z_{av}, which was tested for significant deviation from zero by t-test, and transformed back to r.

Interpretations of these two types of correlation are not the same. If, in the present study, a perfect inter-subject correlation ($r = \pm 1.0$) between [THC] and λ_c existed, it would mean that one can perfectly predict λ_c of a particular subject from the knowledge of his/her [THC]. Usually, however, inter-subject correlations are much lower; and, the closer to zero, the more unreliable the predictions become.

A high average intra-subject correlation means that, on the average, scores on two variables are closely related within a subject, but not necessarily between subjects. Thus, a highly negative average intra-subject correlation between [THC] and λ_c (lower scores indicating poorer performance) would mean that, within a subject, higher plasma levels of THC are associated with poorer tracking performance. Yet this does not imply that, if two subjects are compared, the one with the higher plasma levels performs worse. That would only be the case if both the average intrasubject and the intersubject correlations were strongly negative.

RESULTS

Consumed THC

Six subjects consumed one cigarette, thirteen smoked two and four smoked three. Total THC amounts consumed are given in Table 3.2. Statistical analyses failed to reveal a significant difference between the sexes. It should be noted that these amounts of THC represent both the amount inhaled and the portion that was lost through pyrolysis and side-stream smoke during the smoking process.

Table 3.2 Mean, median and range of amounts of THC consumed, both in absolute values and relative to bodyweight (BW).

	THC consumed (mg)			THC consumed per kg BW (μg/kg)		
	mean	median	range	mean	median	range
Males (N=11)	22.3	18.6	14.7-35.2	324	292	203-524
Females (N=12)	19.4	18.9	11.3-28.2	293	292	194-440
All (N=23)	20.8	18.8	11.3-35.2	308	292	194-524

Plasma Concentrations of the Drug

Mean, median and range of [THC] and [THC-COOH] at each sampling time are shown in Tables 3.3 and 3.4. Maximum [THC] was found in the first sample after smoking at t=40 minutes. Males had somewhat higher [THC] and much higher [THC-COOH] values than females; the difference between both sexes was however rather constant over time, except for [THC] at t=40 where the difference was quite profound. These observations were confirmed by MANOVA that showed a significant *Sex* effect for both [THC] and [THC-COOH] ($F_{1,21}$=4.3 & 9.79; $p<.05$ & .005, respectively), but no significant *Time by Sex* interaction. Since consumed THC amount did not differ between both sexes, the conclusion must either be that males were more efficient smokers than females, or that they absorbed the active ingredient differently.

There was a significant *Time* effect for both [THC] and [THC-COOH] ($F_{3,19}$=14.79 & 11.70, respectively; $p<.001$ in both cases). Univariate trend analysis revealed that both linear, quadratic as well as cubic functions fitted the trend in [THC] over time significantly ($F_{1,21}$=44.56, 38.95 & 29.23; $p<.001$, .001 & .001; p_c=.017, .025 & .05, respectively) due to a rapid decline of [THC] in plasma after the first sample. THC-COOH changes over time were only significantly fitted by a linear trend ($F_{1,21}$=26.92 $p<.001$; p_c=.017).

The relation between consumed THC, relative to body weight, and [THC] was examined by calculation of inter-subject correlations (intra-subject correlations could not be determined from the data because each subject smoked only one dose of THC). These analyses showed moderate inter-subject correlations between both parameters at each sampling time, namely 0.42 ($p<.05$), 0.34 (ns), 0.42 ($p<.05$) and 0.45 ($p<.05$). Yet inspection revealed that the apparent strength of these correlations was almost totally attributable to two males who had consumed the greatest amounts of THC (486 and 524 μg/kg) and had also very high plasma levels of THC (45.9 and 35.5 ng/ml, respectively). When log values of [THC] and consumed THC were used, to normalize the distributions, the correlations were small and not significant. There were no differences between males and females with respect to these correlations.

Table 3.3 Mean, median and range of [THC] in ng/ml.

		t=40	t=100	t=160	t=220
	mean	17.7	5.8	2.8	1.7
Males (N=11)	median	13.3	4.5	2.3	1.3
	range	6.7-45.9	2.5-15.2	1.2-6.8	0.7-5.1
	mean	9.9	3.0	1.4	0.7
Females (N=12)	median	7.0	2.7	1.0	0.6
	range	3.3-19.3	0.3-6.8	0.5-3.2	0.0-1.8
	mean	13.6	4.3	2.1	1.2
All (N=23)	median	9.9	3.5	1.4	0.8
	range	3.3-45.9	0.3-15.2	0.5-6.8	0.0-5.1

Table 3.4 Mean, median and range of [THC-COOH] in ng/ml.

		t=40	t=100	t=160	t=220
	mean	33.9	28.1	25.3	20.8
Males (N=11)	median	25.6	19.6	18.3	13.5
	range	12.9-96.4	12.8-72.4	9.5-63.5	8.0-67.0
	mean	12.4	9.5	8.3	5.6
Females (N=12)	median	9.6	8.2	7.5	5.5
	range	3.3-39.9	0.5-26.8	3.0-15.8	0.0-13.0
	mean	22.7	18.4	16.4	12.8
All (N=23)	median	17.3	13.9	13.6	10.1
	range	3.3-96.4	0.5-72.4	3.0-63.5	0.0-67.0

These results indicate that the between-subject variability in [THC] is not related to the between-subject variability in the consumed amount of THC; in other words, information about [THC] and the time of blood sampling after smoking, of a particular individual, does not reveal how much that subject smoked, nor vice versa.

Perceived "high"

Mean subjective ratings of "high" are shown in Figure 3.1. The subjects consistently reported their peak subjective reaction as being about 70% of the greatest ever experienced. This was achieved shortly after smoking. Their subjective feelings declined, again in a highly consistent

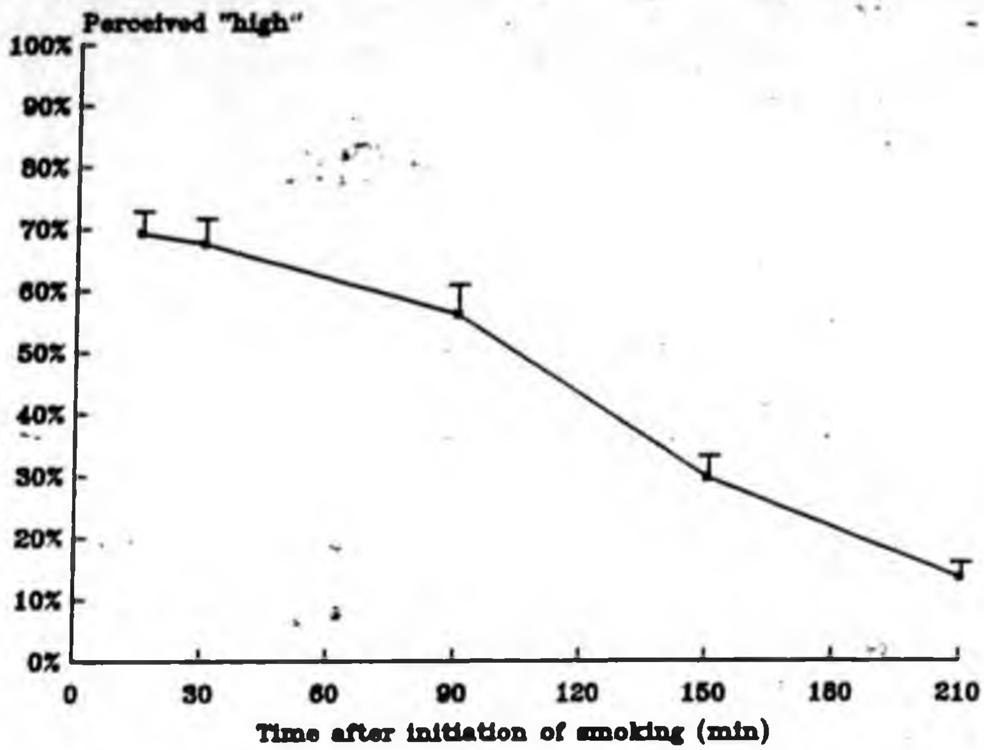

Figure 3.1 Mean (+SE) perceived "high" by *Time*.

manner between subjects, until arriving at a level less than 15% of the greatest ever experienced, at a time 3¼ hours after smoking.

MANOVA revealed a significant *Time* effect ($F_{4,18}$=49.18; $p<.001$). Trend analysis confirmed the impression from the data that the downward trend is best fitted by a linear function ($F_{1,21}$=201.92; $p<.001$).

Willingness to Drive

Figure 3.2 displays percentages of the subjects that declared to be willing to drive under different circumstances of a gradually more compelling nature (*A*. unimportant though gratifying; *B*. important but avoidable; and, *C*. urgent). Only about 20% of the subjects declared their willingness to drive for relatively unimportant reasons (*A* and *B*), but approximately 80% declared that they would do so for an urgent reason (*C*), while experiencing the peak subjective reaction. Willingness to drive gradually rose to about 70% for unimportant reasons, and 100% for an urgent reason, by the end of the test session.

Cochran's test revealed that time-related changes in willingness to drive were statistically significant in all three circumstances ($Q_{df=5}$=46.62, 44.62 & 15.17; $p<.001$, .001 & .01 for situations *A*, *B* & *C*, respectively). McNemar's test showed that the percentage of subjects willing to drive under circumstance *A* was significantly different from baseline until the end of the test session ($p<.001$, .001, .001, .002 & .02; p_c=.01, .013, .017, .025 & .05), while under circumstance *B* changes were only significant until 2½ hours after smoking ($p<.001$, .001 &

.004; p_c=.01, .013 & .017). McNemar's test failed to detect any significant change after smoking relative to baseline for circumstance *C*.

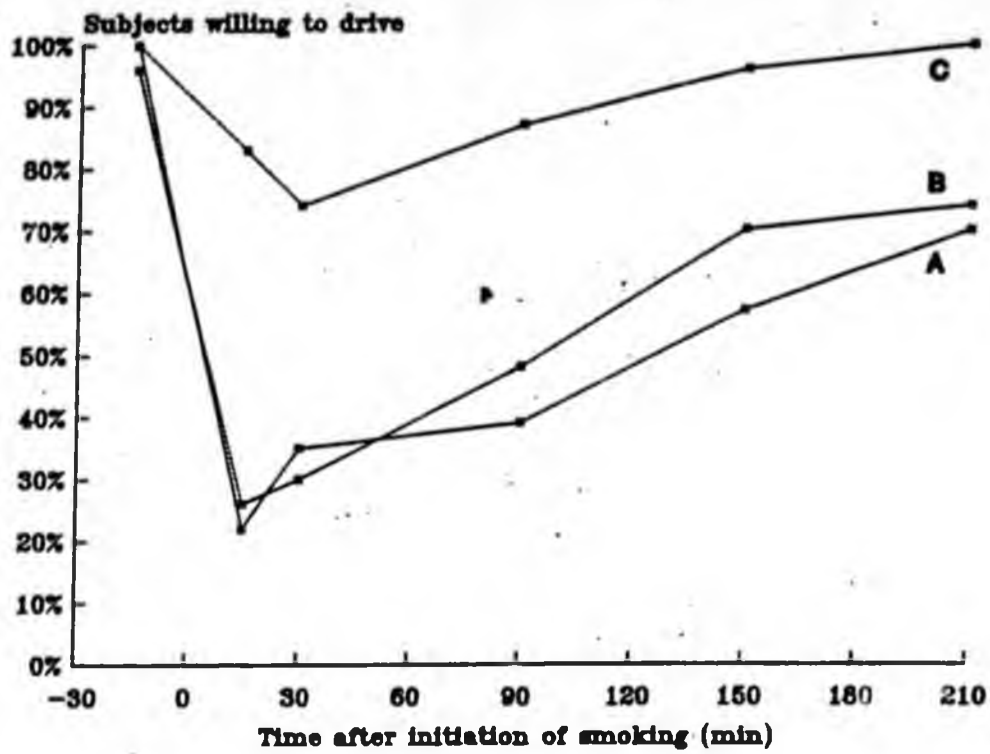

Figure 3.2 Percentage of subjects willing to drive under circumstances *A*, *B* & *C* (see text) by *Time*.

Perceived Alertness, Contentedness and Calmness

Figure 3.3 shows subjects' ratings of perceived alertness, contentedness and calmness. Scores on these factors changed significantly over time ($F_{5,17}$=8.19, 5.79 & 7.02; $p<.001$, .003 & .001, respectively). Subjects felt significantly less alert relative to baseline until about 1½ hours after smoking ($F_{1,22}$=34.67, 20.03 & 16.97; all $p<.001$; p_c=.01, .013 & .017). Separate sequential comparisons of subjective feelings of contentedness provided the same results ($F_{1,22}$=27.24, 19.98 & 9.99; $p<.001$, .001 & .004; p_c=.01, .013 & .017). Feelings of calmness followed a different profile over time. Separate sequential comparisons showed that no significant change occurred during the first few hours after smoking, but at the end of the session subjects felt calmer than they had at baseline ($F_{1,22}$=12.25; $p<.002$; p_c=.01).

Critical Tracking Test

The average frequency at which the subjects lost control (λ_c) was 4.40 rad/s before smoking and fell to 4.15 rad/s in the first test after smoking and gradually rose to baseline level in later tests. MANOVA however failed to show a significant *Time* effect.

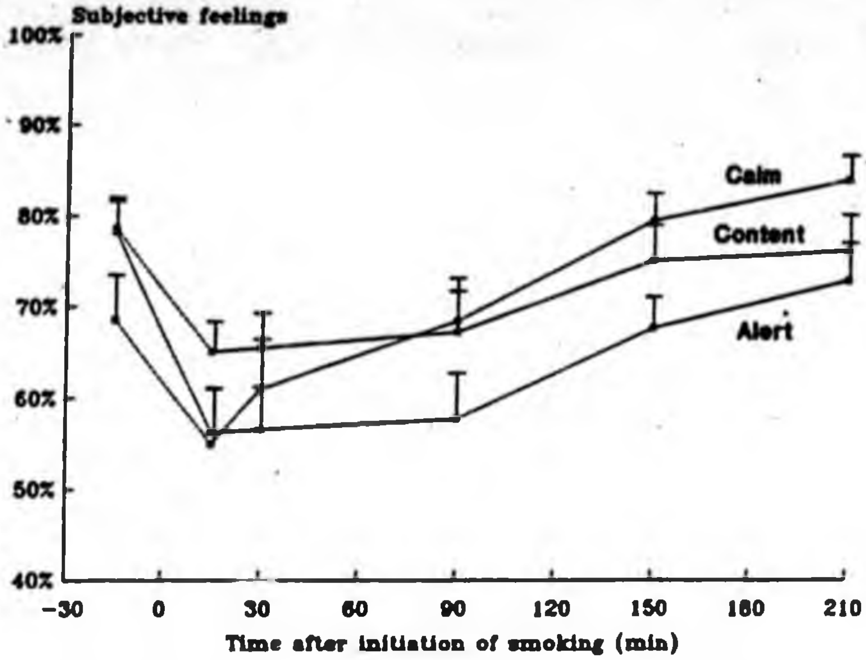

Figure 3.3 Mean (+SE) perceived alertness, contentedness and calmness by *Time*.

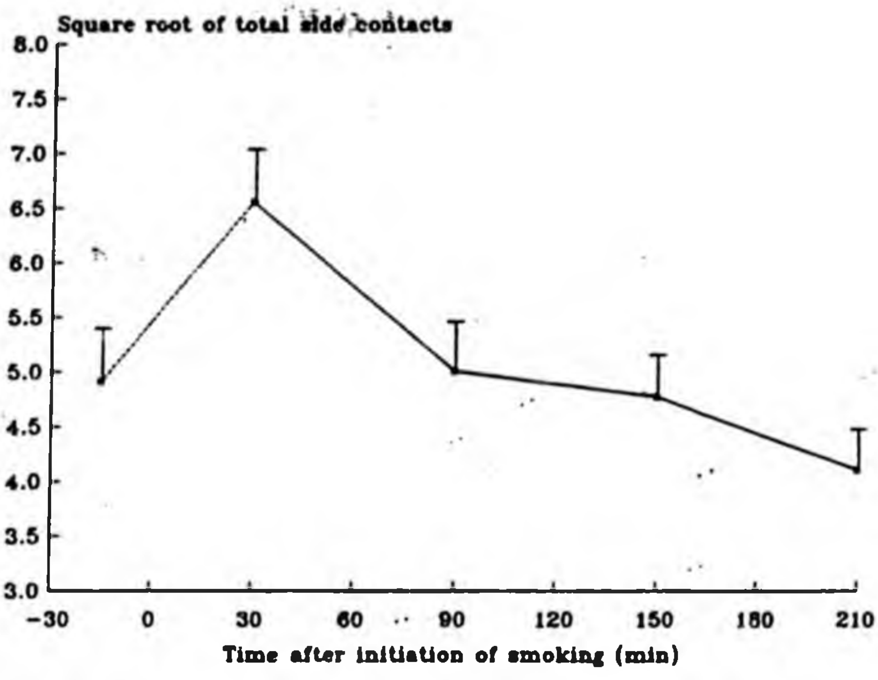

Figure 3.4 Mean (+SE) square root of total number of side contacts in the hand steadiness test by *Time*.

Hand Steadiness Test

Figure 3.4 demonstrates that subjects' hand steadiness diminished after smoking marijuana, but this effect dissipated rapidly after the first test. On the average, the subjects' hand steadiness was even superior at a time two hours after smoking to what it had been initially.

MANOVA revealed a significant *Time* effect ($F_{4,18}$=6.38; $p<.002$). Yet separate comparisons showed that hand steadiness was only significantly different from baseline in the first test after smoking ($F_{1,22}$=16.89; $p<.001$; p_c=.013).

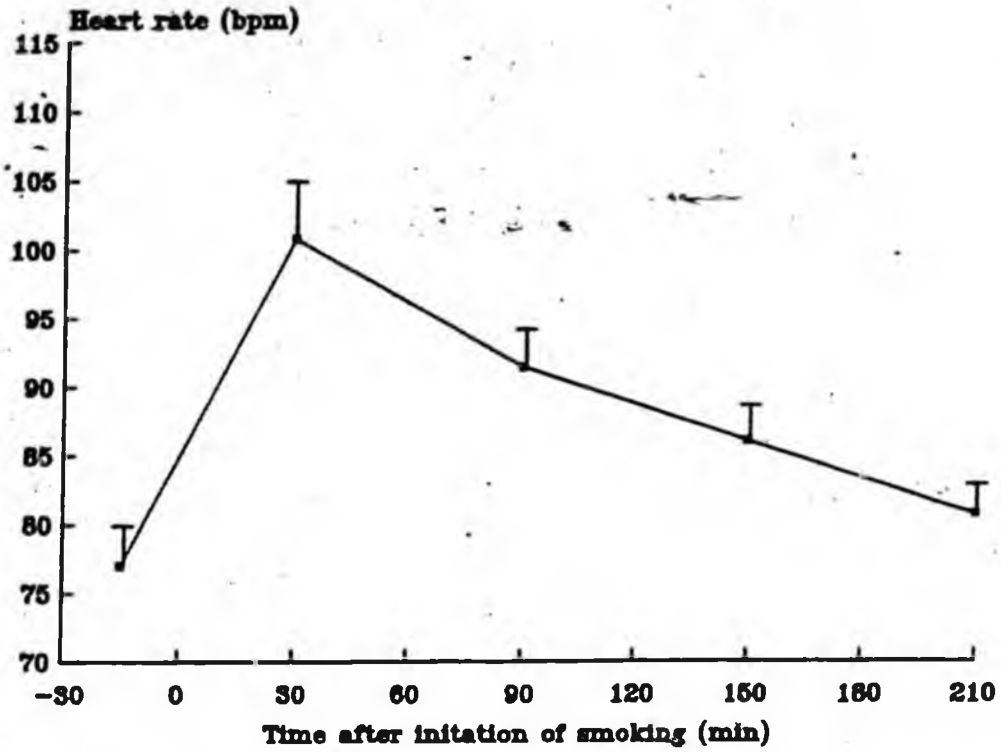

Figure 3.5 Mean (+SE) heart rate by *Time*.

Heart Rate

The subjects' average heart rate, presented in Figure 3.5, varied between 75 and 100 beats per minute (bpm) in close accordance with their subjective feelings. Thirty minutes after smoking, the increase in heart rate varied from 2 to 77 bpm, with a mean elevation of 24 bpm. Heart rate diminished over successive measurements approaching baseline values after 3¼ hours. MANOVA revealed a significant *Time* effect ($F_{4,18}$=10.43; $p<.001$) and separate ANOVA comparisons showed that these elevations were significantly different from baseline at each but the last measurement ($F_{1,22}$=35.64, 21.90, 12.67 & 2.37; $p<.001$, .001, .002 & .14; p_c=.013, .017, .025 & .05, respectively).

Intra-Subject Relations between Variables

Table 3.5 shows the average intra-subject correlations between [THC], $\log_{10}$[THC], and [THC-COOH] with each of the other variables. The log transformation was again applied to achieve a more linear and homeoscadastic relationship between THC values and the other variables. The constant of 1 was added to the raw [THC] values for avoiding negative log transformations. It can be concluded from this table that, within subjects, higher plasma levels of the drug were associated with, and probably produced, increased heart rate, increased feelings of perceived "high", diminished hand steadiness, and diminished feelings of calmness, contentedness and alertness. The correlation with critical tracking performance was not significant, confirming the insensitivity of the test. The log transformation of [THC] did not change the size of the correlations dramatically.

Table 3.5 Average intra-subject correlations (* $p<.05$ ** $p<.01$; 2-tailed).

	[THC]	Log_{10}([THC]+1)	[THC-COOH]
Heart Rate	.79**	.82**	.68**
Perceived "high"	.88**	.95**	.87**
λ_c	-.20	-.22	-.27
Side Contacts	.48*	.45*	.39
Calmness	-.51*	-.38	.02
Contentedness	-.57**	-.59**	-.46*
Alertness	-.64**	-.72**	-.66**

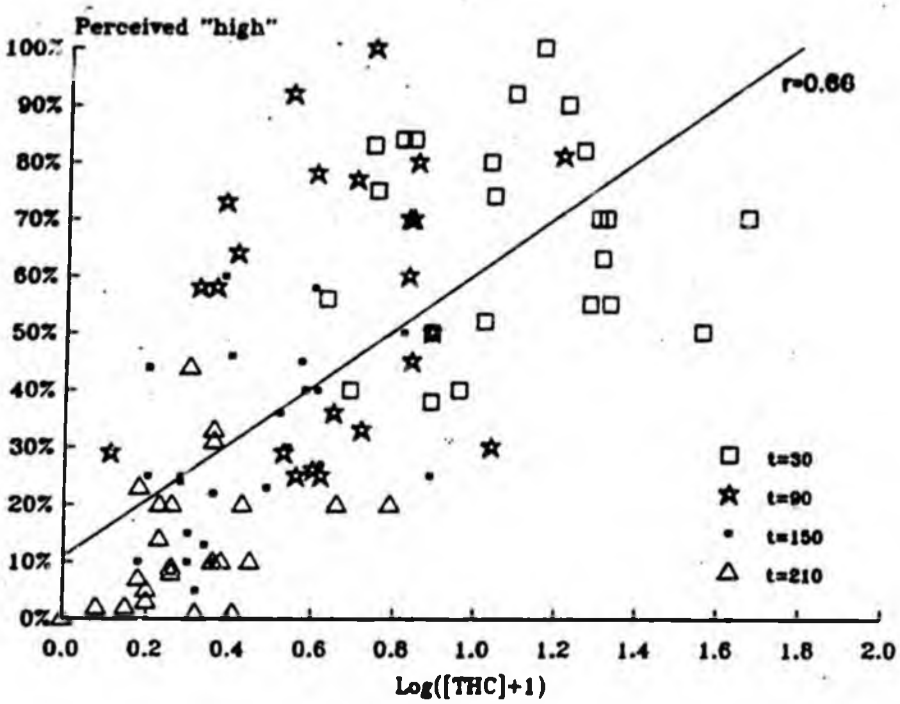

Figure 3.6 Scatter diagram of log([THC]+1) in plasma and perceived "high". Regression line comprising all data is inserted.

Inter-Subject Relations between Variables

Inter-subject correlations between plasma concentrations of the drug and measures of subjective feelings, heart rate and performance were typically low ($r<.50$) at each sampling time. The correlations between log [THC]+1 and perceived "high", for example, were r=0.07 (ns), 0.19 (ns), 0.43 ($p<.05$) and 0.35 (ns), at t=40, 100, 160 and 220 minutes after initiation of smoking, respectively. These low correlations are probably due to "restriction of range", i.e. the variability in both measures is relatively small at each sampling time. If all available data (N=92, 4 measurements of 23 subjects) were included in the correlational computation the highest correlation found was that between log [THC]+1 and perceived "high" (r=0.66; Figure 3.6). In fact, this correlation is a combination of intra-subject and inter-subject correlations, and should therefore only be regarded as an indication of what the correlation might have been if all these data had been independent observations.

DISCUSSION

The pilot study's major purpose was to determine the amount of THC recreational users of cannabis smoke to reach a comfortable "high" and to establish from these results the maximum dose for subsequent driving studies. Median and mean amount of THC consumed were 308 and 292 μg/kg respectively. From these results it was decided that the maximum dose for subsequent driving studies would be 300 μg/kg. This is considerably higher than doses that have usually been administered to subjects in experimental studies (typical, 100-200 μg/kg THC). This could mean either that previous studies' THC doses were lower than those usually consumed by current users, or that the present study's subjects were less efficient smokers and, consequently, smoked more to achieve the same effect. Yet one important point should be raised. Imposed smoking procedures differ considerably between studies on marijuana's effects and can be divided at first glance in two types, self-paced in which subjects may smoke in their customary fashion and machine-paced procedures in which subjects smoke in a prescribed manner with regards to duration of inhalation of smoke and air, holding inhalation, etc. The former method is more realistic while the latter is more controlled. This study applied the former because of the disadvantage of the latter that it might induce unrealistic reactions in some subjects.

One way to contemplate this study's results is to compare the mean [THC] with those found in other studies in which similar procedures were applied with respect to smoking (ad lib fashion) and plasma analysis (GC/MS using a deuterated internal standard) as we did. To the authors' knowledge only one such study has been reported, namely by Ohlsson *et al.* (1980). Marijuana cigarettes containing 19 mg THC were administered to eleven male subjects who were instructed to smoke in their own fashion such as to obtain the maximum desired "high". Subsequent gravimetric estimation showed that a mean of 13.0 mg THC was consumed. [THC] values ranged between 5.4 and 18.0 (mean 12.4) ng/ml 30 minutes after termination of smoking. Only the males of the present study should be included in the comparison with Ohlsson's study, because of the significant difference found between [THC] values of both sexes in the current study. Eleven males in the present study smoked 22.3 mg THC, on average, and their plasma concentrations ranged between 6.7 and 45.9 (mean 17.7) ng/ml 40 minutes after initiation of smoking. Thus, our subjects smoked 70% more THC than Ohlsson's subjects did, resulting in a 43% higher THC level in plasma, as measured 30 minutes after smoking. The average [THC] found in the present study was therefore in the expected direction. This observation may lead to the tentative conclusion that the preferred THC dose to reach a desired "high" in the present study was not due to inefficient smoking but to the fact that current marijuana (or hashish) users do smoke higher THC doses than previously administered in scientific studies.

Other results from the present study showed that perceived "high" and heart rate are very sensitive (psychological and physiological) measures of marijuana intoxication which confirms prior research. Impairments in laboratory tests performance were measured at the time of peak subjective feelings but generally, objective impairment dissipated more rapidly than the feelings themselves. All objective signs of impaired functions were gone within 1.5 hours after smoking. The explanation may be that practice and habituation effects, or both, occurred during the session concealing marijuana's impairment, or, that procedural errors have been made in administering these tests. No definitive answer can be provided and no conclusions can be drawn from this study with respect to marijuana's effects upon performance because of the lack of a control group. The study was simply not designed to estimate these effects, only to indicate whether either of these measures should be considered for inclusion in later studies. If any measure appeared to be systematically related to the inferred changes in THC's pharmacological activity over time, this measure might assume a high degree of practical importance. Correlational analyses, however, showed no strong relationships between [THC] or [THC-COOH] and performance in any test.

An important issue relating to traffic safety is whether subjects would drive a car while under the influence of marijuana. Although all subjects had admitted driving a car while intoxicated at least once before, a majority (about 65%) of the subjects was not willing to drive a car for relatively unimportant reasons shortly after smoking when experiencing the drug's peak subjective reaction. However, most said they would drive. for a very urgent reason. On one hand, this means that the majority of the subjects are aware of a potential marijuana related driving impairment; on the other, a sizable minority (35%) would not refrain from driving a car for unimportant reasons when they are experiencing a "high". These subjects in particular are a source of concern with respect to traffic safety, if marijuana smoking indeed impairs driving performance. Two questions that arise from these contemplations were addressed by the succeeding driving studies; namely, *1.* does marijuana adversely affect driving performance, and *2.* is willingness to drive after marijuana smoking related to driving impairment?

CHAPTER 4 - MARIJUANA AND DRIVING ON A RESTRICTED HIGHWAY

INTRODUCTION

As mentioned in Chapter 1, THC's effects on actual driving performance have been assessed in a relatively small number of studies and only once in the presence of other traffic. The effects of doses up to about 250 μg/kg were modest, if present at all. These findings provided some assurance that it would be safe for subjects to undertake carefully supervised driving tests on normal roads and in traffic, even after treatment with the somewhat higher average dose (i.e. 300 μg/kg) that was preferred by regular marijuana users in the pilot study. Nonetheless normal prudence demanded a demonstration of the test's safety in an environment resembling reality but where neither the subjects nor other road users would be endangered if the optimistic forecast proved false. One objective of the present study was to provide that demonstration using a standard test on a highway closed to other traffic.

The second objective was to define the dose-effect relationship between inhaled THC dose and that parameter of vehicular control which is measured in the standard test; i.e. standard deviation of lateral position (SDLP), an index of "weaving" amplitude the subject allows while attempting to maintain a constant speed and steady lateral position between traffic lane boundaries during uninterrupted highway driving. Alcohol's effects on SDLP were previously measured by Louwerens *et al.* (1985, 1987) in practically the same manner as THC's in this study. The earlier results showing a nearly perfect (r=0.99) exponential relationship between mean blood alcohol concentration (0-0.12 g%) and mean SDLP for 24 "social drinkers", serve admirably for evaluating THC's effects in the present case.

Other objectives were to measure changes in SDLP from tests after placebo to those following separate THC doses of 100, 200 and 300 μg/kg; and, to relate these objective measures of driving impairment to subjective impressions of driving quality and expressed willingness to drive in the same states of intoxication under normal circumstances.

METHODS

Subjects

The same twelve men and twelve women who participated in the pilot study served again as the subjects. Plasma from the pilot study was still not analyzed at the time data collection commenced. The male that apparently did not inhale marijuana smoke was therefore not dropped from the study. As before, his plasma samples showed neither THC nor THC-COOH. Data from this subject had to be again excluded from further analyses. Characteristics of the remaining 23 subjects are shown in the previous chapter (Table 3.1).

Design, Doses and Administration

Marijuana and placebo cigarettes were obtained from the same source as before. The subjects were treated on separate occasions with THC doses of 0, 100, 200, 300 μg/kg. Placebo cigarettes were prepared by ethanol extraction of THC from the plant stock. Marijuana cigarettes were prepared from batches containing 1.75% THC for the two lowest, and 2.57% THC for the highest dose. Cigarettes were cut to different lengths to provide the doses appropriate for the individuals' body weights. It was necessary to provide the five largest subjects with two cigarettes at a time since one would not contain the total dose. Cigarettes were smoked through a plastic holder in a fashion determined by the subject but with the constraint that smoking had to be finished within ten minutes. After cessation of smoking, cigarettes were retained for subsequent gravimetric estimation of THC consumed. These analyses revealed that the average (±SD) amount of consumed THC in the three marijuana conditions was 6.8 (±0.9), 13.6 (±1.9) and 20.4 (±2.8) mg, which equals 94 (±4), 186 (±13) and 282 (±18) μg/kg, respectively, or about 6% less than target doses. Order of treatments were counterbalanced. They were administered subject- and observer-blind (i.e. the investigator who prepared the treatments was not involved in their administration or with data collection).

Testing Procedures

Eight subjects were tested per night and all 24 within a week. Subjects were tested at the same times and on the same days of the week for four consecutive weeks. Breath and urine tests were executed upon the subjects' arrival to check for the presence of alcohol and illicit drugs. If cannabinoids were found in the urine, a blood sample was taken for later verification of the presence of THC. Two subjects commenced smoking at a time at $t=0$ (Table 4.1). Driving tests were performed twice, beginning at $t=40$ and 100 minutes and lasting 15-20 minutes. Blood samples were taken before the driving tests. The subjects' pulse was taken and their performance measured in two laboratory tests that began after the driving tests. Subjective assessments were made immediately after smoking, and before and after the driving tests. Before the start of the experiment, subjects were individually trained to operate the vehicle under generally the same conditions as the tests later occurred.

Table 4.1 Schedule of activities on test-days.

Relative Time (min)	Activity
0-10	Smoking
30-35	Blood Sampling
40-60	Standard Driving Test
70-80	Tracking and Hand Steadiness Tests Heart rate and Blood Pressure
90-95	Blood Sampling
100-120	Standard Driving Test
130-140	Tracking and Hand Steadiness Tests Heart rate and Blood Pressure

Driving Test

The driving test, developed and standardized by O'Hanlon *et al.* (1982, 1986) and applied in more than 40 open- and closed-road studies by three Dutch Institutes during the last decade, measures the ability to control an instrumented vehicle's speed and lateral position. Subjects were instructed to maintain speed at 90 km/h (56 mph), or less if they felt incapable of driving safely at that speed, and a steady lateral position between the delineated boundaries of the traffic lane.

Driving was performed over a 11 km (6.8 mi) section of a primary highway (A76) that connects the Dutch cities of Geleen and Heerlen. Two lanes in the same direction were closed to normal traffic between the hours of 19.00 and 24.00 on three consecutive week-nights over four consecutive weeks of testing. Driving began at one end of the section, involved turning at the other and ended with a return to the origin. A licensed driving instructor accompanied each subject. He was charged with responsibility for ensuring safet at all times and was able to intervene, if necessary, using redundant vehicular controls.

Two Volvo station wagons containing essentially the same instrumentation were employed in the study. The first of a pair of subjects who received treatments together departed from the origin driving one vehicle and was followed by the second driving the other after 2½ minutes. The first subject waited for the arrival of the second at the turning point before returning to the origin. The purpose was to avoid having the subjects, travelling in opposite directions, meet en route. The major instrumentation comprised devices for acquiring continuous analog signals representing steering wheel angle, vehicle speed and lateral position relative to the midline stripe delineation, and a computer system for recording those signals continuously at a 4 Hz sampling rate.

The primary dependent variable was the standard deviation of lateral position (SDLP), which has been shown to be both highly reliable (typical test-retest correlation of 0.7-0.9) and very sensitive to the influence of sedative drugs and alcohol. Other dependent variables were mean speed (SP) and standard deviation of speed (SDSP) and steering wheel angle (SDST).

Questionnaires

The same subjective questionnaires used in the pilot study were administered to the subjects immediately after cessation of smoking ($t=10$) and again at the beginning of each driving test ($t=40$ & 100). At the end of each driving test ($t=60$ & 120), the subjects were required to retrospectively rate their effort made while performing the test (Zijlstra and Van Doorn, 1985; Meyman and Zijlstra, 1986) and subjective driving quality on respective visual-analog scales. Scores on these scales will be expressed as percentage of total scale and percentage of "normal" driving quality, respectively. Questionnaires are enclosed in Appendix A.

Laboratory Tests

Two of the tests employed in the pilot study were also applied here, namely the critical tracking and hand steadiness tests. Exactly the same procedures were employed in their administration as described in the previous chapter.

Physiological Assessments

Heart rate, systolic and diastolic blood pressure were measured by means of a digital blood pressure monitor prior to the hand steadiness test.

Blood Sampling
Blood samples were taken by venepuncture. The samples (2 aliquots containing 10 ml each) were heparinized and centrifuged. The plasma fractions were placed in frozen (-20°C) storage prior to analysis for [THC] and [THC-COOH].

Data Analysis
All data measured on ratio or interval scales were taken in a mixed between-groups, within-subjects MANOVA analysis. *Sex* was the between-groups factor. *Dose* (4 levels) and *Time* after dosing (2 or 3 levels) were factors tested within-subjects. If a significant ($p < .05$) *Dose* effect was found, repeated measures ANOVAs were conducted for testing differences between measures obtained after placebo and each THC dose, separately. Data in these cases were collapsed across *Sex* and *Time* unless the MANOVA analysis had revealed a significant interaction between either factor and *Dose*. In the figures, the mean of the variable is depicted by the height of the bar and its standard error (SE) by the height of the vertical line above the bar.

Separate dose effects were tested using the "Sequential Bonferroni" procedure for adjusting the α-probability criterion (p_c) in accordance with the number of separate comparisons in a given set (Overall and Rhoades, 1987). This means that for the largest of three differences tested at once, p had to be less than $.05/3 = .017$ to be judged significant. For the second, it had to be $< .05/2 = .025$; and for the smallest difference, $p < .05$. The adjustment had the effect of holding the probability of making a type I error at $p \leq .05$ over the entire set of comparisons.

The subjects' expressions of willingness to drive were made on the basis of a dichotomous decision and could not for that reason be analyzed in the same manner as other variables. These data were therefore analyzed using Cochran's Q-statistic test for assessing differences between dosing conditions at each time of testing, separately.

Significant *Sex* effects were generally absent. Results pertaining to differences between the sexes are therefore only reported for the exceptional cases where the differences were significant.

Inter-subject and intra-subject correlations were computed and tested as described in the previous chapter.

RESULTS

Plasma Concentrations of the Drug
Though consumed dose differed little between subjects, [THC] and [THC-COOH] varied enormously. Thirty minutes after smoking 300 μg/kg, for example, [THC] ranged between 1.6 and 59.6 ng/ml. Table 4.2 shows mean, median and range of [THC] and [THC-COOH] by *Dose* and *Time*. Placebo values were not used in the statistical analyses since these were zero in most cases.

As shown by Table 4.2 plasma concentrations of the drug were clearly related to the administered dose and time of blood sampling. MANOVA confirmed this observation yielding a significant *Dose* ($F_{2,20} = 14.65$ & 16.59 for [THC] and [THC-COOH], respectively; both $p < .001$) and *Time* ($F_{1,21} = 50.76$ & 21.16; both $p < .001$) effect. There was a significant *Dose by Time* interaction for [THC] ($F_{2,20} = 10.07$; $p < .001$) and not [THC-COOH]. Though not shown in the table, males had significantly higher [THC-COOH] values, 9 ng/ml on average, than females ($F_{1,21}$=4.49; $p<.05$); average [THC] values were virtually the same for both sexes.

Table 4.2 Mean, median and range of [THC] and [THC-COOH] in ng/ml (N=23).

		100 µg/kg		200 µg/kg		300 µg/kg	
		t=30	*t*=90	*t*=30	*t*=90	*t*=30	*t*=90
[THC]	mean	9.5	3.5	15.9	4.8	20.7	6.2
	median	9.0	3.2	12.0	4.3	19.1	5.6
	range	0.0-21.3	0.0-11.0	1.7-39.3	0.0-11.8	1.6-59.6	0.8-15.4
[THC-COOH]	mean	10.9	9.4	14.2	12.1	17.5	15.2
	median	7.2	4.7	13.4	9.6	13.8	11.4
	range	0.0-61.9	0.0-55.5	2.2-73.9	2.0-65.2	2.6-64.4	2.6-55.4

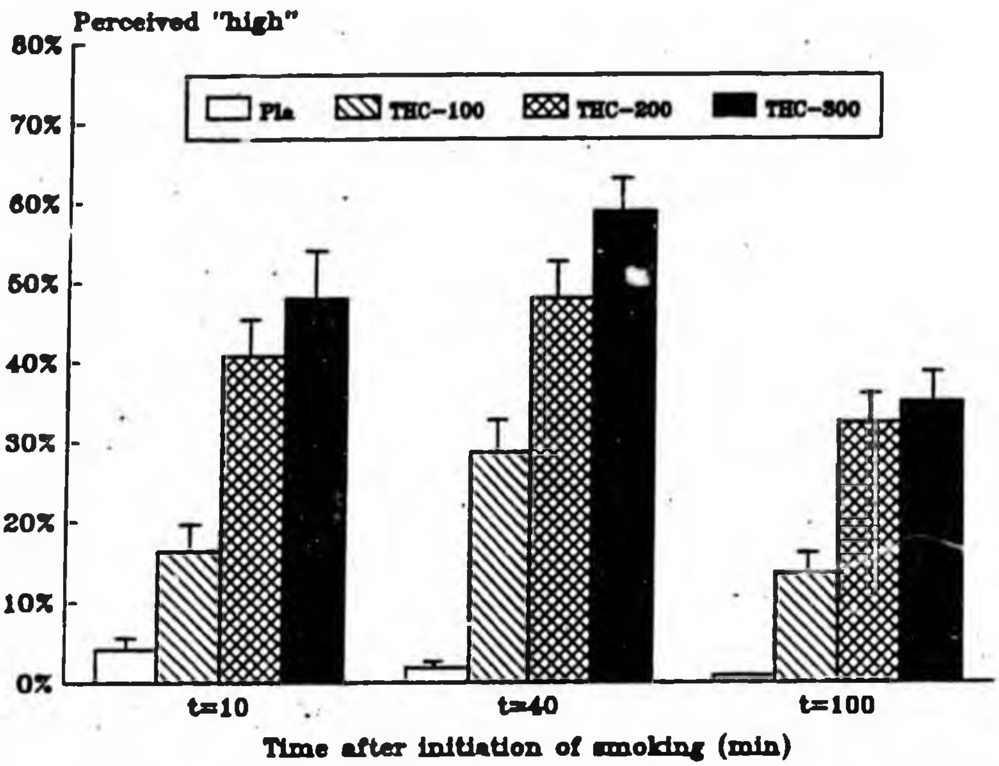

Figure 4.1 Mean (+SE) perceived "high" by *Dose* and *Time*.

Perceived "high"

Average subjective feelings of intoxication ("high") were dose-related and highest just before the first driving test (Figure 4.1). Relative to maximum personal experience, peak levels of intoxication were about 30%, 50% and 60% after 100, 200 and 300 µg/kg doses, respectively.

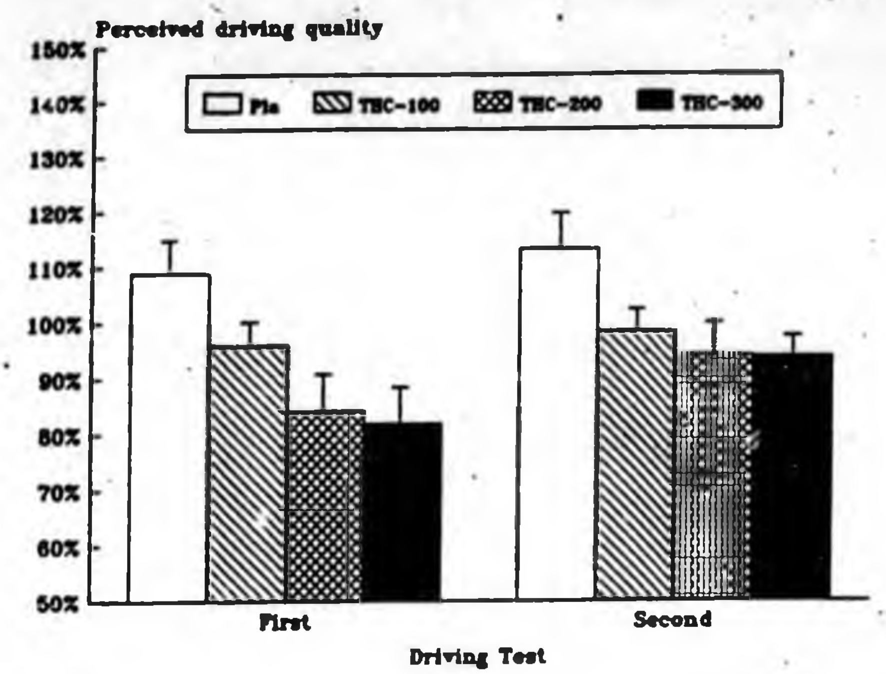

Figure 4.3 Mean (+SE) perceived driving quality, expressed as percentage of "normal", by *Dose* and *Time*.

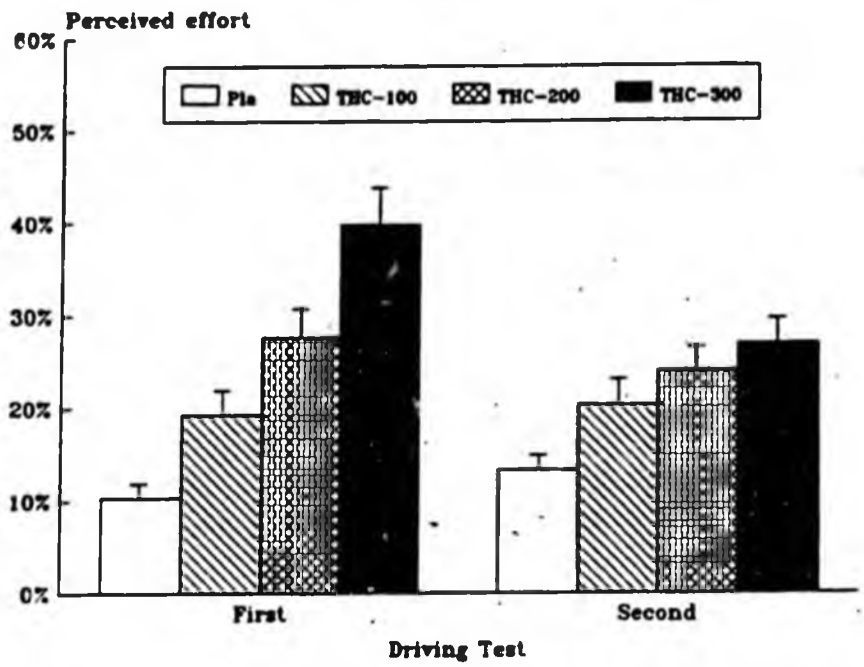

Figure 4.4 Mean (+SE) perceived effort to accomplish the test, expressed as percentage of maximum of scale, by *Dose* and *Time*.

$\mu g/kg$, respectively: $p < .012$, .001 & .001; $p_\epsilon = .05$, .025 & .017) than in the placebo condition. The *Dose by Time* interaction was significant after the two higher doses ($F_{1,22} = 8.45$ & 24.95 for the 200 and 300 $\mu g/kg$, respectively; $p < .008$ & .001; $p_\epsilon = .025$ & .017); i.e. the effort requirement diminished over the interval separating smoking and driving in these conditions.

Willingness to Drive

Table 4.3 presents the percentage of subjects willing to drive under specified conditions of different urgencies (*A*. unimportant though gratifying; *B*. important but avoidable; and, *C*. urgent).

Table 4.3 Percentage of subjects willing to drive under circumstances *A*, *B* & *C* (see text) by *Dose* and *Time*. Rightmost columns display Cochran Q-statistic (df=3) with *p* values.

		0 $\mu g/kg$	100 $\mu g/kg$	200 $\mu g/kg$	300 $\mu g/kg$	Cochran's Q	$p <$
	$t=10$	96	87	48	48	23.54	.001
A	$t=40$	96	65	48	43	23.22	.001
	$t=100$	96	83	65	61	16.40	.001
	$t=10$	91	83	65	57	12.00	.008
B	$t=40$	91	70	48	61	15.14	.002
	$t=100$	91	87	74	57	17.22	.001
	$t=10$	100	96	91	74	13.11	.005
C	$t=40$	100	96	87	74	11.45	.01
	$t=100$	100	96	96	87	6.33	NS

Subjects' responses were similar to those in the pilot study. The lower the administered THC dose and the more urgent the reason for driving, the more subjects declared that they would be willing to drive. According to the subjects' declarations, 40-60% would have driven for unimportant reasons shortly after the two highest doses. However, more than 75% would have driven for an urgent reason. Nearly all would have driven 1½ hours after smoking for an urgent reason when objectively measured driving performance was still impaired. Differences between treatments were significant in all cases, except one: the percentages of subjects who said they would have driven for an urgent reason 100 minutes after initiation of smoking were not different between treatment conditions.

Perceived Alertness, Contentedness and Calmness

Subjective feelings of alertness, contentedness and calmness were all affected by *Dose* ($F_{3,19} = 11.18$, 4.86 & 5.14, respectively; $p < .001$, .011 & .009). After marijuana smoking, subjects felt less alert, content and calm. Significant *Time* effects were found for alertness and calmness ($F_{2,20} = 7.89$ & 8.10, respectively; both $p < .003$): subjects felt more alert and calm later in the session. A significant *Sex by Time* effect was found for feelings of contentedness, females feeling less and males more content later in the session. Separate comparisons showed that all three THC doses produced significantly reduced feelings of alertness ($F_{1,22}$=12.46, 28.94 & 24.80 for the 100, 200 and 300 μg/kg, respectively; $p<.002$, .001 & .001; p_c=.05, .025 & .017). Only the two higher doses produced significantly reduced feelings of contentedness ($F_{1,22}$=8.70 & 15.05 for the 200 and 300 μg/kg, respectively; $p<.007$ & .001; p_c=.025 & .017) and calmness ($F_{1,22}$=14.29 & 11.70 for the 200 and 300 μg/kg, respectively; $p<.001$ & .002; p_c=.017 & .025).

Critical Tracking Test
Subjects' tracking performance, i.e. λ_c, was not affected by THC. Males performed significantly better than females ($F_{1,21}$=12.61; $p<.002$) and performance of all subjects was worse at the second than at the first assessment ($F_{1,21}$=10.89; $p<.003$), but these observations are not of great concern.

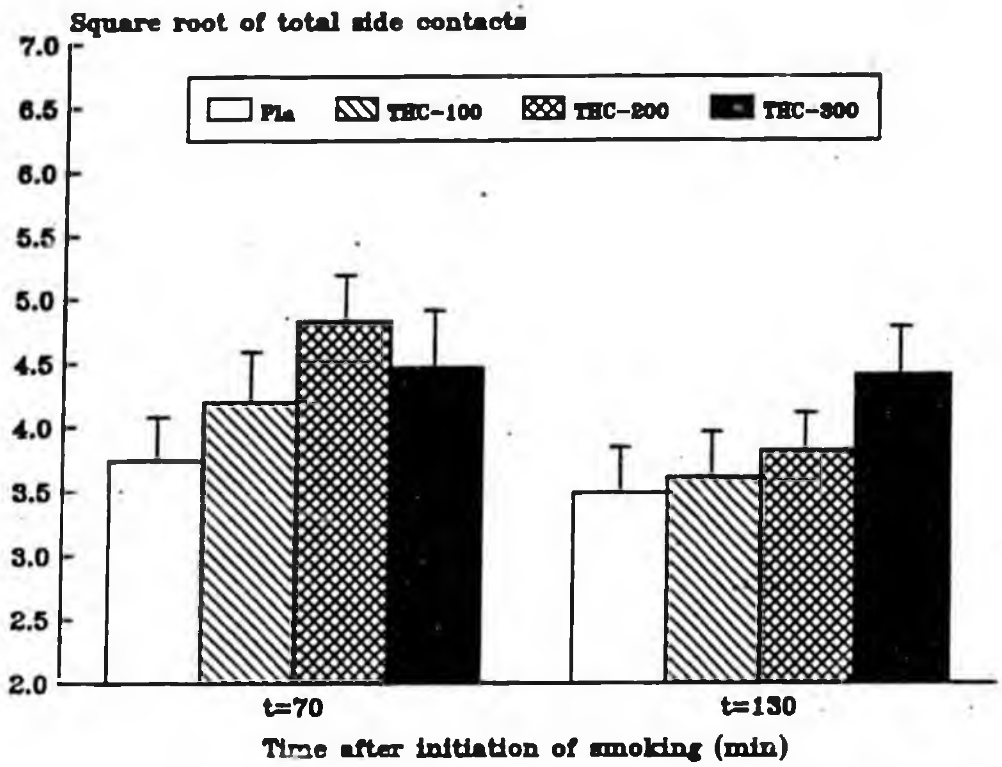

Figure 4.5 Mean (+SE) square root of total number of side contacts in the hand steadiness test by *Dose* and *Time*.

Hand Steadiness Test
Figure 4.5 demonstrates that hand steadiness diminished after all THC doses. MANOVA revealed a significant *Dose* ($F_{3,19}$=5.04; $p<.01$) and *Time* ($F_{1,21}$=8.61; $p<.008$), but no *Dose by Time* effect. This means that marijuana's impairment was still persistent two hours after

smoking. Separate comparisons showed that both higher THC doses, but not the lowest, diminished hand steadiness ($F_{1,22}$=7.67 & 11.76 for the 200 and 300 μg/kg, respectively; $p<.011$ & .002; p_c=.025 & .017).

Heart Rate and Blood Pressure

Heart rate and blood pressure were measured 70 and 130 minutes after the initiation of smoking. Yet as Figure 4.6 demonstrates, heart rate was still elevated in a dose related manner at both assessments. MANOVA confirmed this observation revealing a significant *Dose* effect ($F_{3,19}$=7.71; $p<.001$). Heart rate was always lower at the second assessment resulting in a significant *Time* effect ($F_{1,21}$=24.34; $p<.001$). *Dose by Time* interaction was not significant. Separate comparisons revealed that all three THC doses produced significant heart rate elevations relative to placebo ($F_{1,22}$=9.00, 13.62 & 20.61 for the 100, 200 and 300 μg/kg, respectively; $p<.007$, .001 & .001; p_c=.05, .025 & .017).

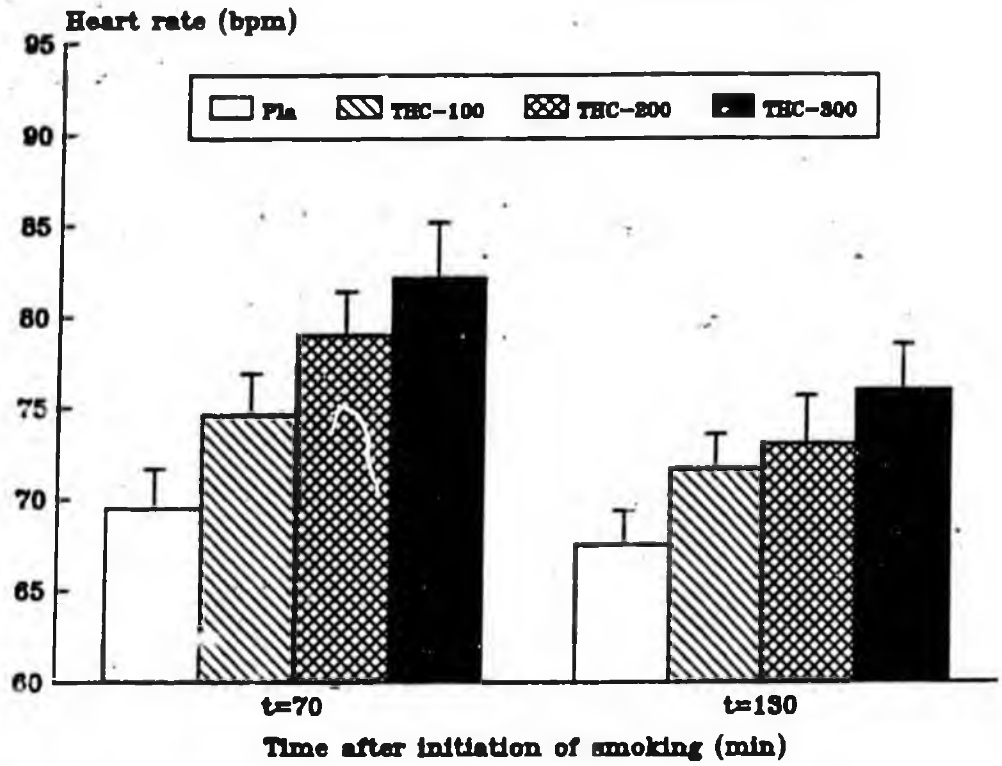

Figure 4.6 Mean (+SE) heart rate by *Dose* and *Time*.

Systolic and diastolic blood pressure measurements were simultaneously analyzed in one "doubly" repeated measures design. This means that both measures are analyzed in one multivariate design. Univariate effects of THC on systolic and diastolic pressures were only tested for significance, separately, if the multivariate *Dose* effect was significant. The lowest THC dose produced slightly lower blood pressure relative to placebo, whereas the highest dose had the opposite effect. Changes in blood pressures varied between -2.0 to +5.8 mmhg. MANOVA failed, however, to reveal either a significant *Dose* or *Dose by Time* effect. The only significant factor was *Time* ($F_{1,21}$=6.92; $p<.005$), indicating that blood pressure decreased significantly from the first to the second assessment: this occurred in both the systolic ($F_{1,21}$=12.92; $p<.002$) and diastolic blood pressure ($F_{1,21}$=4.77; $p<.05$).

Intra-Subject Relations between Variables

Table 4.4 shows the average intra-subject correlations of [THC], [THC-COOH], and SDLP with each of the other variables. The averages were computed from 23 intra-subject correlations, calculated from data obtained at eight sampling times (twice in each condition). The table shows that higher plasma levels of the drug were associated with increased feelings of perceived "high"; higher levels of effort to accomplish the driving test, decreased ratings of subjective driving quality, and increased heart rate. There was no strong relationship, within subjects, between plasma levels of the drug and SDLP. This was because drug concentrations declined between the first and second sampling time, whereas SDLP scores hardly changed. When average intra-subject correlations were computed for the first and second sampling times separately, the correlations between [THC] and SDLP were 0.59 ($p<.01$) and 0.42 ($p<.05$), respectively.

Table 4.4 Average intra-subject correlations (* $p<.05$ ** $p<.01$; 2-tailed).

	[THC]	[THC-COOH]	SDLP
Perceived "high"	.83**	.80**	.41
Perceived Effort	.53**	.58**	.30
Perceived Driving Quality	-.43*	-.44*	-.29
SDLP	.23	.35	1.00
SP	-.35	-.34	.05
SDSP	-.02	.05	.16
λ_c	.11	.07	-.22
Side Contacts	.26	.20	.14
Heart Rate	.49*	.39	.27

Inter-Subject Relations between Variables

Relationship between Drug Levels and Performance. Inter-subject correlations between plasma concentrations of the drug and performance were calculated to determine whether subjects with higher plasma levels of the drug performed poorer than those that had lower plasma levels. Correlations between driving performance and performance in the laboratory were also calculated. The results are presented in Table 4.5. It appeared that correlations involving plasma concentrations were greater when logarithmic values of THC values were used in the computation (1 ng/ml was added to all THC values before the transformation in order to avoid negative log values). Correlations with THC-COOH were generally smaller than those with log THC values; therefore only correlations with log THC values are shown in the table.

Table 4.5 Inter-subject correlations between drug concentrations in plasma and raw performance scores in marijuana conditions (* $p < .05$, ** $p < .01$; 2-tailed).

	100 µg/kg		200 µg/kg		300 µg/kg	
	1st	2nd	1st	2nd	1st	2nd
r(Log([THC]+1),SDLP)	-.23	-.32	-.26	.01	.13	.07
r(Log([THC]+1),SP)	-.68**	-.72**	-.45*	-.39	-.52	-.58**
r(Log([THC]+1),SDSP)	-.37	-.57**	-.52*	-.38	-.27	-.22
r(Log([THC]+1),λ_c)	.33	.51*	.24	.35	.08	.33
r(Log([THC]+1),Side Contacts)	.16	.24	.04	-.19	.31	.47*
r(SDLP,λ_c)	-.47*	-.50*	-.42*	-.56**	-.47*	-.27
r(SDLP,Side Contacts)	.41	.38	.10	.41	.27	.38

Table 4.5 shows that SDLP was not related to prevailing plasma levels of THC. Another driving performance measure, mean speed, was only moderately, yet consistently, related to THC; subjects having high [THC] values drove slower than those having low [THC] values. Driving performance was moderately related to critical tracking; poorer tracking performance on the road (higher SDLPs) concurred with poorer tracking performance in the laboratory (lower λ_cs).

Five percent of the driving tests undertaken in this experiment yielded SDLP scores above the normal limit of 35 cm (Table 4.6). This limit was established by several hundred young and middle-aged volunteers and psychiatric patients who uniformly failed to achieve higher scores in the same test after being treated with placebo in all of the Institute's studies since 1986. It is illuminating to examine the present drivers who drove over the limit with respect to their prior treatments and the plasma concentrations of THC and its metabolite they exhibited at these times.

Table 4.6 Drug levels and SDLPs from those subjects whose SDLPs exceeded 36.0 cm.

Subject	Condition	Trial	[THC] (ng/ml)	[THC-COOH] (ng/ml)	SDLP (cm)
1523	100 µg/kg	2	2.5	3.2	38.7
1503	200 µg/kg	2	1.7	5.1	36.3
1523	200 µg/kg	1	8.8	6.7	39.2
1523	200 µg/kg	2	4.3	4.3	37.0
1527	200 µg/kg	2	10.0	16.2	39.4
1506	300 µg/kg	2	9.8	3.8	36.6
1523	300 µg/kg	1	18.0	11.5	36.9
1523	300 µg/kg	2	5.2	9.2	39.3
1526	300 µg/kg	2	6.7	16.2	36.6

These data are important in two respects. Aberrant driving performance never occurred after placebo smoking, only once after the lowest THC dose and with equal frequency (4x) after both of the higher doses. Moreover, aberrant driving generally occurred during the second and not the first ride in direct opposition to the trend in plasma THC concentrations. From this, it's easy to infer the futility of predicting changes in SDLP, and presumably other aspects of driving performance, from a single [THC] estimation.

Correlations were also computed between drug plasma concentrations and changes in driving performance from placebo to marijuana conditions. These correlations were generally smaller than those involving the raw scores. Thus, [THC] does not predict changes in that performance.

Relationship between Driving Performance and Frequency of Current Use. Subjects were classified into two categories according to the frequency of reported cannabis consumption. Twelve subjects were infrequent users; i.e., between once weekly to once monthly; eleven subjects were classified as frequent users; i.e. at least once weekly but less than daily. SDLP values then entered a repeated measures MANOVA with *Frequency* of use as a between-groups factor, and *Dose* and *Time* as within-subjects factors. MANOVA failed to show a main effect of *Frequency*; interactions of *Frequency* and the other factors were also not significant.

Relation between Driving Performance and Driving under the Influence Experience. Subjects were classified into two categories according to the frequency of reported driving within one hour of cannabis consumption (see Table 3.1). SDLP values then entered a repeated measures MANOVA with *Experience* as a between-groups factor, and *Dose* and *Time* as within-subjects factors. Neither *Experience* nor any interaction was significant.

Relation of Willingness to Drive to Perceived "high" and Driving Performance. The relationship between willingness to drive and changes in SDLP and perceived "high" was determined as follows. Groups were defined by their willingness to drive; i.e., two groups were defined comprising those subjects who would not have driven and those who would, for each combination of condition (4x), sampling time (2x) and urgency of circumstance (3x), separately. Student's 2-tailed t-test for independent means was employed to determine whether the groups had significantly different change scores (drug minus placebo) of SDLP and perceived "high". Thus, 18 different t-test were performed for each variable, SDLP and perceived "high". Criterion for statistical significance was set at .01 because of the large number of tests. No significant differences in SDLP change were found between subjects willing and those reluctant to drive. With respect to changes in perceived "high", only two significant effects were found. Subjects willing to drive under the imagined circumstance *B* ("important but avoidable") at both sampling times in the 200 μg/kg condition felt less "high" than those who would not drive. However, this observation is not of major concern, since it was not supported in the other conditions and circumstances. From these results, it can therefore be concluded that subjects' willingness to drive was not related to either perceived "high" or driving performance.

DISCUSSION

This study demonstrated that marijuana impairs driving performance as measured by an increase in SDLP; all three THC doses significantly affected SDLP relative to placebo. It is remarkable that driving impairment was about the same after the two higher doses. This cannot be due to a ceiling effect, since greater deterioration in road tracking performance has been found after many prescription drugs (e.g. Robbe *et al.*, 1989) and also high doses of alcohol (Louwerens *et al.*, 1987). One possible explanation for the lack of a clear dose related impairment may be that subjects were able to mitigate the effects of the highest dose by "trying harder". Indeed, subjects reported putting more effort in performing the test after smoking the highest THC dose. In other words, subjects tried to overcome the perceived disparity between their actual state and the one required to drive the car efficiently; the higher the THC dose, the greater the disparity between the actual and required states, and the harder they tried to compensate for it.

Though marijuana's adverse effects on SDLP were somewhat smaller in the second test than in the first, no significant interaction was found between the treatments and repetition of the test. This means that the driving performance decrement after smoking marijuana persisted almost undiminished for two hours after smoking.

What is the practical relevance of the size of the effects of marijuana upon lateral position variability? This can be inferred by comparing marijuana's effects to those of alcohol in the same test. As cited above, Louwerens *et al.* (1985, 1987) conducted a study to establish the dose-effect relationship of alcohol. Their study resembled the present one in many aspects: they applied exactly the same driving test, the study was performed on a closed road, and involved the participation of 12 male and 12 female volunteers. They were able to derive an empirical equation for predicting the change in SDLP from placebo levels with increasing blood alcohol concentrations. Mean SDLP began to change significantly at blood alcohol concentration of 0.03 g% and increases exponentially to the point where the vehicle's lateral motion can no longer be restricted to within lane boundaries (at about BAC=0.12-0.15 g%, on the average).

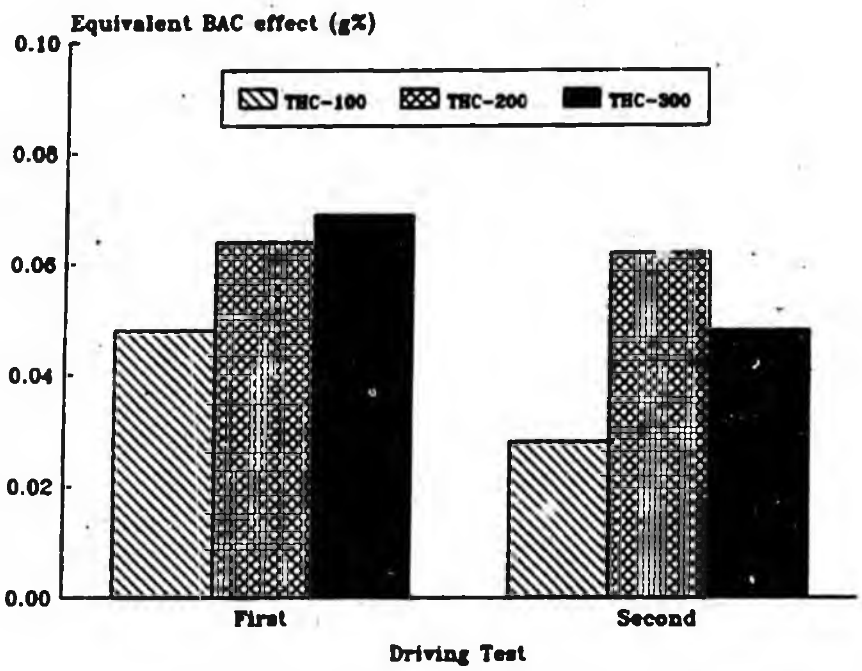

Figure 4.7 Comparison of mean SDLP changes after marijuana smoking to those associated with BAC.

Elevations of the group's mean SDLP in the first and second test after smoking 100, 200 and 300 μg/kg are presented in Figure 4.7, but now as their respective BAC equivalent producing the same driving impairment. Two tentative conclusions can be drawn from these data: first, small doses of THC are capable of impairing driving performance; secondly, performance deterioration is only little worse, yet equivalent to BACs over the Dutch legal limit of 0.05 g%, when much higher doses are smoked.

As mentioned above, mean SDLP values did not change greatly over time. The same can be said of mean subjective driving quality ratings. Yet other parameters did change over time; THC in plasma, perceived "high", heart rate elevation and perceived effort to accomplish the driving test were all less in the second test than in the first. Another important observation was made when the 5% highest SDLPs were examined in greater detail. Nearly all of these scores were recorded in the second rather than the first driving test after smoking higher THC doses. It may be that subjects did not try to compensate as much during the second ride because they felt less intoxicated. Whatever the reason, these results clearly indicate that the behaviorally toxic effect of THC had not yet dissipated. This means that "behavioral intoxication" may outlast physiological and subjective marijuana intoxication, a phenomenon already reported by other investigators (e.g. Reeve *et al.*, 1983; Yesavage *et al.*, 1985). On the other hand, subjects' perceived driving performance, measured retrospectively, did not change from the first to the second test when compared to placebo. Thus, while they felt less intoxicated in the second test they realized that their driving impairment was still the same as in the first test. Subjective feelings of "high" should therefore not be equated with subjective feelings of impairment, as is often done.

Some investigators (Klonoff, 1974; Hansteen *et al.*, 1976) found that marijuana impairs lateral position control as measured by number of cones hit in slalom tests. Others (Casswell, 1979; Attwood *et al.*, 1981) did not find any effect of marijuana upon lateral position control as measured in a similar way as in the present study, presumably due to the low THC dose (6.25 mg in Casswell's study) or the small number of subjects (eight in Attwood's study). Peck *et al.* (1986) found that the number of cones hit decreased after smoking marijuana, probably due to a reduction in speed. Most of these studies also measured alcohol's effects (BACs between 0.04 and 0.10 g%) on lateral position control. It was generally concluded that marijuana's effects were less than alcohol's, especially at BACs of 0.08 g%. Marijuana's effects on lateral position variability were significant, yet not dramatic, in the present study and always less than or equal to the equivalent BAC effect of 0.07 g%. The reduction in mean speed, though small, fits also well with previous findings. It can therefore be concluded that this study's results are in close accordance with previous closed-course driving studies of THC effects on vehicle handling parameters. This implies that simple psychomotor functions involved in driving are impaired by normally consumed THC doses, though not to such an extent that traffic safety is seriously compromised.

Yet disturbing observations of two individuals' attentional deficits were observed; a sudden loss of the ability to shift attention from the prescribed task to an unexpected event (screwdriver on the road) and the lack of anticipation for a normal event (end of circuit). Since perception and attention are important aspects of actual driving, these instances may indicate an unusually hazardous property of THC when the drug is consumed shortly before operating a vehicle. Therefore, the revised conclusion must be: what was measured was only moderately affected by THC, but another major deficit may have existed after the highest dose which bears further examination. One can not conclude whether the standard driving test applied in this study measures the most important deficits.

Important practical implications of the study are whether driving performance decrements can be predicted by prevailing plasma concentrations of the drug. Though average [THC] and [THC-COOH] values were clearly dose-related, driving impairment reached a ceiling before the highest concentrations were achieved. Inter-subject correlations between plasma concentrations of the drug and driving performance after every dose were essentially nil, partly due to the peculiar kinetics of THC. It enters the brain relatively rapidly, although with a perceptible delay relative to plasma concentrations. Once there, it remains even at a time when plasma concentrations approach or reach zero. The conclusion is that driving impairment cannot be predicted by prevailing plasma concentrations of THC or THC-COOH.

Another way of predicting driving impairment was explored; namely, by performance in laboratory tests that might be potential "roadside" tests. Hand steadiness was impaired by marijuana after high doses but not after 100 μg/kg. Performance in this test was not related to driving performance. Previous studies employing the same test (Clark *et al.*, 1970; Milstein *et al.*, 1975) showed greater sensitivity to marijuana-induced impairment of hand steadiness. In those studies subjects were not allowed to rest their hands on the table, which is probably the major reason for the observed difference. In fact, the present and the preceding study merely measured finger rather than hand steadiness. The conclusion must be that hand steadiness was not properly tested, but the results suggest that it is not possible to predict driving impairment by means of hand steadiness performance.

Critical tracking performance was another candidate for being a good "roadside" test. Yet this test failed to show any effect of marijuana which is in conflict with prior research conducted by Sharma and Moskowitz (1975) and more recently Moskowitz *et al.* (1981). They demonstrated that a THC dose of 200 μg/kg impairs critical tracking performance for at least up to 4 hours post-smoking. Peck *et al.* (1986), however, also reported a failure of marijuana alone (1.0 g cigarette containing 1.9% THC) to affect λ_c scores. They hypothesized that their conflicting results could be explained by their subjects' greater cannabis experience and tolerance. Although the same argument could be applied in the present study, it is suspected that the failure to detect significant changes in λ_c after marijuana smoking is due to the particular version employed in this and the pilot study (this group's mean values after placebo were also considerably lower than those commonly found in healthy volunteers). The device used was a commercial PC/AT version of CTT which was originally programmed on a Commodore-64 computer. The latter has been successfully applied in psychopharmacological research by the authors and their colleagues and hitherto appeared as a very sensitive test for drug-related impairment (e.g. Robbe *et al.*, 1989; Ramaekers *et al.*, 1992a). This study was the first in which the commercial PC/AT version was employed, so the conclusion that the software or hardware was not well designed seems inevitable.

All subjects were willing to undertake the driving tests. But test conditions were artificial and the same individuals may or may not have been willing to drive under normal circumstances. Therefore, one questionnaire inquired into the subject's willingness to drive an automobile when experiencing the same drug effect under "normal" conditions. Subjects' willingness to drive was related both to consumed THC dose and urgency. After smoking a low THC dose, nearly all were willing to drive, especially for urgent reasons. After higher doses, fewer were willing to drive under all circumstances. According to what subjects said, they did not become less cautious after inhaling increasingly large doses (unlike what is often reported about alcohol). On the contrary, their caution increased with intoxication. Still, 50% of the subjects reported that they would have driven for an unimportant reason shortly after smoking the two highest THC doses. Since willingness to drive was not related to objective driving impairment, it may be concluded that at least some of the subjects either were not able to appraise their driving performance before they had actually driven or did not consider their impairment as critical.

It is interesting to compare plasma concentrations of THC found after smoking the highest THC dose in this study with those found in the pilot study. The highest dose administered in the present study was comparable to the average dose the same subjects consumed in the pilot study. Mean plasma concentrations of THC after the highest dose in the present study, determined 30 and 90 minutes after initiation of smoking, were 50 and 40% higher than those measured in the pilot study after 40 and 100 minutes. This large difference can only be partially explained by the 10 minutes delay between the two studies' blood sampling schedule. Apparently, subjects smoked more efficiently in this than the previous study. Since most volunteers were used to smoking hashish instead of marijuana, the increased efficiency compared to that in the pilot study may be explained by familiarization with the particular formulation of the drug.

One of the objectives of this study was to determine whether or not the same experimental conditions could be implemented in a study on marijuana's effects on driving on a primary highway public for other traffic. All subjects were willing and able to finish the driving tests without great difficulty. In cases of the exceptional events, the driving instructor was able to control the situation, safely. The effects of marijuana on SDLP were never so large as after many other drugs that had been safely studied in the presence of other traffic. Furthermore, it can be inferred from what subjects said and did that they would not be expected to seek dangerous situations and would be responsive to the instructor's advice. Normal safeguards were deemed sufficient to ensure safety. Hence, the final conclusion was that it would be safe to repeat this study on a normal highway in the presence of other traffic.

CHAPTER 5 - MARIJUANA AND DRIVING ON A NORMAL HIGHWAY IN TRAFFIC

INTRODUCTION

The preceding study showed that the average driving impairment on a closed highway segment was never particularly great after doses of 100, 200 and 300 μg/kg THC (equivalent to impairment at 0.05 to 0.07 g% BAC) making it ethically acceptable to test the same doses' effects on performance in a more natural environment. It seemed essential to do so because the extent to which one can generalize from closed-course testing to the real world is presently unknown. Therefore, the same approach was applied for testing THC's effects on driving performance in a more realistic situation. In particular, the same THC doses were administered to a new group of subjects undertaking similar driving tests, though now on a highway in the presence of other traffic.

The present study was only the second wherein subjects drove in real traffic after receiving THC treatments. It was the first in which subjects inhaled higher "street doses" of THC before driving. Though the preceding study on a closed highway failed to show dramatic effects of high THC doses on high-speed driving, a conservative approach was chosen in designing the present study in order to satisfy the strictest safety requirements. This approach is unique in traffic science but closely follows the procedure used to determine the tolerability of medicinal drugs in human pharmacological research. It is to test THC's effects on actual driving performance in an ascending dose series (below). If any subject would have reacted in an unacceptable manner to a lower dose, he/she would not have been permitted to receive a higher dose.

The major objective of this study was to confirm the relationship between inhaled THC dose and lateral position variability in the context of a standard road tracking test. A secondary objective was to measure performance in another actual driving test (i.e. car following) to determine whether degrees of impairment would correlate between the two tests in a manner indicating a general influence of THC on driving behavior. The third objective was to continue efforts to correlate plasma concentrations of THC and THC-COOH with driving performance impairment as measured in both tests.

METHODS

Subjects

Sixteen new subjects, equally comprised of men and women, were selected according to the same inclusion/exclusion criteria as before. They were individually trained to perform the driving tests in a preliminary "dress rehearsal". Training at laboratory tests continued until each subject achieved satisfactory, asymptotical performance levels.

Plasma analyses after conclusion of the study showed that one female's plasma contained neither THC nor THC-COOH in any sample. It was concluded that this subject had not inhaled smoke, so her data were excluded from further analyses. Characteristics of the remaining 15 subjects are given in Table 5.1. T-tests for independent samples showed that males were heavier smokes than females ($p < .007$). There were no other significant differences between the sexes.

Table 5.1 Mean±SD (range) of subjects' characteristics.

	Males (N=8)	Females (N=7)
Age (yrs)	28.3±7.4 (22-42)	25.0±4.6 (21-34)
Weight (kg)	70.8±7.0 (61.0-83.5)	66.7±7.9 (55.5-79.0)
Weight (lb)	156±15 (134-184)	147±17 (122-174)
Smoking Experience (yrs)	8.3±6.5 (2-21)	6.3±5.9 (1-16)
# Joints/Month	8.3±5.0 (1-16)	2.0±1.4 (1-4)
Driving Experience (yrs)	6.8±5.7 (2-20)	4.9±4.6 (1-15)
Driving Experience (km x 1000)	78±101 (10-320)	38±66 (5-188)
Driving Experience (mi x 1000)	48±63 (6-199)	24±41 (3-117)
# of Subjects Having Driven within 1 Hour following Cannabis Consumption:		
less than 5 times	4	7
5 times or more	4	0

Design, Doses and Administration
The study was conducted according to an ascending dose series design where both active drug and placebo conditions were administered, double-blind, at each of three THC dose levels. THC doses were the same as those used in the previous study, namely 100, 200 and 300 μg/kg.

The lowest dose and placebo were administered in separate First Level treatment conditions spaced a week apart. Half the group received these treatments in the same order, the others in reverse order. Subjects proceeded to the next dose only if, in the driving instructor's opinion, no severe and potentially unsafe drug effects had occurred; and, if the subject was willing to go on to the next level. The intermediate dose and placebo were administered the same way in the Second Level conditions and the decision to proceed was made on the same grounds. The highest dose and placebo were administered the same way in the Third Level conditions to conclude the study.

Marijuana cigarettes were prepared from batches supplied by NIDA, containing 1.77% THC for the lowest, 2.64% THC for the intermediate, and 3.58% THC for the highest dose. Doses were administered by smoking and cigarettes appeared identical at each level of treatment conditions. Cigarettes were smoked through a plastic holder in a fashion determined by the subject but with the constraint that smoking had to be finished within ten minutes. After cessation of smoking, cigarettes were retained for subsequent gravimetric estimation of THC consumed. These analyses revealed that the average (±SD) amount of consumed THC in the three marijuana conditions was 6.9 (±0.7), 13.8 (±1.4) and 20.7 (±2.2) mg, or 100 (±4), 204 (±7) and 299 (±7) μg/kg, respectively.

Testing Procedures
Upon arrival at the laboratory, subjects' breath and urine were tested for the presence of alcohol and cannabinoids. If cannabinoids were found in the urine, a blood sample was taken for later verification of the presence of THC. Two subjects at a time commenced smoking at t=0 (Table

5.2). Thirty minutes after onset of smoking the subjects performed a battery of laboratory tests (tracking, hand steadiness and body sway) and yielded a blood sample. They were then transported to a primary highway (A76, different than in the previous study) between the Dutch cities of Maastricht and Heerlen where the driving tests were performed. Two instrumented vehicles, the same as those in the previous study, were employed in this study. One subject started the car following test (below) in the eastward direction whilst the other subject was sitting in the passenger's seat of the preceding car involved in the same test. The test was conducted on a 16 km (9.9 mi) circuit of the highway and lasted about twelve minutes. At the end of the circuit the car turned at a signalized intersection and parked at a service station, whereupon the subjects reversed roles to repeat the test running in the opposite direction. The new driver reentered the highway and began his/her car following test. After conclusion of the car following test, the subject left the highway at an exit ramp and reentered in the opposite direction on the associated entrance ramp. Thereupon both vehicles parked on the paved shoulder.

Table 5.2 Schedule of activities on test-days.

Relative Time (min)	Activity
0-10	Smoking
30-40	Tracking, Hand Steadiness and Body Sway Tests
40-45	Blood Sampling
55-70	Car Following Test (1st Subject)
70-85	Car Following Test (2nd Subject)
85-135	Standard Driving Test (Both Subjects)
140-155	Car Following Test (1st Subject)
155-170	Car Following Test (2nd Subject)
190-195	Blood Sampling
195-205	Tracking, Hand Steadiness and Body Sway Tests

Both subjects then commenced the standard driving test (below) in separate instrumented vehicles at $t=85$ and $t=88$, respectively. The test circuit was the same as for the car following test. Subjects drove twice around the circuit (in total, 64 km or 40 mi) without stopping in about 50 minutes. At the conclusion of this test, both subjects participated again in the car following test in the same order as before. Subjects were then transported back to the laboratory where they yielded a blood sample and repeated the test battery.

Two pairs of subjects were tested per test night. One pair performed the driving test in daylight, i.e. between 19.30 and 21.30 hours; the other pair commenced driving at 21.30 hours and finished at 23.30 hours in darkness.

Driving Tests

The standard test was the same as described in the previous study (Chapter 4) except for its duration and the presence of other traffic. Subjects were instructed to maintain a constant speed of 95 km/h (59 mph) and a steady lateral position between lane boundaries in the right traffic lane. They were allowed to deviate from this only if it would become necessary to pass a slower vehicle in the same lane. Data from the standard test were analyzed to yield the same performance measures as in the previous study; namely, standard deviation of lateral position (SDLP), mean and standard deviation of speed (SP and SDSP), and standard deviation of steering wheel angle (SDST).

The car following test measures drivers' ability to perceive changes in a preceding vehicle's speed and to react in a manner maintaining a constant headway. It began as the preceding and the following vehicle, respectively driven by one of the driving instructors and the subject, operated in tandem on the slower traffic lane while travelling at a speed of 100 km/h (62 mph). The subject was instructed to maintain a 50 m (164 ft) headway however the preceding vehicle's speed might vary. After driving in this manner for about one minute, the operator of the preceding vehicle released the accelerator pedal allowing its speed to fall to 80 km/h (50 mph). Immediately thereafter, the operator of the preceding vehicle accelerated to 100 km/h (62 mph). The duration of one deceleration and acceleration maneuver was approximately 50 seconds and six to eight, depending upon traffic density, were executed during one test.

The velocity of the leading vehicle was transmitted via telemetry to a receiver in the following vehicle. This signal, along with the following vehicle's own velocity were recorded in parallel, time-coded files on computer files. These data entered a power spectral analysis for yielding phase-delay, modulus or gain and coherence between the vehicle's velocities at the maneuver cycle frequency (i.e. 1/50 s = 0.02 Hz). The average phase-delay between frequencies of 0.01 and 0.03 Hz., encompassing the frequency of the deceleration and acceleration maneuvers, was then calculated and transformed to the time domain to yield a measure of the subject's average reaction time to the movements of the leading vehicle (RT, in seconds). This was taken as the primary dependent variable from the car following test. Gain and coherence were recorded for control purposes. If the test was performed according to instructions, gain should have a value of about 1.0, and coherence, >.90.

During the trials, 3 to 6 direct measurements of separation distance between the following and leading vehicle were made by means of a S-VHS video recording system which was mounted between the following vehicle's front seats facing forward through the windshield. Images of the rear of the preceding vehicle were acquired prior to each deceleration/acceleration maneuver. The camera's internal clock signal was recorded with the video imagery and also converted in an electronic pulse code for simultaneously computer recording along with the two vehicles' speed.

Video imagery recorded throughout the trials were analyzed off-line using an interactive software routine implemented on a IBM-AT computer. A single frame would show the appearance of the preceding vehicle at the moment it begins to decelerate. Next the coordinates of two target markers, spaced 119 cm apart on the rear of the leading vehicle were identified on the display. From this information the distance separating the two vehicles or "headway" was calculated according to the equation,

$$d(\text{in m}) = k\ (1\ m\ /\ \tan(\Theta/2))$$

where k is a proportionally constant and Θ the horizontal angle subtended by the camera lens. Once the starting distance was determined from a single measurement, headway changes during the maneuver were calculated using differential speed according to the equation,

$$\vec{H}(t) = \int V_p\, dt - \int V_f\, dt + H_0$$

where headway varies as a function of time (t) according to the difference between integrals of velocities of preceding and following vehicles (V_p,V_f) plus the headway (H_0) that existed at the beginning of the maneuver. Headway and coefficient of variation of headway (CV-Headway) during maneuvers were taken as secondary dependent variables. The coefficient of variation of headway, and not standard deviation, is preferable because of the latter's confounding by mean headway.

Questionnaires

The same subjective questionnaires used in the previous study were administered to the subjects in the present study. Subjective feelings of "high", present cognitive and emotional state, and subjects' willingness to drive were assessed before the onset and after the conclusion of the driving tests (t=50 and 175). Subjects were also asked about their perception of the administered treatment, whether it was THC or placebo. At the end of each driving test, subjects were required to retrospectively rate the effort given in performing the test and perceived driving quality. Questionnaires are enclosed in Appendix A.

Laboratory Tests

Three tests were administered to the subjects: critical tracking, hand steadiness and body sway. These were also administered in the preceding studies, but the equipment or procedures were changed in this study.

1. Equipment, not procedures, changed in case of the critical tracking test (CTT). The test had shown no sensitivity to treatments administered in the preceding studies, in spite of the fact that other investigators had used the same test for showing significant effects of much lower THC doses. The validity of the particular MS-DOS version used in the preceding studies was doubtful. Therefore an older Commodore-64 version was employed in the present study. This version of the CTT had proven its sensitivity to drug-induced sedation in several previous studies conducted by the authors and their colleagues (e.g. Robbe *et al.*, 1989; Ramaekers *et al.*, 1992a). Test duration was approximately 5 minutes and mean λ_c was the dependent variable.

2. As discussed in the previous chapter, the hand steadiness test examined finger rather than hand steadiness because subjects were allowed to rest their hands on the table. Subjects were not allowed to do this in the present study. The modification was expected to induce greater instability. Therefore, the diameters of holes were increased to avoid ceiling effects of the number of contacts between their sides and the hand-held stylus. The diminishing diameters of the five circular holes were now set to 6.30, 4.70, 3.90, 3.05 and 2.70 mm (0.25, 0.19, 0.15, 0.12 and 0.11 in) respectively. The dependent variable was again the square root of the total number of contacts of the stylus with any side. The test lasted about 3 minutes.

3. Postural instability, or body sway, was measured using the stabilometry method (Kapteyn *et al.*, 1983). It involved the use of a balance platform that measures the location of the vector of force which extends vertically downward from the body's center of gravity and its movement over time. Analog output of force transducers within the platform were digitized

and analyzed to yield simultaneous measures of lateral and sagittal motion around the vertical axis. Subjects were instructed to maintain a static posture while standing over the center of the balance platform with their feet together. Two, 30-second recordings followed. The first with the subject's eyes open, the second with eyes closed. While standing with the eyes open, the subject was required to fixate on a target mounted on the wall from a distance of 2.0 m (6.6 ft). The mean area circumscribed by the vertical vector of force (i.e. curve surface, in mm^2) was taken as the dependent variable (CS-O and CS-C for eyes open and closed, respectively).

Physiological Assessments

The electrocardiogram (ECG) was measured from precordial leads (RC_5), and the interbeat interval (IBI) times were registered continuously during the driving tests. Cardiac interval times were analyzed to yield three different parameters, mean IBI, the coefficient of variation (CV-IBI), and relative amplitude in the power density spectrum between the frequencies of .07 and .14 Hz (PWR-HR).

CV-IBI, is defined as standard deviation of IBI divided by the mean. It is the best measure of IBI variability in the time domain. The coefficient of variation, and not the standard deviation, of IBI is preferable because of the latter's confounding by mean IBI.

PWR-HR is a variability measure within a restricted region of the frequency domain and calculated from the time series of instantaneous heart rates, which are computed at each successive heart beat. It is defined as the integrated amplitude in the power density spectrum between 0.07 and 0.14 Hz.

Mean interbeat interval, and more frequently its reciprocal, mean heart rate, is frequently used for measuring THC's chronotropic cardiac effect. As shown in the previous study, the measure is valuable for assessing the course of the drug's activity over time. However the other measures, CV-IBI and PWR-HR, possess greater psychological significance. They are alternatively used for estimating relative changes in an individual's mental workload, or more correctly the amount of mental effort he must exert for handling a particular workload. In general, both measures vary inversely with the imposed mental workload or the increase in mental effort which is required to cope with a constant workload while maintaining the same level of performance efficiency under the influence of drugs or fatigue (Mulder, 1980; Mulder and Mulder, 1981).

Blood Sampling

Blood samples were obtained from the subjects by venepuncture immediately before they were transported to the test site and immediately after their return, or approximately 35 and 190 minutes after initiation of marijuana smoking. Two aliquots containing 10 ml each were heparinized and centrifuged, and the plasma fractions were placed in frozen storage for later assays to determine [THC] and [THC-COOH]. The analytical procedures were the same as those employed in the preceding studies.

Data Analysis

The first step executed was determining the reliability and consistency of performance and subjective parameters measured in the successive placebo treatment conditions. Test-retest reliability coefficients were determined and mean differences between data collected in successive conditions were tested for significance using repeated measures MANOVA. Previous studies wherein unmedicated subjects performance was repeatedly measured in the standard test have failed to show any significant changes over time intervals as long as one week; and, test-retest reliability coefficients for the SDLP measure have always been higher than $r=.80$. However, intervals separating successive placebo tests were longer in the present study and the reliabilities of measures obtained in the car following test had yet to be determined. For these reasons it appeared necessary to check the consistency of the subjects' performance in the present study.

Subsequently, data from drug and placebo conditions on the first, second and third levels were analyzed separately. Performance variables recorded on ratio or interval scales were subjected to repeated measures MANOVA with *Sex* as a between-groups and *Drug* (placebo versus marijuana) as a within-subjects factor. The effect of *Time* of testing (2 levels) was, if pertinent, simultaneously tested as a within-subjects factor in the same analyses.

It appeared that marijuana's effects on reaction time in the car following test were confounded by mean headway. Reaction times were therefore also analyzed by means of covariance analysis, using headway as the covariate. Covariance analysis estimates what the scores on one variable (in this case, reaction time) would have been if the same "average" score on another variable (in this case, mean headway) would have occurred in all conditions. It allows one to estimate the effects of THC on reaction time independently of those on headway.

Willingness to drive data were analyzed in the same manner as the parametric data. That is, data from drug and placebo conditions on the first, second and third levels were analyzed separately. Thus, data from both sampling times in a drug condition and its respective placebo condition were simultaneously tested for assessing differences in the proportion of subjects willing to drive for a particular reason.

Separate dose effects were tested using the "Sequential Bonferroni" procedure for adjusting the α-probability criterion (p_c) in accordance with the number of separate comparisons in a given set (Overall and Rhoades, 1987). For the largest of three differences tested at once, p had to be less than $.05/3=.017$ to be judged significant. For the second, it had to be $<.05/2=.025$; and for the smallest difference, $p<.05$. The adjustment had the effect of holding the probability of making a type I error at $p\leq.05$ over the entire set of comparisons.

Though data from both the marijuana and respective placebo condition entered MANOVA, figures illustrating the results display mean difference scores (drug - placebo) and standard errors of the difference (SED). The former are depicted by the height of the bars, the latter by the vertical lines above or below the bars. Difference scores were used in order to keep the figures as simple as possible. As a consequence, main effects of *Time* could not be depicted in the figures: a parallel rise or fall in the mean levels of a variable over time would not affect their difference. This is, however, not a major problem, since it is not very interesting to know whether subjects' performance changed in both conditions in the same manner. More interesting is a *Time by Drug* effect, which means that the difference between effects of marijuana and placebo changed over time. This effect would be obvious in the figures.

Significant *Sex* effects were generally absent. Results pertaining to differences between the sexes are therefore mentioned only in the exceptional cases where these were significant.

RESULTS

No subject dropped out during the experiment, neither on their own initiative nor on the driving instructor's. Therefore, the results presented below include data from fifteen subjects at each level of treatment. It was impossible to obtain every blood sample from one woman, even after repeated attempts. Her data were therefore excluded from all analyses involving drug and metabolite plasma concentrations. However, assays of what samples were obtained indicated that she did inhale THC. Consequently, her data were not excluded from other analyses.

Test-Retest Correlations and Consistency of Performance

Correlations between measurements obtained from the successive placebo treatment conditions are shown in Table 5.3. Correlations between repeated SDLP's were somewhat lower than those obtained in earlier studies for "normal" subjects, but were still both highly significant and consistent. Mean and standard deviation of speed were also quite reliable. Steering wheel variability, however, was not a reliable measure.

Table 5.3 Correlations between parameters measured at the same time in the successive placebo treatment conditions (* $p<.05$ ** $p<.01$; one-tailed).

	1st and 2nd placebo		2nd and 3rd placebo		1st and 3rd placebo	
	1st test	2nd test	1st test	2nd test	1st test	2nd test
Standard Driving Test:						
SDLP	.75**		.76**		.72**	
SP	.61**		.84**		.77**	
SDSP	.66**		.69**		.55*	
SDST	-.21		.17		-.62	
Subj. Driv. Quality	.24		.24		.30	
Perceived Effort	.72**		.50*		.56*	
Car Following Test:						
Headway	.73**	.31	.60**	.90**	.67**	-.01
CV-Headway	.48	.19	.36	.40	.55*	.07
RT	.61**	.45*	.81**	.68**	.64**	.09
Subj. Driv. Quality	.51*	.06	.64**	.28	.61**	-.06
Perceived Effort	.72**	.80**	.67**	.69**	.33	.71**
Laboratory Tests:						
λ_c	.68**	.70**	.73**	.87**	.67**	.78**
Side Contacts	.75**	.80**	.84**	.66**	.63**	.63**
CS-O	.43	.49*	.20	.62**	.04	.31
CS-C	.25	.56*	.71**	.18	.37	.41
Other Subjective Feelings:						
Alertness	.44*	.92**	.88**	.78**	.59*	.75**
Contentedness	.52*	.79**	.76**	.77**	.46*	.59**
Calmness	.71**	.34	.87**	.41	.51*	.22

Subjective driving quality ratings were also unreliable, probably due to restriction of range; i.e. most subjects naturally rated their driving performance as about normal (100%) following placebo treatment. Perceived effort ratings were somewhat more reliable, indicating that driving under the conditions of this study was consistently a more effortful occupation for some subjects than others.

Car following parameters were not as reliable as those measured in the standard driving test. Performance in the second ride in the first placebo condition was not related to that in the second ride of the second and third placebo conditions. This means that the test still needs further standardization to reduce the error variance of the measures tested. Ratings of perceived effort in the car following test were only slightly more reliable than those obtained in the standard test. Remarkably, ratings of subjective driving quality were highly reliable in the first car following test, but not in the second.

Hand steadiness and λ_c, but not body sway measures, were highly reliable. Ratings of alertness, contentedness and calmness were moderately reliable. Surprisingly, alertness and contentedness ratings were generally more reliable when measured after driving, in contrast to calmness ratings which were more reliable before the driving tests commenced. Correlations between perceived ratings of "high" were not computed since they were generally very low or zero following placebo.

Mean differences between data collected in successive placebo treatment conditions were tested for significance using repeated measures MANOVA. Only λ_c changed nearly significantly over successive placebo treatment conditions ($F_{2,12}=3.81$; $p<.052$); subjects' performance in this test improved during the study (λ_c=4.6, 4.8 & 5.0, for the respective placebo conditions, averaged across both sampling times). Obviously performance had not reached an asymptotic level during practice trials which preceded the beginning of experimental sessions.

Plasma Concentrations of the Drug

Table 5.4 shows mean, median and range of [THC] and [THC-COOH] by *Dose* and *Time*. Placebo values were not used in the statistical analyses since these were zero in most cases. Therefore, data from all THC conditions were analyzed in one MANOVA. The tabular data indicate that [THC] was related to inhaled THC dose, and fell to about the same level three hours after smoking.

Table 5.4 Mean, median and range of [THC] and [THC-COOH] in ng/ml (N=14).

		100 µg/kg		200 µg/kg		300 µg/kg	
		t=35	*t*=190	*t*=35	*t*=190	*t*=35	*t*=190
[THC]	mean	7.9	0.7	12.0	1.1	16.1	1.5
	median	6.5	0.9	10.0	1.0	15.8	1.5
	range	0.8-17.2	0.0-1.3	1.5-27.1	0.0-2.7	4.7-30.9	0.4-3.2
[THC-COOH]	mean	8.2	4.1	12.2	7.61	15.3	10.0
	median	7.4	4.1	11.2	6.4	13.0	8.2
	range	1.4-19.4	0.0-12.0	2.0-37.2	0.0-32.2	4.2-39.6	1.5-36.3

MANOVA confirmed this impression with significant *Dose* ($F_{2,11}$=20.75; $p<.001$) and *Time* ($F_{1,12}$=54.81; $p<.001$) effects, and *Dose by Time* interaction ($F_{2,11}$=17.80; $p<.001$). Males had somewhat higher [THC] than females and the *Sex* effect approached significance ($F_{1,12}$=4.60; $p<.053$); *Sex by Dose* interaction was not significant.

Plasma levels of the metabolite, THC-COOH, were about the same as those of THC 35 minutes after initiation of smoking, but did not decline as rapidly. Table 5.4 shows that [THC-COOH] was also dose-related at both sampling times. Significant *Dose* ($F_{2,11}$=14.49; $p<.001$) and *Time* ($F_{1,12}$=62.50; $p<.001$) effects, but no *Dose by Time* interaction, were shown by MANOVA.

Perceived "high"

Ratings of "high" after placebo were near zero in most cases. Therefore changes occurring after marijuana smoking, relative to placebo, instead of the raw values, were analyzed by MANOVA. Average subjective feelings of "high" were dose-related and greatest just before the first driving test (Figure 5.1). Relative to maximum personal experience, peak levels of intoxication were

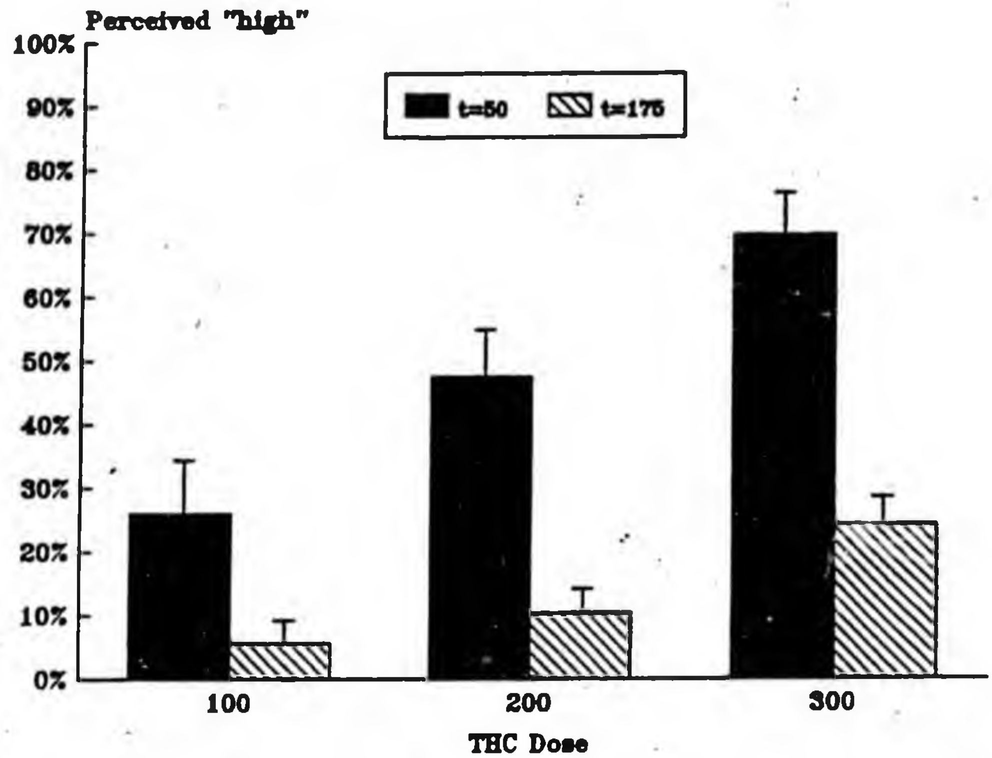

Figure 5.1 Mean (+SED) changes in perceived "high" by *Dose* and *Time*, relative to placebo.

about 30%, 50% and 75% after 100, 200 and 300 μg/kg doses. The approximately linear correspondence between the administered dose and average subjective response was impressive.

Change scores were significantly dose-related ($F_{2,12}$=35.07; $p<.001$) and time-related ($F_{1,13}$=40.25; $p<.001$). The decline in feelings of "high" over time was also dose-related, resulting in a significant *Dose by Time* interaction ($F_{2,12}$=7.87; $p<.007$).

Driving Performance in the Standard Driving Test

All subjects undertook and completed each test in a safe manner; the driving instructors neither terminated any ride prematurely nor intervened while subjects were driving. In other words, the subjects' safety was never compromised.

Figure 5.2 shows the mean changes in SDLP from placebo to marijuana conditions. Performance after consuming THC was worse than after the respective placebo treatment; mean changes in SDLP were 1.1, 1.8 and 2.9 cm for the 100, 200 and 300 μg/kg conditions, respectively. MANOVA showed that SDLP was significantly elevated after inhaling both the higher, but not the lowest, THC doses relative to placebo ($F_{1,13}$=2.66, 6.63 & 10.16 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.13$, .023 & .007; $p_c=.05$, .025 & .017). No significant differences between males and females were discovered.

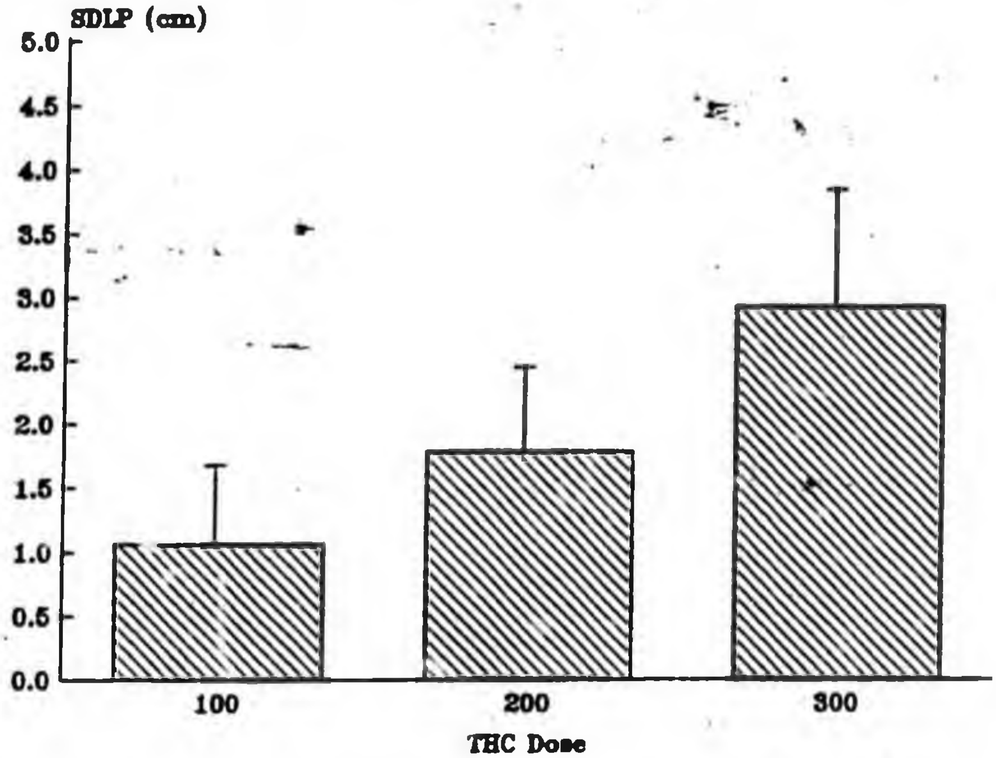

Figure 5.2 Mean (+SED) changes in standard deviation of lateral position in the standard driving test by *Drug*, relative to placebo.

Mean speed was very close to that established as the target by instructions and varied between conditions from 94.5 to 96.1 km/h (58.7 to 59.7 mph). Subjects drove slower following marijuana than following placebo, but the mean differences were quite small: 0.3, 1.1 and 0.5 km/h (0.2, 0.7 and 0.3 mph) for 100, 200 and 300 μg/kg conditions, respectively. MANOVA showed that only the change after the intermediate dose was significant ($F_{1,13}$=8.05; $p<.014$; $p_c=.017$).

Standard deviation of speed was very small in each condition, on average 2.5% of mean speed. Though speed variability increased after smoking THC, the effects were minor and not significant. Standard deviations of steering wheel movements were also not affected by THC; mean changes after smoking THC were essentially nil.

Subjects rated their driving performance in the standard test as about "normal" after smoking placebo and after the lowest dose of THC. Ratings were 90% and 77% of "normal" driving performance following the 200 and 300 μg/kg conditions, respectively. Changes relative to placebo are shown in Figure 5.3. MANOVA demonstrated that changes in perceived driving quality approached the levels of significance required by the "Bonferroni" adjustment after the two higher THC doses ($F_{1,13}=5.29$ & 5.42 for the 200 and 300 μg/kg conditions, respectively; $p<.039$ & .037; $p_c=.025$ & .017), but were not significantly different from placebo after the lowest THC dose.

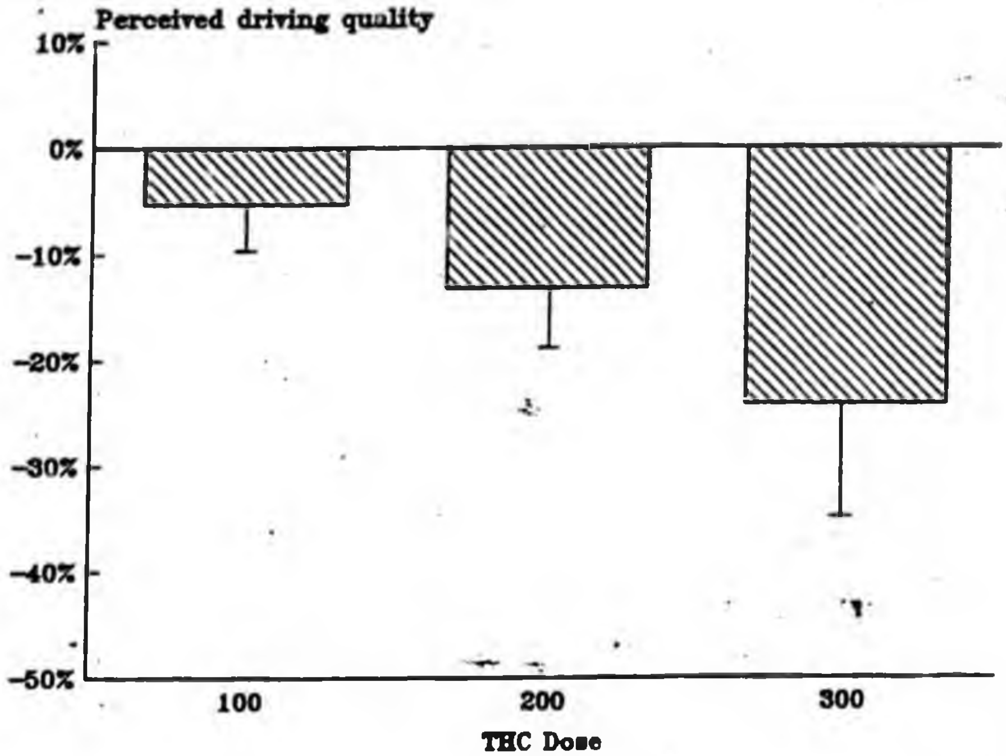

Figure 5.3 Mean (+SED) changes in perceived driving quality in the standard driving test by *Drug*, relative to placebo. Raw scores were expressed as percentage of "normal".

Changes in perceived effort ratings were trivial after the two lower THC doses. Effort did increase from 29% after placebo to 39% following the highest dose. MANOVA failed, however, to reveal any significant effects of THC on perceived effort.

Half of the subjects performed the driving tests in darkness, the other half under daylight conditions. Therefore, repeated measures analysis was again applied to the data, but now with *Light/Darkness* as a between-groups factor. No significant differences were found between the groups for any variable.

Driving Performance in the Car Following Test

All subjects were capable of performing the car following test in each treatment condition. There was no need for the driving instructors to ever intervene or prematurely terminate the test. In one instance, a subject needed the driving instructor's help after smoking the highest THC dose. The subject appeared confused when he took his seat in the car prior to the first car following test. The driving instructor noticed the subject's uncertainty as to what he should do and advised him to turn the engine on. Thereafter, the subject had no problems following the instructions and completing the ride.

Mean headway varied between conditions from 44.5 to 54.9 m (146 to 180 ft); changes relative to placebo are shown in Figure 5.4. It is interesting to note the inverse relationship between THC dose and headway: the lower the dose the greater the headway, especially in the first test after smoking. MANOVA showed that mean headway was significantly increased after smoking the lowest THC dose, relative to placebo ($F_{1,13}=7.57$; $p<.016$; $p_c=.017$); the two higher doses had no significant effect on headway. No significant *Time* or *Drug by Time* effects were found in either THC condition.

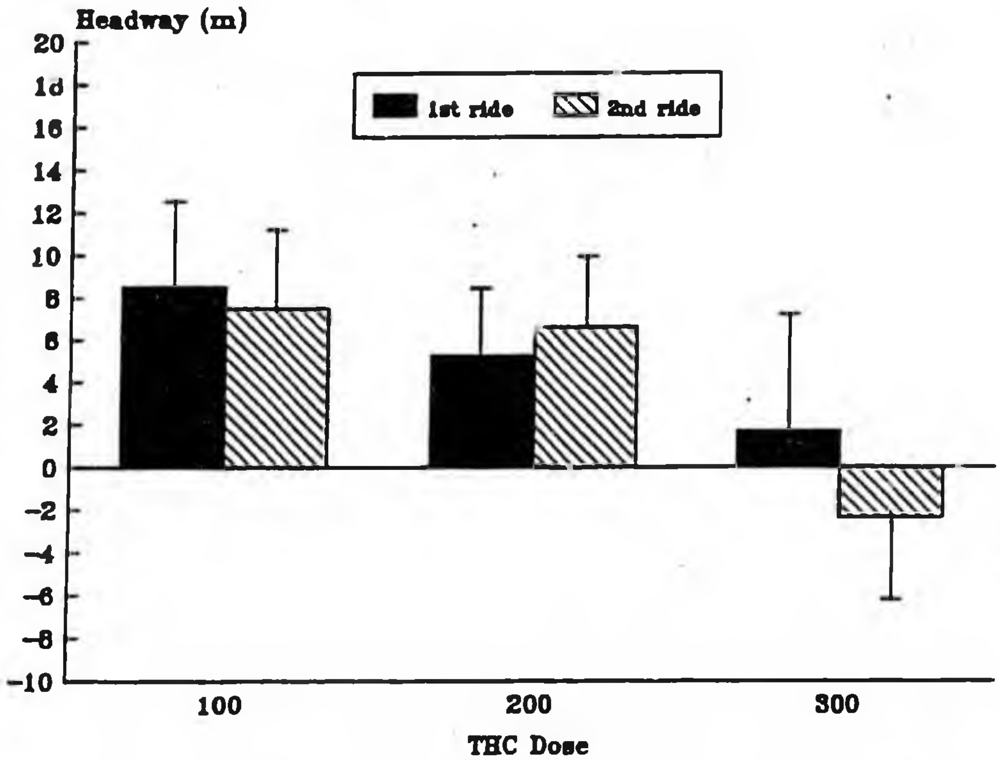

Figure 5.4 Mean (+SEM) changes in headway in the car following test by *Drug* and *Time*, relative to placebo.

Coefficients of variation of headway, expressed as a percentage, were high and varied between conditions from 18.8% to 23.7%. Figure 5.5 shows an inverse relationship between CV-Headway and administered dose, with the exception of the first ride after the highest dose. MANOVA revealed a significant effect following the lowest dose ($F_{1,13}=16.62$; $p<.001$;

p_c=.017), but not the higher doses. *Drug by Time* interaction approached significance following the highest dose ($F_{1,13}$=4.85; $p<.046$; p_c=.017); 300 µg/kg THC produced an increased headway variability in the first test afte smoking, but not in the second.

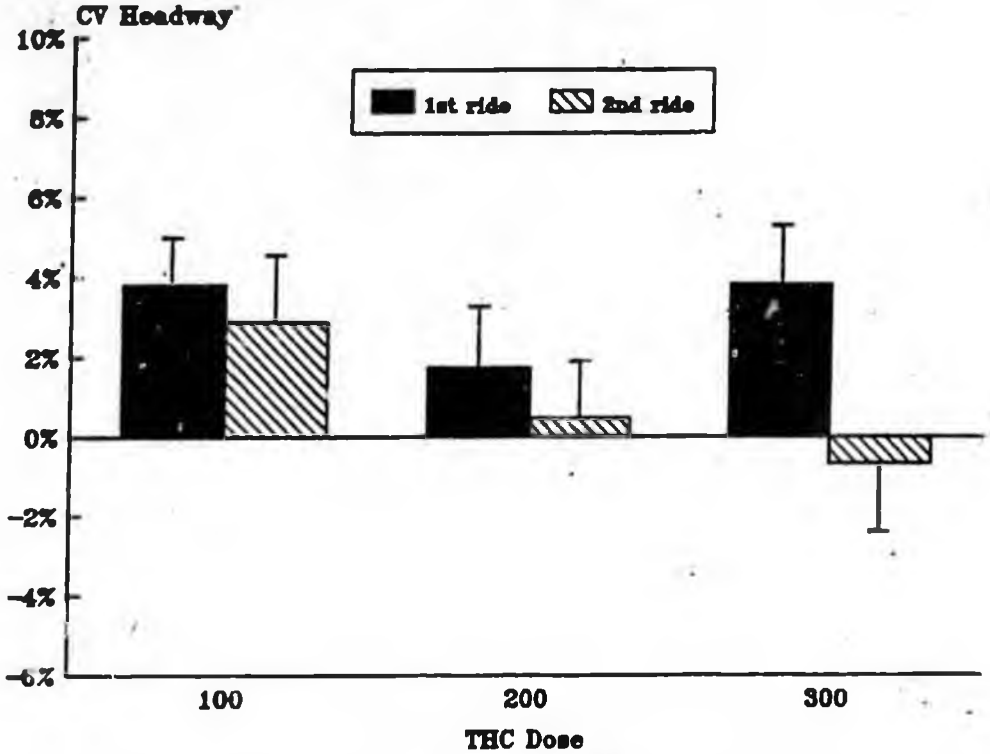

Figure 5.5 Mean (+SED) changes in coefficient of variation of headway in the car following test by *Drug* and *Time*, relative to placebo.

Mean reaction time to perceived changes in the preceding car's speed varied from 1.56 to 2.30 s, between conditions. The changes, shown in Figure 5.6, followed a similar pattern as those of headway; the greatest increase of reaction time occurred after the lowest THC dose, and the smallest after the highest dose. Reaction times were significantly increased after smoking both 100 µg/kg and 200 µg/kg THC, but not 300 µg/kg ($F_{1,13}$=10.78, 6.26 & 1.8, respectively; $p<.006$, .027 & .193; p_c=.017, .025 & .05). Reaction times were, however, strongly related to mean distance (r=0.76, across all conditions). This is understandable: the further apart two cars are, the more difficult it becomes for the subject to perceive changes in the preceding vehicle's velocity.

One may question what the effect of THC on reaction time would have been if subjects had driven at the same mean headway in all conditions? Covariance analysis of reaction time with headway as covariate was applied to answer this question. Figure 5.7 shows the mean changes in adjusted reaction times, from placebo levels. The figure makes clear that the differences in the adjusted reaction times were much less than those in the original ones. Though each THC dose increased reaction time, none did significantly. This means that the elevation in the raw reaction times following the lowest THC dose were simply due to a longer headway.

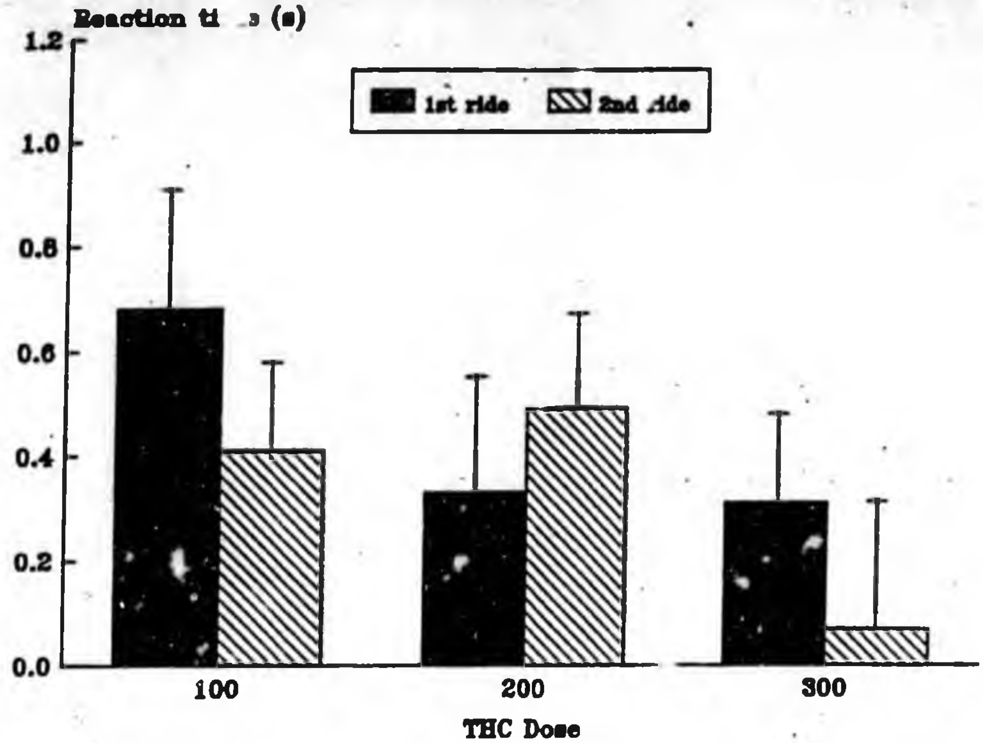

Figure 5.6 Mean (+SED) changes in reaction time in the car following test by *Drug* and *Time*, relative to placebo.

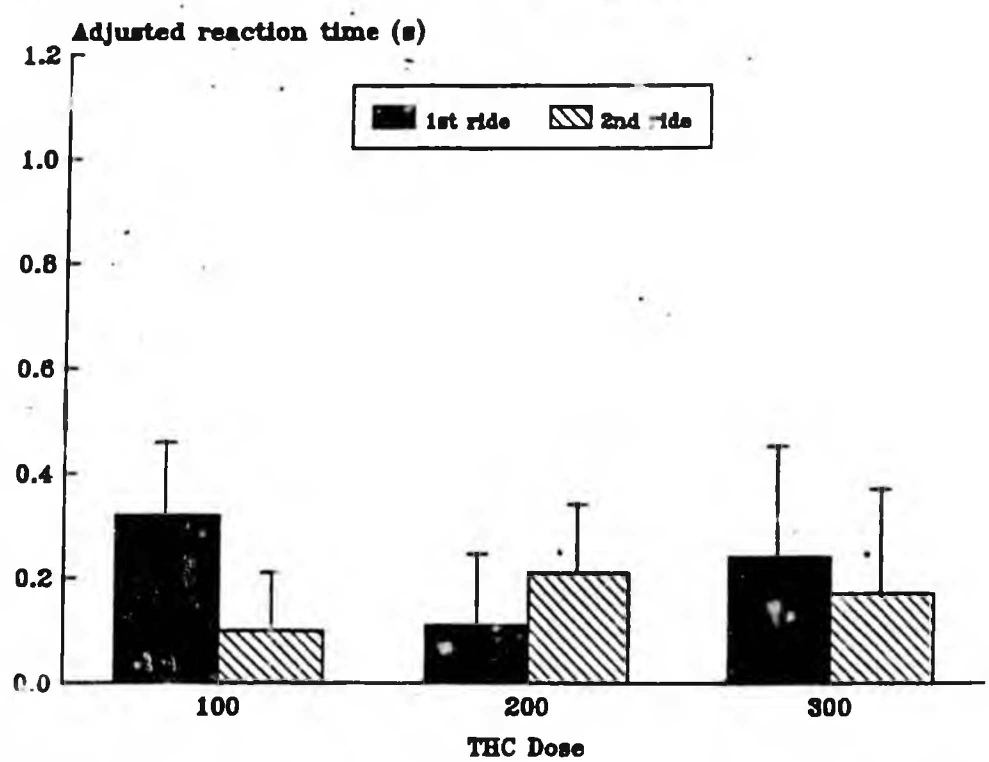

Figure 5.7 Mean (+SED) changes in reaction time, adjusted for changes in headway, in the car following test by *Drug* and *Time*, relative to placebo.

Subjects rated their driving quality in the car following test as somewhat better than normal following each placebo, and worse following each THC dose. Changes from placebo to drug are displayed in Figure 5.8. As for headway and reaction time, there was no clear dose-response

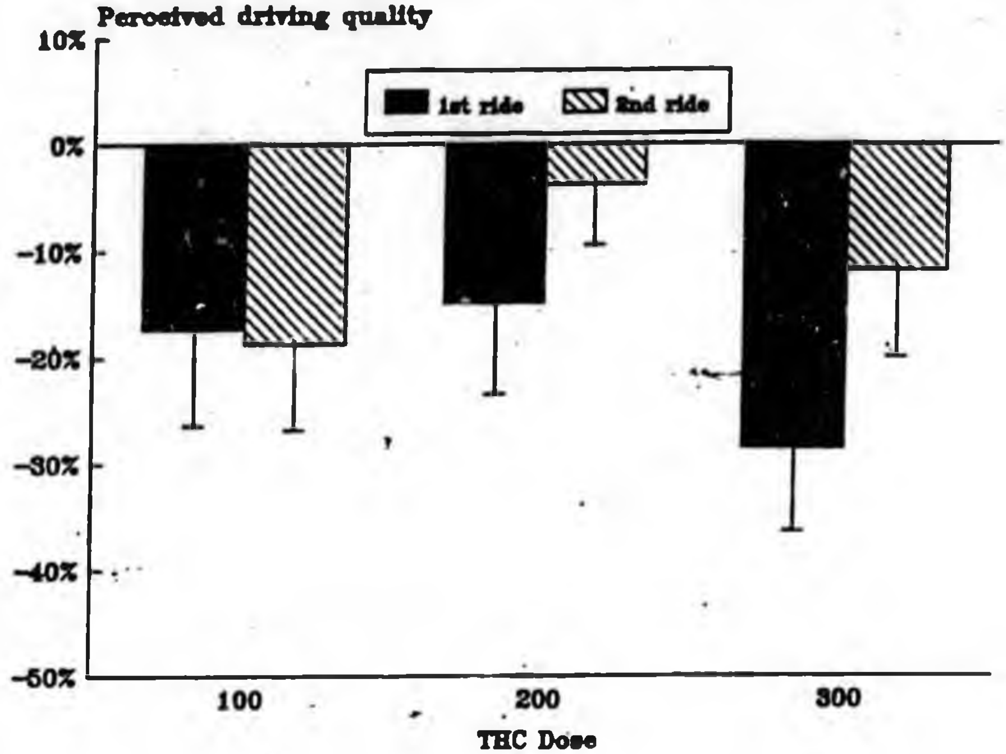

Figure 5.8 Mean (+SED) changes in perceived driving quality in the car following test by *Drug* and *Time*, relative to placebo. Raw scores were expressed as percentage of "normal".

relationship that determined how subjects rated their driving quality. Though they rated it the worst after the highest dose overall their judgement after the lowest dose was nearly as critical. MANOVA demonstrated that driving quality ratings after the highest dose were significantly different from placebo, but those after the lower doses were not ($F_{1,13}$=6.04, 3.19 & 13.84, for the 100, 200 and 300 µg/kg conditions, respectively; $p<.029$, .097 & .003; $p_c=.025$, .05 & .017). Neither *Time* nor *Drug by Time* effects were significant.

Though perceived effort ratings were generally higher following THC than placebo, MANOVA failed to show any significant drug effect.

Willingness to Drive

Table 5.5 presents the percentage of subjects willing to drive under specified conditions of different urgencies (***A.*** unimportant though gratifying; ***B.*** important but avoidable; and ***C.*** urgent). Subjects' responses were similar to those in the previous study. The lower the administered THC dose and the more urgent the reason for driving, the more subjects declared that they would be willing to drive.

Table 5.5 Percentage of subjects willing to drive under circumstances *A*, *B* & *C* (see text) by treatment condition and sampling time.

		0 μg/kg	100 μg/kg	0 μg/kg	200 μg/kg	0 μg/kg	300 μg/kg
A	*t*=50	93	53	93	47	93	27
	t=175	93	80	80	87	93	53
B	*t*=50	100	73	100	60	100	40
	t=175	100	80	100	100	100	67
C	*t*=50	100	93	100	93	100	73
	t=175	100	93	100	93	100	87

Cochran's test showed that the numbers of subjects who would have driven for an unimportant reason following every THC dose were significantly less than after placebo ($Q_{df=3}$=12.0, 13.4 & 21.6 for the 100, 200 and 300 μg/kg conditions, respectively; p<.008, .004 & .0001; p_c=.05, .025 & .017). The same held true for the somewhat more important reason ($Q_{df=3}$=10.2, 18.0 & 21.4 for the 100, 200 and 300 μg/kg conditions, respectively; p<.02, .0004 & .0001; p_c=.05, .025 & .017). In contrast, the numbers of subjects who would have driven for an urgent reason after every THC dose were not significantly different from placebo ($Q_{df=3}$=3.0, 3.0 & 9.4 for the 100, 200 and 300 μg/kg conditions, respectively; p<.40, .40 & .024; p_c=.05, .025 & .017).

Perceived Alertness, Contentedness and Calmness

Table 5.6 shows the mean subjective ratings of alertness, contentedness and calmness, presented as the percentage of maximum scale. Mean subjective ratings generally declined after smoking marijuana, relative to placebo, indicating that subjects then felt less alert, content and calm. MANOVA showed that subjects felt significantly less alert after smoking THC ($F_{1,13}$=12.57, 6.48 & 21.24 for the 100, 200 and 300 μg/kg conditions, respectively; p<.004, .024 & .001; p_c=.025, .05 & .017). Furthermore, a significant *Drug by Time* interaction was found for the 100 μg/kg condition ($F_{1,13}$=13.78; p<.003; p_c=.017), due to the recovery in feelings of alertness from the first to the second time of testing.

Contentedness ratings were only significantly reduced after smoking the highest THC dose ($F_{1,13}$=10.20; p<.007; p_c=.017). *Drug by Time* interaction was significant in the 100 μg/kg condition ($F_{1,13}$=7.71; p<.016; p_c=.017). Calmness ratings also declined after the higher THC doses ($F_{1,13}$=6.05 & 14.65 for the 200 and 300 μg/kg conditions, respectively; p<.029 & .002; p_c=.025 & .017), and *Drug by Time* interaction approached significance in all conditions ($F_{1,13}$=4.33, 6.62 & 5.10 for the 100, 200 and 300 μg/kg conditions, respectively; p<.058, .023 & .042; p_c=.05, .017 & .025).

In summary, subjects felt less alert, content and calm after smoking each THC dose, relative to placebo. The effects were strongest and persisted throughout the testing session after smoking the highest dose.

Table 5.6 Mean (SE) ratings of alertness, contentedness, and calmness by treatment condition and sampling time.

		0 μg/kg	100 μg/kg	0 μg/kg	200 μg/kg	0 μg/kg	300 μg/kg
Alert	t=50	78.3 (3.7)	59.0 (4.3)	76.0 (4.4)	63.9 (4.1)	80.0 (3.4)	57.7 (4.6)
	t=175	69.6 (5.0)	64.7 (4.9)	72.4 (5.5)	66.1 (3.6)	70.6 (4.3)	56.9 (6.2)
Content	t=50	79.3 (2.7)	66.2 (5.1)	77.6 (3.3)	73.6 (3.6)	78.3 (3.4)	67.2 (4.4)
	t=175	72.4 (3.4)	70.3 (4.3)	74.9 (4.4)	73.1 (3.5)	76.7 (3.2)	65.7 (4.9)
Calm	t=50	78.2 (4.2)	64.2 (5.2)	79.5 (4.4)	61.7 (6.8)	79.5 (3.6)	59.6 (5.8)
	t=175	72.5 (5.0)	72.4 (3.8)	75.9 (4.1)	71.3 (4.0)	77.5 (3.5)	70.5 (4.8)

Critical Tracking Test

As shown in Figure 5.9, mean λ_c measured 30 minutes after initiation of smoking diminished in a dose-related manner. Measured 3¼ hours after initiation of smoking, λ_c remained low after

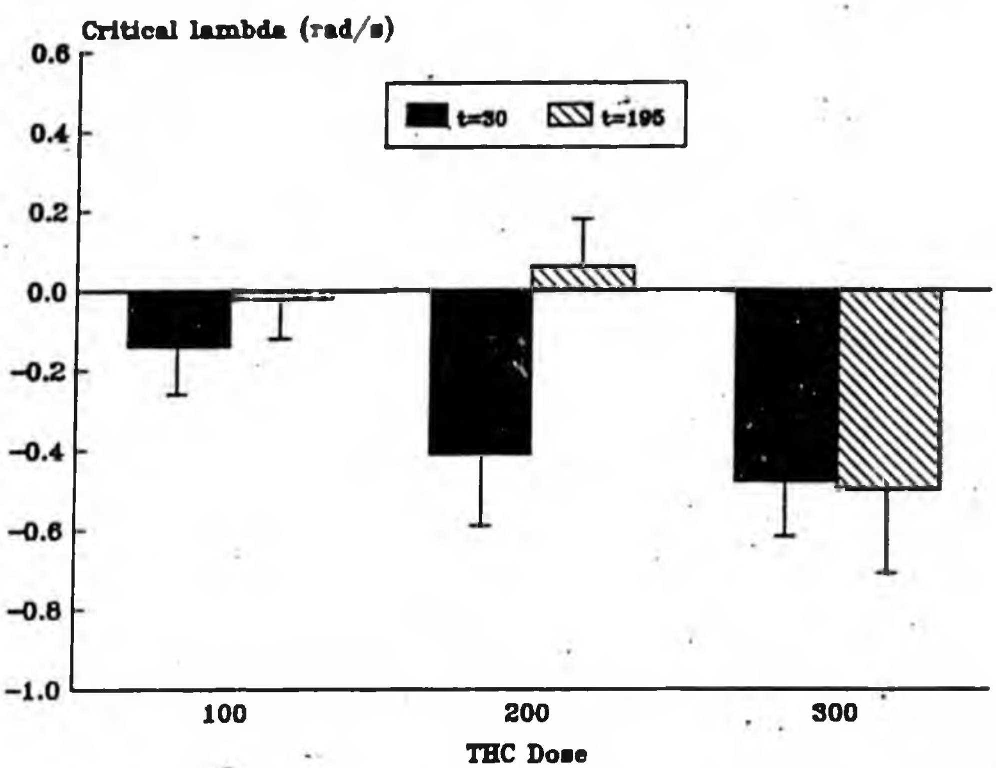

Figure 5.9 Mean (+SED) changes in λ_c in the critical tracking test by *Drug* and *Time*, relative to placebo.

the highest, but not the two lower doses. The lowest THC dose did not affect λ_c significantly. A nearly significant *Drug by Time* interaction was found in the 200 μg/kg condition ($F_{1,13}$=4.69; $p<.05$; $p_c=.017$); i.e. that dose diminished λ_c shortly after smoking, but the effect dissipated after three hours. The highest dose had a significant effect on λ_c ($F_{1,13}=9.03$; $p<.01$; $p_c=.017$), both shortly after smoking and three hours later.

Hand Steadiness Test

Hand steadiness diminished in relation to the dose after marijuana smoking (Figure 5.10). All doses produced significantly greater instability ($F_{1,13}=6.72$, 13.05 & 45.33 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.022$, .003 & .001; $p_c=.05$, .025 & .017).

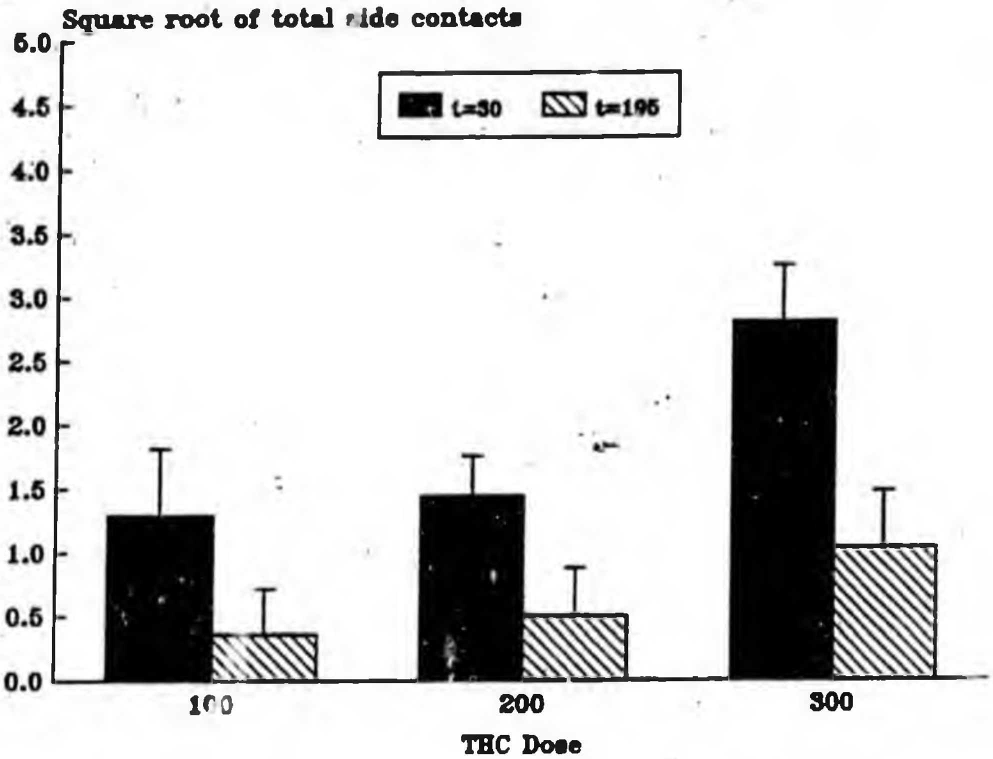

Figure 5.10 Mean (+SED) changes in the square root of total number of side contacts in the hand steadiness test by *Drug* and *Time*, relative to placebo.

Instability diminished after three hours, irrespective of the dose, resulting in significant *Time* effects in each drug-placebo comparison. *Drug by Time* interaction was not significant after the lowest dose, but approached significance after the higher doses ($F_{1,13}=4.51$ & 6.28 for the 200 and 300 μg/kg conditions, respectively; $p<.053$ & .026; $p_c=.025$ & .017).

Body Sway

Mean values for the area circumscribed by the vertical vector of force (i.e. curve surface) are displayed in Table 5.7. Curve surface for subjects standing with eyes-open (CS-O) increased after THC, relative to placebo. These effects approached significance ($F_{1,13}=4.67$, 5.20 & 4.95 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.050$, .040 & .044; $p_c=.050$, .017 & .025). The greatest change from placebo to marijuana smoking was observed in the 200 μg/kg condition, but only in the first test after smoking, resulting in a significant *Drug by Time* interaction ($F_{1,13}$=9.23; $p<.015$; p_c=.017).

Table 5.7 Mean (SE) curve surface (mm^2) in the body sway test, both with eyes open (CS-O) and closed (CS-C), by treatment condition and sampling time.

		0 μg/kg	100 μg/kg	0 μg/kg	200 μg/kg	0 μg/kg	300 μg/kg
CS-O	t=50	29.2 (4.5)	38.7 (4.8)	26.7 (3.2)	42.3 (4.4)	32.9 (4.0)	39.1 (4.3)
	t=175	32.1 (3.8)	43.3 (5.4)	35.5 (5.7)	37.3 (4.8)	31.7 (4.1)	38.5 (3.5)
CS-C	t=50	27.9 (3.9)	53.0 (8.6)	33.7 (6.8)	55.2 (8.8)	36.1 (6.2)	57.7 (11.2)
	t=175	43.3 (6.5)	43.9 (8.3)	40.1 (7.7)	35.2 (5.4)	32.0 (5.5)	36.3 (5.6)

Mean curve surface for the subjects standing with eyes closed (CS-C), increased markedly in the first but not in the second test. The main effect of *Drug* approached significance ($p<.10$) in all three conditions, but *Drug by Time* interactions were significant for the two lower THC doses ($F_{1,13}$=8.86, 7.82 & 3.55 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.011$, .015 & .082; p_c=.017, .025 & .05). Analysis of variance of only the first measurements after smoking revealed that curve surface increased significantly after all THC doses, relative to placebo ($F_{1,14}$=8.66, 10.45 & 4.96 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.011$, .006 & .043; p_c=.025, .017 & .05).

In summary, body sway was affected by all three THC doses, but this effect had dissipated three hours after smoking. Body sway parameters did not discriminate between different THC doses.

Heart Rate

ECG data could not be obtained from every subject in all conditions due to recurrent equipment failures. Though the problem was solved in time to obtain complete data from all 15 subjects in the highest dose conditions, analyses could only be conducted using data from 14 and 9 subjects in the middle- and low-dose conditions. The results of those analyses are summarized in Tables 5.8 and 5.9 for the standard and car following tests, respectively.

Both tables show that driving under the influence of THC is accompanied by shorter interbeat intervals (i.e. increased heart rates) and decreased variation both in the time domain (CV-IBI) and frequency domain between 0.07 and 0.14 Hz (PWR-HR). No clear dose-response relationship was found, except in mean IBI in the car following test.

With respect to the standard driving test, MANOVA showed that all THC doses produced significantly shorter IBIs relative to placebo ($F_{1,7}$=9.07, $F_{1,12}$=7.63 & $F_{1,13}$=21.61 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.02$, .017 & .001; p_c=.05, .025 & .017). CV-IBI was significantly diminished after the two higher doses ($F_{1,12}$=11.52 & $F_{1,13}$=28.90 for the 200 and 300 μg/kg conditions, respectively; $p<.005$ & .001; p_c=.025 & .017), but not the lowest. PWR-HR, on the other hand, was significantly diminished by all THC doses ($F_{1,7}$=18.62 $F_{1,12}$=12.20 & $F_{1,13}$=28.47 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.004$,

.004 & .001; p_c = .025, .05 & .017). Thus, the more specific measure, PWR-HR, which includes only one source of heart rate variability, is more sensitive to THC's effects than CV-IBI, a measure of total variability. In conclusion, both mean IBI and heart rate variability were significantly reduced by all THC doses. Since the latter measure is interpreted as a parameter of mental effort, it can be concluded that subjects needed to invest more effort in driving after smoking marijuana than after placebo.

Table 5.8 Mean interbeat interval time (IBI), coefficient of variation of IBI (CV-IBI), and power density of heart rate (PWR-HR) in the frequency band between 0.07 and 0.14 Hz during the standard driving test.

	N=9		N=14		N=15	
	0 μg/kg	100 μg/kg	0 μg/kg	200 μg/kg	0 μg/kg	300 μg/kg
IBI (ms)	792	721	805	743	797	709
CV-IBI (%)	5.97	4.91	5.40	4.48	5.41	4.15
PWR-HR	1114	666	877	570	862	499

With respect to the car following tests, MANOVA showed that mean IBI decreased significantly after the two higher doses ($F_{1,9}$=9.66 & $F_{1,7}$=26.24 for the 200 and 300 μg/kg conditions, respectively; $p<.013$ & .001; p_c=.025 & .017), but not after the lowest. Mean IBI was always larger during the second ride relative to the first resulting in a significant *Time* effect in all conditions ($F_{1,9}$=52.92, $F_{1,9}$=57.02 & $F_{1,7}$=79.07 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.001$, .001 & .001; p_c= .05, .025 & .017). *Drug by Time* interaction was not significant. This means that subjects were more relaxed when they performed the second than the first car following test, whether they had inhaled THC or placebo.

Table 5.9 Mean interbeat interval time (IBI), coefficient of variation of IBI (CV-IBI), and power density of heart rate (PWR-HR) in the frequency band between 0.07 and 0.14 Hz during the car following tests. Data from the first and second tests are separated by a slash.

	N=9		N=14		N=15	
	0 μg/kg	100 μg/kg	0 μg/kg	200 μg/kg	0 μg/kg	300 μg/kg
IBI (ms)	739/821	697/801	778/859	697/790	750/841	646/755
CV-IBI (%)	5.48/6.31	4.69/4.86	5.18/5.83	3.85/5.25	4.67/5.41	4.05/4.57
PWR-HR	983/1347	608/807	909/1094	438/967	726/993	405/633

CV-IBI was diminished after smoking THC in each condition relative to placebo and these effects were only nearly significant ($F_{1,9}$=7.09, $F_{1,9}$=8.40 & $F_{1,7}$=6.21 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.026$, .018 & .041; p_c=.025, .017 & .05). As in the standard test, PWR-HR was more sensitive to drug induced variability reduction; MANOVA showed that PWR-HR was significantly affected by all doses ($F_{1,9}$=10.46, $F_{1,9}$=6.04 & $F_{1,7}$=9.01 for the 100, 200 and 300 μg/kg conditions, respectively; $p<.010$, .036 & .020; p_c=.017, .05 & .025). Though PWR-HR was generally higher in the second than in the first test, a significant *Time* effect was only found in the 200 μg/kg condition ($F_{1,9}$=8.58; $p<.0168$; p_c=.017). Though subjects felt more relaxed in the second car following test than the first, as measured by IBI, both rides required much the same mental effort, as measured by heart rate variability.

Intra-Subject Relations between Variables

The average intra-subject correlation between [THC] and perceived "high" was, as in the previous study, very high (R=0.90; $p<.01$). The correlation between measured SDLP and [THC] measured before driving was 0.63 ($p<.05$), individual correlations ranging from -.14 to .96; between SDLP and [THC] measured after driving 0.57 ($p<.05$), individual correlations ranging from -.10 to .92. These correlations closely resemble those found in the previous study where SDLP correlated 0.59 and 0.42 in the first and second tests, respectively. This means that the change in driving performance, as measured by SDLP in the standard driving test, is, within individuals, moderately related to the existing [THC]. Performance in the car following test was not significantly correlated with [THC].

The square root of the number of side contacts in the hand steadiness test was significantly correlated to [THC] and perceived "high" (both $r=.66$; $p<.01$). SDLP scores were significantly related to hand instability measured before driving ($r=.52$; $p<.05$), but not with scores obtained after driving ($r=.35$; ns). None of the other laboratory performance measures were either related to plasma concentrations of the drug or to driving performance.

In summary, as [THC] varied within a given individual so did that individual's perceived "high", hand steadiness and SDLP or road tracking error in the standard test.

Inter-Subject Relations between Variables

<u>Relationship between Drug Levels and Performance</u>. Inter-subject correlational analysis between [THC] and [THC-COOH] on one hand and performance parameters on the other failed to reveal any consistent relationship. The most consistent, yet still not strong, relationships found were those involving [THC] on one hand and mean speed in the standard driving test and CTT performance in the laboratory on the other (Table 5.10). Correlations with Log [THC] were generally the same as with [THC]; those with [THC-COOH] were, except a few, generally lower than those with [THC].

The correlations presented in Table 5.10 were derived from raw scores. Another question is whether changes in performance from corresponding placebo levels were related to prevailing [THC]. Correlational analyses showed, however, that these correlations were even smaller than those with the raw scores. Thus, neither [THC] nor [THC-COOH] predicted performance or performance impairment.

Table 5.10 Correlations between [THC] and raw performance scores in the marijuana conditions. If performance was measured only once (like SDLP), then the same scores were correlated with [THC] values as measured before and after the driving tests.

	100 μg/kg		200 μg/kg		300 μg/kg	
	1st	2nd	1st	2nd	1st	2nd
Standard Driving Test:						
SDLP	-.33	.02	-.13	.09	-.25	-.18
SP	-.26	-.18	-.50	-.20	-.55*	-.61
SDSP	-.22	-.14	-.34	-.32	-.20	-.15
Car Following Test:						
Adjusted RT	-.18	.20	.41	.24	.04	.05
Headway	.32	.15	.39	-.02	.18	.05
CV-Headway	-.21	.40	.27	.43	-.29	-.09
Laboratory Tests:						
λ_c	.63*	.31	.48	.27	.45	.18
Side Contacts	.45*	-.38	.54*	.32	.44	.50
OC-O	-.25	-.13	.43	.02	-.38	.06
OC-C	-.05	-.02	.36	-.25	-.26	-.37

Relationship between Driving Impairment and Willingness to Drive. In general, the average road tracking impairment in the standard test of those subjects, who indicated before the driving tests commenced that they would normally not have driven under the imagined circumstances, was greater than of those who would have driven. Statistically, these effects were neither significant when willingness to drive for "unimportant though gratifying" reasons was used as the grouping factor, nor when willingness to drive for "urgent" reasons was used. This was probably due to the small number of subjects who would not have driven under the former condition, and would have driven under the latter condition. When willingness to drive for "important, but avoidable" reasons was used as the grouping factor, no significant difference in road tracking impairment was found between the groups after the highest THC dose; but, following the two lower doses, subjects who would not have driven were significantly more impaired than those who would have driven ($F_{1,13}$=10.38 & 6.93 for the 100 and 200 μg/kg conditions, respectively; $p<.007$ & .021; p_c=.017 & .025).

Relationship between Driving Performance and Other Measures. In the previous study, SDLP was moderately correlated with λ_c from the CTT. The present study showed the same pattern of correlations i.e. -.41 and -.50 in the 100 μg/kg condition, -.49 and -.37 in the 200 μg/kg condition, and -.58 ($p<.05$) and -.54 ($p<.05$) in the 300 μg/kg condition. Despite the interesting theoretical aspects of these consistent results, correlations of such magnitude are generally considered too low for predictive purposes. Performance in the car following test was not significantly correlated with λ_c. Neither hand steadiness nor body sway were related to performance in the standard driving test or the car following test.

As in the previous study, repeated measures analysis of SDLP in the standard test was repeated with reported *Frequency* of cannabis smoking as a between-subjects factor. MANOVA failed to reveal any significant effect.

The relationship between test performance and previous experience of driving under the influence could not be determined: too few indicated having driven in that condition more than a few times (Table 5.1).

DISCUSSION

The conservative approach of administering THC according to an ascending, placebo controlled, dose series achieved its purpose of ensuring the subjects' safety. All were able to complete the series without suffering any untoward reaction while driving. However it is fair to ask whether this approach could have conceivably biased the results toward minimization of the drug's effects. We have three reasons for believing that this was not the case. Driving performance during successive repetitions of the standard highway driving test after placebo smoking was relatively constant, so that the reference for judging effects of every dose's effects was essentially the same. The measured mean changes in SDLP after the lowest and highest THC doses in the present study were about what they had been in the previous study where dose orders were counterbalanced. Finally, there was apparently one dose sequence effect on car following performance but it was the opposite of any which could bias the results toward minimizing THC's effects. Such a bias would have existed if the subjects choose to operate more cautiously as doses ascended. Yet as described below, they appeared to operate most cautiously in the car following test after the lowest dose. If any bias existed in this test it was toward maximizing, rather than minimizing THC effects.

Road tracking performance in the standard test was impaired in a dose-related manner by THC. The 100 μg/kg dose produced a slight elevation in mean SDLP (1.1 cm), albeit nearly significant. The 200 μg/kg dose produced a significant elevation (1.8 cm), of dubious practical relevance. The 300 μg/kg dose produced a highly significant elevation (2.9 cm) which may be viewed as practically relevant but unexceptional in comparison with similarly measured effects of many medicinal drugs.

For example, diazepam given for one week in its lowest therapeutic dose (5 mg, thrice daily) caused anxious patients to drive with a mean SDLP about 7 cm higher than their premedication baseline (Van Laar *et al.*, 1992). Furthermore, THC's effects on SDLP were, after the 100, 200 and 300 μg/kg doses in this study, about the same as those of BACs = 0.02, 0.04 and 0.06 g% according to the empirical equation described by Louwerens *et al.* (1985, 1987). The comparison reinforces our impression of the relevance of SDLP changes after THC. The two lower doses produced elevations less than the lowest BAC associated with intoxication and an elevated risk of causing a traffic accident (i.e. 0.05 g%; Borkenstein *et al.*, 1964; Council on Scientific Affairs, 1985), whereas the highest dose, and one preferred by the drug's users, produced a marginally greater elevation. But even this change in SDLP can not, by itself, be taken to indicate exceptional impairment.

It is often reported that subjects compensate for THC's adverse effects on driving abilities by operating at slower than normal speeds, especially through curves or slaloms. Our subjects were instructed to maintain a speed of 95 km/h (58 mph) unless compelled to slow down for safety reasons. Following marijuana smoking they drove with an average speed that was only slightly lower (maximum, 1 km/h or 0.6 mph) than after placebo and very close to the prescribed level. They apparently felt that it was within their capability to safely perform this relatively simple task while operating at the normal highway speed.

The objective of confirming results obtained in the previous closed highway study was achieved in this one. It should be recalled that subjects' SDLPs were measured twice on the former occasion; i.e. in 22 km (13.7 mi) trials beginning 40 and 100 minutes after the initiation of smoking. The timing of the second trial most closely corresponded to that in the present study so their respective results will serve as the basis for comparison. Mean SDLP elevations after the lowest and highest doses differed little between the two studies: 100 μg/kg, 1.4 and 1.1 cm; and 300 μg/kg, 2.4 and 2.9 cm, respectively. Mean SDLP elevations after the 200 μg/kg dose differed somewhat between studies, being 3.3 cm in the first case and 1.8 in the second. Yet the results of the first study were anomalous in two respects. Not only did the former group's reaction in the 2nd trial exceed that in the 1st trial following the 200 μg/kg dose, it was also greater than their 2nd trial reaction after the 300 μg/kg dose. Both results were in contradiction to plasma THC concentrations measured at these times. Thus the peculiar elevation in mean SDLP during the 2nd trial after the intermediate dose was probably a consequence of sampling error. That it was not replicated in the present study should dispel any notions to the contrary.

The car following test was implemented for the first time in the present study. In it, subjects maintained a headway of 45-50 m (148-164 ft) while driving in the successive placebo conditions. They lengthened mean headway by 8, 6 and 2 m (26.2, 19.7 and 6.6 ft) in the corresponding THC conditions after 100, 200 and 300 μg/kg, respectively. The initially large drug-placebo difference and its subsequent decline is a surprising result in need of an explanation. If one considers that changes in headway after THC results from impaired distance perception, the inverse relationship between administered dose and mean headway defies explanation. But if one considers these differences as the results of the subjects' caution in approaching the task under the influence of THC on successive occasions, another explanation seems plausible.

Performing the car following test in the company of investigators while under the influence of THC was a novel experience for all subjects. Neither the investigators nor the subjects could predict how the latter would be able to operate the vehicle. The former were somewhat apprehensive and it would not be surprising if the latter were also, particularly, on the first occasion the test was performed after THC inhalation. Subjects were required to match their vehicle's speed with that of the preceding vehicle's and so were unable to reduce velocity as a compensatory action. They could however maintain a longer headway and thereby slightly increase their margin of safety which might be needed if THC retarded their reactions. We believe they did so after receiving the lowest THC dose. When nothing untoward happened and the subjects' confidence in their ability to control the vehicle grew, they apparently tended to diminish headway after each of the succeeding doses so that it came progressively closer to the distance measured after all of the placebo treatments. Thus our explanation for the initial difference between headways maintained after THC and placebo, and why it diminished in subsequent pairs of these conditions, is that the subjects' caution was greatest the first time they undertook the test under the influence of THC and progressively less thereafter.

The only other plausible explanation is that lower THC doses induce a greater sense of caution than higher doses. There is of course no way to determine which of the two explanations is valid from the results of this study. But the fact that the subjects reported feeling less calm and content as the doses increased seems to contradict the notion that they simultaneously became less cautious. Whatever explanation is favored, it is clear that large doses of THC have little effect on mean headway during car following.

Reaction time to changes in the preceding vehicle's speed increased following THC treatment, relative to placebo. The administered THC dose was inversely related to the change in reaction time, as it was to headway. Mean increases in reaction time were 0.55, 0.41 and 0.19 s following the 100, 200 and 300 μg/kg dose, respectively. However, reaction time data were confounded with headway. That is, increased reaction times were partly due to longer headway. Statistical adjustment for this confounding resulted in smaller and non-significant increases in reaction time following marijuana treatment, the greatest impairment (0.32 s) being observed in the first test following the lowest THC dose. Headway variability followed a similar pattern as mean headway and reaction time; the greatest impairment was found following the lowest dose.

A secondary objective of the study was to determine whether degrees of impairment would correlate between the two tests in a manner indicating a general influence of THC on driving behavior. The results obtained in this study showed that this was not the case; a significant dose-related impairment was found with road tracking, but not with car following. Test duration can not have been the critical point, since the standard test in the previous study was of the same duration as the present car following test.

The car following test was both less sensitive and reliable than it could be following the removal of certain procedural flaws. Intervals between successive maneuvers were practically constant and the preceding vehicle's deceleration was both abrupt an stereotyped. Thus the occurrence and nature of the maneuvers were highly predictable for the subjects.

Greater irregularity in both the timing of maneuvers and the profile of velocity changes would probably increase the sensitivity of the test. After the fact we recognized that the indirect and discontinuous method used for measuring headway produced a degree of error variance which appreciably reduced the reliability of these data. Equipment has become available since the initiation of this study which now makes it possible to measure headway directly and continuously (i.e. an inexpensive pulsed laser reflection recording system). Use of this equipment should increase the reliability of headway measurement in future applications of this test. Finally, the greatest source of error variance was the procedure of allowing the subject to assume, within limits, whatever headway he/she chooses. Whether this is a flaw or not depends upon one's desire to measure or control headway at the beginning of maneuvers. However the subject's choice of headway is certainly a factor which inflates reaction time error variance. Adjusting the data statistically to overcome the confounding effect of headway on reaction time is only a partial solution to the problem. We would probably have been wiser to strictly enforce headway control in order to increase the reliability of reaction time measurements and their sensitivity to drug effects.

Without trying to minimize the impact of procedural errors on the data, it is doubtful whether any flaw or all in combination seriously obscured a practically important THC effect. SDLP recorded in the standard highway driving test was about as sensitive to low-dose THC effects as any of the traditional laboratory performance measures taken in the study. Moreover the average intra-subject correlation between [THC] and SDLP was as high or higher than any measured between the drug's plasma concentration and another performance variable. This relationship could not have been measured if SDLP were not one of the most sensitive parameters known for measuring the effects of THC. The fact that car following performance was less sensitive does not mean that it would have failed to reveal effects of practical importance if these truly existed. SDLP showed no such effects even after the highest dose.

The reasons why SDLP and not car following performance showed the modest impairing effects of THC may have less to do with the inadequacy of the latter test than to the difference between what the two tests measure. SDLP is controlled by a very fast and high capacity human information processing system which operates in a wholly "automatic" manner. That is, outside of conscious control. The process is relatively impervious to environmental changes as shown again by the high reliability of SDLP under repeated placebo conditions in the present study. It is, however, highly vulnerable to internal factors that retard the flow of information through the system. THC and other drugs are among these factors. When they interfere with the process to elevate SDLP there is very little the afflicted individual can do in way of compensation. Car following performance on the other hand depends upon more discrete perception of events leading to a conscious decision, a response selection and its execution. Performing the test involves far more sustained attention and conscious effort than does road tracking in the standard test. Because car following performance is under conscious control and well within the speed limitations of "cognitive" compensatory mechanisms it is possible for individuals to recognize their deficiencies and correct them by effort that increases attention. In short, any deficiencies that THC might have otherwise produced may have been overcome by the subjects' compensatory effort. The cost of effort focused on accomplishing a task is however accompanied by less capacity left for performing another in parallel. The subjects indeed related that their investment of effort in the first car following test increased with the administered dose, and relative to corresponding placebo levels, more so than in the standard driving test. Though these differences were not statistically significant in either case, they were in line with the significant reduction in heart rate variability, that occurred independently of mean rate changes after every THC dose, including the lowest. Together the findings support the premise that THC increases the requirement for compensatory effort during car following which maintains constant performance, but possibly reduces the capacity for undertaking any activity in parallel. Coupled with THC's reputably adverse effect on the ability to divide attention between tasks performed simultaneously (Smiley, 1986), the net effect might constitute a more serious impediment to safe driving than any observed in this study. It will be interesting to explore this possibility in further research.

Subjects' report of their willingness to drive under specified conditions of different urgencies were similar to those in the previous study. The lower the administered THC dose, and the more urgent the reason for driving, the more subjects declared that they would be willing to drive. Furthermore, there was a tendency for subjects who would normally not have driven to be more impaired in road tracking than those who would. Apparently these subjects recognized their respective degrees of impairment while under the influence of every THC dose. This is supported by the subjects' judgments of their own driving quality which changed in a realistic dose related manner after marijuana smoking.

Critical tracking and hand steadiness tests were more sensitive to THC induced impairment than in the previous study. This confirms our impression that the earlier CTT version was poorly conceived. It also indicates that applying the correct procedures for measuring hand steadiness is very important; i.e. subjects should not be allowed to rest their hand on the table while performing the test. Both tests showed dose-related impairment shortly after cessation of smoking. When the tests were repeated three hours later, hand instability was still present though to a lesser degree. The effect of the highest but not the two lower doses on CTT performance persisted undiminished from the first to the second test, or over a 3-hour period after smoking.

These results partially confirm results obtained by Sharma and Moskowitz (1975). They found that THC 200 μg/kg had a virtually undiminished effect on tracking performance for up to four hours. The time course of postural instability after marijuana smoking followed a different profile. All THC doses increased body sway to the same extent shortly after cessation of smoking but none did three hours later.

An important practical objective of this study was to determine whether degrees of driving impairment can be accurately predicted from either measured concentrations of THC in plasma or performance measured in potential roadside "sobriety" tests of tracking ability or hand and posture stability. These results, like many reported before, indicate that none of these measures accurately predicts changes in actual driving performance under the influence of THC. CTT performance came closest but even its correlation with driving was only $r=.50$. However, that test might well be included in a battery of similarly predictive tests, measuring different abilities, to collectively yield a single more predictive index of impairment.