ADDITIONAL SCIENTIFIC DATA CONSIDERED BY THE DRUG ENFORCEMENT ADMINISTRATION IN EVALUATING JON GETTMAN'S PETITION TO INITIATE RULEMAKING PROCEEDINGS TO RESCHEDULE MARIJUANA

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INTRODUCTION

On July 10, 1995, Jon Gettman petitioned the Drug Enforcement Administration (DEA) to initiate rulemaking proceedings to reschedule marijuana. Marijuana is currently listed in schedule I of the Controlled Substances Act (CSA). Mr. Gettman proposed that DEA promulgate a rule stating that "there is no scientific evidence that [marijuana has] sufficient abuse potential to warrant schedule I or II status under the [CSA]."

In accordance with the CSA, DEA gathered the necessary data and, on December 17, 1997, forwarded that information along with Mr. Gettman's petition to the Department of Health and Human Services (HHS) for a scientific and medical evaluation and scheduling recommendation. On January 17, 2001, HHS forwarded to DEA its scientific and medical evaluation and scheduling recommendation. The CSA requires DEA to determine whether the HHS scientific and medical evaluation and scheduling recommendation and "all other relevant data" constitute substantial evidence that the drug should be rescheduled as proposed in the petition. 21 USC 811(b). This document contains an explanation of the "other relevant data" that DEA considered.

In deciding whether to grant a petition to initiate rulemaking proceedings, DEA must consider eight factors specified in 21 USC 811(c). The information contained in this document is organized according to these eight factors.

1) ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE.

Evaluation of the abuse potential of a drug is obtained, in part, from studies in the scientific and medical literature. There are many preclinical indicators of a drug's behavioral and psychological effects that, when taken together, provide an accurate prediction of the human abuse liability. Specifically,

these include assessments of the discriminative stimulus effects, reinforcing effects, conditioned stimulus effect, effects on operant response rates, locomotor activity, effects on food intake and other behaviors, and the development of tolerance and dependence (cf., Brady et al., 1990; Preston et al., 1997). Clinical studies of the subjective and reinforcing effects in substance abusers, interviews with substance abusers, clinical interviews with medical professionals, and epidemiological studies provide quantitative data on abuse liability in humans and some indication of actual abuse trends (cf., deWit and Griffiths, 1991).

Evidence of actual abuse and patterns of abuse are obtained from a number of substance abuse databases, and reports of diversion and trafficking. Specifically, data from Drug Abuse Warning Network (DAWN), Poison Control Centers, System To Retrieve Investigational Drug Evidence (STRIDE), seizures and declarations from U.S. Customs, DEA Drug Theft Reports and other diversion and trafficking data bases are indicators of the pattern, scope, duration and significance of abuse.

Reinforcing effects in animals:

As described by the petitioner, the preponderance of preclinical studies using animal models had, to recently, shown that Δ^9-THC had minimal activity in behavioral paradigms predictive of reinforcing efficacy (i.e., self-administration paradigms; Harris et al., 1974; Pickens et al., 1973; Deneau and Kaymakcalan, 1971). In general, Δ^9-THC had been shown to be relatively ineffective in maintaining self-administration behavior by either the intravenous or oral routes (Kaymakcalan, 1973; Harris et al., 1974; Carney et al., 1977; Mansbach et al., 1994). Under limited experimental parameters, Δ^9-THC self-administration was demonstrated after animals were either first trained to self-administer PCP, after a chronic cannabinoid history was established or when maintained at 80% reduced body weight (Pickens et al., 1973; Deneau and Kaymakcalan, 1971; Takahashi and Singer, 1979). However, Tanda, Munzar and Goldberg of the Intramural Preclinical Pharmacology Section of the NIDA (2000) have clearly demonstrated that THC can act as a strong reinforcer of drug-taking behavior in an experimental animal model, the squirrel monkey, as it does in humans. The self-administration behavior was comparable in intensity to that maintained by cocaine under identical conditions and was obtained using a range of doses similar to those self-administered by

humans smoking a single marijuana cigarette.

Although the neuropharmacological actions of Δ^9-THC suggest a powerful brain substrate underlying its rewarding and euphorigenic effects, behavioral studies of Δ^9-THC's rewarding effects had been inconclusive. Several reasons for the previous inability by a number of laboratories to demonstrate self-administration of Δ^9-THC in animals may be its relatively slow-onset, its long-lasting behavioral effects and its insolubility in physiological saline or water for injection (Mansbach et al., 1994). Similar findings have been found in the animal literature with nicotine - an avid reinforcer in humans. The strength of THC, like nicotine, as a reinforcer in animals may be more dependent on supplementary strengthening by ancillary stimuli than is the case for other drugs (cf Henningfield, 1984).

In other behavioral and pharmacological tests used to assess reinforcing efficacy, Δ^9-THC produced significant effects. Specifically, Δ^9-THC augments responding for intracranial self-stimulation by decreasing the reinforcing threshold for brain stimulation reward. It also dose-dependently enhances dopamine efflux in forebrain nuclei associated with reward and this enhanced efflux occurs locally in the terminal fields within brain reward pathways (Gardner and Lowinson, 1991; Gardner, 1992; Chen et al., 1993, 1994). In conditioned place preference procedures, Δ^9-THC (2.0 and 4.0 mg/kg, i.p.) produced significant dose-dependent increases in preference for the drug paired chamber, the magnitude of which was similar to that seen with 5.0 mg/kg cocaine and 4.0 mg/kg morphine (Leprore et al., 1995). However, Δ^9-THC also produced a conditioned place aversion and conditioned taste aversion (Leprore et al., 1995; Parker and Gillies, 1995). The development of taste aversions with drug administrations that also produce place preferences have been described as somewhat of a "drug paradox" by Goudie; however, this has been found to occur within the "therapeutic window" of all known drugs of abuse (cf Goudie, 1987). Goudie has concluded that drugs can possess both reinforcing and aversive properties at the same doses. This fact may underlie the reciprocal relationship between the behavioral effects of THC, CBD, and THC+CBD combinations, discussed below.

Drug Discrimination in Animals

Preclinical drug discrimination studies with Δ^9-THC are

predictive of the subjective effects of cannabinoid drugs in humans and serve as animal models of marijuana and THC intoxication in humans (Balster and Prescott, 1992; Wiley et al., 1993b, 1995). In a variety of species it has been found that Δ^9-THC shares discriminative stimulus effects with cannabinoids that bind to CNS cannabinoid receptors with high affinity (Compton et al., 1993; Järbe et al., 1989; Gold et al., 1992; Wiley et al., 1993b, 1995b; Järbe and Mathis, 1992) and that are psychoactive in humans (Balster and Prescott, 1992). Furthermore, recent studies show that the discriminative stimulus effects of Δ^9-THC are mediated via the CB_1 receptor subtype (Pério et al., 1996).

Chronic Δ^9-THC administration to rats produced tolerance to the discriminative stimulus effects of Δ^9-THC, but not to its response rate disruptions. Specifically, tolerance to the stimulus effects of Δ^9-THC increased 40-fold when supplemental doses of up to 120 mg/kg/day Δ^9-THC were administered under conditions of suspended training (Wiley et al., 1993a).

The discriminative stimulus effects of Δ^9-THC appear to be pharmacologically specific as non-cannabinoid drugs typically do not elicit cannabimimetic effects in drug discrimination studies (Browne and Weissman, 1981; Balster and Prescott, 1992, Gold et al., 1992; Barrett et al., 1995; Wiley et al., 1995a). Furthermore, these studies show that high doses of Δ^9-THC produce marked response rate disruption, immobility, ataxia, sedation and ptosis in rhesus monkeys and rats (Wiley et al., 1993b; Gold et al., 1992; Martin et al., 1995).

Clinical Abuse Potential

Both marijuana and THC can serve as positive reinforcers in humans. Marijuana and Δ^9-THC produced profiles of behavioral and subjective effects that were similar regardless of whether the marijuana was smoked or taken orally, as marijuana in brownies, or orally as THC-containing capsules, although the time course of effects differed substantially. There is a large clinical literature documenting the subjective, reinforcing, discriminative stimulus, and physiological effects of marijuana and THC and relating these effects to the abuse potential of marijuana and THC (e.g., Chait et al., 1988; Lukas et al., 1995; Kamien et al., 1994; Chait and Burke, 1994; Chait and Pierri, 1992; Foltin et al., 1990; Azorlosa et al., 1992; Kelly et al., 1993, 1994; Chait and Zacny, 1992; Cone et al., 1988; Mendelson and Mello, 1984).

These listed studies represent a fraction of the studies performed to evaluate the abuse potential of marijuana and THC. In general, these studies demonstrate that marijuana and THC dose-dependently increases heart rate and ratings of "high" and "drug liking", and alters behavioral performance measures (e.g., Azorlosa et al., 1992; Kelly et al., 1993, 1994; Chait and Zacny, 1992; Kamien et al., 1994; Chait and Burke, 1994; Chait and Pierri, 1992; Foltin et al., 1990; Cone et al., 1988; Mendelson and Mello, 1984). Marijuana also serves as a discriminative stimulus in humans and produces euphoria and alterations in mood. These subjective changes were used by the subjects as the basis for the discrimination from placebo (Chait et al., 1988).

In addition, smoked marijuana administration resulted in multiple brief episodes of euphoria that were paralleled by rapid transient increases in EEG alpha power (Lukas et al., 1995); these EEG changes are thought to be related to CNS processes of reinforcement (Mello, 1983).

To help elucidate the relationship between the rise and fall of plasma THC and the self-reported psychotropic effects, Harder & Rietbrock (1997) measured both the plasma levels of THC and the psychological "high" obtained from smoking a marijuana cigarette containing 1% THC. As can be seen from these data, a rise in plasma THC concentrations results in a corresponding increase in the subjectively reported feelings of being "high". However, as THC levels drop the subjectively reported feelings of "high"

remain elevated. The subjective effects seem to lag behind plasma THC levels. Similarly, Harder and Rietbrock compared lower doses of 0.3% THC-containing and 0.1% THC-containing cigarettes in human subjects.

As can be clearly seen by these data, even low doses of marijuana, containing 1%, 0.3% and even 0.1% THC, typically referred to as "non-active", are capable of producing subjective reports and physiological markers of being "high".

THC and its major metabolite, 11-OH-THC, have similar psychoactive and pharmacokinetic profiles in man (Wall et al., 1976; DiMarzo et al., 1998; Lemberger et al., 1972). Perez-Reyes et al. (1972) reported that THC and 11-OH-THC were equipotent in generating a "high" in human volunteers. However, the metabolite, 11-OH-THC, crosses the blood-brain barrier faster than the parent THC compound (Ho et al., 1973; Perez-Reyes et al., 1976). Therefore, the changes in THC plasma concentrations in humans may not be the best predictive marker for the subjective and physiological effects of marijuana in humans. Cocchetto et al. (1981) have used hysteresis plots to clearly demonstrate that plasma THC concentration is a poor predictor of simultaneous occurring physiological (heart rate) and psychological ("high") pharmacological effects. Cocchetto et al. demonstrated that the time course of tachycardia and psychological responses lagged behind the plasma THC concentration-time profile. As recently summarized by Martin & Hall (1997,1998)

> there is no linear relationship between blood [THC] levels and pharmacological effects with respect to time, a situation that hampers the prediction of cannabis-induced impairment based on THC blood levels (p90).

Physical dependence in animals

There are reports that abrupt withdrawal from Δ^9-THC can produce a mild spontaneous withdrawal syndrome in animals, including increased motor activity and grooming in rats, decreased seizure threshold in mice, increased aggressiveness, irritability and altered operant performance in rhesus monkeys (cf., Pertwee, 1991). The failure to observe profound withdrawal signs following abrupt discontinuation of the drug may be due to Δ^9-THC's long half-life in plasma and slowly waning levels of drug that continue to permit receptor adaptation.

Recently the discovery of a cannabinoid receptor antagonist demonstrates that a profound precipitated withdrawal syndrome can be produced in Δ^9-THC tolerant animals after twice daily injections (Tsou et al., 1995) or continuous infusion (Aceto et al., 1995, 1996).

Physical dependence in humans

Signs of withdrawal in humans have been demonstrated after studies with marijuana and Δ^9-THC. Although the intensity of the withdrawal syndrome is related to the daily dose and frequency of administration, in general, the signs of Δ^9-THC withdrawal have been relatively mild (cf., Pertwee, 1991). This withdrawal syndrome has been compared to that of short-term, low dose treatment with opioids, sedatives, or ethanol, and includes changes in mood, sleep, heart rate, body temperature, and appetite. Other signs such as irritability, restlessness, tremor, mild nausea, hot flashes and sweating have also been noted (cf., Jones, 1980, 1983).

Chait, Fischman, & Schuster (1985) have demonstrated an acute withdrawal syndrome or "hangover" occurring approximately 9 hours after a single marijuana smoking episode. Significant changes occurred on two subjective measures and on a time production task. In 1973, Cousens & DiMascio reported a similar "hangover" effect from acute administrations of Δ^9-THC. The hangover phenomenon or continued "high", in the Cousens & DiMascio study, occurred 9 hrs after drug administration and was associated with some residual temporal disorganization, as well. These residual or hangover effects may mimic the withdrawal syndrome, both qualitatively and quantitatively, which is expressed after chronic marijuana exposure. This acute hangover may reflect a true acute withdrawal syndrome similar to that experienced from high acute alcohol intake. The presence of an acute withdrawal syndrome after drug administration has been suggested to represent a physiological compensatory rebound by which chronic administration of the drug will eventually potentiate and produce dependence and the potential for continued abuse (Gauvin, Cheng & Holloway, 1993).

Crowley et al. (1998) screened marijuana users for DSM-IIIR dependence criteria. Of the 165 males and 64 female patients that met the criteria, 82.1% were found to have co-morbid conduct disorders; 17.5% had major depression; and 14.8% had a diagnosis

of attention-deficit/hyperactivity disorder. These results also showed that most patients claimed to have "serious problems" from cannabis use. The data also indicated that for adolescents with conduct problems, cannabis use was not benign, and that the drug served as a potent reinforcer for further cannabis usage, producing dependence and withdrawal.

Kelly & Jones (1992) quantified concentrations of THC and its metabolites in both plasma and urine after a 5 mg intravenous dose of THC was administered to frequent and infrequent marijuana smokers. The frequent smokers were users who smoked marijuana almost daily for at least two years. The infrequent smokers were users who smoked marijuana no more than two to three times per month but had done so for at least two years. Pharmacokinetic parameters after intravenously administered THC revealed no significant differences between frequent and infrequent marijuana users on area under the time-effect curve (AUC), volume of distribution, elimination half-lives of parent THC and metabolites in plasma and urine. There were also no group differences in metabolic or renal clearances. The authors concluded that there was no evidence for metabolic or dispositional tolerance between the two groups of subjects. Kelly and Jones also reported that tolerance was not evident in heart rate, diastolic blood pressure, skin temperature, and the degree of psychological "high" from the i.v. administration of THC.

In two separate reports, Haney et al. have recently described abstinence symptoms of an acute withdrawal syndrome following high (30 mg q.i.d.) and low (20 mg q.i.d) dose administrations of oral THC (Haney et al., 1999a) and following 5 puffs of high (3.1%) and low (1.8%) THC-containing smoked marijuana cigarettes (Haney et al., 1999b). Abstinence from oral THC increased ratings of "anxious", "depressed", and "irritable", and decreased the reported quantity and quality of sleep and decreased food intake by 20-30% compared to baseline. Abstinence from as low as 5 controlled puffs of active marijuana smoking increased ratings of "anxious", "irritable" and "stomach pain", and significantly decreased food intake. The 5 controlled puffs of 5 second duration each were drawn from 2 separate marijuana cigarettes (3 puffs from one, 2 puffs from the other. The smoke was held for 40 seconds and then exhaled. All subjects reported significant increases on subjective measures of "high", "good drug effect", and "stimulated", as well as "mellow", "content", and "friendly" as a result of this limited and controlled draw of THC. Both of these studies have delineated a withdrawal syndrome

from concentrations of THC significantly lower than those reported in any other previous study and, for the first time, clearly identified a marijuana withdrawal syndrome detected at low levels of THC exposure that do not produce tolerance. The abstinence syndrome was not limited to subjective state changes but was also quantified using a cognitive/memory test battery.

In a related study, Khouri et al (1999) found that long-term heavy marijuana users became more aggressive during abstinence from marijuana than did former or infrequent users. Previous dependence studies have relied largely on patients' subjective reports of a range of symptoms. Khouri et al. examined a single symptom - aggression. The authors concluded that marijuana abstinence is associated with unpleasant behavioral symptoms that may contribute to continued marijuana use.

Kouri & Pope (2000) examined three groups of marijuana users during a 28-day supervised abstinence period. Current marijuana users experienced significant increases in anxiety, irritability, physical tension, and physical symptoms and decreases in mood and appetite during marijuana withdrawal. These symptoms were most pronounced during the initial 10 days of abstinence, bust some were present for the entire 28-day withdrawal period. The findings from this study reveal that chronic heavy users of marijuana experience a number of withdrawal symptoms during abstinence and clearly demonstrate a "marijuana dependence syndrome" in humans.

These data suggest that dependence on THC may in fact be an important consequence of repeated, daily exposure to cannabinoids and that daily marijuana use may be maintained, at least in part, by the alleviation of abstinence symptoms. Relevant to the present petition, the Haney et al. study is the first report demonstrating this syndrome with extremely low concentrations of THC.

Results of THC Dose Comparison Studies:

There are reports in the scientific literature that evaluated dose-related subjective and reinforcing effects of *Cannabis sativa* in humans. These studies have assessed the subjective and reinforcing effects of *cannabis* cigarettes containing different potencies of THC and/or which have manipulated the THC dose by varying the volume of THC smoke inhaled (Azorlosa et al., 1992; Lukas et al., 1995; Chait et al.,

1988; Chait and Burke, 1994; Kelly et al., 1993).

Chait et al. (1988) studied the discriminative stimulus effects of smoked marijuana cigarettes containing THC contents of 0%, 0.9%, 1.4%, 2.7%. Marijuana smokers were trained to discriminate smoked marijuana from placebo using 4 puffs of a 2.7%-THC cigarettes. Subjective ratings of "high", and physiological measures (i.e., heart rate) were significantly and dose-dependently increased after smoking the 0.9%, 1.4%, 2.7%. Marijuana cigarettes containing 1.4% THC completely substituted for 2.7%-THC on drug identification tasks, however, 0.9%-THC did not. The authors found that the onset of discriminative stimulus effects was within 90 seconds after smoking began (after the first two puffs). Since the 1.4%-THC cigarette substituted for 2-puffs of the 2.7%-THC cigarette, the authors estimate that an inhaled dose of THC as low as 3 mg can produce discriminable subjective effects.

Similarly, Lukas et al. (1995) reported that marijuana cigarettes containing either 1.26% or 2.53% THC produced significant and dose-dependent increases in level of intoxication and euphoria in male occasional marijuana smokers. Four of the six subjects that smoked the 1.26%-THC cigarette reported marijuana effects and 75% of these subjects reported euphoria. All six of the subjects that smoked 2.53% THC reported marijuana effects and euphoria. Peak levels of self-reported intoxication occurred at 15 and 30 minutes after smoking and returned to control levels by 90-105 minutes. There was no difference between latency to or duration of euphoria after smoking either the 1.26% or 2.53% THC cigarettes. The higher dose-marijuana cigarette produced a more rapid onset and longer duration of action than the lower dose marijuana cigarette (1.26% THC). Plasma THC levels peaked 5-10 minutes after smoking began; the average peak level attained after the low- and high-dose marijuana cigarette was 36 and 69 ng/ml respectively.

In order to determine marijuana dose-effects on subjective and performance measures over a wide dose range, Azorlosa et al. (1992) evaluated the effects of 4, 10, or 25 puffs from marijuana cigarettes containing 1.75 or 3.55% THC in seven male moderate users of marijuana. Orderly dose-response curves were produced for subjective drug effects, heart rate, and plasma concentration, as a function of THC content and number of puffs. After smoking the 1.75% THC cigarette, maximal plasma THC levels were 57 ng/ml immediately after smoking, 18.3 ng/ml 15 minutes

after smoking, 10.3 ng/ml 30 minutes after smoking, and 7.7 ng/ml 45 minutes after smoking.

The study also showed that subjects could smoke more of the low THC cigarette to produce effects that were similar to the high THC dose cigarette (Azorlosa et al., 1992). There were nearly identical THC levels produced by 10-puff low-THC cigarette (98.6 ng/ml) and 4-puff high THC cigarette (89.4 ng/ml). Similarly, the subjective effects ratings, including high, stoned, impaired, confused, clear-headed and sluggish, produced under the 10 puff low- and high-THC and 25 puff low-THC conditions did not differ significantly from each other.

As with most drugs of abuse, higher doses of marijuana are preferred over lower dose. Although not preferred, these lower doses still produce cannabimimetic effects. Twelve regular marijuana smokers participated in a study designed to determine the preference of a low potency (0.64%-THC) vs. a high potency (1.95%-THC) marijuana cigarette (Chait and Burke, 1994). The subjects first sampled the marijuana of two different potencies in one session, then chose which potency and how much to smoke. During sampling sessions, there were significant dose-dependent increases in heart rate and subjective effects, including ratings of peak "high", strength of drug effects, stimulated, and drug liking. During choice sessions, the higher dose marijuana was chosen over the lower dose marijuana on 87.5% of occasions. Not surprising, there was a significant positive correlation between the total number of cigarettes smoked and the ratings of subjective effects, strength of drug effect, drug "liking", expired air carbon monoxide, and heart rate increases. The authors state it is not necessary valid to assume that the preference observed in the present study for the high-potency marijuana was due to greater CNS effects from its higher THC content. The present study found that the low- and high-potency marijuana cigarettes also differ on several sensory dimensions; the high-potency THC was found to be reported as "fresher" and "hotter". Other studies found that marijuana cigarettes containing different THC contents varied in sensory dimensions (cf., Chait et al., 1988; Nemeth-Coslett et al., 1986).

As summarized by Martin & Hall for the United Nations only a small amount of cannabis (e.g. 2-3 mg of available THC) is required to produce a brief pleasurable high for the occasional user and a single joint may be sufficient for two or three individuals. Using these data and those of Harder & Reitbroch

(1997, above), a one gram cigarette containing 1% THC containing cannabis, would contain 10 mg of THC - a dose well capable of producing a social high.

Carlini et al. (1974) examined 33 subjects who smoked marijuana cigarettes with different ratios of constituent cannabinoids. The plant containing 0.82% THC produced larger than expected results based on the estimates from the THC content. Smoking a 250 mg cigarette containing 5.0 mg of Δ^9-THC induced more reactions graded 3 and 4 than 10 or 20 mg of Δ^9-THC. It was further observed that the psychological effects (subjective "high") started around 10 min after the end of the inhalation, and reached a maximum 20 to 30 min later, subsiding within 1 to 3 hrs. The peak of psychological disturbances, therefore, did not coincide in time with the peak of pulse rate effects. Carlini et al., suggested that other constituents of the marijuana were interacting synergistically with the THC to potentiate the subjective response induced by the smoking of the cigarette. Karniol and colleagues (1973,1974) have clearly demonstrated that cannabidiol (CBD) blocks some of the effects induced by THC, such as increased pulse rates and disturbed time perception. More importantly, CBD blocked some of the psychological effects of THC, but not by altering the quantitative or intensity of the psychological reactions. CBD seemed better able to block the aversive effects of THC. CBD changed the symptoms reported by the subjects in such a way that the anxiety component produced by THC administration was actually reduced. The animal subjects of one study showed greater analgesia scores with a CBD+THC combination (1973) and the human subjects from the other study (1974) showed less anxiety and panic but reported more pleasurable effects. CBD may be best seen as an "entourage" compound (Mechoulam, Fride, DiMarzo, 1998) which is administered along with THC and results in a functional potentiation of THC's behavioral and subjective effects. This potentiation can be in both the intensity and/or duration of the high induced by marijuana. According to Paris & Nahas (1984) the CBD:THC ratio in industrial or fiber type hemp is 2:1. Relevant to the current petition, the CBD:THC ratio producing the greatest increase in euphoria in the Karniol et al. studies was 2:1 (60:30 mg).

Jones & Pertwee(1972) were first to report that the presence of cannabidiol inhibited the metabolism of THC and its active metabolite. These data were soon replicated by Nilsson et al., (1973). Bronheim et al., (1995) examined the effects of CBD on the pharmacokinetic profile of THC content in both blood and

brains of mice. CBD pretreatments produced a modest elevation in THC-blood levels; area under the kinetics curve of THC was increased by 50% as a function of decreased clearance. CBD pretreatments also modestly increased the C_{max}, AUC, and half-life of the major THC metabolites in the blood. The THC kinetics function showed a 7- to 15-fold increase in the area under the curve, a 2- to 4-fold increase in the half-life, as well as the t_{max}. CBD pretreatments resulted in large increases in area under the curves and half-lives of all the THC metabolites in the mice brains. The inhibition of the metabolism of THC and its psychoactive metabolites by CBD may underlie the potentiation in the subjective effects of THC by CBD in humans.

In addition to THC, hemp material contains a variety of other substances (e.g., Hollister, 1974), including other cannabinoids such as cannabidiol (CBD) and cannabinol (CBN). One comprehensive review described the activities of 300 cannabinoid compound in preclinical models (Razdan, 1986). Since CBD is always present in preparations of *cannabis*, it may represent a high CBD:THC ratio in the case of low THC *cannabis*. Therefore, it is important to understand the interactions of cannabidiol and Δ^9-THC.

Structure-activity studies of cannabinoid compounds characterized cannabidiol in relationship to Δ^9-THC and other cannabinoids (Martin et al., 1981; Little et al., 1988). These and other studies have found that cannabidiol was inactive and did not produce neuropharmacological effects or discriminative stimulus, subjective effects and behavioral effects predictive of psychoactive subjective effects (Howlett, 1987; Howlett et al., 1992; c.f., Hiltunen and Järbe, 1986; Perez-Reyes et al., 1973; Zuardi et al., 1982; Karniol et al., 1974).

Other studies have reported that cannabidiol has cannabinoid properties, including anticonvulsant effects in animal and human models (Consroe et al., 1981; Carlini & Cunha, 1981; Doyle and Spence, 1995), hypnotic effects (Monti, 1977), anxiolytic effects (Musty, 1984; Onaivi, Geen,& Martin, 1990; Guimarães et al., 1990; 1994) and rate-decreasing effects on operant behavior (Hiltunen et al., 1988).

Experiments with cannabidiol in combination with THC have found that certain behavioral responses induced by THC (i.e., operant, schedule-controlled responding) were attenuated by cannabidiol (Borgen and Davis, 1974; Brady and Balster, 1980;

Consroe et al., 1977; Dalton et al., 1976; Kraniol and Carlini, 1973; Karniol et al., 1974; Welburn et 1976; Zuardi and Karniol, 1983; Zuardi et al., 1981, 1982; Hiltunen et al., 1988). However, other affects produced by THC are augmented or prolonged by the combined administration of CBD and THC or marijuana extract (Chesher and Jackson, 1974; Hine et al., 1975a,b; Fernandes et al., 1974; Karniol and Carlini, 1973; Musty and Sands, 1978; Zuardi and Karniol, 1983; Zuardi et al., 1984). Still other studies did not report any behavioral interaction between the CBD and THC (Bird et al., 1980; Browne and Weissman, 1981; Hollister and Gillespie, 1975; Järbe and Henricksson, 1974; Järbe et al., 1977; Mechoulam et al., 1970; Sanders et al., 1979; Ten Ham and DeLong, 1975).

A study to characterize the interaction between CBD and THC was conducted using preclinical drug discrimination procedures. Rats and pigeons trained to discriminate the presence or absence of THC, and tested with CBD administered alone and in combinations with THC (Hiltunen and Järbe, 1986).

Specifically, in rats trained to discriminate 3.0 mg/kg, i.p. THC, CBD (30.0 mg/kg) was administered alone and in combination with THC (0.3 and 1.0 mg/kg, i.p.). In pigeons trained to discriminate 0.56 mg/kg, i.m. THC, CBD (17.5 mg/kg) was administered alone and in combination with THC (0.1, 0.3, and 0.56 mg/kg, i.m.). CBD prolonged the discriminative stimulus effects of THC in rats, but did not change the time-effect curve for THC in pigeons. In pigeons, the administration of CBD did not produce any differential effect under a fixed ratio schedule of reinforcement (Hiltunen and Järbe, 1986).

These data suggest that CBD may somehow augment or prolong the actions of THC in rats and had no effect in pigeons. In the present study, the CBD/THC ratios ranged from 30:1 to 100:1 in rats and enhanced the stimulus effects of THC. However, similar CBD/THC ratios in pigeons (31:1, 58:1 and 175:1) did not result in any changes to THC's discriminative stimulus or response rate effects (Hiltunen and Järbe, 1986).

It should be noted that cannabidiol can be easily converted to delta-9- and delta-8-tetrahydrocannabinol. Even industrial hemp plant material (leaves), containing high concentrations of CBD, can be treated in clandestine laboratories to convert the CBD to delta-9-tetrahydrocannabinol (Mechoulam, 1973) converting a supposedly innocuous weed into a potent smoke product.

In conclusion, the "entourage" compound, cannabidiol, does contribute to all of the effects ascribed to THC, however it also appears to lack cannabimimetic properties. However, there is no credible scientific evidence that CBD is a pharmacological antagonist at the cannabinoid receptor (Howlett, Evans, & Houston, 1992). There is clear evidence that CBD can functionally antagonize some of the aversive effects of THC (Dewey, 1986). The data from the scientific literature cited above, clearly demonstrate the ability of CBD to modify some very specific effects of THC. Most importantly, relative to the euphorigenic effects of THC (which contributes to its abuse liability), CBD appears to potentiate the psychological or subjective effects of THC by potentiating the blood and brain THC and 11-OH-THC levels and by functionally blocking the aversive (anxiety-like) properties of THC.

Abuse Liability Summary:

Preclinical and clinical experimental data demonstrate that marijuana and Δ^9-THC have similar abuse liabilities (i.e., drug discrimination, self-administration, subjective effects). Both preclinical and clinical studies show that discontinuation of either marijuana or Δ^9-THC administration produces a mild withdrawal syndrome. The effects of THC are dose-dependent and several studies have found that low-potency THC is behaviorally active and can produce cannabimimetic-like subjective and physiological effects.

ACTUAL ABUSE

There are dozens of data collection and reporting systems that are useful for monitoring the United States' problem with abuse of licit and illicit substances. These data collection and reporting systems provide quantitative data on many factors related to abuse of a particular substance, including incidence, pattern, consequence and profile of the abuser of specific substances (cf., Larsen et al., 1995).

Evidence of actual abuse is defined by episodes/mentions in the databases indicative of abuse/dependence. Some of the databases that are utilized by DEA to provide data relevant to actual abuse of a substance include the Drug Abuse Warning Network (DAWN), National Household Survey on Drug Abuse, Monitoring the Future survey, FDA's Spontaneous Adverse Events

Reports, the American Association of Poison Control Centers database and reports of the Community Epidemiology Work Group (CEWG).

Drug trafficking and diversion data provide strong evidence that a drug or other substance is being abused. In order to determine the pattern, incidence, and consequences of abuse and the demographics of abusers of a particular substance to be controlled, DEA relies on data collected from a number of sources, including the United States government as well as state and local law enforcement groups. Information from these sources often provides a first indication of an emerging pattern of abuse of a particular drug or substance, and when taken together with other data sources provide strong evidence that can be used in determining a substance's placement in the schedules listed in the CSA.

The evidence from epidemiological studies conclude that marijuana use alone and in combination with other illicit drugs is increasing. The most recent "Monitoring the Future Study", documented increases in lifetime, annual and current (within the past 30 days) and daily use of marijuana by eighth and tenth graders; this increasing trend began in the early 1990's.

Similarly, according the NIDA's "National Household Survey", marijuana use is increasing with the greatest increase among the younger age groups (12-17 years of age). The frequency of marijuana use in the past year increases significantly among 12-17 year olds. This survey also found that youths who used marijuana at least once in their lives were more likely to engage in violent or other antisocial behaviors.

Marijuana is the most readily available illicit drug in the United States. Cannabis is cultivated in remote locations and frequently on public lands. Major domestic outdoor cannabis cultivation areas are found in California, Hawaii, Kentucky, New York and Tennessee. Significant quantities of marijuana were seized from indoor cultivation operations; there were 3,532 seizures in 1996 compared to 3,348 seized in 1995. Mexico is the major source of foreign marijuana, along with lesser amounts from Colombia and Jamaica (NNICC, 1996).

Domestically, marijuana is distributed by groups or individuals, ranging from large sophisticated organizations with

controlled cultivation and interstate trafficking, to small independent traffickers at the local level.

(2) SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN

Cannabis sativa is unique in that it is the only botanical source of the terpenophenolic substances referred to as cannabinoids which are responsible for the psychoactive effects of *Cannabis*. There are roughly 60 different cannabinoids found in *Cannabis* (Nahas, 1984; Murphy & Bartke, 1992; Agurell, Dewey & Willette, 1984) but the psychoactive properties of *Cannabis* are attributed to one or two of the major cannabinoid substances, namely delta-9-tetrahydrocannabinol and delta-8-tetrahydrocannabinol. In fresh, carefully dried marijuana, up to 95% of their cannabinoids are present as (-)-delta-9-(*trans*)-tetrahydrocannabinol carboxylic acid (Nahas, 1984; Murphy & Bartke, 1992; Agurell, Dewey & Willette, 1984). The acid form is not psychoactive, but is readily decarboxylated upon heating to yield delta-9-tetrahydrocannabinol (neutral form). Therefore, plant material could be very high in its "pro-drug" acid form and very low in neutral form but still be very potent when smoked.

There are two primary factors that influence THC content: genetic predisposition and environmental influences. Genetic factors are considered predominant in determining cannabinoid content, although, fluctuations in weather conditions have greatly enhanced or diminished the THC content.

Paris & Nahas (1984) have admonished that marijuana is not a single uniform plant like many of those encountered in nature, but a rather deceptive weed with several hundred variants. The intoxicating substances prepared from *Cannabis* vary considerably in potency according to the varying mixtures of different parts of the plant, and according to the techniques of fabrication. According to Paris & Nahas, this basic botanical fact has been overlooked by physicians and educators, who have written about marijuana as a simple, single substance, which uniformly yields a low concentration of a single intoxicant. In addition to changes due to its own genetic plasticity, marijuana has been modified throughout the ages by environmental factors and human manipulations, and is not yet a stabilized botanical species (Paris & Nahas, 1984).

According to Paris & Nahas (1984) the terminology used by Fetterman et al. (1970, 1971) is somewhat misleading, especially with respect to their contention that environmental factors, including climate, are not as important as heredity in determining the cannabinoid content of cutigens. The analyses of Fetterman et al., (1970) were performed according to the technique by Doorenbos et al., (1971) on plant materials from variants that had been cut at the stem beneath the lowest leaves and air-dried. Seeds, bracts, flowers, leaves and small stems were then stripped from the plant. Most of the small stems were removed by a 10-mesh screen, and the seeds were eliminated with a mechanical seed separator. This preparation of marijuana contains less seed and stem than most of the illicit material available in the United States. Cannabinoids were then extracted from the plant material and analyzed by standard techniques.

Other systems of separating *Cannabis* into drug, intermediate and non-drug type have been developed. These are typically determined by chemical analyses based upon the method described by Doorenbos (1971) which utilizes manicured portions of the *Cannabis* plant only in determining percent concentration.

Cannabis sativa has been referred to as a widely distributed and unstabilized species. *Cannabis* exhibits extreme polymorphism (ability to alter, change) in different varieties, dependent upon many factors. For example, there are at least twenty strains which are cultivated for fiber. There have been many attempts to classify *Cannabis* as a function of intoxicant properties or fiber properties. Such classification efforts are dependent upon the age of the sample. And there is no totally reliable classification system based on a single chemical analysis. The plasticity of the genus has prevented the development of such a system (Turner *et al.* 1980a,b).

In a study where twelve strains of *Cannabis* were grown out of doors in Southern England (Fairbairn and Liebmann, 1974, Fairbairn et al., 1971), the following were determined:

1. Warm climate are not necessary for high THC content.
2. There is considerable THC content variation within and between plants.
3. Quantitative results of tetrahydrocannabinol concentration (THC) are highly dependent upon the specific plant part sampled, the stage of

growth and the size of sample.

4. Certain strains of *Cannabis* can be THC or cannabidiol (CBD) rich which does not seem to be dependent upon environmental conditions.
5. However, growing the same strain of *Cannabis* under different lighting conditions can produce plants that range from 2.4 to 4.42% THC concentration (based upon an analysis of the upper leaves). And finally,
6. THC concentration are dramatically higher on dried flowering or vegetative tops of the plants relative to middle or lower portions.

In a similar study on the characterization of *Cannabis* accessions with regard to cannabinoid content, *vis-a-vis* other plant characters (deMeijer, 1992), it was determined that:

1. there exists considerable variation within and among accessions for cannabinoid content;
2. mean cannabinoid content is strongly affected by year of cultivation;
3. there is no strict relationship between chemical and non-chemical traits; and,
4. it is uncommon, but some accessions combine high bark fiber content and considerable psychoactive potency.

In 1993 de Meijer reported the results of a government (Netherlands) funded industrial hemp project designed to investigate the stem quality, yield, and a comparative analysis to wood fibers. deMeijer found that the commercial grade industrial hemp seeds, germplasms derived from <0.3% THC chemovars, demonstrated a significant variation in the average THC content which ranged from 0.06 to 1.77% in the female dry leaf matter. deMeijer concluded by stating,

> Although high bark fiber content does not necessarily exclude high THC content, most fiber cultivars have very low THC content and thus possess no psychoactive potency

While the data from his own study refutes these conclusions he does conclude that the industrial hemp plant does not preclude high THC content.

A review of these and other studies in the scientific literature, indicate that THC concentrations vary within portions of the *Cannabis* plant (Hanus et al., 1989, 1975). In some studies, the concentration of THC can increase as much as 100% from leafy to flowering portions of the same plant. THC concentrations are known to be elevated on the upper portions of the plant. In a study published by Fairbairn and Liebmann, (1974) there was considerable variations between the flowering tops (bracts, flowers, immature fruits at the ends of shoots) and leafy portions of some specimens. THC content decreases with age and length of leaves (Paris & Nahas, 1984, p 25). The lower, more developed leaves have a low cannabinoid content and the top leaves have a high cannabinoid content, especially when they are associated with the bracts of the plant. Cannabinoids are localized in the upper third of the "stalk" and in the flowers. Therefore, the THC content of specific portions of a plant, which on a whole plant basis did not exceed 1%, could significantly exceed this threshold. Very few marijuana users actually "smoke" the leaves. It is the colas or the flowering portions of the plants which are utilized and these are exactly the portions of the plant which would be expected to have the highest concentration of THC.

It is clearly recognized that *Cannabis* presents a high degree of genetic plasticity which results in extreme polymorphism in its different varieties. The hemp first grown in the United States for fiber was of European origin. The type basic to modern American fiber production, known as Kentucky, came originally from China. In Europe, there are five to six varieties with one considered "exceptional" - the Kymington. The plasticity of the European fiber variety has been clearly shown (Bouquet, 1951; Hamilton, 1912, 1915). European cultigens planted in dry, warm areas of Egypt to supply fiber for rope-making were found to produce, within several generations, plants with high psycho-active ingredients and very little fiber. *Cannabis sativa's* botanical and chemical characteristics change markedly as a result of environmental factors and human manipulation. Doorenbos et al., (1971) cultivated a Mexican and Turkish variant in Mississippi for three consecutive generations. During that period, the Δ^9-THC content did not change in the Mexican variant but increased in the Turkish variant. In the more controlled environment of a phytotron (light, humidity, and nutrition controlled), Braut-Boucher (1978), Braut-Boucher & Petiard (1981), Braut-Boucher, Paris, & Cosson (1977) and Paris et al., (1975) found that the cannabinoid concentrations rose over a

similar three year period. The concentrations rose more sharply in cool environments (22-12°C: day-night) than in warm environments (32-12°C). Some authors have hypothesized that immediate environmentally caused changes are individual plant reactions, whereas the progressive changes over generations are linked with whole populations and constitute a true natural selection. Whether this evolution is caused by a change of genetic equilibrium (caused by the environment), or by a modification of the genetic capacity (over time), is impossible to say (Paris & Nahas, 1984).

In 1974 through 1976 the University of Mississippi cultivated 7 variants of 12 Cannabis plants discovered and collected in 1973 from different areas of Mexico. Cannabinoid content was analyzed weekly during the cultivation period. Turner, Elsohly, Lewis, Lopez-Santibanez & Carranza (1982) summarized their findings as follows:

> In 1974, vegetative plants of ME-H, ME-K, ME-L, ME-N and ME-O, at 13 weeks of age had higher Δ^9-THC content that at weeks 12 and 14. They showed minimum Δ^9-THC content at week 15. For the most part, 1974 staminate and pistillate plants grown in Mississippi produced a low Δ^9-THC concentration.....
>
> In all variants, the average Δ^9-THC was higher in 1976 than in 1974. Also, a greater fluctuation of Δ^9-THC was observed in 1976 than in 1974.

These results further establish that *Cannabis Sativa L.* is not a stable hybrid plant, but rather, represents characteristics more similar to an unstable weed.

Marijuana chemistry is complex and cannot be simplified or extrapolated from any one or two "active compounds". As early as 1974 this fact was recognized by the United Nations Division on Narcotic Drugs (UN Doc, 1974). As highlighted by Turner (1980), the chemistry of THC is not the chemistry of marijuana and the pharmacology of marijuana is not the pharmacology of THC. Recent findings do suggest that the interactions between cannabinoids is one of many critical factors in the analysis of the psychopharmacology of marijuana.

According to Jones (1980), because of exposure to a wide range of plant material and the cultural labeling (almost like advertising) of much of the marijuana experience, marijuana users are particularly subject to the effects of nonpharmacological variables that alter the subjective response to marijuana intoxication (Jones 1971, 1980; Cappell & Pliner, 1974; Becker 1967). As reviewed by Jones (1971), a number of studies suggest that experienced marijuana users are more subject to "placebo reactions"; that is, a degree of intoxication disproportionate to the THC content of the material. This seems particularly true if the individuals are exposed to low potency marijuana (<1.0% THC). Jones believes that this is a result of experience and practice at recognizing minimal physiologic cues together with the smell, taste and other sensations associated with smoking a marijuana cigarette (Jones 1980, 1971). Becker 1967 and Cappell & Pliner (1974) have described a number of psychological factors (expectancy, social setting, etc.) that appear to synergistically interact to help generate the subjective experiences engendered by marijuana smoking.

Domino, Rennick, & Pearl (1976) administered THC injected into tobacco cigarettes to male volunteers. Similar to findings described by Isbell et al., (1967) they report that 50 μg of THC into the cigarettes produced a "social high", while 250 μg /kg was "hallucinogenic". Taking 80 kg as the mean weight of their subjects the authors concluded that a 4.0 mg total THC dose produced a "social high"; a hallucinogenic dose was 20 mg total THC by inhalation. A standard 1g cigarette of 1% THC fibre-type hemp provides 10 mg of THC. Even allowing for a 50% loss of THC from sidestream smoke and pyrolysis, smoking this cigarette provides more than enough THC to produce a "social high".

In 1968 Weil, Norman, & Nelsen described a set of studies examining the physiological and psychological aspects of smoked marijuana. The first batch of Mexican grown marijuana used in the study was found to contain only 0.3% THC by weight. The potency of this product was considered to be "low" by the experimenters on the basis of the doses needed to produce symptoms of intoxication in the chronic users. This low potency marijuana was able to produce a "high", but only with two 1 gram cigarettes. A second batch was used in later studies. Weil, Norman, & Nelsen report that marijuana assayed at 0.9% THC (a quantity slightly less than the 1% THC limit set forth by the petitioners) was rated by the chronic users in the study to be "good, average" marijuana, neither exceptionally strong nor exceptionally weak

compared to the usual supplies. Users consistently reported symptoms of intoxication after smoking about 0.5 grams of the 0.9% THC containing marijuana (half a joint). With the high dose of marijuana (2.0 grams of 0.9% THC containing marijuana) all chronic users became "high" by their own accounts and in the judgment of experimenters who had observed many persons under the influence of marijuana.

Agurell & Leander (1971) examined the physiological and psychological effects of low THC-containing cannabis in experienced users. They reported that 14-29% of the cannabinoid content of the cigarette was transferred to the main stream smoke. Based on qualitative and quantitative analyses, Agurell & Leander demonstrated that as little as 3-5 mg of THC was needed to be absorbed by the lung in order to produce a "normal biological high". Further, they found that as little as 1 mg of absorbed THC was discriminable by all of their chronic user subjects.

In 1982, Barnett, Chiang, Perez-Reyes, & Owens had six subjects smoke a 1% THC-containing (industrial hemp, as defined by the petitioner) marijuana cigarette. Significant heart rate and subjective measures of "high" were measured for 2 hours after each cigarette.

In 1971 Jones reported on the wide variability in THC concentrations found in street samples:

> Specimens gathered in the midwestern United States contained only 0.1 - 0.5% THC. Thirty specimens selected from seized samples in the Bureau of Narcotics and Dangerous Drugs Laboratory in San Francisco all contained less than 1% THC. Samples from the State of California Bureau of Narcotic enforcement analyzed in our laboratory contained as little as 0.1% THC and a maximum of 0.9%....In a survey done in Ontario, Canada, Marshman and Gibbons found that of 36 samples alleged to be marijuana with high cannabinoid content, 34% contained no marijuana at all, and much of the rest was cut with other plant substances. A generous assumption is that marijuana generally available in the United States averages about 1.0% THC.

It must be acknowledged that the THC content of domestically grown and imported marijuana has increased since these reports.

However, the description by Weil, Zinberg & Nelson (1968), Agurell & Leander (1971), Jones (1971) and Barnett et al. (1982) highlight the historical importance of low THC concentrations contained in marijuana which provided the basis for the marijuana culture that developed in the 1970s. The incident described by Jones was not an isolated case of the inadvertent misrepresentation of the THC content of marijuana extracts. Caldwell et al., (1969) found that the NIMH-supplied marijuana that they reported to have contained 1.3% THC was analyzed by two independent laboratories and found to contain as little as 0.2 to 0.5% THC. Similarly, according to Paton & Pertwee (1973) the THC content of material used by Clark & Nakashima (1968), Weil et al., (1968), Weil & Zinberg (1969), and Crancer et al., (1969) must be expected to be one-third to one-sixth less than stated. This means that the positive results of all of these studies were the result of a surprisingly low THC-containing (<1.0%) marijuana. The early scientific data on the subjective effects of marijuana were generated with these samples by experienced smokers smoking material in this potency range. These experienced marijuana smokers were reporting that these marijuana samples were of "average quality" (Mechoulam, 1973).

In an early study, Jones (1971) utilized 1 gram of plant material with a THC concentration of 0.9% (9 mg of THC). Experienced marijuana smokers were asked to freely smoke marijuana cigarettes for 10 minutes. The smoking topography of the smokers widely varied and was not controlled in this set of experiments. Subjects were asked to smoke the entire cigarette. Subjective state was measured by asking the subjects to make global estimates of his degree of intoxication on a 0-100 scale. A score of 0 was defined as "sober" and a score of 100 as the most intoxicated or most "stoned" they had ever been in any social situation. At the end of the session (about 3 hrs), the subject also filled out a 272-item symptom checklist (SDEQ: subjective drug effects questionnaire) which taps some of the more unusual emotional, perceptual and cognitive effects produced by psychoactive drugs. The mean potency rating was 61 for the marijuana containing only 9 mg of THC. There was a tremendous range in the rating made by individual smokers. Jones concluded that the smokers may obtain intermittent reinforcement from THC but where much of the behavior and subsequent response is maintained by "conditioned reinforcers" such as the whole ritual of lighting up, the associated stimuli of smell, taste, visual stimuli and so on.

Manno, Kiplinger, Haine, Bennett, & Forney (1970) asked subjects to smoke an entire 1 gram cigarette containing 1% THC (10 mg; low potency). The subjects were told to take 2 to 4 seconds to inhale and to hold the draw for 30 to 60 seconds. The expired smoke was collected and analyzed for THC content, as well. During the experiment the subjects smoked the entire cigarette; in all cases, less than 0.5 mg of THC remained in the residue of each cigarette. Manno et al. reported that the quantity of THC or other cannabinols present in a marijuana cigarette was not a reliable indicator of the amount of cannabinols that were delivered in the smoke of the cigarette. Controlled smoking experiments through a manufactured smoking machine demonstrated that approximately 50% of the Δ^9-THC originally present in the cigarette was delivered unchanged in the smoke. Manno et al. concluded that a dose of approximately 5 mg of Δ^9-THC was delivered which was estimated to be an administered dose in the range of 50 to 75 μg per kilogram. These low potency marijuana cigarettes produced significant motor and mental performance measures on the pursuit meter test, delayed auditory feedback, verbal output, reverse reading, reverse counting, progressive counting, simple addition, subtraction, addition +7, subtract +7, and color differentiation. These low potency cigarettes also produced significant pulse rate increases and significant increases on a somatic symptoms checklist. Unsolicited verbal comments from the subjects verified that the subjects were "high" on these low potency marijuana cigarettes.

Kiplinger, Manno, Rodda, Forney, Haine, Ease, & Richards (1971) conducted a randomized block, double-blind study designed to establish a dose-response analysis of the THC content in marijuana using a variety of behavioral and subjective effects measures. Marijuana cigarettes were manufactured to deliver doses of 0, 6.25, 12.5, 25, and 50 μg/kg of Δ^9-THC. Based on an average 70 kg man, the total delivered doses of THC were 0, 0.43, 0.875, 1.75, and 3.5 mg. Based on the assumption of a 50% loss of THC from pyrolysis and sidestream smoke these doses would be equivalent to smoking cigarettes containing 0, 0.08%, 0.16%, 0.3%, and 0.7% THC containing hemp. The lower concentrations of THC were used because these doses are found in the weaker "hemp" or fiber type marijuana commonly grown in the United States. All doses of THC, including the two lowest doses, increased the subjective ratings on both the ARCI and Cornell Medical Indexes, produced heart-rate increases, increased motoric decrements in pursuit meter, and produced decrements in mental performance using the delayed auditory feedback test. Most importantly, 80%

of subjects correctly identified the lowest dose (6.25 μg/kg; 0.43 mg THC) as active marijuana. The authors suggested that even lower doses might have measurable effects. Holtzman (1971) has suggested that one of the best predictors of a drug's abuse liability is the identification of the substance as "drug-like" by experienced drug users. The identification of the lowest dose of marijuana in the Kiplinger et al. and the other studies, discussed above, clearly suggests that industrial "fiber-type" marijuana has abuse potential.

Many of the studies examining the behavioral effects of marijuana in animals have chosen to administer THC because of the difficulties in controlling and administering exact doses within and between subjects when using pyrolyzed forms of marijuana to animals. Accurate small-animal smoke delivery systems are not yet available. The lack of water solubility of Δ^9-THC has made its administration and absorption a difficult problem for pharmacologists. Many different methods for suspending, solubilizing, or emulsifying Δ^9-THC have been used. None of these methods are without difficulty and without influence on absorption and pharmacological activity. The fact that many methods have been used by various investigators makes quantitative comparisons difficult.

Δ^9-THC is the primary active ingredient of marijuana that produces the subjective "high" associated with smoking the plant material and is the chemical basis for *cannabis* abuse. Studies in several species of laboratory animals, including rhesus monkeys, rats and pigeons, have found pharmacological specificity for Δ^9-THC at the cannabinoid receptors, and for cannabinoid drugs that bind with high affinity to brain cannabinoid receptors, and is psychoactive in humans and animals (Browne and Weissman, 1981; Balster and Prescott, 1992; Compton et al., 1993; Wiley et al., 1995a,b). In general, the doses that produce its acute therapeutic effects and its cannabimimetic effects are similar (Devine et al., 1987; Consroe and Sandyk, 1992).

Central Nervous System Effects

It has been reported that in man, doses above 1 milligram of Δ^9-THC absorbed by smoking marijuana are sufficient to cause a "high" (Agurell et al., 1986). Further, Agurell et al. (1986) suggested based on mouse data, that a pronounced "high" would be caused by the presence of as little as 10 micrograms of Δ^9-THC in

the brain, immediately after smoking a marijuana cigarette. These conclusions, based on a diverse array of pharmacokinetic studies, suggest that "fiber-type" marijuana clearly has the capacity to deposit these levels of THC into the brain of man soon after smoking a 1% THC-containing marijuana cigarette (assuming the typical "joint" of 1 g, with 10mg THC). Δ^9-THC exerts its most prominent effects on the CNS and the cardiovascular system. Administration of Δ^9-THC via smoked *cannabis* is associated with decrements in motivation, cognition, judgement, memory, motor coordination, and alterations in perception (especially time perception), sensorium, and mood (cf., Jaffe, 1993). Most commonly Δ^9-THC produces an increase in well-being and euphoria accompanied by feelings of relaxation and sleepiness. The consequences produced by Δ^9-THC-induced behavioral impairments can greatly impact the public health and safety, given that individuals may be attending school, working, or driving a motor vehicle under the influence of the drug (i.e., marijuana).

Preclinical studies show that Δ^9-THC produces decrements in short-term memory, as evidenced by disruptions in acquisition and performance of maze behavior, conditioned emotional responses, and passive avoidance responses, impairment on the retention in delayed matching and alternation tests, and increases in resistance to extinction (Drew and Miller, 1974, Nakamura et al., 1991; Järbe and Mathis, 1992; Lichtman and Martin, 1996). Recent studies in rats found that these Δ^9-THC-induced impairments in spatial working memory were reversible after long abstinence (Nakamura et al., 1991) and can be blocked by the cannabinoid receptor antagonist SR141716A (Lichtman and Martin, 1996).

Memory disturbances are one of the well-documented effects of Δ^9-THC and marijuana on human behavior (Mendelson et al., 1974; Jaffe, 1993; Hollister, 1986; Chait and Pierri, 1992). Clinical investigators of Δ^9-THC and marijuana's effects in memory have suggested that the drug produces a deficit in memory for recent events, and inhibition of the passage of memory from short-term to long-term storage (Drew and Miller, 1974; Darley 1973a,b).

Heishman, Huestis, Henningfield, & Cone (1990) demonstrated cognitive performance decrements in marijuana smokers. Performance remained impaired on arithmetic and recall tests on the day after smoke administration. The authors suggested that performance decrements from smoking two to four marijuana

cigarettes may be evident for 24 to 31 hours. These data identify a particular set of performance decrements which characterize a marijuana-induced abstinence syndrome in man.

Cardiovascular Effects

In humans, Δ^9-THC produces an increase in heart rate, an increase in systolic blood pressure while supine, decreases in blood pressure while standing, and a marked reddening of the conjunctivae (cf., Jaffe, 1993). The increase in heart rate is dose-dependent and its onset and duration varies but lags behind the peak of Δ^9-THC levels in the blood.

Respiratory Effects:

Marijuana smoking produces inflammation, edema, and cell injury in the tracheobronchial mucosa of smokers and may be a risk factor for lung cancer (Sarafian et al., 1999). Smoke from marijuana has been shown to stimulate intermediate levels of reactive oxygen species. A brief, 30-minute exposure to marijuana smoke, regardless of the THC content, also induced necrotic cell death that increased steadily up to 48 hours after administration. Sarafian et al., concluded that marijuana smoke containing THC is a potent source of cellular oxidative stress that could contribute significantly to cell injury and dysfunction in the lungs of smokers.

The low incidence of carcinogenicity may be related to the fact that intoxication from marijuana does not require large amounts of smoked material. This may be especially true today since marijuana has been reported to be more potent now than a generation ago and individuals typically titrate their drug consumption to consistent levels of intoxication. However, several cases of lung cancer in young marijuana users with no have been reported (Fung et al., 1999).

However, a recent study (Zhang et al., 1999, below) has suggested that marijuana use may dose-dependently interact with mutagenic sensitivity, cigarette smoking and alcohol use to increase the risk of head and neck cancer. THC is known to suppress macrophage natural killer cells and T-lymphocytes and reduce resistance to viral and bacterial infections. As shown below, Zhu et al., demonstrated that THC probably interacts with the T-cell cannabinoid CB2 receptor to produce these effects. As shown in the figure, below, these researchers found that THC

promoted tumor growth in two immunocompetent mice lines. In two different weakly immunogenic murine lung cancer models, intermittent administration of THC led to accelerated growth of tumor implants compared with treatment with placebo alone. The immune inhibitory cytokines IL-10 and TGF-beta were augmented, while IFN-gamma was down-regulated at both the tumor site and in the spleens of THC-treated mice. This has been the first clear demonstration that THC promotes tumor growth and supports the epidemiological evidence of an increased risk of cancer among marijuana smokers.

In a recent comprehensive review of the existing literature base, Carriot & Sasco (2000) reported that users under the age of 40 years of age were more susceptible to squamous-cell carcinoma of the upper aerodigestive tract, particularly of the tongue and larynx, and possibly the lung. Others tumors being suspected are non-lymphoblastic acute leukemia and astrocytoma. In head and neck cancer carcinogenicity was observed for regular (i.e. more than once a day for years) cannabis smokers. Moreover, cannabis increases the risk of head and neck cancer in a dose-response manner for frequency and duration of use. THC seems to have a specific carcinogenic effect different from that of the pyrolysis products produced by (nicotine) cigarette smoking.

(3) THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE.

In general, the petitioner argues that the chemistry, toxicology and pharmacology of marijuana has been subjected to extensive study and peer review, and have been well characterized in the scientific literature. In addition, the discovery of the cannabinoid receptor has shed new light on the effects of marijuana and its mechanism of action.

The literature cited by the petitioner (Tashkin et al., 1987, 1988, 1990, 1991, 1993; Barbers et al., 1991; Sherman et al., 1991a, 1991b; Wu et al., 1992) provide data about the effects of marijuana smoke on the lungs, which, by the petitioner's own admission, is inherently unhealthy. Data show that smoking marijuana is associated with more tar than cigarettes and holding your breath (a common practice of marijuana smokers) increases carbon monoxide concentration. His assertion that Schedule I policy makes promoting safer marijuana smoking habits impossible has no basis in law (exact citations are found in petition).

Pulmonary effects of smoked marijuana include bronchodilation after acute exposure. Chronic bronchitis and pharyngitis are associated with repeated pulmonary illness. With chronic marijuana smoking, large airway obstruction and cellular inflammatory abnormalities appear in bronchial epithelium (Adams and Martin, 1996). Chronic marijuana use is associated with the same types of health problems as cigarette smoking: increased frequency of bronchitis, emphysema and asthma. The ability of alveolar macrophages to inactivate bacteria in the lung is impaired. Local irritation and narrowing of airways also contribute to problems in these patients.

Work by Perez-Reyes et al. (1991) and Agurell et al. (1989) provides data about the pharmacokinetics of THC from smoked marijuana.

When marijuana is smoked, THC in the form of an aerosol in the inhaled smoked is absorbed within seconds and delivered to the brain rapidly and efficiently. Peak venous blood levels 75-150 ng/ml usually occur by the end of smoking a cigarette and level of THC in the arterial system is probably much higher (Agurell et al., 1986).

Toxicity by definition is the ability of an agent to produce injury or cause harm (morbidity/mortality). It is not clear that the effects of marijuana use are "well-established," but what is known about the psychoactive effects, lung effects, endocrine effects etc. would suggest that smoking marijuana is not benign.

The cardiovascular effects of smoked or oral marijuana have not presented any health problems for healthy and relatively young users. However, marijuana smoking by older patients, particularly those with some degree of coronary artery disease, is likely to pose greater risks because of the resulting increased cardiac work, increased catecholamines, carboxyhemoglobin and postural hypotension (Benzowitz and Martin, 1996; Hollister, 1988).

The endocrine system effects include moderate depression of spermatogenesis and sperm motility and decrease in plasma testosterone on males. Prolactin, FSH, LH, and GH levels are decreased in females (Mendelson and Mello, 1984). Relatively little study has been done on human female endocrine or reproductive function.

THC and other cannabinoids in marijuana have immunosuppressant properties producing impaired cell-mediated and humoral immune system responses. THC and other cannabinoids suppress antibody formation, cytokine production, leukocyte migration and killer-cell activity (Adams and Martin, 1996).

Marijuana may cause membrane perturbations in cells. At the marijuana conference in July, 1995 sponsored by NIH, NIDA and DHHS, Dr. Cabral stated that THC effects body functions by accumulating in fatty tissue. While a receptor-based mechanism of action has been determined, localized and characterized it is not clear that this necessarily negates membrane (high fatty acids) effects.

Mechanisms for marijuana's psychoactive effects were thought to be through interactions of the lipid component of cell membranes. The discovery of the cannabinoid receptor has changed that thinking and it is now believed that most of the effects of marijuana are mediated through cannabinoid receptors. Receptors are located in brain areas concerned with memory, cognition and motor coordination. An endogenous ligand, anandamide, has been identified but not studied in humans (Thomas et al, 1996). A specific THC antagonist, SR141716A, produces intense withdrawal signs and behaviors in rodents that have been exposed to THC for even a relatively short period of time (Adams and Martin, 1996). Clinical pharmacology of the antagonist has not been studied in humans.

Most of what is known about human pharmacology of smoked marijuana comes from experiments with plant material containing about 2 percent THC or less. Very few controlled studies have been done with elderly, inexperienced or unhealthy users and data suggest that adverse effects may differ from healthy volunteers (Hollister 1986, 1988).

Most of what is written about the pharmacological effects of marijuana is inferred from experiments on pure THC. The amount of Cannabidiol and other cannabinoids in smoked marijuana could

modify the effects of THC.

Tolerance to marijuana's psychoactive effect probably results from down regulation of cannabinoid receptors which is a form of desensitization of neuronal cells. In general, tolerance to marijuana's effects is often associated with an increased dependence liability. Data indicate that people escalate the amount of marijuana they smoke and continue to use marijuana despite negative consequences. These are classic signs of developing dependence.

After repeated smoked or oral marijuana doses, marked tolerance is rapidly acquired to many of marijuana's effects: cardiovascular, autoimmune and many subjective effects. After exposure is stopped, tolerance is lost with similar rapidity (Jones et al., 1981)

Withdrawal symptoms and signs appearing within hours after cessation of repeated marijuana use have been reported in clinical settings (Duffy and Milan, 1996; Mendelson et al., 1984). Typical symptoms and signs were restlessness, insomnia, irritability, salivation, diarrhea, increased body temperature and sleep disturbances (Jones et al., 1981).

Data on the immune system indicates that marijuana does effect the body's ability to resist microbes including bacteria, viruses and fungi and decreases the body's antitumor activity. THC effects macrophages, T-lymphocytes and B-lymphocyts. A THC receptor has been found in the spleen. These effects may be receptor mediated. In a person with compromised immune function marijuana could pose a health risk.

Acute effects of transient anxiety, panic, feelings of depression and other dysphoric moods have been reported by 17 percent of regular marijuana users in a large study (Tart, 1971). Whether marijuana can produce lasting mood disorders or schizophrenia is less clear (IOM, 1982). Chronic marijuana use can be associated with behavior characterized by apathy and loss of motivation along with impaired educational performance (Pope and Yurgelun-Todd, 1996).

DEA has found that since HHS's last medical and scientific evaluation on marijuana (1986), there have been a significant number of new findings relating to THC:

1. cannabinoid receptors have been identified in the brain and spleen;
2. the CNS cannabinoid receptor has been cloned;
3. an endogenous arachidonic acid derivative ligand (anandamide) has been identified;
4. a high density of cannabinoid receptors have been located in the cerebral cortex, hippocampus, striatum and cerebellum; and
5. an antagonist to the cannabinoid receptor has been developed

In addition, a significant body of literature has been amassed regarding the effects of marijuana. For example:

1. studies on the acute and chronic effects of marijuana on the endocrine system;
2. effect of marijuana on learning and memory;
3. effect of marijuana on pregnant females and their offspring development;
4. effect on the immune system;
5. effect on the lungs; and
6. effects of chronic use with regard to tolerance, dependence and "amotivational syndrome."

While many of the petitioner's arguments are based on new research findings, the interpretation of those findings requires clarification.

As was pointed out by the NIH expert committee on the medical utility of marijuana, marijuana is not a single drug. It is a variable and complex mixture of plant parts with a varying mix of biologically active material. Characterizing the clinical pharmacology is difficult especially when the plant is smoked or eaten. Some of the inconsistency or uncertainty in scientific reports describing the clinical pharmacology of marijuana results from the inherently variable potency of the plant material. Inadequate control over drug dose together with the use of research subjects with variable experience in using marijuana contributes to the uncertainty about what marijuana does or does not do

There are studies in the scientific literature that have evaluated dose-related subjective and reinforcing effects of *Cannabis sativa* in humans. These studies have assessed the subjective and reinforcing effects of *cannabis* cigarettes containing different potencies of THC and/or which have manipulated the THC dose by varying the volume of THC smoke inhaled (Azorlosa et al., 1992; Lukas et al., 1995; Chait et al., 1988; Chait and Burke, 1994; Kelly et al., 1993; Kipplinger et al, 1971, Manno et al., 1970).

Chait et al. (1988) studied the discriminative stimulus effects of smoked marijuana cigarettes containing THC contents of 0%, 0.9%, 1.4%, 2.7%. Marijuana smokers were trained to discriminate smoked marijuana from placebo using 4 puff of a 2.7%-THC cigarettes. Subjective ratings of "high", mean peak "high" scores, and physiological measures (i.e., heart rate) were significantly and dose-dependently increased after smoking the 0.9%, 1.4%, 2.7%. Marijuana cigarettes containing 1.4% THC completely substituted for 2.7%-THC on drug identification tasks, however, 0.9%-THC did not. The authors found that the onset of discriminative stimulus effects was within 90 seconds after smoking began (after the first two puffs). Since the 1.4%-THC cigarette substituted for 2-puffs of the 2.7%-THC cigarette, the authors estimate that an inhaled dose of THC as low as 3 mg can produce discriminable subjective effects.

Similarly, Lukas et al. (1995) reported that marijuana cigarettes containing either 1.26% or 2.53% THC produced significant and dose-dependent increases in level of intoxication and euphoria in male occasional marijuana smokers. Four of the six subjects that smoked the 1.26%-THC cigarette reported marijuana effects and 75% of these subjects reported euphoria. All six of the subjects that smoked 2.53% THC reported marijuana effects and euphoria. Peak levels of self-reported intoxication occurred at 15 and 30 minutes after smoking and returned to control levels by 90-105 minutes. There was no difference between latency to or duration of euphoria after smoking either the 1.26% or 2.53% THC cigarettes. The higher dose-marijuana cigarette produced a more rapid onset and longer duration of action than the lower dose marijuana cigarette (1.26% THC). Plasma THC levels peaked 5-10 minutes after smoking began; the average peak level attained after the low- and high-dose marijuana cigarette was 36 and 69 ng/ml respectively.

In order to determine marijuana dose-effects on subjective

and performance measures over a wide dose range, Azorlosa et al. (1992) evaluated the effects of 4, 10, or 25 puffs from marijuana cigarettes containing 1.75 or 3.55% THC in seven male moderate users of marijuana. Orderly dose-response curves were produced for subjective drug effects, heart rate, and plasma concentration, as a function of THC content and number of puffs. After smoking the 1.75% THC cigarette, maximal plasma THC levels were 57 ng/ml immediately after smoking, 18.3 ng/ml 15 minutes after smoking, 10.3 ng/ml 30 minutes after smoking, and 7.7 ng/ml 45 minutes after smoking.

The study also show that subjects could smoke more of the low THC cigarette to produced effects that were similar to the high THC dose cigarette (Azorlosa et al., 1992). There were nearly identical THC levels produced by 10-puff low-THC cigarette (98.6 ng/ml) and 4-puff high THC cigarette (89.4 ng/ml). Similarly, the subjective effects ratings, including high, stoned, impaired, confused, clear-headed and sluggish, produced under the 10 puff low- and high-THC and 25 puff low-THC conditions did not differ significantly from each other.

As with most drugs of abuse, higher doses of marijuana are preferred over lower dose. Although not preferred, these lower doses still produce cannabimimetic effects. Twelve regular marijuana smokers participated in a study designed to determine the preference of a low potency (0.64%-THC) vs. a high potency (1.95%-THC) marijuana cigarette (Chait and Burke, 1994). The subjects first sampled the marijuana of two different potencies in one session, then chose which potency and how much to smoke. During sampling sessions, there were significant dose-dependent increases in heart rate and subjective effects, including ratings of peak "high", strength of drug effects, stimulated, and drug liking. During choice sessions, the higher dose marijuana was chosen over the lower dose marijuana on 87.5% of occasions. Not surprising, there was a significant positive correlation between the total number of cigarettes smoked and the ratings of subjective effects, strength of drug effect, drug "liking", expired air carbon monoxide, and heart rate increases. The authors state it is not necessary valid to assume that the preference observed in the present study for the high-potency marijuana was due to greater CNS effects from its higher THC content. The present study found that the low- and high-potency marijuana cigarettes also differ on several sensory dimensions; the high-potency THC was found to "fresher" and "hotter". Other studies found that marijuana cigarettes containing different THC

contents varied in sensory dimensions (cf., Chait et al., 1988; Nemeth-Coslett et al., 1986).

As described above in Factors 1 and 2, there are data to show that the effects of THC are dose-dependent and several studies have found that low-potency THC is behaviorally active and can produce cannabimimetic-like subjective and physiological effects. Preclinical and clinical experimental data demonstrate that marijuana and Δ^9-THC have similar abuse liabilities (i.e.,drug discrimination, self-administration, subjective effects). Both preclinical and clinical studies show that discontinuation of either marijuana and Δ^9-THC administration produces a mild withdrawal syndrome. Most of what is known about human pharmacology of smoked marijuana comes from experiments with plant material containing about 2-3% percent THC or less, in cigarette form provided by NIDA (cf., NIDA, 1996). Very few controlled studies have been done with elderly, inexperienced or unhealthy users and data suggests that adverse effects may differ from healthy volunteers (Hollister 1986, 1988).

Cannabidiol (CBD) does not have psychotomimetic properties and does not appear to produce a subjective "high" in human subjects (Musty, 1984). This does not mean that CBD does not have CNS effects or that it does not contribute to the subjective high produced by the cannabinoids. CBD has been clearly shown to have anti-convulsant effects as demonstrated by several techniques such as electroshock-induced seizures, kindled seizures, pentylenetetrazole-induced seizures (Carlini et al., 1973; Izquierdo & Tannhauser, 1973). The suggestion that CBD does not have abuse liability is based in part on the findings that CBD does not produce THC-like discriminative stimulus effects in animals (Ford, Balster, Dewey, Rosecrans, & Harris, 1984; but see below). However, these tests were conducted with CBD administered alone and at only one or two time-points (however, see Jarbe below). The normal route of administration of THC and CBD in humans is by smoking. This mode of administration provides a variable proportion of cannabinoid ratios to the individual subject. As stated above, the chemistry of marijuana is not just the chemistry of Δ^9-THC , but at a minimum, a combination of cannabinoids. According to Turner (1980) kinetic interactions have been reported to occur among the cannabinoids since the early 1970s. Control studies with varying ratios of cannabinoid administrations and complete time-effect functions have still not been conducted.

Domino, Domino, & Domino (1984) have shown that the rate-of-change of the subjective high after marijuana administration does not follow the rate-of-change of plasma or brain THC levels. While plasma THC function show a sharp ascending limb and exponential decline after administration, the subjective "high" peaks after the peak in THC and shows a protracted slow decline. The proportional ratios between the cannabinoids and their metabolites in inhaled marijuana, acting as entourage substances, may have emergent properties that cannot be ascribed to any one component of the complex stimulus administered in the smoke (Gauvin & Baird, 1999). These cannabinoid ratios may play a critical role in the initiation, maintenance, and relapse of marijuana smoking.

CBD has been clearly shown to have anxiolytic (Guimarães et al, 1990, 1994; Musty, 1984; Onaivi, Green & Martin, 1990; Zuardi et al., 1982) and antipsychotic (Zuardi et al., 1995; Zuardi, Antunes Rodrigues, & Cunha, 1991)effects in both animal and man. In the sense that many studies which have examined the subjective profiles of marijuana have demonstrated an "anxiety" component to THC and marijuana use, it should not be surprising that CBD's anxiolytic effects block some of these discriminative properties. However, it should not be concluded from these results that CBD's anxiolytic properties do not have or cannot acquire reinforcing efficacy. It has been suggested that the affective baseline of the drug abuser plays a critical role in the stimulus properties of drugs (Gauvin, Harland & Holloway, 1989). The anxiolytic properties of CBD may serve to diminish the anxiety states associated with many psychopathological states, thus effectively functioning as a "negative reinforcer". As such, CBD may function to increase the likelihood of its administration by its ability to remove the negative affective states in anxious patients. A number of authors have summarized the process by which marijuana smokers "learn to get high" (cf Jones, 1971, 1980; Cappell & Pliner, 1974). Karniol et al., (1974) have clearly demonstrated that the co-administration of CBD with THC actually blocks the anxiety induced by Δ^9-THC, leaving the subjects less tense and potentiating the reinforcing effects of the THC as demonstrated by the subjects verbal reports of enjoying the experience even more. Very few experienced marijuana smokers report symptoms of anxiety (cf Jones, 1971, 1980; Petersen, 1980). The relief of the anxiety and/or psychotomimetic properties of THC by the co-administration of CBD may effectively function as a "negative reinforcer", increasing the likelihood of continued abuse.

Other studies have reported that cannabidiol has cannabinoid properties, including anticonvulsant effects in animal and human models (Consroe et al., 1981; Carlini et al., 1981; Doyle and Spence, 1995), hypnotic effects (Monti et al., 1977), and rate-decreasing effects on operant behavior (Hiltunen et al., 1988). Experiments with cannabidiol in combination with THC have found that certain behavioral responses induced by THC (i.e., operant, schedule-controlled responding) were attenuated by cannabidiol (Borgen and Davis, 1974; Brady and Balster, 1980; Consroe et al., 1977; Dalton et al., 1976; Karniol and Carlini, 1973; Karniol et al., 1974; Welburn et 1976; Zuardi and Karniol, 1983; Zuardi et al., 1981, 1982; Hiltunen et al., 1988). However, other affects produced by THC are augmented or prolonged by the combined administration of CBD and THC or marijuana extract (Chesher and Jackson, 1974; Hine et al., 1975a,b; Fernandes et al., 1974; Karniol and Carlini, 1973; Musty and Sands, 1978; Zuardi and Karniol, 1983; Zuardi et al., 1984). Still other studies did not report any behavioral interaction between the CBD and THC (Bird et al., 1980; Browne and Weissman, 1981; Hollister and Gillespie, 1975; Järbe and Henricksson, 1974; Järbe et al., 1977; Mechoulam et al., 1970; Sanders et al., 1979; Ten Ham and DeLong, 1975).

A study to characterize the interaction between CBD and THC was conducted using preclinical drug discrimination procedures. Rats and pigeons trained to discriminate the presence or absence of THC, and tested with CBD administered alone and in combinations with THC (Hiltunen and Järbe, 1986).Specifically, in rats trained to discriminate 3.0 mg/kg, i.p. THC, CBD (30.0 mg/kg) was administered alone and in combination with THC (0.3 and 1.0 mg/kg, i.p.). In pigeons trained to discriminate 0.56 mg/kg, i.m. THC, CBD (17.5 mg/kg) was administered alone and in combination with THC (0.1, 0.3, and 0.56 mg/kg, i.m.). CBD prolonged the discriminative stimulus effects of THC in rats, but did not change the time-effect curve for THC in pigeons. In pigeons, the administration of CBD did not produce any differential effect under a fixed ratio schedule of reinforcement (Hiltunen and Järbe, 1986).

These data suggest that CBD may somehow augment or prolong the actions of THC in rats and had no effect in pigeons. In the present study, the CBD/THC ratios ranged from 30:1 to 100:1 in rats and enhanced the stimulus effects of THC. However, similar CBD/THC ratios in pigeons (31:1, 58:1 and 175:1) did not result in any changes to THC's discriminative stimulus or response rate effects (Hiltunen and Järbe, 1986).

In conclusion, although cannabidiol does contribute to the other effects of *cannabis*, it appears to lack cannabimimetic properties. In addition, there does not appear to be a scientific consensus that cannabidiol pharmacologically antagonizes, in a classic sense, the effects of THC. Certain functional blockades have been demonstrated. As presented in the scientific literature cited above, the ability of cannabidiol to modify the effects of THC may be specific to only some effects of THC. Most importantly, CBD appears to potentiate the euphorigenic and reinforcing effects of THC which suggests that the interaction between THC and CBD is synergistic and may actually contribute to the abuse of marijuana.

(4) ITS HISTORY AND CURRENT PATTERN OF ABUSE

The federal databases documenting the actual abuse of marijuana are distributed and maintained by the HHS, therefore, we acknowledge and concur with HHS's review of this factor analysis.

(5) THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE.

The basis of the petition to remove marijuana from Schedules I and II is not based on data required by 21 USC 811 (c) (i.e., the scope, duration, and significance of use of the substances).

The petitioner seems to assume that the concept, use of an illegal substance is abuse of that substance, is a concept which is universally held to the exclusion of any other definition of abuse of a substance. While this concept is valid in general terms because marijuana is not a legitimately marketed product therefore it has no legitimate use, holding that all adhere to this definition of abuse denigrates the intellectual capacity of all researchers who investigate the topic. The petitioner neglects to recognize the efforts of the DHHS and many groups which expend a great deal of time and money in research efforts directed toward developing and implementing drug-abuse prevention programs. The petitioner also rejects the notion that there are individuals who abuse marijuana even though the National Household Survey, to which the petitioner refers, would indicate that is the case.

It has not been established that marijuana is effective in treating any medical condition. (NIH Workshop on the Medical Utility of Marijuana, 1997) At this time, there is no body of

knowledge to which a physician can turn to learn which medical condition in which patient will be ameliorated at which dosage schedule of smoked marijuana nor can he/she determine in which patient the benefits will exceed the risks associated with such treatment. The petitioner, therefore, is advocating that individuals become their own physicians, a notion that even primitive man found unsatisfactory.

There is nothing absolute in the placement of a substance into a particular CSA schedule. The placement of a substance in a CSA schedule is the government's mechanism for seeing that the availability of certain psychoactive substances is limited to the industrial, scientific and medical needs which are accepted as being legitimate. The placement of a substance into Schedule I does not preclude research of that substance, nor does it preclude development of a marketable product. The National Institute on Drug Abuse, an element of the Department of Health and Human Services, convened a conference in 1995 and with NIDA's parent organization, the National Institutes of Health, assembled an ad hoc group of experts in 1997 to address issues related to the use, abuse, and medical utility of marijuana. With regard to the medical utility of marijuana, the experts concluded that the scientific process should be allowed to evaluate the potential therapeutic effects of marijuana for certain disorders, dissociated from the societal debate over the potential harmful effects of nonmedical marijuana use. All decisions on the ultimate usefulness of a medical intervention are based on a benefit/risk calculation, and marijuana should be no exception to this generally accepted principle.

The cause and effect relationship which the petitioner poses is neither substantiated nor relevant. Estimates are useful when attempting to allocate resources but they are not necessary for effective eradication of marijuana. Each year, millions of plants are destroyed before their product reaches the market. In addition, federal law enforcement activities result in the seizure of another million or more pounds of product annually.

As reviewed by Gledhill, Lee, Strote, & Wechsler (2000), rates of illicit drug use, especially marijuana, have risen uniformly among the youth in the United States in the past decade and remained steady at the end of the 1990s despite efforts to reduce prevalence. Between 1991 and 1997, rates of past 30-day marijuana use had more than doubled among U.S. 10th grade secondary school students and more than tripled among seniors, after a decade of decline. Between 1997 and 1999, rates of

marijuana use among secondary school students declined for the first time in the 1990s mainly among the older students (16-17 yrs old).

Disturbing are the findings that marijuana use is steadily increasing among 8th, 10th and 12th graders at all prevalence levels. According to the 1996 survey results from the Monitoring the Future Study, 45% of seniors and 35% of 10th graders claimed to have used marijuana at least once. Among eighth graders, annual prevalence rates more nearly tripled 1992 to 1996. Accompanying the increased use of marijuana among High School seniors is a decreasing perceived risk or harm of marijuana use (Johnston et al., 1996). In reality, the harm associated with the abuse of marijuana is increasing; the marijuana emergency room and treatment admission rates continue to increase in recent years.

Gledhill-Hoyt, Lee, Strote, & Wechsler (2000) examined rates and patterns of marijuana use among different types of students and colleges in 1999, and changes in use since 1993. 15,403 students in 1993, 14,724 students in 1997, and 14,138 students in 1999 were assessed. The prevalence of past 30-day and annual marijuana use increased in nearly all student demographic subgroups, and at all types of colleges. Nine out of 10 students (91%) who used marijuana in the past 30 days had used other illicit drugs, smoked cigarettes, and/or engaged in binge drinking. Twenty-nine percent of past 30-day marijuana users first used marijuana and 34% began to use marijuana regularly at or after the age of 18, when most were in college.

Coffey, Lynskey, Wolfe, & Patton (2000) examined predictors of cannabis use initiation, continuity and progression to daily use in adolescents. Over 2,000 students were examined. Peer cannabis use, daily smoking, alcohol use, antisocial behavior and high rates of school-level cannabis use were associated with middle-school cannabis use and independently predicted high-school uptake. Cannabis use persisted into high-school use in 80% of all middle-school users. Middle-school use independently predicted incidents in high-school daily use in males, while high-dose alcohol use and antisocial behavior predicted incidence of daily use in high school females. The authors also found that cigarette smoking was an important predictor of both initiation and persisting cannabis use.

Farrelly et al., (2001) reviewed the NHSDA from 1990 through

1996 and compared those statistics with State law enforcement policies and prices that affect marijuana use in the general public. These authors found evidence that both higher fines for marijuana possession and increased probability of arrest decreased the probability that a young adult will use marijuana. These new data refute the petitioner's suggestion that legal control of marijuana does not have a dampening effect on its use.

(6) WHAT, IF ANY, RISKS ARE THERE TO PUBLIC HEALTH:

There are human data demonstrating that marijuana and Δ^9-THC produce an increase in heart rate, an increase in systolic blood pressure while supine, and decreases in blood pressure while standing (cf., Jaffe, 1993). The increase in heart rate is dose-dependent and its onset and duration correlate with levels of Δ^9-THC in the blood.

When DEA evaluates a drug for control or rescheduling, the question of whether the substance creates dangers to the public health, in addition to, or because of, its abuse potential must be considered. A drug substances' risk to the public health manifests itself in many ways. Abuse of a substance may affect the physical and/or psychological functioning of an individual abuser. In addition, it may have disruptive effects on the abuser's family, friends, work environment, and society in general. Abuse of certain substances leads to a number of antisocial behaviors, including violent behavior, endangering others, criminal activity, and driving while intoxicated. Data examined under this specific factor of the CSA ranges from preclinical toxicity to postmarketing adverse reactions in humans. DEA reviews data from many sources, including forensic laboratory analyses, crime laboratories, medical examiners, poison control centers, substance abuse treatment centers, and the scientific and medical literature.

Adverse effects associated with marijuana and THC as determined by clinical trials, FDA adverse drug effects and World Health Organization data, are described elsewhere (cf., Chait and Zacny, 1988; Chait and Zacny, 1992; Cone et al., 1988; and Pertwee, 1991). A recent press release from the Substance Abuse and Mental Health Service Administration reported that adolescents, age 12 to 17, who use marijuana weekly are nine times more likely than non-users to experiment with illegal drugs or alcohol; six times more likely to run away from home; five times more likely to steal; nearly four times more likely to engage in violence; and three times more likely to have thoughts about committing suicide. It was also reported that adolescents

also associated social withdrawal, physical complaints, anxiety, and depression, attention problems, and thoughts of suicide with past-year marijuana use (SAMHSA, 1999). Budney, Novy, & Hughes (1999) have recently examined the withdrawal symptomology in chronic marijuana users seeking treatment for their dependence. The majority of the subjects (85%) reported that they had experienced symptoms of at least moderate severity and 47% experienced greater than four symptoms rated as severe. The most reported mood symptoms associated with the withdrawal state were irritability, nervousness, depression, and anger. Some of the behavioral characteristics of the marijuana withdrawal syndrome were craving, restlessness, sleep disruptions, strange dreams, changes in appetite, and violent outbursts. These data clearly support the validity and clinical significance of a marijuana withdrawal syndrome in man.

Toxic Effects of Marijuana and THC

Although a median lethal dose (LD_{50}) of THC has not been established in humans, it has been found in laboratory animals (Phillips et al., 1971). In mice, the LD_{50} for THC was 481.9, 454.9 and 28.6 mg/kg after oral, intraperitoneal, and intravenous routes of administration. In rats, the LD_{50} for THC (extracted from marijuana) was 666.0, 372.9 and 42.5 mg/kg after oral, intraperitoneal, and intravenous routes of administration. Another study examined the toxicity of THC in rats, dogs and monkeys (Thompson et al., 1972). Similarly this study found that in rats, the LD_{50} for THC was 1140.0, 400.0 and 20.0 mg/kg after oral, intraperitoneal, and intravenous routes of administration. There was no LD_{50} attained in monkeys and dogs by the oral route. Over 3000 mg/kg of THC was administered without lethality to dogs and monkeys. A dose of about 1000 mg/kg was the lowest dose that caused death in any animal. Behavioral changes in the survivors included sedation, huddled postures, muscle tremors, hypersensitivity to sound and immobility.

The cause of death in the rats and mice after oral THC was profound depression leading to dyspnea, prostration, weight loss, loss of righting reflex, ataxia, and severe decreases in body temperature leading to cessation of respiration from 10 to 40 hours after a single oral dose (Thompson et al., 1972). No consistent pathologic changes were observed in any organs. The cause of death in dogs or monkeys (when it rarely occurred) did not appear to be via the same mechanism as in the rats.

In humans, the estimated lethal dose of intravenous dronabinol [(-)-Δ^9-THC] is 30 mg/kg (2100 mg/70 kg). In

antiemetic studies, significant CNS symptoms were observed following oral doses of 0.4 mg/kg (28 mg/70 kg) (PDR, 1997). Signs and symptoms of mild dronabinol intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia. Following moderate dronabinol intoxication patients may experience memory impairment, depersonalization, mood alterations, urinary retention, and reduced bowel motility. Signs and symptoms of severe dronabinol intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Dronabinol may produce panic reactions in apprehensive patients or seizures in those with an existing seizure disorder (PDR, 1997).

Thus, large doses of THC ingested by mouth were not often associated with toxicity in dogs, nonhuman primates and humans. However, it did produce fatalities in rodents as a result of profound CNS depression. Thus, the evidence from studies in laboratory animals and human case reports indicates that the lethal dose of THC is quite large. The adverse effects associated with THC use are generally extensions of the CNS effects of the drug and are similar to those reported after administration of marijuana (cf., Chait and Zacny, 1988; Chait and Zacny, 1992; Cone et al., 1988; and Pertwee, 1991).

Health and Safety Risks of Δ^9-THC Use

The recent Institute of Medicine report on the scientific basis for the medicinal use of cannabinoid products stated the following:

> Not surprisingly, most users of other illicit drugs have used marijuana first. In fact, most drug users begin with alcohol and nicotine before marijuana - usually before they are of legal age. In the sense that marijuana use typically precedes rather than follows initiation of other illicit drug use, it is indeed a "gateway" drug (Institute of Medicine Report 1999, p. ES.7).

Golub and Johnson (1994) examined the developmental pathway followed by a sample of persons who became serious drug abusers. Of the 837 persons sampled 84% had onset to more serious drugs by the time of the interviews. Most of the sample reported having used marijuana (91%). Two-thirds of the drug abusers reported having used marijuana prior to onset to more serious drugs and an additional 19% reported having onset to marijuana and more

serious drugs in the same year. These data strongly suggest that marijuana does plan an important role on the pathway to more serious drugs use. Further, the proportion who onset to marijuana before or in the same year as more serious drugs was reported to have increased substantially with time from a low of 78% for persons born from 1928 to 1952 to 95% for the most recent birth cohort of the study (1968-1973). These findings further suggest that marijuana's role as a gateway to more serious substance sue has become more pronounced over time.

Ferguson & Horwood (2000)have examined the relationship between cannabis use in adolescence and the onset of other illicit drug use. Data were gathered over the course of a 21 year longitudinal study of a birth cohort of 1,265 children. By the age of 21, just over a quarter of this cohort reported using various forms of illicit drugs on at least one occasion. In agreement with the predictions of a "stage-theory" of the "gateway hypothesis" there was strong evidence of a temporal sequence in which the use of cannabis preceded the onset of the use of other illicit drugs. Of those reporting the use of illicit drugs, all but three (99%) had used cannabis prior to the use of other illicit drugs. However, the converse was not true and the majority (63%) of those using cannabis did not progress to the use of other forms of illicit drugs. In addition, to these findings there was a strong dose-response relationship between the extent of cannabis use and the onset of illicit drug use. The analysis suggested that those using cannabis in any given year on at least 50 occasions had hazards of using other illicit drugs that were over 140 times higher than those who did not use in the year. Furthermore, hazards of the onset of other illicit drug use increased steadily with increasing cannabis use. The very strong gradient in risk reflected the facts that: (1) among non-users of cannabis the use of other forms of illicit drugs was almost non-existent and (2) among regular users of cannabis the use of other illicit drugs was common. To address the issue of "confounding factors", the associations between cannabis use and the onset of illicit drug use were adjusted for a series of prospectively measured confounding factors that included measures of social disadvantage, family functioning, parental adjustment, individual characteristics, attitudes to drug use and early adolescent behavior. After adjustments for these factors, there was still evidence of strong dose-response relationships between the extent of cannabis use in a given year and the onset of illicit drug use - the hazards of the onset of illicit drug use was 100 times those of non-users.

Critics of the "gateway theory" point to the presence of other confounding factors and processes that encourage both cannabis use and other forms of illicit drug use. Despite these factors, the Ferguson & Horwood (2000) study provide a compelling set of results that support the hypothesis that cannabis use may encourage other forms of illicit drug use, including the following:

1. Temporal sequence: There was clear evidence that the use of cannabis almost invariably preceded the onset of other forms of illicit drug use.

2. Dose-Response: There was clear evidence of a very strong and consistent dose-response relationship in which increasing cannabis use was associated with increasing risks of the onset of illicit drug use.

3. Resilience to control for confounding: Even following control for a range of prospectively measured social, family and individual factors, strong and consistent associations remained between cannabis use and the onset of other forms of illicit drug use. And,

4. Specificity of associations: The association could not be explained as reflecting a more general process of transition to adolescent deviant behavior since even after control for contemporaneously assessed measures of juvenile offending, alcohol use, cigarette smoking, unemployment and related measures, strong and consistent relationships between cannabis use and the onset of other forms of illicit drugs remained.

A suggested view of the "gateway hypothesis" states that the use of cannabis may be associated with increasing risks of other forms of illicit drug use, with this relationship being mediated by affiliations with deviant peers and other non-observed processes that may encourage those who use cannabis (and particularly heavy users) to experiment with, and use, other illicit drugs.

While marijuana is clearly not the only gateway to the use of other illicit drugs it is one of the three most typical drugs

in the adolescent's armamentarium. The increased avenues to imported and "home-grown" marijuana which contain behaviorally-active doses of THC and CBD pose a serious threat to the health and well-being of this dimension of society.

Taylor et al (2000) evaluated the relationship between cannabis dependence and respiratory symptoms and lung function in young adults, 21 years of age, while controlling for the effects of cigarette smoking. The researchers found significant respiratory symptoms and changes in spirometry occur in cannabis-dependent individuals at age 21 years, even though the cannabis smoking history is of relatively short duration. The likelihood of reporting a broad range of respiratory symptoms was significantly increased in those who were either cannabis-dependent or smoked tobacco or both compared to non-smokers. The symptoms most frequently and significantly associated with cannabis dependence were early morning sputum production (144% greater prevalence than non-smokers). Overall, respiratory symptoms in study members who met strict criteria for cannabis dependence were comparable to those of tobacco smokers consuming 1-10 cigarettes daily. In subjects who were both tobacco users and were cannabis-dependent, some effects seem to be additive, notably early morning sputum production, which occurred 8 times more frequently than non-smokers.

One of the greatest concerns to society regarding Δ^9-THC is the behavioral toxicity produced by the drug. Δ^9-THC intoxication is associated with impairments in memory, motor coordination, cognition, judgement, motivation, sensation, perception and mood (cf., Jaffe, 1993). The consequences produced by Δ^9-THC-induced behavioral impairments can greatly impact the individual and society in general. These impairments result in occupational, household, or airplane, train, truck, bus or automobile accidents, given that individuals may be attending school, working, or operating a motor vehicle under the influence of the drug. In the most general sense, impaired driving can be seen as a failure to exercise the expected degree of prudence or control necessary to ensure road safety. The operations of a motor vehicle are clearly a skilled performance that requires controlled and flexible use of a person's intellectual and perceptual resources. Cannabis interferes with resource allocations in both cognitive and attentional tasks.

In 1999, Ehrenreich et al., examined the detrimental effects of chronic interference by cannabis with the endogenous cannabinoid systems during peripubertal development in humans. As an index of cannabinoid action, visual scanning and other

attentional factors were examined in 99 individuals who exclusively used cannabis. Early-onset cannabis use (onset before the age of 16) showed significant impairments in attention in adulthood. These persistent attentional deficits may interact with the activities of daily living, such as operating an automobile.

Kurzthaler et al., (1999) examined the effects of cannabis on a cognitive test battery and driving performance skills. The demonstrated significant impairments in the verbal memory and the trail making tests in this study reflect parallel compromises in associative control that is acknowledged as a cognitive process inherent in memory function immediately after smoking cannabis. Applied to the question of driving ability, the authors suggest that the missing functions would signify that a driver under acute cannabis influences would not be able to use acquired knowledge from earlier experiences adequately to ensure road safety.

Recently, the National Highway Traffic Safety Administration (NHTSA; 1998, 1999, 2000) conducted a study with the Institute for Human Psychopharmacology at Maastricht University in The Netherlands. Low dose and high dose THC administered alone, and with alcohol were examined in two on-road driving situations: (1) the Road Tracking Test, measuring a driver's ability to maintain a constant speed of 62 mph and a steady lateral position between the boundaries of the right traffic lane; and (2) the Car Following Test, measuring a drivers' reaction times and ability to maintain distance between vehicles while driving 164 ft. behind a vehicle that executed a series of alternating accelerations and decelerations. Both levels of THC alone, and alcohol alone, significantly impaired performances on BOTH road tests compared with baseline. Alcohol and the high dose of THC produced 36% decrements in reaction time; because the test vehicles were traveling at 59 mph, the delayed reaction times meant that the vehicle traveled, on average, an additional 139 feet beyond the point where the subjects began to decelerate. Even the lower dose of THC by itself retarded reaction times by 0.9 seconds. The NHTSA concluded that even in low to moderate doses, marijuana impairs driving performance.

In a related analysis, Yesavage, Leirer, Denari, & Hollister (1985) examined the acute and delayed effects of smoking one marijuana cigarette containing 1.9% THC (19 mg of THC)on aircraft pilot performance. Ten private pilot licensed subjects were trained in a flight simulator prior to marijuana exposure. Flight simulator performance was measured by the number of

aileron (lateral control), elevator (vertical control) and throttle changes; the size of these control changes; the distance off the center of the runway on landing; and the average lateral and vertical deviation from an ideal glideslope and center line over the final mile of the approach. Compared to baseline performance, significant differences occurred in all variables at 1 and 4 hours after smoking, except for the numbers of throttle and elevator changes at 4 hours. Most importantly, at 24 hours after a single marijuana cigarette, there were significant impairments in the number and size of aileron (lateral control) changes, size of elevator changes, distance off-center on landing, and vertical and lateral deviations on approach to landing. Interestingly, despite these performance deficits, the pilots reported no significant subjective awareness of their impairments at 24 hours. It is noteworthy that a fatal crash in which a pilot had a positive THC screen involved similar landing misjudgments.

In addition to causing unsafe conditions, marijuana use results in decreased performance and lost productivity in the workplace, including injuries, absenteeism, and increased health care costs. A NIDA report on drugs in the workplace summarized the prevalence of marijuana use in the workplace and its impact on society. This report found that in 1989, one in nine working people (11%) reported current use of marijuana (Gust and Walsh, 1989). Recent DAWN data and other surveys indicate that marijuana use is increasing, especially among younger and working age individuals.

Bray, Zarkin, Ringwalt, & Qi (2000) estimated the impact of age of dropout on the relationship between marijuana use and high school dropouts using four longitudinal surveys from students in the Southeastern U.S. public school system. Their results suggested that marijuana initiation was positively related to high school dropout. Although the magnitude and the significance of the relationship varied with age of dropout and the other substances used, the overall effect represented an odds-ratio of approximately 2.3. These data suggest that an individual is approximately 2.3 times more likely to drop out of school than an individual who has not initiated marijuana use.

When DEA evaluates a drug for control or rescheduling, whether the substance creates dangers to the public health, in addition to or because of its abuse potential, must be considered. The risk to the public health of a substance may manifest itself in many ways. Abuse of a substance may affect the physical and/or psychological functioning of an individual

abuser, it may have disruptive effects on the abuser's family, friends, work environment, and society in general. Abuse of certain substances leads to a number of antisocial behaviors, including violent behavior, endangering others, criminal activity, and driving while intoxicated. Data examined under this factor ranges from preclinical toxicity to postmarketing adverse reactions in humans. DEA reviews data from many sources, including forensic laboratory analyses, crime laboratories, medical examiners, poison control centers, substance abuse treatment centers, and the scientific and medical literature.

In its official report titled "Marijuana and Medicine: Assessing the Science Base", the Institute of Medicine highlighted a number of risks to the public health as a result of cannabis consumption:

1) Cognitive impairments associated with acutely administered marijuana limit the activities that people would be able to do safely or productively. For example, no one under the influence of marijuana or THC should drive a vehicle or operate potentially dangerous equipment (Page 107).

2) The most compelling concerns regarding marijuana smoking in HIV/AIDS patients are the possible effects of marijuana on immunity. Reports of opportunistic fungal and bacterial pneumonia in AIDS patients who used marijuana suggest that marijuana smoking either suppresses the immune system or exposes patients to an added burden of pathogens. In summary, patients with pre-existing immune deficits due to AIDS should be expected to be vulnerable to serious harm caused by smoking marijuana. The relative contribution of marijuana smoke versus THC or other cannabinoids is not known. (Page 116-117)

3) DNA alterations are known to be early events in the development of cancer, and have been observed in the lymphocytes of pregnant marijuana smokers and in those of their newborns. This is an important study because the investigators were careful to exclude tobacco smokers; a problem in previous studies that cited mutagenic effects of marijuana smoke. (Page 118-119)

4) ...factors influence the safety of marijuana or cannabinoid drugs for medical use: the delivery system, the use of plant material, and the side effects of cannabinoid drugs. (1) Smoking marijuana is clearly harmful, especially in people with chronic conditions, and is not an ideal drug delivery

system. (2) Plants are of uncertain composition, which renders their effects equally uncertain, so they constitute an undesirable medication. (Page 127)

(7) ITS PSYCHIC OR PHYSIOLOGICAL DEPENDENCE LIABILITY.

The "dopaminergic hypothesis of drug abuse" is not the only explanation for the neurochemical actions of drugs. The nucleus accumbens/ventral striatum areas of the brain, typically referred to as simply the Nucleus Accumbens (NAc), represents a critical site for mediating the rewarding or hedonic properties of several classes of abused drugs, including alcohol, opioids, and psychomotor stimulants (Gardner & Vorel, 1998; Koob, 1992; Koob et al., 1998; Wise, 1996; Wise & Bozarth, 1987). It is generally appreciated that all of these drugs augment extracellular dopamine levels in the NAc and that this action contributes to their rewarding properties. However, recent evidence also suggests that many drugs of abuse have dopamine-independent interactions with Nac neuronal activity (Carlezon & Wise, 1996; Chieng & Williams, 1998; Koob, 1992; Martin et al., 1997; Yuan et al., 1992). Recent studies conducted at the Cellular Neurobiology Branch of the NIDA by Hoffman & Lupica (2001) concluded that THC modulates NAc glutamatergic functioning of dopamine. These authors suggested that increases in Nac dopamine levels may be a useful neurochemical index of drug reward but do not fully account for the complex processing of fast synaptic activity by this neuromodulator in the Nac. Moreover, because both glutamatergic and GABAergic inputs to medium spiny neurons are directly inhibited by dopamine, as well as by drugs of abuse. It is likely that these effects contribute to the abuse liability of marijuana.

In addition, the petitioner's global statements about the role of dopamine, the reinforcing effects of marijuana and other drugs, and the predictive validity of animal self-administration studies with marijuana and abuse potential in humans are not supported by the scientific literature. For example:

1) There are drugs that do not function through dopaminergic systems that are self-administered by animals and humans (i.e., barbiturates, benzodiazepines, PCP).

2) There are drugs that are readily self-administered by animals that are not abused by man (antihistamines)

3) There are drugs that are abused by humans that are not readily self-administered by animals (hallucinogens and hallucinogenic phenethylamines, nicotine, caffeine).

4) There are drugs that have no effect on dopamine that are self-administered by animals and not abused by humans (i.e., antihistamines).

Physical Dependence in Animals

Abrupt withdrawal from Δ^9-THC can produce a mild spontaneous withdrawal syndrome in animals, including increased motor activity and grooming in rats, decreased seizure threshold in mice and increased aggressiveness, irritability and altered operant performance in rhesus monkeys (cf., Pertwee, 1991). The failure to observe profound withdrawal signs following abrupt discontinuation of Δ^9-THC may be due to (1) its long half-life in plasma and (2) slowly waning levels of Δ^9-THC and its metabolites that continue to permit receptor adaptation.

Recently the discovery of a cannabinoid receptor antagonist demonstrates that a profound precipitated withdrawal syndrome can be produced in Δ^9-THC tolerant animals after twice daily injections (Tsou et al., 1995) or continuous infusion (Aceto et al., 1995, 1996). In rats continuously infused with low doses Δ^9-THC for four days, the cannabinoid antagonist precipitated a behavioral withdrawal syndrome, including scratching, face rubbing, licking, wet dog shakes, arched back and ptosis (Aceto et al., 1996). This chronic low dose regimen consisted of 0.5, 1, 2, 4 mg/kg/day Δ^9-THC on days 1 through 4; 5 and 25-fold higher Δ^9-THC doses were used for the medium and high dose regimens, respectively. The precipitated withdrawal syndrome was dose-dependently more severe in the medium and high THC dose groups.

Physical Dependence in Humans

Signs of withdrawal have been demonstrated after studies with Δ^9-THC. Although the intensity of the withdrawal syndrome is related to the daily dose and frequency of administration, in general, the signs of Δ^9-THC withdrawal have been relatively mild (cf., Pertwee, 1991). This withdrawal syndrome has been compared to that of a short-term, low dose treatment with an opioid or ethanol, and includes changes in mood, sleep, heart rate body temperature, and appetite. Other signs such as irritability, restlessness, tremor mild nausea, hot flashes and sweating have also been noted (cf., Jones, 1983).

A withdrawal syndrome was reported after the discontinuation of oral THC in volunteers receiving dronabinol dosages of 210 mg/day for 12 to 16 consecutive days (PDR, 1997). This was 42-times the recommended dose of 2.5 mg, b.i.d. Within 12 hours after discontinuation, these volunteers manifested withdrawal symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours after THC discontinuation, there was an intensification of withdrawal symptoms to include "hot flashes", sweating, rhinorrhea, loose stools, hiccoughs, and anorexia. These withdrawal symptoms gradually dissipated over the next 48 hours. EEG changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt challenge. Patients also complained of disturbed sleep for several weeks after discontinuation of high doses of dronabinol. The intensity of the cannabinoid withdrawal syndrome is related by the chronic dose and by the frequency of chronic administration. There is also evidence that the cannabinoid withdrawal symptoms can be reversed by the administration of marijuana and Δ^9-THC, or by treatment with a barbiturate (hexobarbital) or ethanol (Pertwee, 1991).

An acute withdrawal syndrome or "hangover" has been reported by Chait, Fischman, & Schuster (1985) developing approximately 9 hours after smoking a 1 g marijuana cigarette containing 2.9% THC. Five of twelve subjects reported themselves as "dopey and hung over" the morning after smoking the single cigarette. In a 10 second and 30 second time-production task significant marijuana hangover effects were found. The effect on the time production task is of interest since the effect obtained the morning after smoking marijuana was opposite to that observed acutely after smoking marijuana. These data may suggest an opponent compensatory rebound which may underlie the development of tolerance over periods of chronic marijuana exposure. Scores

on the benzedrine-group (BG) scale, a stimulant scale of the Addiction Research Center Inventory (ARCI) consisting mainly of terms relating to intellectual efficiency and energy, were significantly higher the morning after marijuana smoking, as well. Chait, Fischman, & Schuster also reported increases on the amphetamine (A) scale of the ARCI, a measure of the dose-related effects of d-amphetamine. Cousens & DiMascio (1973) have previously reported a similar "hangover" and "speed of thought alterations" in subjects the morning after they had received a 30 mg oral dose of Δ^9-THC. Like the "hangover" associated with high dose ethyl alcohol consumption, the hangover from marijuana may be qualitatively identical to, and differ only on an intensity dimension from, the withdrawal syndrome produced from chronic consumption (cf Gauvin, Cheng, Holloway, 1993).

As described above, Haney et al. have recently described abstinence symptoms of an acute withdrawal syndrome following high (30 mg q.i.d.) and low (20 mg q.i.d) dose administrations of oral THC (Haney et al., 1999a) and following 5 puffs of high (3.1%) and low (1.8%) THC-containing smoked marijuana cigarettes (Haney et al., 1999b). Both of these studies have delineated a withdrawal syndrome from concentrations of THC significantly lower than those reported in any other previous study and, for the first time, clearly identified a marijuana withdrawal syndrome detected at low levels of THC exposure that do not produce tolerance. These data suggest that dependence on THC may in fact be an important consequence of repeated, daily exposure to cannabinoids and that daily marijuana use may be maintained, at least in part, by the alleviation of abstinence symptoms.

As stated above, Budney, Novy, & Hughes (1999) have recently examined the withdrawal symptomology in chronic marijuana users seeking treatment for their dependence. The majority of the subjects (85%) reported that they had experienced symptoms of at least moderate severity and 47% experienced greater than four symptoms rated as severe. The most reported mood symptoms associated with the withdrawal state were irritability, nervousness, depression, and anger. Some of the behavioral characteristics of the marijuana withdrawal syndrome were craving, restlessness, sleep disruptions, strange dreams, changes in appetite, and violent outbursts. These data clearly support the validity and clinical significance of a marijuana withdrawal syndrome in man. Large-scale population studies have also reported significant rates of cannabis dependence (Kessler et al., 1994; Farrell et al., 1998), particularly in prison and homeless populations. Similar reports of cannabis dependence in withdrawal in other populations have been previously discussed

(above; Crowley et al (1998); Kouri & Pope (2000)).

Psychological Dependence in Humans

In addition to the physical dependence produced by abrupt withdrawal from Δ^9-THC, psychological dependence on Δ^9-THC can also be demonstrated. Case reports and clinical studies show that frequency of Δ^9-THC use (most often as marijuana) escalates over time, there is evidence that individuals increase the number, doses, and potency of marijuana cigarettes. Data have clearly shown that tolerance to the stimulus effects of the drug develops which could lead to drug seeking behavior (Pertwee, 1991; Aceto et al., 1996; Kelly et al., 1993, 1994; Balster and Prescott, 1992; Mendelson et al., 1976; Mendelson and Mello, 1985; Mello, 1989). Several studies have reported that patterns of marijuana smoking and increased quantity of marijuana smoked were related to social context and drug availability (Kelly et al., 1994; Mendelson and Mello, 1985; Mello, 1989). There have been, however, other studies which have demonstrated that the magnitude of many of the behavioral effects produced by Δ^9-THC and other synthetic cannabinoids lessens with repeated exposure while also demonstrating that tolerance did not develop to the euphorigenic activity, or the "high" from smoked marijuana (Dewey, 1986; Perez-Reyes et al., 1991). Recent electrophysiological data from animals suggests that the response of VTA dopamine neurons do not diminish during repeated exposure to cannabinoids, and that this may underlie the lack of tolerance to the euphoric effects of marijuana even with chronic use (Wu & French, 2000).

The problems of psychological dependence associated with marijuana (THC) abuse are apparent from DAWN reports and survey data from the National Household Survey on Drug Abuse and the Monitoring the Future study. These databases show that the incidence of chronic daily marijuana use and adverse events associated with its use are increasing, especially among the young. At the same time, perception of risk has decreased and availability is widespread (cf., NIDA, 1996). These factors contribute to perpetuating the continued use of the marijuana.

(8) WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THIS SUBCHAPTER.

According to the legal definition, marijuana (Cannabis sativa *L.*) is not an immediate precursor of a scheduled controlled substance. However, cannabidiol is a precursor for delta-9-tetrahydrocannabinol, a Schedule I substance under the CSA.

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