DEPARTMENT OF JUSTICE

Drug Enforcement Administration

Notice of Denial of Petition

By letter dated March 20, 2001, the Drug Enforcement Administration (DEA) denied a petition to initiate rulemaking proceedings to reschedule marijuana. Because DEA believes that this matter is of particular interest to members of the public, the agency is publishing below the letter sent to the petitioner (denying the petition), along with the supporting documentation that was attached to the letter.

Dated: March 28, 2001.

Donnie R. Marshall,

Administrator.

U.S. Department of Justice,

Drug Enforcement Administration,
Washington, D.C. 20537

March 20, 2001.

Jon Gettman:

Dear Mr. Gettman: On July 10, 1995, you petitioned the Drug Enforcement Administration (DEA) to initiate rulemaking proceedings under the rescheduling provisions of the Controlled Substances Act (CSA). Specifically, you petitioned DEA to propose rules, pursuant to 21 U.S.C. 811(a), that would amend the schedules of controlled substances with respect to the following controlled substances: marijuana; tetrahydrocannabinols; dronabinol; and nabilone. Although you grouped these substances together in your petition, the scheduling analysis differs for each. To avoid confusion, DEA is providing you with a separate response for each of the controlled substances that you proposed be rescheduled. This letter responds to your petition to reschedule marijuana.

Summary

You requested that DEA remove marijuana from schedule I based on your assertion that ''there is no scientific evidence that [it has] sufficient abuse potential to warrant schedule I or II status under the [CSA].'' In accordance with the CSA rescheduling provisions, DEA gathered the necessary data and forwarded that information and your petition to the Department of Health and Human Services (HHS) for a scientific and medical evaluation and scheduling recommendation. HHS concluded that marijuana does have a high potential for abuse and therefore recommended that marijuana remain in schedule I. Based on the HHS evaluation and all other relevant data, DEA has concluded that there is no substantial evidence that marijuana should be removed from schedule I. Accordingly, your petition to initiate rulemaking proceedings to reschedule marijuana is hereby denied.

Detailed Explanation

A. Statutory Requirements and Procedural History

The CSA provides that the schedules of controlled substances established by Congress may be amended by the Attorney General in rulemaking proceedings prescribed by the Administrative Procedure Act. 21 U.S.C. 811(a). The Attorney General has delegated this authority to the Administrator of DEA. 28 CFR 0.100.

As you have done, any interested party may petition the Administrator to initiate rulemaking proceedings to reschedule a controlled substance. 21 U.S.C. 811(a); 21 CFR 1308.43(a). Before initiating such proceedings, the Administrator must gather the necessary data and request from the Secretary of HHS a scientific and medical evaluation and recommendation as to whether the controlled substance should be rescheduled as the petitioner proposes. 21 U.S.C. 811(b); 21 CFR 1308.43(d). The Secretary has delegated this function to the Assistant Secretary for Health.[1]

The recommendations of the Assistant Secretary are binding on the Administrator with respect to scientific and medical matters. Id. If the Administrator determines that the evaluations and recommendations of the Assistant Secretary and ''all other relevant data'' constitute substantial evidence that the drug that is the subject of the petition should be subject to lesser control or removed entirely from the schedules, he shall initiate rulemaking proceedings to reschedule the drug or remove it from the schedules as the evidence dictates. 21 U.S.C. 811(b); 21 CFR 1308.43(e). In making such a determination, the Administrator must consider eight factors:

(1) The drug's actual or relative potential for abuse;

(2) Scientific evidence of its pharmacological effect, if known;

(3) The state of current scientific knowledge regarding the drug;

(4) Its history and current pattern of abuse;

(5) The scope, duration, and significance of abuse;

(6) What, if any, risk there is to the public health;

(7) The drug's psychic or physiological dependence liability; and

(8) Whether the drug is an immediate precursor of a substance already controlled under the CSA.

21 USC 811(c).

In this case, you submitted your petition by letter dated March 10, 1995. After gathering the necessary data, DEA referred the petition to HHS on December 17, 1997, and requested from HHS a scientific and medical evaluation and scheduling recommendation. HHS forwarded its scientific and medical evaluation and scheduling recommendation to DEA on January 17, 2001.

B. HHS Scientific and Medical Evaluation and Other Relevant Data Considered by DEA

Attached to this letter is the scientific and medical evaluation and scheduling recommendation that HHS submitted to DEA.[2] Also attached is a document prepared by DEA that specifies other data relevant to your petition that DEA considered.

C. Basis for Denial of Your Petition: The Evidence Demonstrates That Marijuana Does Have A High Potential For Abuse

Your petition rests on your contention that marijuana does not have a ''high potential for abuse'' commensurate with schedule I or II of the CSA. The Assistant Secretary has concluded, based on current scientific and medical evidence, that marijuana does have a high potential for abuse commensurate with schedule I. The additional data gathered by DEA likewise reveals that marijuana has a high potential for abuse. Indeed, when the HHS evaluation is viewed in combination with the additional data gathered by DEA, the evidence overwhelmingly leads to the conclusion that marijuana has a high potential for abuse.

Accordingly, there is no statutory basis for DEA to grant your petition to initiate rulemaking proceedings to reschedule marijuana. For this reason alone, your petition must be denied.

D. A Schedule I Drug With a High Potential For Abuse and No Currently Accepted Medical Use or Safety for Use Must Remain Classified In Schedule I

DEA's denial of your petition is based exclusively on the scientific and medical findings of HHS, with which DEA concurs, that lead to the conclusion that marijuana has a high potential for abuse. Nonetheless, independent of this scientific and medical basis for denying your petition, there is a logical flaw in your proposal that should be noted.

You do not assert in your petition that marijuana has a currently accepted medical use in treatment in the United States or that marijuana has an accepted safety for use under medical supervision. Indeed, the HHS scientific and medical evaluation reaffirms expressly that marijuana has no currently accepted medical use in treatment in the United States and a lack of accepted safety for use under medical supervision.

Nor do you dispute that marijuana is a drug of abuse. That is, you do not contend that marijuana has no potential for abuse such that it should be removed entirely from the CSA schedules. Rather, your contention is that marijuana has less than a ''high potential for abuse'' commensurate with schedules I and II and, therefore, it cannot be classified in either of these two schedules.

Congress established only one schedule—schedule I—for drugs of abuse with ''no currently accepted medical use in treatment in the United States'' and ''lack of accepted safety for use * * * under medical supervision.'' 21 USC 812(b). To be classified in schedules II through V, a drug of abuse

[1] As set for in a memorandum of understanding entered in to by HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the CAS, with the concurrence of NIDA. 50 FR 9518 (1985).

[2] To avoid confusion, those parts of the HHS document that are not relevant to your petition with respect to marijuana (*i.e.,* those parts that are relevant only to the scheduling of tetrahydrocannabinols, dronabinol, or nabilone) have been redacted from the attachment. The HHS evaluation of these other substances will be addressed when DEA responds (in separate letters) to your petitions with respect to these other substances.

must have a ''currently accepted medical use in treatment in the United States.'' [3] *Id.* This is why the CSA allows practitioners to prescribe only those controlled substances that are listed in schedules II through V. 21 USC 829. Drugs listed in schedule I, by contrast, may not be prescribed for patient use; they may only be dispensed by practitioners who are conducting FDA-approved research and have obtained a schedule I research registration from DEA. 21 USC 823(f); 21 CFR 5.10(a)(9), 1301.18, 1301.32.

That schedule I controlled substances are characterized by a lack of accepted medical use was recently reiterated by Congress, when it declared, in a provision entitled, ''NOT LEGALIZING MARIJUANA FOR MEDICINAL USE'':

It is the sense of the Congress that—

(1) certain drugs are listed on Schedule I of the Controlled Substances Act if they have a high potential for abuse, lack any currently accepted medical use in treatment, and are unsafe, even under medical supervision;

(2) the consequences of illegal use of Schedule I drugs are well documented, particularly with regard to physical health, highway safety, and criminal activity;

(3) pursuant to section 401 of the Controlled Substances Act, it is illegal to manufacture, distribute, or dispense marijuana, heroin, LSD, and more than 100 other Schedule I drugs;

(4) pursuant to section 505 of the Federal Food, Drug and Cosmetic Act, before any drug can be approved as a medication in the United States, it must meet extensive scientific and medical standards established by the Food and Drug Administration to ensure it is safe and effective;

(5) *marijuana and other Schedule I drugs have not been approved by the Food and Drug Administration to treat any disease or condition.*

* * * * *

Pub. L. No. 105–277, Div. F., 112 Stat. 2681–760 to 2681–761 (1998) (emphasis added).

Thus, when it comes to a drug that is currently listed in schedule I, if it is undisputed that such drug has no currently accepted medical use in treatment in the United States and a lack of accepted safety for use under medical supervision, and it is further undisputed that the drug has at least some potential for abuse sufficient to warrant control under the CSA, the drug must remain in schedule I. In such circumstances, placement of the drug in schedules II through V would conflict with the CSA since such drug would not meet the criterion of ''a currently accepted medical use in treatment in the United States.'' 21 USC 812(b).

Therefore, even if one were to assume, theoretically, that your assertions about marijuana's potential for abuse were correct (*i.e.,* that marijuana had some potential for abuse but less than the ''high potential for abuse'' commensurate with schedules I and II), marijuana would not meet the criteria for placement in schedules III through V since it has no currently accepted medical use in treatment in the United States—a determination that is reaffirmed by HHS in the attached medical and scientific evaluation.

For the foregoing reasons, your petition to reschedule marijuana cannot be granted under the CSA and is, therefore, denied.

Sincerely,

Donnie R. Marshall,
Administrator.
Attachments.

Department of Health and Human Services,

Office of the Secretary, Office of the Public Health and Science, Assistant Secretary for Health, Surgeon General, Washington, D.C. 20201.

January 17, 2001.

Mr. Donnie R. Marshall,
Deputy Administrator, Drug Enforcement Administration, Washington, D.C. 20537.

Dear Mr. Marshall: In response to your request dated December 17, 1997, and pursuant to the Controlled Substances Act (CSA), 21 U.S.C. § 811 (b), (c), and (f), the Department of Health and Human Services (DHHS) recommends that marijuana * * * continue to be subject to control under Schedule I. * * * Marijuana and the tetrahydrocannabinols are currently controlled under Schedule I of the CSA. Marijuana continues to meet the three criteria for placing a substance in Schedule I of the CSA under 21 U.S.C. 812(b)(1). As discussed in the attached analysis, marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision. Accordingly, HHS recommends that marijuana * * * continue to be subject to control under Schedule I of the CSA.

You will find enclosed two documents prepared by FDA's Controlled Substance Staff that are the bases for the recommendations.

Sincerely yours,

David Satcher,
Assistant Secretary for Health and Surgeon General.
Enclosure.

Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act

A. Background

On July 10, 1995, Mr. Jon Gettman submitted a petition to the Drug Enforcement Administration (DEA) requesting that proceedings be initiated to repeal the rules and regulations that place marijuana and the tetrahydrocannabinols in Schedule I of the Controlled Substances Act (CSA) and dronabinol and nabilone in Schedule II of the CSA. The petition contends that evidence of abuse potential is insufficient for each substance or class of substances to be controlled in Schedule I or II of the CSA. In December 1997, the DEA Administrator requested that the Department of Health and Human Services (DHHS) develop scientific and medical evaluations and recommendations as to the proper scheduling of the substances at issue, pursuant to 21 U.S.C. 811(b).

This document responds to the portion of the petition that concerns marijuana * * *.

In accordance with 21 U.S.C. 811(b), the DEA has gathered information, and the Secretary of DHHS has considered eight factors in a scientific and medical evaluation, to determine how to schedule and control marijuana (Cannabis sativa) under the CSA. The eight factors are: actual or relative potential for abuse, scientific evidence of pharmacological effects, scientific knowledge about the drug or substance in general, history and current patterns of abuse, the scope and duration and significance of abuse, the risk (if any) to public health, psychic or physiologic dependence liability, and whether the substance is an immediate precursor of a substance that is already controlled. If appropriate, the Secretary must also make three findings—related to a substance's abuse potential, legitimate medical use, and safety or dependence liability—and then a recommendation. This evaluation presents scientific and medical knowledge under the eight factors, findings in the three required areas, and a recommendation.

Administrative responsibilities for evaluating a substance for control under the CSA are performed by the Food and Drug Administration (FDA), with the concurrence of the National Institute on Drug Abuse (NIDA), as described in the Memorandum of Understanding (MOU) of March 8, 1985 (50 FR 9518–20).

Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to the scheduling of marijuana are considered below. The weight of the scientific and medical evidence considered under these factors supports the three findings that: (1) Marijuana has a high potential for abuse, (2) marijuana has no currently accepted medical use in treatment in the United States, and (3) there is a lack of accepted evidence about the safety of using marijuana under medical supervision.

B. Evaluating Marijuana Under the Eight Factors

This section presents scientific and medical knowledge about marijuana under the eight required factors.

[3] A controlled substance in schedule II must have either ''a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.'' 21 USC 812(b)(2)(B).

1. Its Actual or Relative Potential for Abuse

The CSA defines marijuana as the following:

All parts of the plant Cannabis Sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination. 21 U.S.C. 802(16).

The term ''abuse'' is not defined in the CSA. However, the legislative history of the CSA suggests the following in determining whether a particular drug or substance has a potential for abuse:

a. Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

b. There is a significant diversion of the drug or substance from legitimate drug channels.

c. Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances.

d. The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community. Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91–1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603.

In considering these concepts in a variety of scheduling analyses over the last three decades, the Secretary has analyzed a range of factors when assessing the abuse liability of a substance. These factors have included the prevalence and frequency of use in the general public and in specific sub-populations, the amount of the material that is available for illicit use, the ease with which the substance may be obtained or manufactured, the reputation or status of the substance ''on the street'', as well as evidence relevant to population groups that may be at particular risk.

Abuse liability is a complex determination with many dimensions. There is no single test or assessment procedure that, by itself, provides a full and complete characterization. Thus, no single measure of abuse liability is ideal. Scientifically, a comprehensive evaluation of the relative abuse potential of a drug substance can include consideration of the drug's receptor binding affinity, preclinical pharmacology, reinforcing effects, discriminative stimulus effects, dependence producing potential, pharmacokinetics and route of administration, toxicity, assessment of the clinical efficacy-safety database relative to actual abuse, clinical abuse liability studies and the public health risks following introduction of the substance to the general population. It is important to note that abuse may exist independent of a state of physical dependence, because drugs may be abused in doses or in patterns that do not induce physical dependence.

Animal data and epidemiological data are both used in determining a substance's abuse liability. While animal data may help the Secretary draw conclusions on the abuse liability of a substance, data regarding human abuse, if available, is given greater weight. For example, even if a compound fails to display abuse liability in animal laboratory testing, positive evidence of abuse liability in humans is given greater weight. Epidemiological data can also be an important indicator of actual abuse and may, in some circumstances, be given greater weight than laboratory data. Thus, in situations where the epidemiological data indicates that a substance is abused, despite the lack of positive abuse liability indications in animal or human laboratory testing, the abuse liability determination may rest more heavily on the epidemiological data. Finally, evidence of clandestine production and illicit trafficking of a substance are also important factors to consider as this evidence sheds light on both the demand for a substance as well as the ease with which it can be obtained.

The Secretary disagrees with Mr. Gettman's assertion that ''[t]he accepted contemporary legal convention for evaluating the abuse potential of a drug or substance is the relative degree of self-administration the drug induces in animal subjects.'' As discussed above, self-administration tests that identify whether a substance is reinforcing in animals are but one component of the scientific assessment of the abuse potential of a substance. Positive indicators of human abuse liability for a particular substance, whether from laboratory studies or epidemiological data, are given greater weight than animal studies suggesting the same compound has no abuse potential.

Throughout his petition, Mr. Gettman argues that while many people ''use'' marijuana, few ''abuse'' it. He appears to equate abuse with the level of physical dependence and toxicity resulting from marijuana use. Thus, he appears to be arguing that a substance that causes only low levels of physical dependence and toxicity must be considered to have a low potential for abuse. The Secretary does not agree with this argument. Physical dependence and toxicity are not the only factors that are considered in determining a substance's abuse potential. The actual use and frequency of use of a substance, especially when that use may result in harmful consequences such as failure to fulfill major obligations at work or school, physical risk-taking, or even substance-related legal problems, are indicative of a substance's abuse potential.

a. *There is evidence that individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.*

Marijuana is a widely used substance. The pharmacology of the psychoactive constituents of marijuana (including delta^{9}-THC, the primary psychoactive ingredient in marijuana) has been studied extensively in animals and humans and is discussed in more detail below in Section 2, ''Scientific Evidence of its Pharmacological Effects, if Known.'' Although it is difficult to determine the full extent of marijuana abuse, extensive data from the National Institute on Drug Abuse (NIDA) and from the Substance Abuse Mental Health Services Administration (SAMHSA) are available. These data are discussed in detail in Section 4 ''Its History and Current Pattern of Abuse;'' Section 5, ''The Scope, Duration, and Significance of Abuse;'' and Section 6, ''What, if any Risk There is to the Public Health.''

According to the National Household Survey on Drug Abuse (NHSDA), of the 14.8 million Americans who used illicit drugs on a monthly basis in 1999, 11.2 million used marijuana. In 1998, 1.6 million children between the ages of 12 and 17 used marijuana for the first time. (See the discussion of the 1999 NHSDA in Section 4). A 1999 survey of 8th, 10th, and 12th grade students indicates that marijuana is the most widely used illicit drug in this age group. By 12th grade, 37.8% of students report having used marijuana in the past year, and 23.1% report using it monthly. (See the

discussion of the Monitoring the Future Study in Section 4). Primary marijuana abuse accounts for 13% of the admissions to treatment facilities for substance abuse, with 92% of those admitted having used marijuana for the first time by age 18. (See discussion of the Treatment Episode Data Set in Section 4).

The Drug Abuse Warning Network (DAWN) is a national probability survey of hospitals with emergency departments (EDs). DAWN is designed to obtain information on ED episodes that are induced by or related to the use of an illegal drug or the non-medical use of a legal drug. DAWN recently reported 87,150 ED drug mentions for marijuana/hashish in 1999, representing 16 % of all drug-related episodes in 1999. (See discussion of DAWN in Section 4). In 1999, DAWN data show that out of 664 medical examiner marijuana-related episodes, there were 187 deaths in persons who had used marijuana alone. While marijuana has a low level of toxicity when compared to other drugs of abuse, there are a number of risks resulting from both acute and chronic use of marijuana. These risks are discussed in full in sections 2 and 6 below.

b. *There is significant diversion of the substance from legitimate drug channels.*

Because cannabis is currently available through legitimate channels for research purposes only, there is limited legitimate use of this substance and thus limited potential for diversion. The lack of significant diversion of investigational supplies may also result from the ready availability of cannabis of equal or greater potency through illicit channels.

The magnitude of the demand for marijuana is, however, evidenced by the Drug Enforcement Administration (DEA) / Office of National Drug Control Policy (ONDCP) statistics. Data on marijuana seizures can often highlight trends in the overall trafficking patterns. The DEA's Federal-Wide Drug Seizure System (FDSS) provides information on total federal drug seizures. FDSS reports total federal seizures of 699 metric tons of marijuana in fiscal year 1997, 825 metric tons in fiscal year 1998 and 1,175 metric tons in fiscal year 1999 (ONDCP, 2000).

c. *Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances.*

The 1998 NHSDA suggests that 6.8 million individuals use marijuana on a weekly basis (SAMHSA, 1998), confirming that marijuana has reinforcing properties for many individuals. The FDA has not approved a new drug application for marijuana, although research under several INDs is currently active. Based on the large number of individuals who use marijuana, it can be concluded that the majority of individuals using cannabis do so on their own initiative, not on the basis of medical advice from a practitioner licensed to administer the drug in the course of professional practice.

d. *The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.*

Two drug products that contain cannabinoid compounds that are structurally related to the active components in marijuana are already regulated under the CSA. These are Marinol (dronabinol, delta^9-THC), which is a Schedule III drug, and nabilone, which is a Schedule II drug. All other cannabinoid compounds that are structurally related to the active components in marijuana are listed as Schedule I drugs under the CSA. Cannabinoid compounds constitute a distinct pharmacological class that is unrelated to other drugs currently listed in the CSA. The primary psychoactive compound in botanical marijuana is delta^9-tetrahydrocannabinol (delta^9-THC). Other cannabinoids also present in the marijuana plant likely contribute to the psychoactive effects. Individuals administer the constituents of marijuana by burning the material and inhaling (smoking) many of its combustible and vaporized products. The route of administration of a drug is one component of its abuse potential. Most psychoactive drugs exert their maximum subjective effects when blood levels of the drug are rapidly increased. Inhalation of drugs permits a rapid delivery and distribution of the drug to the brain. The intense psychoactive drug effect, which can be rapidly achieved by smoking, is often called a ''rush'' and generally is considered to be the effect desired by the abuser. This effect explains why marijuana abusers prefer the inhalation, intravenous or intranasal routes rather than oral routes of administration. Such is also the case with cocaine, opium, heroin, phencyclidine, and methamphetamine (Wesson & Washburn, 1990).

2. Scientific Evidence of Its Pharmacological Effects, If Known

We concur with the petitioner that there is abundant scientific data available on the neurochemistry, toxicology, and pharmacology of marijuana. This section includes a scientific evaluation of marijuana's neurochemistry and pharmacology, central nervous system effects including human and animal behavior, pharmacodynamics of central nervous system effects, cognitive effects, cardiovascular and autonomic effects, endocrine system effects and immunological system effects. The overview presented below relies upon the most current research literature on cannabinoids.

Neurochemistry and Pharmacology of Marijuana

To date, a total of 483 natural constituents have been identified in marijuana of which approximately 66 belong to the general group known as cannabinoids (Ross and ElSohly, 1995). The cannabinoids appear to be unique to marijuana, and most of those occurring naturally have already been identified. Within the cannabinoids, delta^9-tetrahydrocannabinol (delta^9-THC) is considered the major psychoactive constituent of marijuana. Since the elucidation of the structure and discovery of the function of delta^9-THC, in 1964 by Gaoni and Mechoulam, cannabis and cannabinoid research has flourished. Substantial discoveries on the pharmacology, biochemistry and behavioral mechanisms of action of the cannabinoids have been accomplished, and laid the scientific foundations for a better understanding of the effects of marijuana.

There is conclusive evidence of the existence of at least two cannabinoid receptors, CB_1 and CB_2, and it is now known that some of the pharmacological effects of cannabinoids are mediated through activation of these receptors. The cannabinoid receptors belong to the G-protein-coupled receptors family and present a typical seven transmembrane-spanning domain structure. Many G-protein coupled receptors are linked to adenylate cyclase, and stimulation of these receptors might result, either in inhibition or activation of adenylate cyclase, depending on the receptor system. Cannabinoid receptors are linked to an inhibitory G protein (Gi), meaning that when activated, inhibition of the activity of adenylate cyclase occurs, thus preventing the conversion of ATP to the second messenger cyclic AMP (cAMP). Examples of inhibitory-coupled receptors include opioid,

muscarinic,″ $_2$-adrenoreceptors, dopamine (D_2) and serotonin (5-HT_1) among others. The pharmacological relevance of the adenylate cyclase inhibition has been difficult to determine (Adams and Martin, 1996).

Advances in molecular biology allowed the cloning of a cannabinoid receptor (Matsuda *et al.,* 1990), first from rat brain origin followed by the cloning of the human receptor (Gerard *et al.,* 1991) therefore offering definitive evidence for a specific cannabinoid receptor. Autoradiographic studies have provided information on the distribution of cannabinoid receptors. CB_1 receptors are present in the brain and spinal cord and in certain peripheral tissues. The distribution pattern of these receptors within the central nervous system is heterogeneous. It is believed that the localization of these receptors in various regions of the brain, such as basal ganglia, cerebellum, hippocampus and cerebral cortex, may explain cannabinoid interference with movement coordination and effects on memory and cognition. Concentration of CB_1 receptors is considerably lower in peripheral tissues than in the central nervous system (Henkerham *et al.,* 1990 and 1992). CB_2 receptors have been detected only outside the central nervous system. Their occurrence has been shown to be primarily in immune tissues such as leukocytes, spleen and tonsils and it is believed that the CB_2-type receptor is responsible for mediating the immunological effects of cannabinoids (Galiegui *et al.,* 1995).

Recently it has been shown that CB_1 but not CB_2 receptors inhibit N- and Q type calcium channels and activate inwardly rectifying potassium channels. Inhibition of the N-type calcium channels decreases neurotransmitter release from several tissues and this may the mechanism by which cannabinoids inhibit acetylcholine, noradrenaline and glutamate release from specific areas of the brain. These effects might represent a potential cellular mechanism underlying the antinociceptive and psychoactive effects of cannabinoids (Ameri, 1999).

Several synthetic cannabinoid agonists have been synthesized and characterized and selective antagonists for both receptors have been identified. In 1994, SR–141716A, the first selective antagonist with CB_1 selectivity was identified, and more recently the selective CB_2 receptor antagonist, SR-144528, was described (Rinaldi-Carmona *et al.,* 1994 and 1998). In general, antagonists have proven to be invaluable tools in pharmacology. They allow the identification of key physiological functions by the receptors, through the blockade of their responses.

Delta^9-THC displays similar affinity for CB_1 and CB_2 receptors but behaves as a weak agonist for CB_2 receptors as judged by inhibition of adenylate cyclase. The identification of synthetic cannabinoid ligands deprived of the typical THC-like psychoactive properties, that selectively bind to CB_2 receptors, supports the idea that the psychotropic effects of cannabinoids are mediated through the activation of CB_1-receptors (Hanus *et al.,* 1999). Furthermore, cannabinoid agonists such as delta^9-THC and the synthetic ones, WIN–55,212–2 and CP–55,940, produce hypothermia, analgesia, hypoactivity and cataplexy. These effects are reversed by the selective CB_1 antagonist, SR–141716A, providing good evidence for the involvement of a CB_1 receptor mediated mechanism.

In addition, the discovery of the endogenous cannabinoid receptor agonists, anandamide and arachidonyl glycine (2–AG) confirmed the belief of a central cannabinoid neuromodulatory system. Indeed, cannabinoid and their endogenous ligands are present in central as well as peripheral tissues. Mechanisms for the synthesis and metabolism of anandamide have been described. The physiological roles of endogenous cannabinoids are not yet fully characterized, although it has been the target of large research efforts (Martin *et al.,* 1999).

In conclusion, progress in cannabinoid pharmacology, including the characterization of the cannabinoid receptors, isolation of endogenous cannabinoid ligands, synthesis of agonists and antagonists with diverse degree of affinity and selectivity for cannabinoid receptors, have provided the foundation for the elucidation of the specific effects mediated by cannabinoids and their roles in psychomotor disorders, memory, cognitive functions, analgesia, antiemesis, intraocular and systemic blood pressure modulation, broncodilation, and inflammation.

The reinforcing properties of a number of commonly abused drugs such as amphetamine, cocaine, alcohol, morphine and nicotine, have been explained by the effects of these drugs in the activation of dopaminergic pathways in certain areas of the brain and in particular the mesolimbic dopaminergic system (Koob, 1992). It has been demonstrated that delta^9-THC increases dopamine activity in reward relevant circuits in the brain (French, 1997; Gessa, *et al.* 1998), but the mechanism of these effects and the relevance of these findings in the context of the abuse potential of marijuana is still unknown.

Central Nervous System Effects

Human Behavioral Effects

As with other psychoactive drugs, the response that an individual has to marijuana is dependent on the set (psychological and emotional orientation) and setting (circumstances) under which the individual takes the drug. Thus, if an individual uses marijuana while in a happy state of mind among good friends, the responses are likely to be interpreted as more positive than if that individual uses the drug during a crisis while alone.

The mental and behavioral effects of marijuana can vary widely among individuals, but common responses, described by Wills (1998) and others (Adams and Martin 1996; Hollister 1986a, 1988a; Institute of Medicine 1982) are listed below:

(1) Dizziness, nausea, tachycardia, facial flushing, dry mouth and tremor can occur initially

(2) Merriment, happiness and even exhilaration at high doses

(3) Disinhibition, relaxation, increased sociability, and talkativeness

(4) Enhanced sensory perception, giving rise to increased appreciation of music, art and touch

(5) Heightened imagination leading to a subjective sense of increased creativity

(6) Time distortions

(7) Illusions, delusions and hallucinations are rare except at high doses

(8) Impaired judgement, reduced co-ordination and ataxia, which can impede driving ability or lead to an increase in risk-taking behavior

(9) Emotional lability, incongruity of affect, dysphoria, disorganized thinking, inability to converse logically, agitation, paranoia, confusion, restlessness, anxiety, drowsiness and panic attacks may occur, especially in inexperienced users or in those who have taken a large dose

(10) Increased appetite and short-term memory impairment are common

Humans demonstrate a preference for higher doses of marijuana (1.95% delta^9-THC) over lower doses (0.63% delta^9-THC) (Chaitand Burke, 1994), similar to the dose preference exhibited for many other drugs of abuse.

Animal Behavioral Effects

- Predictors of Reinforcing Effects (Self-Administration and Conditioned Place Preference)

One indicator of whether a drug will be reinforcing in humans is the self-administration test in animals. Self-

administration of marijuana, LSD, sigma receptor agonists, or cholinergic antagonists is difficult to demonstrate in animals. However, when it is known that humans voluntarily consume a particular drug for its pleasurable effects, the inability to establish self-administration with that drug in animals has no practical importance. This is because the animal test is only useful as a rough predictor of human behavioral response in the absence of naturalistic data. Thus, the petitioner is incorrect that the accepted legal convention for abuse potential is self-administration in animals and that because marijuana does not induce self-administration in animals, it has a lower abuse potential than drugs that easily induce self-administration in animals. Similarly, the petitioner is incorrect that the difficulty in inducing self-administration of marijuana in animals is due to a lack of effect on dopamine receptors. In fact, dopamine release can be stimulated indirectly by marijuana, following direct action of the drug on cannabinoid receptors. However, it is important to note that while self-administration in animals has been correlated with dopamine function, both pleasurable and painful stimuli can evoke dopaminergic responses. Dopamine functioning does not determine scheduling under the CSA.

Naïve animals will not typically self-administer cannabinoids when they must choose between saline and a cannabinoid. However, a recent report shows that when squirrel monkeys are first trained to self-administer intravenous cocaine, they will continue to bar-press at the same rate when THC is substituted for cocaine, at doses that are comparable to those used by humans who smoke marijuana (Tanda *et al.,* 2000). This effect was blocked by the cannabinoid receptor antagonist, SR 141716. These data demonstrate that under specific pretreatment conditions, an animal model of reinforcement by cannabinoids now exists for future investigations. Additionally, mice have been reported to self-administer WIN 55212, a CB_1 receptor agonist with a non-cannabinoid structure (Martellotta *et al.,* 1998). There may be a critical dose-dependent effect, though, since aversive effects, rather than reinforcing effects, have been described in rats with high doses of WIN 55212 (Chaperon *et al.,* 1998) as well as delta^9-THC (Sanudo-Pena *et al.,* 1997). The cannabinoid antagonist, SR 141716, counteracted these aversive effects.

The conditioned place preference (CPP) test also functions as a predictor of reinforcing effects. Animals show CPP to cannabinoids, but only at mid-dose levels. However, cannabinoid antagonists also induce CPP, suggesting that occupation of the cannabinoid receptor itself, may be responsible.

• Drug Discrimination Studies

Animals, including monkeys and rats (Gold *et al.,* 1992) as well as humans (Chait, 1988) can discriminate cannabinoids from other drugs or placebo. Discriminative stimulus effects of delta^9-THC are pharmacologically specific for marijuana-containing cannabinoids (Balster and Prescott, 1992, Barrett *et al.,* 1995, Browne and Weissman, 1981, Wiley *et al.,* 1993, Wiley *et al.,* 1995). Additionally, the major active metabolite of delta^9-THC, 11-OH-delta^9-THC, also generalized to the stimulus cue elicited by delta^9-THC (Browne and Weissman, 1981). Twenty-two other cannabinoids found in marijuana also fully substituted for delta^9-THC. The discriminative stimulus effects of the cannabinoid group appear to provide unique effects because stimulants, hallucinogens, opioids, benzodiazepines, barbiturates, NMDA antagonists and antipsychotics have not been shown to substitute for delta^9-THC.

Pharmacodynamics of CNS Effects

Psychoactive effects occur within seconds after smoking marijuana, while the onset of effects after oral administration is 30–60 min. After a single moderate smoked dose, most mental and behavioral effects are measurable for approximately 4 to 6 hours (Hollister 1986, 1988). Venous blood levels of delta^9-THC or other cannabinoids correlate poorly with intensity of effects and character of intoxication (Agurell *et al.* 1986; Barnett *et al.* 1985; Huestis *et al.* 1992a). There does not appear to be a ''hangover'' syndrome following acute administration of marijuana containing 2.1% delta^9-THC (Chait, 1985).

We agree with the petitioner that clinical studies do not demonstrate tolerance to the ''high'' from marijuana. This may be related to recent electrophysiological data showing that the ability of THC to increase neuronal firing in the ventral tegmental area (a region known to play a critical role in drug reinforcement and reward) is not reduced following chronic administration of the drug (Wu and French, 2000). On the other hand, tolerance can develop in humans to marijuana-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood and certain behavioral changes (Jones *et al.,* 1981).

Repeated use of many drugs leads to the normal physiological adaptations of tolerance and dependence and is not a phenomenon unique to drugs of abuse. Down-regulation of cannabinoid receptors has been suggested as the mechanism underlying tolerance to the effects of marijuana (Rodriguez de Fonseca *et al.,* 1994, Oviedo *et al.,* 1993). By pharmacological definition, tolerance does not indicate the physical dependence liability of a drug.

Physical dependence is a condition resulting from the repeated consumption of certain drugs. Discontinuation of the drug results in withdrawal signs and symptoms known as withdrawal or abstinence syndrome. It is believed that the withdrawal syndrome probably reflects a rebound of certain physiological effects that were altered by the repeated administration of the drug. These pharmacological events of physical dependence and withdrawal are not associated uniquely with drugs of abuse. Many medications such as antidepressants, beta-blockers and centrally acting antihypertensive drugs that are not associated with addiction can produce these effects after abrupt discontinuation.

Some authors describe a marijuana withdrawal syndrome consisting of restlessness, irritability, mild agitation, insomnia, sleep EEG disturbances, nausea and cramping that resolves in days (Haney *et al.,* 1999). This syndrome is mild compared to classical alcohol and barbiturate withdrawal phenomena, which may include agitation, paranoia, and seizures. Marijuana withdrawal syndrome has more frequently been reported in adolescents who were admitted for substance abuse treatment or under research conditions upon discontinuation of daily administration.

According to the American Psychiatric Association, Diagnostic and Statistical Manual (DSM–IV–TR™, 2000), the distinction between occasional use of cannabis and cannnabis dependence or abuse can be difficult to make because social, behavioral, or psychological problems may be difficult to attribute to the substance, especially in the context of use of other substances. Denial of heavy use is common, and people appear to seek treatment for cannabis dependence or abuse less often than for other types of substance-related disorders.

Although pronounced withdrawal symptoms can be provoked from the administration of a cannabinoid antagonist in animals who had received chronic THC administration, there is no overt withdrawal syndrome behaviorally in animals under conditions of natural discontinuation following chronic THC administration.

This may be the result of slow release of cannabinoids from adipose storage, as well as the presence of the major metabolite, 11-OH-delta^9-THC, which is also psychoactive.

Cognitive Effects

Acute administration of smoked marijuana impairs performance on tests of learning, associative processes, and psychomotor behavior (Block *et al.,* 1992). These data demonstrate that the short-term effects of marijuana can interfere significantly with an individual's ability to learn in the classroom or to operate motor vehicles. Administration of 290 ug/kg delta^9-THC in a smoked marijuana cigarette by human volunteers impaired perceptual motor speed and accuracy, two skills that are critical to driving ability (Kurzthaler *et al.,* 1999). Similarly, administration of 3.95% delta^9-THC in a smoked marijuana cigarette increased dysequilibrium measures as well as the latency in a task of simulated vehicle braking at a rate comparable to an increase in stopping distance of 5 feet at 60 mph (Liguori *et al.,* 1998).

The effects of marijuana may not resolve fully until at least a day after the acute psychoactive effects have subsided. A study at the National Institute on Drug Abuse (NIDA) showed residual impairment on memory tasks 24 hours after volunteer subjects had smoked 0, 1, or 2 marijuana cigarettes containing 2.57% delta^9-THC on two occasions the previous day (Heishman *et al.,* 1990). However, later studies at NIDA showed that there were no residual alterations in subjective or performance measures the day after subjects were exposed to 1.8%, or 3.6% smoked delta^9-THC, indicating that the residual effects of smoking a single marijuana cigarette are minimal (Fant *et al.,* 1998). A John Hopkins study examined marijuana's effects on cognition on 1,318 participants over a 15-year period and reported there were no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis, nor any male-female differences. The authors concluded that ''these results * * * seem to provide strong evidence of the absence of a long-term residual effect of cannabis use on cognition.'' (Lyketsos *et al.,* 1999).

Age of first use may be a critical factor in persistent impairment resulting from chronic marijuana use. Individuals with a history of marijuana-only use that began before the age of 16 were found to perform more poorly on a visual scanning task measuring attention than individuals who started using marijuana after that age (Ehrenreich *et al.,* 1999). However, the majority of early-onset marijuana users do not go on to become heavy users of marijuana, and those that do tend to associate with delinquent social groups (Kandel and Chen, 2000).

An individual's drug history may play a role in the response that person has to marijuana. Frequent marijuana users (greater than 100 times) were better able to identify a drug effect from low dose delta^9-THC than infrequent users (less than 10 times) and were less likely to experience sedative effects from the drug (Kirk and deWit, 1999). This difference in experiential history may account for data showing that reaction times are not altered by acute administration of marijuana in long term marijuana users (Block and Wittenborn, 1985), suggesting that behavioral adaptation or tolerance can occur to the acute effects of the drug in the absence of evidence for dependence.

The impact of *in utero* marijuana exposure on a series of cognitive tasks had been studied in children at different stages of development. Differences in several cognitive domains distinguished the 4-year-old children of heavy marijuana users. In particular, memory and verbal measures were negatively associated with maternal marijuana use (Fried and Watkinson, 1987). Maternal marijuana use was predictive of poorer performance on abstract/visual reasoning tasks, although it was not associated with an overall lowered IQ in 3-year old children (Griffith *et al.,* 1994). At 6 years of age, prenatal marijuana history was associated with an increase in omission errors on a vigilance task, possibly reflecting a deficit in sustained attention, was noted (Fried *et al.,* 1992). Recently, it had been speculated that prenatal exposure may affect certain behaviors and cognitive abilities that fall under the construct termed executive function, that is, not associated with measures of global intelligence. It was postulated that when tests evaluate novel problem-solving abilities as contrasted to knowledge, there is an association between executive function and intelligence. In a recent study (Fried *et al.,* 1998), the effect of prenatal exposure in 9–12 year old children was analyzed, and similarly to what was shown in other age groups, *in utero* marijuana exposure was negatively associated with executive function tasks that require impulse control, visual analysis and hypothesis testing and it was not associated with global intelligence.

Cardiovascular and Autonomic Effects

Single smoked or oral doses of delta^9-THC ingestion produce tachycardia and unchanged or increased blood pressure (Capriotti *et al.,* 1988, Benowitz and Jones, 1975). However, prolonged delta^9-THC ingestion produces significant heart rate slowing and blood pressure lowering (Benowitz and Jones, 1975). Both plant-derived cannabinoids and the endogenous ligands have been shown to elicit hypotension and bradycardia via activation of peripherally located CB_1 receptors (Wagner *et al.,* 1998). The mechanism of these effects were suggested in that study to include presynaptic CB_1 receptor mediated inhibition of norepinephrine release from peripheral sympathetic nerve terminals, with the possibility of additional direct vasodilation via activation of vascular cannabinoid receptors.

Impaired circulatory responses to standing, exercise, Valsalva maneuver, and cold pressor testing following THC administration suggest a state of sympathetic insufficiency. Tolerance developed to the orthostatic hypotension, possibly related to plasma volume expansion, but did not develop to the supine hypotensive effects. During chronic marijuana ingestion, nearly complete tolerance was shown to have developed to the tachycardia and psychological effects when subjects were challenged with smoked marijuana. Electrocardiographic changes were minimal despite the large cumulative dose of THC. (Benowitz and Jones, 1975)

Cardiovascular effects of smoked or oral marijuana have not been shown to result in any health problems in healthy and relatively young users. However, marijuana smoking by older patients, particularly those with some degree of coronary artery or cerebrovascular disease, is postulated to pose greater risks, because of the resulting increased cardiac work, increased catecholamines, carboxyhemoglobin, and postural hypotension (Benowitz and Jones 1981; Hollister 1988).

As a comparison, the cardiovascular risks associated with use of cocaine are quite serious, including cardiac arrhythmias, myocardial ischemia, myocarditis, aortic dissection, cerebral ischemia, stroke and seizures.

Respiratory Effects

Transient bronchodilation is the most typical effect following acute exposure to marijuana. The petitioner is correct that marijuana does not suppress respiration in a manner that leads to death. With long-term use of marijuana, there can be an increased frequency of pulmonary illness from chronic bronchitis and pharyngitis. Large-airway obstruction, as evident on pulmonary function tests, can also occur with

chronic marijuana smoking, as can cellular inflammatory histopathological abnormalities in bronchial epithelium (Adams and Martin 1996; Hollister 1986).

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. Several cases of lung cancer in young marijuana users with no history of tobacco smoking or other significant risk factors have been reported (Fung *et al.* 1999). However, a recent study (Zhang *et al.,* 1999) 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. The association of marijuana use with carcinomas remains controversial.

Endocrine System Effects

In male human volunteers, neither smoked THC (18 mg/marijuana cigarette) nor oral THC (10 mg t.i.d. for 3 days and on the morning of the fourth day) altered plasma prolactin, ACTH, cortisol, luteinizing hormone or testosterone levels (Dax *et al.,* 1989). Reductions in male fertility by marijuana are reversible and only seen in animals at concentrations higher than those found in chronic marijuana users.

Relatively little research has been performed on the effects of experimentally administered marijuana on human female endocrine and reproductive system function. Although suppressed ovulation and other ovulatory cycle changes occur in nonhuman primates, a study of human females smoking marijuana in a research hospital setting did not find hormone or menstrual cycle changes like those in monkeys that had been given delta^{9}-THC (Mendelson *et al.,* 1984a).

THC reduces binding of the corticosteroid dexamethasone in hippocampal tissue from adrenalectomized rats, suggesting a direct interaction with the glucocorticoid receptor. Chronic THC administration also reduced the number of glucocorticoid receptors. Acute THC releases corti-costerone, but tolerance developed with chronic THC administration. (Eldridge *et al.,* 1991)

Immune System Effects

Immune functions can be enhanced or diminished by cannabinoids, dependent on experimental conditions, but the effects of endogenous cannabinoids on the immune system are not yet known. The concentrations of THC that are necessary for psychoactivity are lower than those that alter immune responses.

A study presented by Abrams and coworkers at the University of California, San Francisco at the XIII International AIDS Conference investigated the effect of marijuana on immunological functioning in 62 AIDS patients who were taking protease inhibitors. Subjects received one of three treatments, three times a day: Smoked marijuana cigarette containing 3.95% THC; oral tablet containing THC (2.5 mg oral dronabinol); or oral placebo. There were no changes in HIV RNA levels between groups, demonstrating no short-term adverse virologic effects from using cannabinoids. Additionally, those individuals in the cannabinoid groups gained more weight than those in the placebo group (3.51 kg from smoked marijuana, 3.18 kg from dronabinol, 1.30 kg from placebo) (7/13/00, Durban, South Africa).

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

This section discusses the chemistry, human pharmacokinetics, and medical uses of marijuana.

Chemistry

According to the DEA, three forms of cannabis (that is, Cannabis sativa L. and other species) are currently marketed illicitly in the U.S.A. These cannabis derivatives include marijuana, hashish and hashish oil.

Each of these forms contains a complex mixture of chemicals. Among these components the twenty-one carbon terpenes found in the plant as well as their carboxylic acids, analogues, and transformation products are known as cannabinoids (Agurell *et al.,* 1984, 1986; Mechoulam, 1973). The cannabinoids appear to be unique to marijuana and most of the naturally-occurring have been identified. Among the cannabinoids, delta^{9}-tetrahydrocannabinol (delta^{9}-THC, alternate name delta^{1}-THC) and delta-8-tetrahydrocannabinol (delta^{8}-THC, alternate name delta^{6}-THC) are the only compounds in the plant, which show all of the psychoactive effects of marijuana. Because delta^{9}-THC is more abundant than delta^{8}-THC, the activity of marijuana is largely attributed to the former, which is considered the main psychoactive cannabinoid in cannabis. Delta^{8}-THC is found only in few varieties of the plant (Hively *et al.,* 1966). Other cannabinoids, such as cannabidiol (CBD) and cannabinol (CBN), has been characterized. CBD is not considered to have cannabinol-like psychoactivity, but is thought to have significant anticonvulsant, sedative, and anxiolytic activity (Adams and Martin, 1996; Agurell *et al.,* 1984, 1986; Hollister, 1986).

Marijuana is a mixture of the dried flowering tops and leaves from the plant (Agurell *et al.* 1984; Graham 1976; Mechoulam 1973) and is variable in content and potency (Agurell *et al.* 1986; Graham 1976; Mechoulam 1973). Marijuana is usually smoked in the form of rolled cigarettes. The other cannabis forms are also smoked. Potency of marijuana, as indicated by cannabinoid content, has been reported to average from as low as one to two percent to as high as 17 percent.

Delta^{9}-THC is an optically active resinous substance, insoluble in water and extremely lipid soluble. Chemically is known as (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo-[b,d]pyran-1-ol or (-)-delta^{9}-(trans)-tetrahydrocannabinol. The pharmacological activity of delta^{9}-THC is stereospecific; the (-)-trans isomer is 6–100 times more potent than the (+)-trans isomer (Dewey *et al.,* 1984).

The concentration of delta^{9}-THC and other cannabinoids in marijuana varies greatly depending on growing conditions, parts of the plant collected (flowers, leaves stems, etc), plant genetics, and processing after harvest (Adams and Martin , 1996; Agurell *et al.,* 1984; Mechoulam, 1973). Thus, there are many variables that can influence the strength, quality and purity of marijuana as a botanical substance. In the usual mixture of leaves and stems distributed as marijuana, the concentration of delta^{9}-THC ranges from 0.3 to 4.0 percent by weight. However, specially grown and selected marijuana can contain 15 percent or even more delta^{9}-THC. Thus, a one-gram marijuana cigarette might contain as little as 3 milligrams or as much as 150 milligrams or more of delta^{9}-THC among several other cannabinoids. As a consequence, the clinical pharmacology of pure delta^{9}-THC may not always be expected to have the same clinical pharmacology of smoked marijuana containing the same amount of delta^{9}-THC (Harvey, 1985). Also, the lack of consistency of concentration of delta^{9}-THC in botanical marijuana from diverse sources makes the interpretation of clinical data very difficult. If marijuana is to be investigated more widely for medical use, information and data regarding the chemistry, manufacturing and specifications of marijuana must be developed. 21 CFR 314.50(d)(1)

describes the data and information that should be included in the chemistry, manufacturing and controls section of a new drug application (NDA) to be reviewed by FDA.

Hashish consists of the cannabinoid-rich resinous material of the cannabis plant, which is dried and compressed into a variety of forms (balls, cakes *etc.*). Pieces are then broken off, placed into pipes and smoked. Cannabinoid content in hashish has recently been reported by DEA to average 6 percent.

Hash oil is produced by extracting the cannabinoids from plant material with a solvent. Color and odor of the extract vary, depending on the type of solvent used. Hash oil is a viscous brown or amber-colored liquid that contains approximately 15 percent cannabinoids. One or two drops of the liquid placed on a cigarette purportedly produce the equivalent of a single marijuana cigarette.

Human Pharmacokinetics

Marijuana is generally smoked as a cigarette (weighing between 0.5 and 1.0 gram), or in a pipe. It can also be taken orally in foods or as extracts of plant material in ethanol or other solvents. Pure preparations of delta^9-THC and other cannabinoids can be administered by mouth, rectal suppository, intravenous injection, or smoked.

The absorption, metabolism, and pharmacokinetic profile of delta^9-THC (and other cannabinoids) in marijuana or other drug products containing delta^9-THC are determined by route of administration and formulation (Adams and Martin 1996; Agurell *et al.* 1984, 1986). When marijuana is administered by smoking, delta^9-THC in the form of an aerosol in the inhaled smoke is absorbed within seconds. The delta^9-THC is delivered to the brain rapidly and efficiently as would be expected of a very lipid-soluble drug. The delta^9-THC bioavailability from smoked marijuana, i.e., the actual absorbed dose as measured in blood, varies greatly among individuals. Bioavailability can range from one percent to 24 percent with the fraction absorbed rarely exceeding 10 to 20 percent of the delta^9-THC in a marijuana cigarette or pipe (Agurell *et al.* 1986; Hollister 1988a). This relatively low and quite variable bioavailability results from significant loss of delta^9-THC in side-stream smoke, from variation in individual smoking behaviors, from cannabinoid pyrolysis, from incomplete absorption of inhaled smoke, and from metabolism in the lungs. A smoker's experience is likely an important determinant of the dose that is actually absorbed (Herning *et al.* 1986; Johansson *et al.* 1989). Venous blood levels of delta^9-THC or other cannabinoids correlate poorly with intensity of effects and character of intoxication (Agurell *et al.* 1986; Barnett *et al.* 1985; Huestis *et al.* 1992a).

After smoking, venous levels of delta^9-THC decline precipitously within minutes, and within an hour are about 5 to 10 percent of the peak level (Agurell *et al.,* 1986, Huestis *et al.,* 1992a, 1992b). Plasma clearance of delta^9-THC is approximately 950 mL/min or greater, thus approximating hepatic blood flow. The rapid disappearance of delta^9-THC from blood is largely due to redistribution to other tissues in the body, rather than to metabolism (Agurell *et al.,* 1984, 1986). Metabolism in most tissues is relatively slow or absent. Slow release of delta^9-THC and other cannabinoids from tissues and subsequent metabolism results in a long elimination half-life. The terminal half-life of delta^9-THC is estimated to range from approximately 20 hours to as long as 10 to 13 days, though reported estimates vary as expected with any slowly cleared substance and the use of assays of variable sensitivities.

In contrast, following an oral dose of delta^9-THC or marijuana, maximum delta^9-THC and other cannabinoid blood levels are attained after 2 to 3 hours (Adams and Martin 1996; Agurell *et al.* 1984, 1986). Oral bioavailability of delta^9-THC, whether pure or in marijuana, is low and extremely variable, ranging between 5 and 20 percent (Agurell *et al.* 1984, 1986). There is inter-and intra-subject variability, even when repeatedly dosed under controlled and ideal conditions. The low and variable oral bioavailability of delta^9-THC is a consequence of its first-pass hepatic elimination from blood and erratic absorption from stomach and bowel. Because peak effects are slow in onset, typically one or two hours after an oral dose, and variable in intensity, it is more difficult for a user to titrate the oral delta^9-THC dose than with marijuana smoking. When smoked, the active metabolite, 11-hydroxy-delta^9-THC, probably contributes little to the effects since relatively little is formed, but after oral administration, metabolite levels produced may exceed that of delta^9-THC and thus contribute greatly to the pharmacological effects of oral delta^9-THC or marijuana. Delta^9-THC is metabolized via microsomal hydroxylation to more than 80, active and inactive, metabolites (Lemberger *et al.,* 1970, Lemberger *et al.,* 1972a, 1972b) of which the primary active metabolite was 11-OH-delta^9-THC. This metabolite is approximately equipotent to delta^9-THC in producing marijuana-like subjective effects (Agurell *et al.,* 1986, Lemberger and Rubin, 1975). Following oral administration of radioactive-labeled delta^9-THC, it has been confirmed that delta^9-THC plasma levels attained by the oral route are low relative to those levels after smoking or intravenous administration. The half-life of delta^9-THC has been determined to be 23–28 hours in heavy marijuana users, but 60–70 hours in naive users (Lemberger *et al.,* 1970).

Characterization of the pharmacokinetics of delta^9-THC and other cannabinoids from smoked marijuana is difficult (Agurell *et al.*, 1986, Herning *et al.*, 1986, Heustis *et al.*, 1992a) in part because a subject's smoking behavior during an experiment cannot be easily controlled or quantified by the researcher. An experienced marijuana smoker can titrate and regulate the dose to obtain the desired acute psychological effects and to avoid overdose and/or minimize undesired effects. Each puff delivers a discrete dose of delta^9-THC to the body. Puff and inhalation volume changes with phase of smoking, tending to be highest at the beginning and lowest at the end of smoking a cigarette. Some studies found frequent users to have higher puff volumes than less frequent marijuana users. During smoking, as the cigarette length shortens, the concentration of delta^9-THC in the remaining marijuana increases; thus, each successive puff contains an increasing concentration of delta^9-THC.

Cannabinoid metabolism is extensive. There are at least 80 probable biologically inactive, but not completely studied, metabolites formed from delta^9-THC (Agurell *et al.*, 1986; Hollister, 1988a). In addition to the primary active metabolite, 11-hydroxy-delta^9-THC, some inactive carboxy metabolites have terminal half-lives of 50 hours to 6 days or more. The latter substances serve as long term markers of earlier marijuana use in urine tests. Most of the absorbed delta^9-THC dose is eliminated in feces, and about 33 percent in urine. Delta^9-THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-delta^9-THC. The glucuronide is excreted as the major urine metabolite along with about 18 nonconjugated metabolites. Frequent and infrequent marijuana users are similar in the way they metabolize delta^9-THC (Agurell *et al.*, 1986).

Medical Uses for Marijuana

FDA has not approved a new drug application for marijuana, although there are several INDs currently active. There is suggestive evidence that

marijuana may have beneficial therapeutic effects in relieving spasticity associated with multiple sclerosis, as an analgesic, as an antiemetic, as an appetite stimulant and as a bronchodilator, but there is no data from controlled clinical trials to support a new drug application for any of these indications. Data of the risks and potential benefits of using marijuana for these various indications must be developed to determine whether botanical marijuana, or any cannabinoid in particular, has a therapeutic role.

In February 1997, a NIH-sponsored workshop analyzed available scientific information and concluded that ''in order to evaluate various hypotheses concerning the potential utility of marijuana in various therapeutic areas, more and better studies would be needed'' (NIH, 1997). In addition, in March 1999, the Institute of Medicine (IOM) issued a detailed report that supports the absolute need for evidence-based research into the effects of marijuana and cannabinoid components of marijuana, for patients with specific disease conditions. The IOM report also emphasized that smoked marijuana is a crude drug delivery system that exposes patients to a significant number of harmful substances and that ''if there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives.'' As such, the IOM recommended that clinical trials should be conducted with the goal of developing safe delivery systems (Institute of Medicine, 1999). Additionally, State-level public initiatives, including referenda in support of the medical use of marijuana have generated interest in the medical community for high quality clinical investigation and comprehensive safety and effectiveness data.

The Department of Health and Human Services (DHHS) is committed to providing ''research-grade marijuana for studies that are the most likely to yield usable, essential data'' (DHHS, 1999). The opportunity for scientists to conduct clinical research with botanical marijuana has increased due to changes in the process for obtaining botanical marijuana from the National Institute on Drug Abuse, the only legal source of the drug for research. Studies published in the current medical literature demonstrate that clinical research with marijuana is being conducted in the US under FDA-authorized Investigational New Drug applications. In May 1999, DHHS provided guidance on the procedures for providing research-grade marijuana to scientists who intend to study marijuana in scientifically valid investigations and well-controlled clinical trials (DHHS, 1999). This action was prompted by the increasing interest in determining through scientifically valid investigations whether cannabinoids have medical use.

4. Its History and Current Pattern of Abuse

To assess drug abuse patterns and trends, data from different sources such as National Household Survey on Drug Abuse (NHSDA), Monitoring the Future (MTF), Drug Abuse Warning Network (DAWN), and Treatment Episode Data Set (TEDS) have been analyzed. These indicators of marijuana use in the United States are described below:

National Household Survey on Drug Abuse

The National Household Survey on Drug Abuse (NHSDA, 1999) is conducted by the Department of Health and Human Service's Substance Abuse and Mental Health Services Administration (SAMHSA) annually. This survey has been the primary source of estimates of the prevalence and incidence of alcohol, tobacco and illicit drug use in the US. It is important to note that this survey identifies whether an individual used a drug during a certain period, but not the amount of the drug used on each occasion. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. Persons excluded from the survey include homeless people who do not use shelters, active military personnel, and residents of institutional group quarters, such as jails and hospitals. In 1999, 66,706 individuals were interviewed.

According to the 1999 NHSDA, illicit drug use involved approximately 14.8 million Americans (6.7% of the US population) on a monthly basis. The most frequently used illicit drug was marijuana, with 11.2 million Americans (5.1% of the US population) using it monthly. The 1999 NHSDA no longer provides data on the weekly or daily use of any drug, so these statistics are unavailable for marijuana. The NHSDA estimated that 76.4 million Americans (34.6% of the population) have tried marijuana at least once during their lifetime. Thus, 14.7% of those who try marijuana go on to use it monthly. NHSDA data from 1999 show that 57% of illicit drug users only use marijuana on a monthly basis, which corresponds to 8.44 million persons (3.8% of the US population). However, there are no data available on marijuana-only use as a percent of use of any drug.

An estimated 2.3 million persons of all ages used marijuana for the first time in 1998, of whom 1.6 million were between the ages of 12–17. (Information on when people first used a substance is collected on a retrospective basis, so this information is always one year behind information on current use.) This represents a slight reduction in new marijuana users from 1997, when the rate was 2.6 million people of all ages and 1.8 million for those 12–17 years old. Trends for marijuana use were similar to the trends for any illicit use. There were no significant changes between 1998 and 1999 for any of the four age groups, but an increasing trend since 1997 among young adults age 18–25 years (12.8 % in 1997, 13.8 % in 1998, and 16.4 % in 1999) and a decreasing trend since 1997 for youths age 12–17 years (9.4 % in 1997, 8.3 % in 1998, and 7.0 % in 1999).

Monitoring the Future

Monitoring the Future (MTF, 1999) is a national survey that tracks drug use trends among American adolescents. The MTF has surveyed 8th, 10th and 12th graders every spring in randomly selected U.S. schools since 1975 for 12th graders and since 1991 for 8th and 10th graders. This survey is conducted by the Institute for Social Research at the University of Michigan under a grant from NIDA. The 1999 sample sizes were 17,300, 13,900, and 14,100 in 8th, 10th, and 12th grades, respectively. In all, about 45,000 students in 433 schools participated. Because multiple questionnaire forms are administered at each grade level, and because not all questions are contained in all forms, the numbers of cases upon which a particular statistic are based can be less than the total sample.

Comparisons between the MTF and students sampled in the NHSDA (described above) have generally shown NHSDA prevalence to be lower than MFT estimates, in which the largest difference occurred with 8th graders. The MTF survey showed the use of illegal drugs by adolescents leveled off in 1997 and then declined somewhat for most drugs in 1998. Also, the 1998-year survey showed that for the first time since 1991 an increase in the percentage of 8th graders who said marijuana is a risk to their health.

Illicit drug use among teens remained steady in 1999 in all three grades, as did the use of a number of important specific drugs such as marijuana, amphetamines, hallucinogens taken as a class, tranquilizers, heroin, and alcohol. Marijuana is the most widely used illicit drug. For 1999, the annual prevalence rates in grades 8, 10, and 12,

respectively, are 17%, 32%, and 38%. Current monthly prevalence rates are 9.7%, 19.4% and 23.1%. (See Table 1), whereas current daily prevalence rates (defined as the proportion using it on 20 or more occasions in the prior thirty days) are 1.4%, 3.8%, and 6.0%.

TABLE 1.—TRENDS IN ANNUAL AND MONTHLY PREVALENCE OF USE OF VARIOUS DRUGS FOR EIGHTH, TENTH, AND TWELFTH GRADERS

[Entries are precentages]

Grade	Annual			30-Day		
	1997	1998	1999	1997	1998	1999
Any illicit drug (a)						
8th	22.1	21.0	20.5	12.9	12.1	12.2
10th	38.5	35.0	35.9	23.0	21.5	22.1
12th	42.4	41.4	42.1	26.2	25.6	25.9
Any illicit drug other than cannabis (a)						
8th	11.8	11.0	10.5	6.0	5.5	5.5
10th	18.2	16.6	16.7	8.8	8.6	8.6
12th	20.7	20.2	20.7	10.7	10.7	10.4
Marijuana/hashish						
8th	17.7	16.9	16.5	10.2	9.7	9.7
10th	34.8	31.1	32.1	20.5	18.7	19.4
12th	38.5	37.5	37.8	23.7	22.8	23.1
Cocaine						
8th	2.8	3.1	2.7	1.1	1.4	1.3
10th	4.7	4.7	4.9	2.0	2.1	1.8
12th	5.5	5.7	6.2	2.3	2.4	2.6
Heroin (b)						
8th	1.3	1.3	1.4	0.6	0.6	0.6
10th	1.4	1.4	1.4	0.6	0.7	0.7
12th	1.2	1.0	1.1	0.5	0.5	0.5

Source. The Monitoring the Future Study, the University of Michigan.

a. For 12th graders only: Use of ''any illicit drug'' includes any use of marijuana, LSD, other hallucinogens, crack, other cocaine, or heroin, or any use of other opiates, stimulants, barbiturates, or tranquilizers not under a doctor's orders. For 8th and 10th graders: The use of other opiates and barbiturates has been excluded, because these younger respondents appear to over-report use (perhaps because they include the use of nonprescription drugs in their answers).

b. In 1995, the heroin question was changed in three of six forms for 12th graders and in two forms for 8th and 10th graders. Separate questions were asked for use with injection and without injection. Data presented here represents the combined data from all forms. In 1996, the heroin question was changed in the remaining 8th and 10th grade forms.

Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN, 1998) is a national probability survey of hospitals with emergency departments (EDs) designed to obtain information on ED episodes that are induced by or related to the use of an illegal drug or the non-medical use of a legal drug. The DAWN system provides information on the health consequences of drug use in the United States as manifested by drug-related visits to emergency departments (ED episodes). DAWN captures the non-medical use of a substance either for psychological effects, dependence, or suicide attempt. The ED data come from a representative sample of hospital emergency department's which are weighted to produce national estimates. As stated in DAWN methodology, ''the terms 'ED drug abuse episode' or 'ED episode' refer to any ED visit that was induced by or related to drug abuse. Similarly, the terms 'ED drug mention' or 'ED mention' refer to a substance that was mentioned in a drug abuse episode. Up to 4 substances can be reported for each ED episode. Thus, the number of ED mentions will always equal or exceed the number of ED episodes.''

Many factors can influence the estimates of ED visits, including trends in the ED usage in general. Some drug users may have visited EDs for a variety of reasons, some of which may have been life threatening, whereas others may have sought care at the ED for detoxification because they needed certification before entering treatment. It is important to note that the variable ''Motive'' applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to the specific drug for which the tables have been created. DAWN data do not distinguish the drug responsible for the ED visit from others used concomitantly. The DAWN report itself states, ''Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED contact may be more relevant to the other drug(s) involved in the episode.''

In 1999, there were an estimated 554,932 drug-related ED episodes and 1,015,206 ED drug mentions from these drug-related episodes. Nationally, the number of ED episodes and mentions remained relatively stable from 1998 to 1999. The 4 drugs mentioned most frequently in ED reports—alcohol-in-combination (196,277 mentions), cocaine (168,763), marijuana/hashish (87,150), and heroin/morphine (84,409)—were statistically unchanged from 1998 to 1999. Marijuana/hashish mentions represented 16% of all drug-related episodes in 1999. For adolescent patients age 12–17, there was no statistical change from 1998 to 1999 in drug use for any drug category (Table 2). There was no a statistically significant change in the number of marijuana/hashish mentions, heroin/morphine of cocaine from 1998 to 1999.

TABLE 2.—ESTIMATED NUMBER OF EMERGENCY DEPARTMENT DRUG EPISODES, DRUG MENTIONS AND MENTIONS FOR SELECTED DRUGS FOR TOTAL COTERMINOUS US BY YEAR FOR 1997–1999

	1997	1998	1999
Drug episodes	527,058	542,544	554,932
Drug mentions	943,937	982,856	1,015,206
Cocaine	161,087	172,014	168,763
Heroin/Morphine	72,010	77,645	84,409
Marijuana/Hashish	64,744	76,870	87,150

Source: Office of applied studies, SAMHSA, Drug Abuse Warning Network, 1999 (03/2000 update). Note: These estimates are based on a representative sample of non-federal, short-stay hospitals with 24-hour emergency departments in the U.S.

There were no statistically significant increases in marijuana/hashish mentions on the basis of age, gender, or race/ethnicity subgroups between 1998 and 1999, although a 19% increase in marijuana/hashish mentions (from 22,907 to 27,272) among young adults age 18 to 25 was observed.

Approximately 15 percent of the emergency department marijuana/hashish mentions involved patients in the 6–17 years of age, whereas this age group only accounts for less than 1 percent of the emergency department heroin/morphine and approximately 2 percent of the cocaine emergency department mentions. Most of the emergency department heroin/morphine and cocaine mentions involved subjects in the 26–44 years of age range.

Marijuana/hashish is likely to be mentioned in combination with other substances, particularly with alcohol and cocaine. Marijuana use as a single drug accounted for approximately 22% of the marijuana episodes. Single use of cocaine and heroin accounted for 29% and 47% of the cocaine and heroine episodes respectively.

The petitioner asserts that ''common household painkillers'' and benzodiazepines produce more ED visits than marijuana and that marijuana users are no more likely to be seen in EDs

than other chronic drug users. DAWN data do not confirm the petitioner's assertions. For 1999, the estimated rate of mentions of selected drugs per 100,000 population is 69.4 for cocaine, 35.8 for marijuana/hashish, 34.7 for heroin/morphine, 17.5 for alprazolam/diazepam/lorazepam, and 16.9 for aspirin/acetaminophen. The estimated rate of mentions of marijuana/hashish per 100,000 population is similar to that of heroin/morphine, but approximately twice that of aspirin/acetaminophen and that of alprazolam/diazepam/lorazepam. However, marijuana estimated rate of mentions/100,000 population is approximately half that of cocaine.

These drugs are easily distinguished by the motivation for their use. In 1999, marijuana/hashish mentions were related to episodes in which the motive for drug intake was primarily dependence (34.2%) followed by recreational use (28%), suicide (11.5%) and other psychic effects (8.1%). DAWN defines ''psychic effects'' as a conscious action to use a drug to improve or enhance any physical, emotional, or social situation or condition. The use of a drug for experimentation or to enhance a social situation, as well as the use of drugs to enhance or improve any mental, emotional, or physical state, is reported to DAWN under this category. Examples of the latter include anxiety, stay awake, help to study, weight control, reduce pain and to induce sleep. A different pattern is observed for tranquilizers (alprazolam/diazepam/lorazepam) and aspirin/acetamipnophen. Alprazolam/diazepam/lorazepam mentions were primarily related to episodes where the motive for drug intake was primarily suicide (approximately 58%), followed by dependence (approximately 17%), other psychic effects (approximately 11%), and recreational use (approximately 5%). For the use of aspirin/acetaminophen the primary motive of the episode was suicide (80%), other psychic effects (9%) and recreational use (2%).

DAWN also collects information on drug-related deaths from selected medical examiner offices from more than 40 metropolitan areas. In 1997 and 1998, there were 678 and 595 marijuana-related death mentions, representing 7.1 and 5.9 percent of the total drug abuse deaths for each year respectively. Medical examiner data also showed that in the majority of the mentions, marijuana was used concomitantly with cocaine, heroin and alcohol.

Treatment Episode Data Set

The Treatment Episode Data Set (TEDS, 1998) system is part of SAMHSA's Drug and Alcohol Services Information System (Office of Applied Science, SAMHSA). TEDS comprises data on treatment admissions that are routinely collected by States in monitoring their substance abuse treatment systems. The TEDS report provides information on the demographic and substance use characteristics of the 1.5 million annual admissions to treatment for abuse of alcohol and drugs in facilities that report to individual State administrative data systems. It is important to note that TEDS is an admission-based system, and TEDS admissions do not represent individuals, because a given individual admitted to treatment twice within a given year would be counted as two admissions. TEDS includes facilities that are licensed or certified by the State substance abuse agency to provide substance abuse treatment and that are required by the States to provide TEDS client-level data. Facilities that report TEDS data are those that receive State alcohol and/or drug agency funds for the provision of alcohol and/or drug treatment services. The primary goal for TEDS is to monitor the characteristics of treatment episodes for substance abusers.

Primary marijuana abuse accounted for 13% of TEDS admissions in 1998, the latest year for which data are available. In general, most of the individuals admitted for marijuana were white young males. Marijuana use began at an early age among primary marijuana admissions and more than half of the admitted patients had first used marijuana by the age of 14 and 92% by the age of 18. More than half of marijuana treatment admissions were referred through the criminal justice system.

Approximately one-third of those who were admitted for primary marijuana abuse use the drug daily. Between 1992 and 1998, the proportion of admissions for primary marijuana use increased from 6% to 13%, whereas the proportion of admissions for primary cocaine use declined from 18% in 1992 to 15% in 1998. The proportion of opiate admissions increased from 12% in 1992 to 15% in 1998 and alcohol accounted for about half (47%) of all TEDS admissions in 1998. Marijuana has not been associated with other drugs in 30.8% of the primary marijuana admissions that corresponds to 4.1% of all admissions. Secondary use of alcohol was reported by 38.2% of the marijuana admissions and secondary cocaine use was reported by 4% of admissions for primary marijuana abuse. The combination marijuana/alcohol/cocaine accounts for 8.5% of marijuana primary admissions and 1.1% of all admissions.

The TEDS Report concludes that, ''Overall, TEDS admissions data confirm that those admitted to substance abuse treatment have problems beyond their dependence on drugs and alcohol, being disadvantaged in education and employment when compared to the general population after adjusting for age, gender, and race/ethnicity distribution differences between the general population and the TEDS. It is not possible to conclude cause and effect from TEDS data—whether substance abuse precedes or follows the appearance of other life problems—but the association between problems seems clear.''

NIDA's Community Epidemiology Work Group (CEWG, 1999)

The CEWG is a network composed of epidemiologic and ethnographic researchers from major metropolitan areas of the United States and selected countries from abroad that meets semiannually to discuss the current epidemiology of drug abuse. Large-scale databases used in analyses include TEDS; DAWN; the Arrestee Drug Abuse Monitoring (ADAM) program funded by the National Institute of Justice; information on drug seizures, price, and purity from the Drug Enforcement Administration; Uniform Crime Reports maintained by the Federal Bureau of Investigation and Poison Control Centers. These data are enhanced with qualitative information obtained from ethnographic research, focus groups, and other community-based sources. Although data from TEDS and DAWN have been previously discussed this document, the analysis offered by the CEWG gives a more descriptive overview of individual geographical areas. In 1999, marijuana indicators were stable in 17 of the 21 CEWG areas. Indicators were mixed in two areas (Atlanta and Baltimore) and increased in two (Los Angeles and St. Louis). Despite the stability of certain indicators, marijuana abuse remains a serious problem in CEWG areas. In Atlanta, marijuana is the second most prevalent drug on the market and is increasingly used by a wide variety of people mostly white males and young adolescents. In St. Louis, marijuana indicators are increasing and DAWN marijuana ED mentions rose 33.3% from the last half of 1998 to the first half of 1999. Treatment admissions rose 40.1% from the second half of 1998 to the first

half of 1999, and another 9.6% in the second half of 1999.

In recent years, the proportion of primary marijuana abusers entering drug abuse treatment programs has been increasing in many CEWG cities. For example, between 1998 and the first semester of 1999, drug treatment admissions for primary marijuana abuse increased from 15.2% to 20.3% in Atlanta. In the first half of 1999, primary marijuana abusers represented 18.8% of drug treatment admissions in New York City compared with 16.6% in the first half of 1998. In the first half of 1999, primary marijuana abuse represented 41.2% of all drug treatment admissions in Denver and totaled 3,179. The number of primary marijuana admissions in St. Louis increased dramatically in the first half of 1999, representing 40.8% of treatment admissions.

The CEWG reports an increase in problems associated with marijuana that they attribute to the drug's greater availability/potency, its relative low cost, and a public attitude that use of marijuana is less risky than use of other drugs.

5. The Scope, Duration, and Significance of Abuse

According to the National Household Survey on Drug Abuse and the Monitoring the Future study, marijuana remains the most extensively used illegal drug in the US, with 34.6% of individuals over age 12 (76.4 million) and 49.7% of 12th graders having tried it at least once in their lifetime. While the majority of individuals (85.3%) who have tried marijuana do not use the drug monthly, 11.2 million individuals (14.7%) report that they used marijuana within the past 30 days. An examination of use among various age cohorts demonstrates that monthly use occurs primarily among college age individuals, with use dropping off sharply after age 25.

The Drug Abuse Warning Network data show that among 18–25 year olds, there was a 19% increase in 1999 for marijuana emergency department mentions. The fact that this age cohort had the greatest degree of acute adverse reactions to marijuana might be expected given that this group has the largest prevalence of marijuana use. Marijuana was commonly associated with alcohol and cocaine.

According to 1999 DAWN data, there were 187 deaths mentions where marijuana was the only drug reported, out of the total 664 medical examiners episodes involving marijuana in 1999. In the majority of the medical examiners episodes marijuana was associated with alcohol, cocaine, and morphine.

Data from the Treatment Episode Data Set confirm that 69% of admissions to drug treatment programs for primary marijuana abuse also had concurrent use of alcohol and other drugs. The TEDS report also emphasizes that individuals who are admitted for drug treatment have multiple disadvantages in education and employment compared to the general population. Individuals most likely to develop dependence on marijuana have a higher rate of associated psychiatric disorders or are socializing with a delinquent crowd.

6. What, if Any, Risk There is to the Public Health

The risk to the public health as measured by quantifiers such as emergency room episodes, marijuana-related deaths, and drug treatment admissions is discussed in full in sections 1, 4, and 5 above. Accordingly, this section focuses on the health risks to the individual user. All drugs, both medicinal and illicit, have a broad range of effects on the individual user that are dependent on dose and duration of usage. It is not uncommon for a FDA approved drug product to produce adverse effects even at doses in the therapeutic range. Such adverse responses are known as ''side effects''. When determining whether a drug product is safe and effective for any indication, FDA performs a thorough risk-benefit analysis to determine whether the risks posed by the drug product's potential or actual side effects are outweighed by the drug product's potential benefits. As marijuana is not approved for any use, any potential benefits attributed to marijuana use have not been found to be outweighed by the risks. However, cannabinoids have a remarkably low acute lethal toxicity despite potent psychoactivity and pharmacologic actions on multiple organ systems.

The consequences of marijuana use and abuse are discussed below in terms of the risk from acute and chronic use of the drug to the individual user (IOM, 1999) (see also the discussion of the central nervous system effects, cognitive effects, cardiovascular and autonomic effects, respiratory effects, and the effect on the immune system in Section 2):

Risks from acute use of marijuana:

Acute use of marijuana causes an impairment of psychomotor performance, including performance of complex tasks, which makes it inadvisable to operate motor vehicles or heavy equipment after using marijuana. People who have or are at risk of developing psychiatric disorders may be the most vulnerable to developing dependence on marijuana. Dysphoria is a potential response in a minority of individuals who use marijuana.

Risks from chronic use of marijuana:

Marijuana smoke is considered to be comparable to tobacco smoke in respect to increased risk of cancer, lung damage, and poor pregnancy outcome. An additional concern includes the potential for dependence on marijuana, which has been assessed to be rare among the general population but more common among adolescents with conduct disorder and individuals with psychiatric disorders. Although a distinctive marijuana withdrawal syndrome has been identified, it is mild and short-lived.

The Diagnostic and Statistical Manual (DSM–IV–SR, 2000) of American Psychiatric Association states that the consequences of cannabis abuse are as follows:

> [P]eriodic cannabis use and intoxication can interfere with performance at work or school and may be physically hazardous in situations such as driving a car. Legal problems may occur as a consequence of arrests for cannabis possession. There may be arguments with spouses or parents over the possession of cannabis in the home or its use in the presence of children. When psychological or physical problems are associated with cannabis in the context of compulsive use, a diagnosis of Cannabis Dependence, rather than Cannabis Abuse, should be considered.

Individuals with Cannabis Dependence have compulsive use and associated problems. Tolerance to most of the effects of cannabis has been reported in individuals who use cannabis chronically. There have also been some reports of withdrawal symptoms, but their clinical significance is uncertain. There is some evidence that a majority of chronic users of cannabinoids report histories of tolerance or withdrawal and that these individuals evidence more severe drug-related problems overall. Individuals with Cannabis Dependence may use very potent cannabis throughout the day over a period of months or years, and they may spend several hours a day acquiring and using the substance. This often interferes with family, school, work, or recreational activities. Individuals with Cannabis Dependence may also persist in their use despite knowledge of physical problems (*e.g.,* chronic cough related to smoking) or psychological problems (*e.g.,* excessive sedation and a decrease in goal-oriented activities resulting from repeated use of high doses).

7. Its Psychic or Physiologic Dependence Liability

Tolerance can develop to marijuana-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood and behavioral changes (Jones *et al.,* 1981). Down-regulation of cannabinoid receptors has been suggested as the mechanism underlying tolerance to the effects of marijuana (Rodriguez de Fonseca *et al.,* 1994). Pharmacological tolerance does not indicate the physical dependence liability of a drug.

In order for physical dependence to exist, there must be evidence for a withdrawal syndrome. Although pronounced withdrawal symptoms can be provoked from the administration of a cannabinoid antagonist in animals who had received chronic THC administration, there is no overt withdrawal syndrome behaviorally in animals under conditions of natural discontinuation following chronic THC administration. The marijuana withdrawal syndrome is distinct but mild compared to the withdrawal syndromes associated with alcohol and heroin use, consisting of symptoms such as restlessness, mild agitation, insomnia, nausea and cramping that resolve after 4 days (Budney *et al.,* 1999; Haney *et al.,* 1999). These symptoms are comparable to the decreased vigor, increased fatigue, sleepiness, headache, and reduced ability to work seen with caffeine withdrawal (Lane *et al.,* 1998). However, marijuana withdrawal syndrome has only been reported in adolescents who were inpatients for substance abuse treatment or in individuals who had been given marijuana on a daily basis during research conditions. Physical dependence on marijuana is a rare phenomenon compared to other psychoactive drugs and if it develops, it is milder when marijuana is the only drug instead of being used in combination with other drugs.

TEDS data for 1998 show that 37.9% of admissions for treatment for primary marijuana use met DSM IV criteria for cannabis dependence, whereas 27.7% met DSM IV criteria for cannabis abuse. Taken in the context of the total number of admissions, a DSM IV diagnosis for cannabis dependence represented 6.6%, and a diagnosis for cannabis abuse represented 4.9%, of all subjects admitted to treatment. In contrast, opioid and cocaine dependence was the DSM diagnosis of 12.2% and 12.6% of all admissions, respectively. (See Section 6 regarding marijuana abuse and dependence).

According to the NHSDA, data discussed above in Section 1, 6.8 million Americans used marijuana weekly in 1998. In addition, the DAWN data discussed in Section 4 indicates that 34.2% of the 87,150 ED marijuana mentions in 1999 were related to episodes in which the motive for drug intake was primarily dependence. It should be emphasized that the patient-reported ''motive'' for the drug intake applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to one specific drug. DAWN data do not distinguish the drug responsible for the ED visit from others used concomitantly. Finally, the CEWG data discussed in Section 4 above reports an increase in the proportion of primary marijuana users entering drug abuse treatment programs. Thus, there is evidence among a certain proportion of marijuana users for a true psychological dependence syndrome.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under This Article

Marijuana is not an immediate precursor of another controlled substance.

C. Findings and Recommendation

After considering the scientific and medical evidence presented under the eight factors above, FDA finds that marijuana meets the three criteria for placing a substance in Schedule I of the CSA under 21 U.S.C. 812(b)(1). Specifically:

1. Marijuana Has a High Potential for Abuse

11.2 million Americans used marijuana monthly in 1999 and 1998 data indicate that 6.8 million Americans used marijuana weekly. A 1999 study indicates that by 12th grade, 37.8% of students report having used marijuana in the past year, and 23.1 % report using it monthly. In 1999, 87,150 emergency department episodes were induced by or related to the use of marijuana/hashish, representing 16% of all drug-related episodes. The primary motive for drug intake in 34.2 % of those episodes was reported to be dependence. DAWN data from that same year show that out of 664 medical examiner episodes involving marijuana, marijuana was the only drug reported in 187 deaths. In recent years, the proportion of primary marijuana abusers entering drug abuse treatment programs has been increasing in major U.S. cities, ranging from 19% in New York City to 41% in St. Louis and Denver.

Data show that humans prefer higher doses of marijuana to lower doses, demonstrating that marijuana has dose-dependent reinforcing effects. Marijuana has relatively low levels of toxicity and physical dependence as compared to other illicit drugs. However, as discussed above, physical dependence and toxicity are not the only factors to consider in determining a substance's abuse potential. The large number of individuals using marijuana on a regular basis and the vast amount of marijuana that is available for illicit use are indicative of widespread use. In addition, there is evidence that marijuana use can result in psychological dependence in a certain proportion of the population.

2. Marijuana Has No Currently Accepted Medical Use in Treatment in the United States

The FDA has not approved a new drug application for marijuana. The opportunity for scientists to conduct clinical research with marijuana has increased recently due to the implementation of DHHS policy supporting clinical research with botanical marijuana. While there are INDs for marijuana active at the FDA, marijuana does not have a currently accepted medical use for treatment in the United States nor does it have an accepted medical use with severe restrictions.

A drug has a ''currently accepted medical use'' if all of the following five elements have been satisfied:

a. The drug's chemistry is known and reproducible;

b. There are adequate safety studies;

c. There are adequate and well-controlled studies proving efficacy;

d. The drug is accepted by qualified experts; and

e. The scientific evidence is widely available.

Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994).

Although the chemistry of many cannabinoids found in marijuana have been characterized, a complete scientific analysis of all the chemical components found in marijuana has not been conducted. Safety studies for acute or subchronic administration of marijuana have been carried out through a limited number of Phase 1 clinical investigations approved by the FDA, but there have been no studies that have scientifically assessed the efficacy of marijuana for any medical condition. A material conflict of opinion among experts precludes a finding that marijuana has been accepted by qualified experts. At this time, it is clear

that there is not a consensus of medical opinion concerning medical applications of marijuana.

Alternately, a drug can be considered to have ''a currently accepted medical use with severe restrictions'' (21 U.S.C. 812(b)(2)(B)). Although some evidence exists that some form of marijuana may prove to be effective in treating a number of conditions, research on the medical use of marijuana has not progressed to the point that marijuana can be considered to have a ''currently accepted medical use with severe restrictions.''

3. There Is a Lack of Accepted Safety for Use of Marijuana Under Medical Supervision

There are no FDA-approved marijuana products. Marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. As discussed earlier, the known risks of marijuana use are not outweighed by any potential benefits. In addition, the agency cannot conclude that marijuana has an acceptable level of safety without assurance of a consistent and predictable potency and without proof that the substance is free of contamination. If marijuana is to be investigated more widely for medical use, information and data regarding the chemistry, manufacturing and specifications of marijuana must be developed. Therefore, FDA concludes that, even under medical supervision, marijuana has not been shown to have an acceptable level of safety.

FDA therefore recommends that marijuana be maintained in Schedule I of the CSA.

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Additional Scientific Data Considered by the Drug Enforcement Administration in Evaluating Jon Gettman's Petition To Initiate Rulemaking Proceedings To Reschedule Marijuana

Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, March 2001

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 U.S.C. 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 U.S.C. 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 al.,* 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; Jäarbe 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 (Guimães *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 al.,* 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 U.S.C. 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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[FR Doc. 01–9306 Filed 4–17–01; 8:45 am]
BILLING CODE 4410–09–P