U.S. Department of Justice - Drug Enforcement Administration

Schedule of Controlled Substances: Maintaining Marijuana in Schedule I of the Controlled Substances Act

Background, Data, and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b)

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BACKGROUND

On November 30, 2011, Governors Lincoln D. Chafee of Rhode Island and Christine O. Gregoire of Washington submitted a petition to the Drug Enforcement Administration (DEA) to initiate proceedings for a repeal of the rules or regulations that place marijuana[38] in schedule I of the Controlled Substances Act (CSA). The petition requests that marijuana[39] and "related items" be rescheduled in schedule II of the CSA. The petitioners claim that:

1. Cannabis has accepted medical use in the United States;
2. Cannabis is safe for use under medical supervision;
3. Cannabis for medical purposes has a relatively low potential for abuse, especially in comparison with other schedule II drugs.

The DEA accepted this petition for filing on January 30, 2012.

The Attorney General may by rule transfer a drug or other substance between schedules of the CSA if she finds that such drug or other substance has a potential for abuse, and makes the findings prescribed by 21 U.S.C. 812(b) for the schedule in which such drug is to be placed. 21 U.S.C. 811(a)(1). The Attorney General has delegated this responsibility to the Acting Administrator of the DEA. 28 C.F.R. § 0.100(b).

In accordance with 21 U.S.C. 811(b), after gathering the necessary data, the DEA submitted the petition and necessary data to the Department of Health and Human Services (HHS) on June 11, 2013, and requested that HHS provide a scientific and medical evaluation and scheduling recommendation for marijuana. In documents dated

[38] The Controlled Substances Act (CSA) defines marijuana as: "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 there from), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination." 21 U.S.C. 802(16). Note that "marihuana" is the spelling used in the CSA. This document uses the spelling that is more common in current usage, "marijuana."

[39] Petitioners defined marijuana as all cultivated strains of cannabis.

June 3 and June 25, 2015, the acting Assistant Secretary for Health of the HHS[40] recommended to the DEA that marijuana continue to be controlled in Schedule I of the CSA, and provided to the DEA its scientific and medical evaluation titled "Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act." The HHS's recommendations are binding on the DEA as to scientific and medical matters. 21 U.S.C. 811(b).

Before initiating proceedings to reschedule a substance, the CSA requires the Acting Administrator to determine whether the HHS scheduling recommendation, scientific and medical evaluation, and "all other relevant data" constitute substantial evidence that the drug should be rescheduled as proposed. 21 U.S.C. 811(b). The Acting Administrator must determine whether there is substantial evidence to conclude that the drug meets the criteria for placement in another schedule based on the criteria set forth in 21 U.S.C. 812(b). The CSA requires that both the DEA and the HHS consider the eight factors specified by Congress in 21 U.S.C. 811(c). This document lays out those considerations and is organized according to the eight factors. As DEA sets forth in detail below, the evidence shows:

1. Actual or relative potential for abuse. Marijuana has a high potential for abuse. Preclinical and clinical data show that it has reinforcing effects characteristic of drugs of abuse. National databases on actual abuse show marijuana is the most widely abused drug, including significant numbers of substance abuse treatment admissions. Data on marijuana seizures show widespread availability and trafficking.

2. Scientific evidence of its pharmacological effect. The scientific understanding of marijuana, cannabinoid receptors, and the endocannabinoid system continues to be studied and elucidated. Marijuana produces various pharmacological effects, including subjective (e.g., euphoria, dizziness, disinhibition), cardiovascular, acute and chronic respiratory, immune system, and prenatal exposure effects, as well as behavioral and cognitive impairment.

3. Current scientific knowledge. There is no currently accepted medical use for marijuana in the United States. Marijuana sources are derived from numerous cultivated strains and may have different levels of Δ^9-THC and other cannabinoids. Under the five-element test for currently accepted medical use discussed in more detail below and upheld by the Court of Appeals for the District of Columbia in Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994) (hereinafter "ACT"), there is no complete scientific analysis of marijuana's chemical components; there are not adequate

[40] As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of the NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations.

safety studies; there are not adequate and well-controlled efficacy studies; there is not a consensus of medical opinion concerning medical applications of marijuana; and the scientific evidence regarding marijuana's safety and efficacy is not widely available. To date, scientific and medical research has not progressed to the point that marijuana has a currently accepted medical use, even under conditions where its use is severely restricted.

4. History and current pattern of abuse. Marijuana continues to be the most widely used illicit drug. In 2014, there were 22.2 million current users. There were also 2.6 million new users, most of whom were less than 18 years of age. During the same period, marijuana was the most frequently identified drug exhibit in federal, state, and local forensic laboratories.

5. Scope, duration, and significance of abuse. Abuse of marijuana is widespread and significant. In 2014, for example, an estimated 6.5 million people aged 12 or older used marijuana on a daily or almost daily basis over a 12-month period. In addition, a significant proportion of all admissions for substance abuse treatment are for marijuana/hashish as their primary drug of abuse. In 2013, 16.8% of all such admissions--281,991 over the course of the year--were for primary marijuana/hashish abuse.

6. Risk, if any, to public health. Together with the health risks outlined in terms of pharmacological effects above, public health risks from acute use of marijuana include impaired psychomotor performance, impaired driving, and impaired performance on tests of learning and associative processes. Chronic use of marijuana poses a number of other risks to the public health including physical as well as psychological dependence.

7. Psychic or physiological dependence liability. Long-term, heavy use of marijuana can lead to physical dependence and withdrawal following discontinuation, as well as psychic or psychological dependence. In addition, a significant proportion of all admissions for treatment for substance abuse are for primary marijuana abuse; in 2013, 16.8% of all admissions were for primary marijuana/hashish abuse, representing 281,991 individuals.

8. Immediate precursor. Marijuana is not an immediate precursor of any controlled substance.

As specified in 21 U.S.C. 812(b)(1), in order for a substance to be placed in schedule I, the Acting Administrator must find that:

A. The drug or other substance has a high potential for abuse.
B. The drug or other substance has no currently accepted medical use in treatment in the United States.
C. There is a lack of accepted safety for use of the drug or other substance under medical supervision.

To be classified in another schedule under the CSA (e.g., II, III, IV, or V), a substance must have a "currently accepted medical use in treatment in the United States." 21 U.S.C. 812(b)(2)–(5). A substance also may be placed in schedule II if it is found to have "a currently accepted medical use with severe restrictions." 21 U.S.C. 812(b)(2). If a controlled substance has no such currently accepted medical use, it must be placed in schedule I. See Notice of Denial of Petition, 66 FR 20038 (Apr. 18, 2001) ("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.'").

A drug that is the subject of an approved new drug application (NDA) or abbreviated new drug application (ANDA) under Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), is considered to have a currently accepted medical use in treatment in the United States for purposes of the CSA . The HHS stated in its review, however, that FDA has not approved any NDA for marijuana for any indication.

In the absence of NDA or ANDA approval, DEA has established a five-element test for determining whether the drug has a currently accepted medical use in treatment in the United States. Under this test, a drug will be considered to have a currently accepted medical use only if the following five elements are satisfied:

1. The drug's chemistry is known and reproducible;
2. There are adequate safety studies;
3. There are adequate and well-controlled studies proving efficacy;
4. The drug is accepted by qualified experts; and
5. The scientific evidence is widely available.

(57 FR 10499, 10506 (March 26, 1992)). *See also* ACT, 15 F.3d at 1135.

As discussed in Factor 3, below, HHS concluded, and DEA agrees, that the scientific evidence is insufficient to demonstrate that marijuana has a currently accepted medical use under the five-element test. The evidence was insufficient in this regard also when the DEA considered petitions to reschedule marijuana in 1992 (57 FR 10499),[41] in 2001 (66 FR 20038), and in 2011 (76 FR 40552)[42]. Little has changed since 2011 with respect to the lack of clinical evidence necessary to establish that marijuana has a currently accepted medical use. No studies have scientifically assessed the efficacy and full safety profile of marijuana for any specific medical condition.

The limited existing clinical evidence is not adequate to warrant rescheduling of marijuana under the CSA. To the contrary, the data in this scheduling review document show that marijuana continues to meet the criteria for schedule I control under the CSA for the following reasons:

[41] *See* Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131 (D.C. Cir. 1994).
[42] *See* Americans for Safe Access v. DEA, 706 F.3d 438 (D.C. Cir. 2013)(rhg den. 2013).

1. Marijuana has a high potential for abuse.
2. Marijuana has no currently accepted medical use in treatment in the United States.
3. Marijuana lacks accepted safety for use under medical supervision.

FACTOR 1: THE DRUG'S ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

Marijuana is the most commonly abused illegal drug in the United States. It is also the most commonly used illicit drug by high school students in the United States. Further, marijuana is the most frequently identified drug by state, local and federal forensic laboratories. Marijuana's main psychoactive ingredient, Δ^9-tetrahydrocannabinol (Δ^9-THC),[43] is an effective reinforcer in laboratory animals, including primates and rodents. These animal studies both predict and support the observations that marijuana produces reinforcing effects in humans. Such reinforcing effects can account for the repeated abuse of marijuana.

A. Indicators of Abuse Potential

The HHS has concluded in its document, "Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act," that marijuana has a high potential for abuse. The finding of "abuse potential" is critical for control under the Controlled Substances Act (CSA). Although the term is not defined in the CSA, guidance in determining abuse potential is provided in the legislative history of the Act (Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 2 (1970), reprinted in 1970 U.S.C.C.A.N. 4566, 4603). Accordingly, the following items are indicators that a drug or other substance has potential for abuse:

- *There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or*

- *There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or*

- *Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or*

- *The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such*

[43] The terms Δ^9-THC and THC are used interchangeably though out this document.

drugs, 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.

Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

In its recommendation, the HHS analyzed and evaluated data on marijuana as applied to each of the above four criteria. The analysis presented in the recommendation (HHS, 2015) is discussed below:

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

   The HHS stated that some individuals are taking marijuana in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community. Data from national databases on actual abuse of marijuana support the idea that a large number of individuals use marijuana. In its recommendation (HHS, 2015), the HHS presented data from the National Survey on Drug and Health (NSDUH) of the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Monitoring the Future (MTF) survey of the National Institute on Drug Abuse (NIDA), and the DEA has since updated this information. The most recent data from SAMHSA's NSDUH in 2014 reported that marijuana was the most used illicit drug. Among Americans aged 12 years and older, an estimated 22.2 million Americans used marijuana within the past month according to the 2014 NSDUH. In 2004, an estimated 14.6 million individuals reported using marijuana within the month prior to the study. The estimated rates in 2014 thus reflect an increase of approximately 7.6 million individuals over a 10-year period. According to the 2013 NSDUH report, an estimated 19.8 million individuals reported using marijuana. Thus, over a period of one year (2013 NSDUH – 2014 NSDUH), there was an estimated increase of 2.4 million individuals in the United States using marijuana.

   The results from the 2015 Monitoring the Future survey of 8^{th}, 10^{th}, and 12^{th} grade students indicate that marijuana was the most widely used illicit drug in these age groups. Current monthly use was 6.5% of 8^{th} graders, 14.8% of 10^{th} graders, and 21.3% of 12^{th} graders. The Treatment Episode Data Set (TEDS) in 2013 reported that marijuana abuse was the primary factor in 16.8 percent of non-private substance-abuse treatment facility admissions. In 2011, SAMHSA's Drug Abuse Warning Network (DAWN) reported that marijuana was mentioned in 36.4% (455,668 out of approximately 1.25 million) of illicit drug-related Emergency Department (ED) visits.

Data on the extent and scope of marijuana abuse are presented under Factors 4 and 5 of this analysis. Discussion of the health effects of marijuana is presented under Factor 2, and the assessment of risk to the public health posed by acute and chronic marijuana abuse is presented under Factor 6 of this analysis.

2. *There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels.*

In accordance with the CSA, the only lawful source of marijuana in the United States is that produced and distributed for research purposes under the oversight of NIDA and in conformity with United States obligations under the Single Convention on Narcotic Drugs.[44] The HHS stated that there is a lack of significant diversion from legitimate drug sources, but that this is likely due to high availability of marijuana from illicit sources. Marijuana is not an FDA-approved drug product. Neither a New Drug Application (NDA) nor a Biologics License Application (BLA) has been approved for marketing in the United States. However, the marijuana used for nonclinical and clinical research represents a very small amount of the total amount of marijuana available in the United States and therefore information about marijuana diversion from legitimate sources is limited or not available.

The DEA notes that the magnitude of the demand for illicit marijuana is evidenced by information from a number of databases presented under Factor 4. Briefly, marijuana is the most commonly used illegal drug in the United States. It is also the most commonly used illicit drug by American high schoolers. Marijuana is the most frequently identified drug in state, local, and federal forensic laboratories, with increasing amounts of both domestically grown and of illicitly smuggled marijuana.

Given that marijuana has long been the most widely trafficked and abused controlled substance in the United States, and that all aspects of such illicit activity are entirely outside of the closed system of distribution mandated by the CSA, it may well be the case that there is little thought given to diverting marijuana from the small supplies produced for legitimate research purposes. Thus, the lack of data indicating diversion of marijuana from legitimate channels to the illicit market is not indicative of a lack of potential for abuse of the drug.

[44] See 76 FR 51403, 51409-51410 (2011) (discussing cannabis controls required under the Single Convention).

3. *Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.*

   The HHS stated that the FDA has not evaluated or approved an NDA or BLA for marijuana for any therapeutic indication. Consistent with federal law, therefore, an individual legitimately can take marijuana based on medical advice from a practitioner only by participating in research that is being conducted under an Investigational New Drug (IND) application. The HHS noted that there are several states as well as the District of Columbia which have passed laws allowing for individuals to use marijuana for purported "medical" use under certain circumstances, but data are not available yet to determine the number of individuals using marijuana under these state laws. Nonetheless, according to 2014 NSDUH data, 22.2 million American adults currently use marijuana (SAMHSA, 2015a). Based on the large number of individuals who use marijuana and the lack of an FDA-approved drug product, the HHS concluded that the majority of individuals using marijuana do so on their own initiative rather than by following medical advice from a licensed practitioner.

4. *The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, 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.*

   Marijuana and its primary psychoactive ingredient, Δ^9-THC, are controlled substances in schedule I under the CSA.

   The HHS stated that one approved, marketed drug product contains synthetic Δ^9-THC, also known as dronabinol, and another approved, marketed drug product contains a cannabinoid-like synthetic compound that is structurally related to Δ^9-THC, the main active component in marijuana. Both products are controlled under the CSA.

   Marinol is a schedule III drug product containing synthetic Δ^9-THC (dronabinol) formulated in sesame oil in soft gelatin capsules. Marinol was approved by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who did not respond to conventional anti-emetic treatments. In 1992, FDA approved Marinol for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Marinol was originally placed into

schedule II and later rescheduled to schedule III under the CSA due to the low reports of abuse relative to marijuana.

Cesamet is a drug product containing the schedule II substance nabilone, a synthetic substance structurally related to Δ^9-THC. Cesamet was approved for marketing by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. All other naturally occurring cannabinoids in marijuana and their synthetic equivalents with similar chemical structure and pharmacological activity are already included as schedule I drugs under the CSA.

B. Abuse Liability Studies

In addition to the indicators suggested by the CSA's legislative history, data as to preclinical and clinical abuse liability studies, as well as actual abuse, including clandestine manufacture, trafficking, and diversion from legitimate sources, are considered in this factor.

Abuse liability evaluations are obtained from studies in the scientific and medical literature. There are many preclinical measures of a drug's effects that when taken together provide an accurate prediction of the human abuse liability. Clinical studies of the subjective and reinforcing effects in humans and epidemiological studies provide quantitative data on abuse liability in humans and some indication of actual abuse trends. Both preclinical and clinical studies have clearly demonstrated that marijuana and Δ^9-THC possess the attributes associated with drugs of abuse: they function as a positive reinforcer to maintain drug-seeking behavior, they function as a discriminative stimulus, and they have dependence potential.

Preclinical and most clinical abuse liability studies have been conducted with the psychoactive constituents of marijuana, primarily Δ^9-THC and its metabolite, 11-hydroxy-Δ^9-THC. Δ^9-THC's subjective effects are considered to be the basis for marijuana's abuse liability. The following studies provide a summary of that data.

1. Preclinical Studies

Δ^9-THC, the primary psychoactive component in marijuana, is an effective reinforcer in laboratory animals, including primates and rodents, as these animals will self-administer Δ^9-THC. These animal studies both predict and support the observations that Δ^9-THC, whether smoked as marijuana or administered by other routes, produces reinforcing effects in humans. Such reinforcing effects can account for the repeated abuse of marijuana.

a. Drug Discrimination Studies

The drug discrimination paradigm is used as an animal model of human subjective effects (Solinas et al., 2006) and is a method where animals are

able to indicate whether a test drug is able to produce physical or psychological changes similar to a known drug of abuse. Animals are trained to press one bar (in an operant chamber) when they receive a known drug of abuse and another bar when they receive a placebo. When a trained animal receives a test drug, if the drug is similar to the known drug of abuse, it will press the bar associated with the drug.

Discriminative stimulus effects of Δ^9-THC have specificity for the pharmacological effects of cannabinoids found in marijuana (Balster and Prescott, 1992; Browne and Weissman, 1981; Wiley et al., 1993; Wiley et al., 1995). As mentioned by the HHS, the discriminative stimulus effects of cannabinoids appear to be unique because abused drugs of other classes including stimulants, hallucinogens, opioids, benzodiazepines, barbiturates, NMDA antagonists, and antipsychotics do not fully substitute for Δ^9-THC.

Laboratory animals including monkeys (McMahon et al., 2009), mice (McMahon et al., 2008), and rats (Gold et al., 1992) are able to discriminate cannabinoids from other drugs and placebo. The major active metabolite of Δ^9-THC, 11-hydroxy-Δ^9-THC, generalizes to Δ^9-THC (Browne and Weissman, 1981). In addition, according to the HHS, twenty-two other cannabinoids found in marijuana also substitute for Δ^9-THC. At least one cannabinoid, CBD, does not substitute for Δ^9-THC in rats (Vann et al., 2008).

b. Self-Administration Studies

Animal self-administration behavior associated with a drug is a commonly used method for evaluating if the drug produces rewarding effects and for predicting abuse potential (Balster, 1991; Balster and Bigelow, 2003). Drugs that are self-administered by animals are likely to produce rewarding effects in humans. As mentioned in the HHS review document, earlier attempts to demonstrate self-administration of Δ^9-THC were unsuccessful and confounded by diet restrictions, animal restraint, and known analgesic activity of Δ^9-THC at testing doses (Tanda and Goldberg, 2003; Justinova et al., 2003). Self-administration of Δ^9-THC was first demonstrated by Tanda et al. (2000). Tanda et al. (2000) showed that squirrel monkeys that were initially trained to self-administer cocaine (30 µg/kg, i.v.) self-administered 2 µg/kg Δ^9-THC (i.v.) and at a rate of 30 injections per one hour session. Tanda et al. (2000) used a lower dose of Δ^9-THC that was rapidly delivered (0.2 ml injection over 200 ms) than in previous self-administration studies such that analgesic activity of Δ^9-THC was not a confounding factor. The authors also stated that the doses were comparable to those doses used by humans who smoke marijuana. A CB1 receptor antagonist (SR141716) blocked this rewarding effect of THC.

Justinova et al. (2003) were able to demonstrate self-administration of Δ^9-THC in drug-naïve squirrel monkeys (no previous exposure to other drugs).

The authors tested the monkeys with several doses of Δ^9-THC (1, 2, 4, 8, and 16 µg/kg, i.v.) and found that the maximal rates of self-administration were observed with the 4 µg/kg/infusion. Subsequently, Braida et al. (2004) reported that rats will self-administer Δ^9-THC when delivered intracerebroventricularly (i.c.v.), but only at the lowest doses tested (0.01 – 0.02 µg/infusion, i.c.v.).

Self-administration behavior with Δ^9-THC was found to be antagonized in rats and squirrel monkeys by rimonabant (SR141716A, CB1 antagonist) and the opioid antagonists (naloxone and naltrexone) (Tanda et al., 2000; Braida et al., 2004; Justinova et al., 2004).

c. Conditioned Place Preference Studies

Conditioned place preference (CPP) is a behavioral assay where animals are given the opportunity to spend time in two distinct environments: one where they previously received a drug and one where they received a placebo. If the drug is reinforcing, animals in a drug-free state will choose to spend more time in the environment paired with the drug when both environments are presented simultaneously.

CPP has been demonstrated with Δ^9-THC in rats but only at low doses (0.075 – 1.0 mg/kg, i.p.; Braida et al., 2004). Rimonabant (0.25 – 1.0 mg/kg, i.p.) and naloxone (0.5 – 2.0 mg/kg, i.p.) antagonized Δ^9-THC-mediated CPP (Braida et al., 2004). However, in another study with rats, rimonabant was demonstrated to induce CPP at doses ranging from 0.25 – 3.0 mg/kg (Cheer et al., 2000). Mice without µ-opioid receptors did not exhibit CPP to Δ^9-THC (paired with 1 mg/kg Δ^9-THC, i.p.) (Ghozland et al., 2002).

2. Clinical Studies

In its scientific review (HHS, 2015), the HHS provided a list of common subjective psychoactive responses to cannabinoids based on information from several references (Adams and Martin, 1996; Gonzalez, 2007; Hollister, 1986; Hollister, 1988; Institute of Medicine, 1982). Furthermore, Maldonado (2002) characterized these subjective responses as pleasurable to most humans and are generally associated with drug-seeking and/or drug-taking. Later studies (Scherrer et al., 2009; Zeiger et al., 2010) reported that high levels of positive psychoactive effects correlate with increased marijuana use, abuse, and dependence. The list of the common subjective psychoactive effects provided by the HHS (HHS, 2015) is presented below:

1) Disinhibition, relaxation, increased sociability, and talkativeness.
2) Increased merriment and appetite, and even exhilaration at high doses.

3) Enhanced sensory perception, which can generate an increased appreciation of music, art, and touch.
4) Heightened imagination, which can lead to a subjective sense of increased creativity.
5) Initial dizziness, nausea, tachycardia, facial flushing, dry mouth, and tremor.
6) Disorganized thinking, inability to converse logically, time distortions, and short-term memory impairment.
7) Ataxia and impaired judgment, which can impede driving ability or lead to an increase in risk-taking behavior.
8) Illusions, delusions, and hallucinations that intensify with higher doses.
9) Emotional lability, incongruity of affect, dysphoria, agitation, paranoia, confusion, drowsiness, and panic attacks, which are more common in inexperienced or high-dosed users.

The HHS mentioned that marijuana users prefer higher concentrations of the principal psychoactive component (Δ^9-THC) over lower concentrations. In a clinical study with marijuana users (n = 12, usage ranged from once a month to 4 times a week), subjects were given a choice of 1.95% Δ^9-THC marijuana or 0.63% Δ^9-THC marijuana after sampling both marijuana cigarettes in two choice sessions. The marijuana cigarette with high THC was chosen in 21 out of 24 choice sessions or 87.5% of the time (Chait and Burke, 1994). Furthermore, in a double-blind study, frequent marijuana users (n = 11, usage at least 2 times per month with at least 100 occasions) when given a low-dose of oral Δ^9-THC (7.5 mg) were able to distinguish the psychoactive effects better than occasional users (n = 10, no use within the past 4 years with 10 or fewer lifetime uses) and also experienced fewer sedative effects (Kirk and de Wit, 1999).

Marijuana has also been recognized by scientific experts to have withdrawal symptoms (negative reinforcement) following moderate and heavy use. As discussed further in Factor 7, the DEA notes that the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) included a list of withdrawal symptoms following marijuana [cannabis] use (DSM-5, 2013).

C. Actual Abuse of Marijuana - National Databases Related to Marijuana Abuse and Trafficking

Marijuana continues to be the most widely used illicit drug. Evidence of actual abuse can be defined by episodes/mentions in databases indicative of abuse/dependence. The HHS provided in its recommendation (HHS, 2015) information relevant to actual abuse of marijuana including data results from the National Survey on Drug Use and Health (NSDUH), a Monitoring the Future (MTF) survey, the Drug Abuse Warning Network (DAWN), and the Treatment Episode Data Set (TEDS). These data sources provide quantitative information on many factors related to abuse of a particular substance,

including incidence and patterns of use, and profile of the abuser of specific substances. The DEA is providing updated information from these databases in this discussion. The DEA also includes data on trafficking and illicit availability of marijuana from DEA databases including the National Forensic Laboratory Information System (NFLIS) and the National Seizure System (NSS), formerly the Federal-wide Drug Seizure System (FDSS), as well as other sources of data specific to marijuana, including the Potency Monitoring Project and the Domestic Cannabis Eradication and Suppression Program (DCE/SP).

1. National Survey on Drug Use and Health (NSDUH)

The National Survey on Drug Use and Health (NSDUH) is conducted annually by the Department of Health and Human Service's Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA is the primary source of estimates of the prevalence and incidence of pharmaceutical drugs, illicit drugs, alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals.

According to the 2014 NSDUH report, marijuana was the most commonly used and abused illicit drug. That data showed that there were 22.2 million people who were past month users (8.4%) among those aged 12 and older in the United States. (Note: NSDUH figures on marijuana use include hashish use; the relative proportion of hashish use to marijuana use is very low). Marijuana had the highest rate of past-year dependence or abuse in 2014. The NSDUH report estimates that 3.0 million people aged 12 or older used an illicit drug for the first time in 2014; a majority (70.3%) of these past year initiates reported that their first drug used was marijuana. Among those who began using illicit drugs in the past year, 65.6%, 70.3%, and 67.6% reported marijuana as the first illicit drug initiated in 2012, 2013, and 2014 respectively. In 2014, the average age of marijuana initiates among 12- to 49-year-olds was 18.5 years. These usage rates and demographics are relevant in light of the risks presented.

Marijuana had the highest rate of past year dependence or abuse of any illicit drug in 2014. The 2014 NSDUH report stated that 4.2 million persons were classified with substance dependence or abuse of marijuana in the past year (representing 1.6% of the total population aged 12 or older, and 59.0% of those classified with illicit drug dependence or abuse) based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition (DSM-IV).

Among past year marijuana users age 12 or older, 18.5% used marijuana on 300 or more days within the previous 12 months in 2014. This translates into 6.5 million people using marijuana on a daily or almost daily basis over a 12-month period, significantly more than the estimated 5.7 million daily or almost daily

users in just the year before. Among past month marijuana users, 41.6% (9.2 million) used the drug on 20 or more days in the past month, a significant increase from the 8.1 million who used marijuana 20 days or more in 2013.

2. Monitoring the Future (MTF)

Monitoring the Future (MTF) is an ongoing study which is funded under a series of investigator-initiated competing research grants from the National Institute on Drug Abuse (NIDA). MTF tracks drug use trends among American adolescents in the 8th, 10th, and 12th grades. According to its 2015 survey results, marijuana was the most commonly used illicit drug, as was the case in previous years. Approximately 6.5% of 8th graders, 14.8% of 10th graders, and 21.3% of 12th graders surveyed in 2015 reported marijuana use during the past month prior to the survey. A number of high school students in 2015 also reported daily use in the past month, including 1.1%, 3.0%, and 6.0% of 8th, 10th, and 12th graders, respectively.

3. Drug Abuse Warning Network (DAWN), Emergency Department (ED) Visits

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related hospital emergency department (ED) visits to track the impact of drug use, misuse, and abuse in the United States. For the purposes of DAWN, the term "drug abuse" applies if the following conditions are met: (1) the case involved at least one of the following: use of an illegal drug, use of a legal drug contrary to directions, or inhalation of a non-pharmaceutical substance; and (2) the substance was used for one of the following reasons: because of drug dependence, to commit suicide (or attempt to commit suicide), for recreational purposes, or to achieve other psychic effects. Importantly, many factors can influence the estimates of ED visits, including trends in overall use of a substance as well as trends in the reasons for ED usage. For instance, some drug users may visit EDs for life-threatening issues while others may visit to seek care for detoxification because they needed certification before entering treatment. Additionally, DAWN data do not distinguish the drug responsible for the ED visit from other drugs that may have been used concomitantly. As stated in a DAWN report, "Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED visit may be more relevant to the other drug(s) involved in the episode."

In 2011, marijuana was involved in 455,668 ED visits out of 2,462,948 total ED visits involving all abuse or misuse in the United States and out of 1.25 million visits involving abuse or misuse of illicit drugs (excluding alcohol-related visits), as estimated by DAWN. This is lower than the number of ED visits involving cocaine (505,224) and higher than the number of ED visits involving heroin (258,482) and stimulants (e.g., amphetamine, methamphetamine) (159,840). Visits involving the other major illicit drugs, such as MDMA, GHB, LSD and other hallucinogens, PCP, and inhalants, were much less frequent, comparatively.

In young patients, marijuana is the illicit drug most frequently involved in ED visits, according to DAWN estimates, with 240.2 marijuana-related ED visits per 100,000 population ages 12 to 17, 443.8 per 100,000 population ages 18 to 20, and 446.9 per 100,000 population ages 21 to 24.

4. Treatment Episode Data Set (TEDS) System

The Treatment Episode Data Set (TEDS) system is part of the SAMHSA Drug and Alcohol Services Information System and is a national census of annual admissions to state licensed or certified, or administratively tracked, substance abuse treatment facilities. The TEDS system contains information on patient demographics and substance abuse problems of admissions to treatment for abuse of alcohol and/or drugs in facilities that report to state administrative data systems. For this database, the primary substance of abuse is defined as the main substance of abuse reported at the time of admission. TEDS also allows for the recording of two other substances of abuse (secondary and tertiary).

In 2011, the TEDS system included 1,928,792 admissions to substance abuse treatment; in 2012 there were 1,801,385 admissions; and in 2013 there were 1,683,451 admissions. Marijuana/hashish was the primary substance of abuse for 18.3% (352,397) of admissions in 2011; 17.5% (315,200) in 2012; and 16.8% (281,991) in 2013. Of the 281,991 admissions for marijuana/hashish treatment in 2013, 24.3% used marijuana/hashish daily. Among those treated for marijuana/hashish as the primary substance in 2013, 27.4% were ages 12 to 17 years and 29.7% were ages 18 to 24 years. Those admitted for marijuana/hashish were mostly male (72.6%) and non-Hispanic (82.2%). Non-hispanic whites (43.2%) represented the largest ethnic group of marijuana admissions.

5. Forensic Laboratory Data

Data on marijuana seizures from federal, state, and local forensic laboratories have indicated that there is significant trafficking of marijuana. The National Forensic Laboratory System (NFLIS) is a program sponsored by the Drug Enforcement Administration's Office of Diversion Control. NFLIS systematically collects drug identification results and associated information from drug exhibits encountered by law enforcement and analyzed in federal, state, and local forensic laboratories. NFLIS is a comprehensive information system that includes data from 278 individual forensic laboratories that report more than 91% of the drug caseload in the U.S. NFLIS captures data for all drugs and chemicals identified and reported by forensic laboratories. More than 1,700 unique substances are represented in the NFLIS database.

Data from NFLIS showed that marijuana was the most frequently identified drug in federal, state, and local laboratories from January 2004 through December

2014. Marijuana accounted for between 29.47% and 34.84% of all drug exhibits analyzed annually during that time frame (Table 1).

Table 1. NFLIS Federal, State and Local Forensic Laboratory Data of Marijuana Reports (other than hashish)

Year	Reports	Percent of Total Reports
2004	454,582	34.42%
2005	483,134	32.53%
2006	520,060	32.55%
2007	525,668	33.66%
2008	526,420	34.07%
2009	536,888	34.30%
2010	544,418	34.91%
2011	495,937	33.42%
2012	485,591	32.02%
2013	452,839	30.70%
2014	432,989	29.27%
2015*	341,162	26.73%

NFLIS database queried 03-23-2016, by date of submission, all drugs reported
*2015 data are still being reported to NFLIS due to normal lag time.

Since 2004, the total number of reports of marijuana and the amount of marijuana encountered federally has remained high (see data from Federal-wide Drug Seizure System and Domestic Cannabis Eradication and Suppression Program below).

6. Federal-wide Drug Seizure System

The Federal-wide Drug Seizure System (FDSS) contains information about drug seizures made within the jurisdiction of the United States by the Drug Enforcement Administration, the Federal Bureau of Investigation, United States Customs and Border Protection, and United States Immigration and Customs Enforcement. It also records maritime seizures made by the United States Coast Guard. Drug seizures made by other Federal agencies are included in the FDSS database when drug evidence custody is transferred to one of the agencies identified above. FDSS is now incorporated into the National Seizure System (NSS), which is a repository for information on clandestine laboratory and contraband (chemicals and precursors, currency, drugs, equipment and weapons). FDSS reports total federal drug seizures [in kilograms (kg)] of substances such as cocaine, heroin, MDMA, methamphetamine, and cannabis (marijuana and hashish). The yearly volume of cannabis seized (Table 2), consistently exceeding a thousand metric tons per year, shows that cannabis is very widely trafficked in the United States.

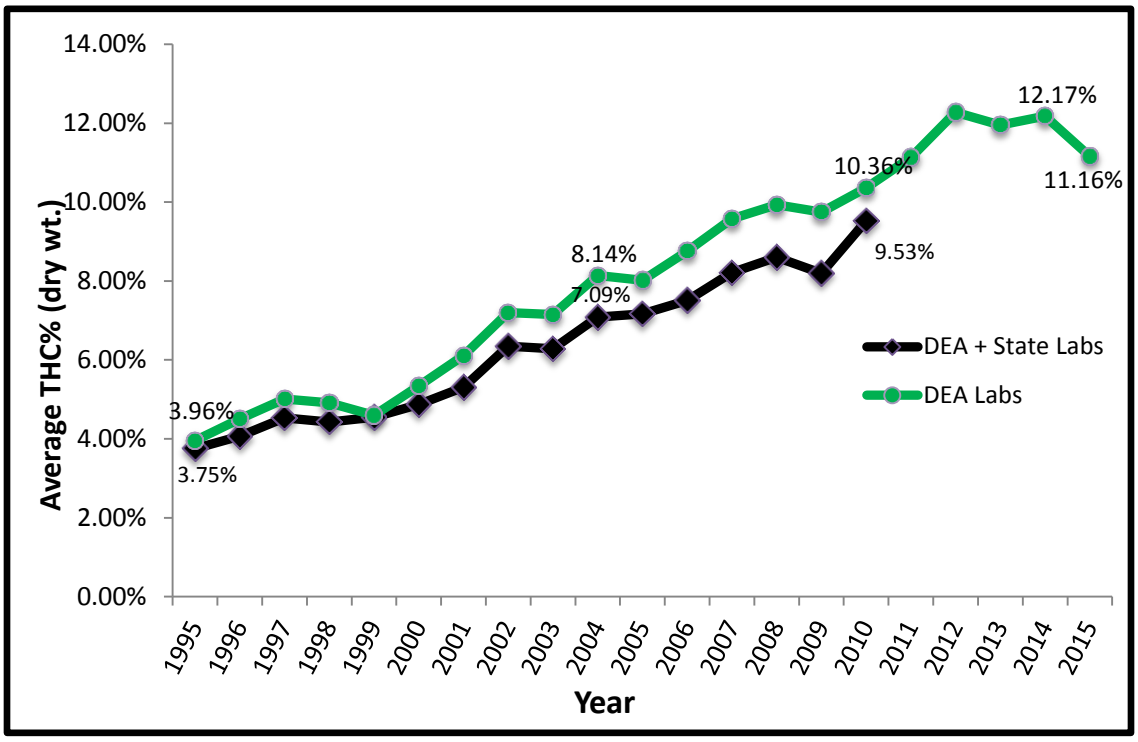
Table 2. Total Federal Seizures of Cannabis (Expressed in Kg)
(Source: NSS, U.S. Seizures, EPIC System Portal, queried 08-05-2015)

	2010	2011	2012	2013	2014
Cannabis	**4,071,328**	**3,622,256**	**2,756,439**	**2,622,494**	**1,768,277**
Marijuana	4,070,850	3,621,322	2,754,457	2,618,340	1,767,741
Hashish	478	934	1,982	4,154	536

7. Potency Monitoring Project

The University of Mississippi's Potency Monitoring Project (PMP), through a contract with the National Institute on Drug Abuse (NIDA), analyzes and compiles data on the Δ^9-THC concentrations of marijuana, hashish and hash oil samples provided by DEA regional laboratories and by state and local police agencies. After 2010, PMP has analyzed only marijuana samples provided by DEA regional laboratories. As indicated in Figure 1, the percentage of Δ^9-THC increased from 1995 to 2010 with an average THC content of 3.75% in 1995 and 9.53% in 2010. In examining marijuana samples only provided by DEA laboratories, the average Δ^9-THC content was 3.96% in 1995 in comparison to 11.16% in 2015.

Figure 1. Average Percentage of Δ^9-THC in Samples of Seized Marijuana (1995 – 2015)*
(Source: The University of Mississippi Potency Monitoring Program, Quarterly Report # 131)



*PMP discontinued analysis of state samples after 2010.
**Data for 2015 are incomplete. Figure 1 contains percentage of Δ^9-THC data through Dec. 22. Due to lack of funding, 4,177 samples haven't yet been analyzed.

8. The Domestic Cannabis Eradication and Suppression Program

The Domestic Cannabis Eradication and Suppression Program (DCE/SP) was established in 1979 to reduce the supply of domestically cultivated marijuana in the United States. The program was designed to serve as a partnership between federal, state, and local agencies. Only California and Hawaii were active participants in the program at its inception. However, by 1982 the program had expanded to 25 states and by 1985 all 50 states were participants. Cannabis is cultivated in remote locations and frequently on public lands and illicitly grown in all states. Data provided by the DCE/SP (Table 3) show that in the United States in 2014, there were 3,904,213 plants eradicated in outdoor cannabis cultivation areas compared to 2,597,798 plants in 2000. Significant quantities of marijuana were also eradicated from indoor cultivation operations. There were 396,620 indoor plants eradicated in 2014 compared to 217,105 eradicated in 2000.

Table 3. Domestic Cannabis Eradication, Outdoor and Indoor Plants Seized, 2000–2014 (Source: Domestic Cannabis Eradication/Suppression Program)

	2000	2001	2002	2003	2004
Outdoor	2,597,798	3,068,632	3,128,800	3,427,923	2,996,144
Indoor	217,105	236,128	213,040	223,183	203,896
Total	2,814,903	3,304,760	3,341,840	3,651,106	3,200,040

	2005	2006	2007	2008	2009
Outdoor	3,938,151	4,830,766	6,599,599	7,562,322	9,980,038
Indoor	270,935	400,892	434,728	450,986	414,604
Total	4,209,086	5,231,658	7,034,327	8,013,308	10,394,642

	2010	2011	2012	2013	2014
Outdoor	9,866,766	6,226,288	3,631,582	4,033,513	3,904,213
Indoor	462,419	509,231	302,377	361,727	396,620
Total	10,329,185	6,735,519	3,933,959	4,395,240	4,300,833

The recent statistics from these various surveys and databases show that marijuana continues to be the most commonly used illicit drug, with considerable rates of heavy abuse and dependence. They also show that marijuana is the most readily available illicit drug in the United States.

Petitioners' major comments in relation to Factor 1 and the Government's responses

1) In Exhibit B, the petitioners compared the effects of marijuana to currently controlled schedule II substances and made repeated claims about the comparative effects.

The HHS noted that comparisons between marijuana and schedule II substances are difficult because of differences in the actions of different pharmacological classes of schedule II drugs in the CSA. The HHS notes that schedule II substances include stimulant-like drugs (e.g. cocaine, amphetamine), opioids (e.g. fentanyl, oxycodone), depressant drugs (e.g., pentobarbital), dissociative anesthetics (e.g. phencyclidine), and naturally occurring plant components (e.g. coca leaves and poppy straw). The mechanism of action of Δ^9-THC and marijuana, which act primarily through the cannabinoid receptors (discussed further in Factor 2) are completely different from the above-mentioned classes of schedule II substances. The HHS concludes that the differences in the mechanisms of action in the various classes of schedule II substances make it inappropriate to compare the range of those substances with marijuana.

Furthermore, as noted by the HHS, many substances scheduled under the CSA are evaluated within the context of drug development using data submitted under a New

Drug Application (NDA). However, the petitioners have not identified a specific indication for use of marijuana and therefore the HHS notes that an appropriate comparator based on indication cannot be identified.

2) The petitioners indicated that the actual or relative potential of abuse of marijuana is low. The petitioners state, "*Some researchers claim that cannabis is not particularly addictive. Experts assert that cannabis's addictive potential parallels caffeine's."* (Exhibit B, page 19, lines 20-21). Furthermore, petitioners stated that, "*Cannabis use indicates a lower likelihood of addiction and abuse potential as compared to other substances."* (Exhibit B, page 22, lines 12-13).

Under the CSA, for a substance to be placed in schedule II, III, IV, or V, it must have a currently accepted medical use in treatment in the United States.[45] As DEA has previously stated, Congress established only one schedule, schedule I, for drugs of abuse with "no currently accepted medical use in treatment in the United States." 76 FR 40552 (2011). Thus, any attempt to compare the relative abuse potential of schedule I substance to that of a substance in another schedule is inconsequential since a schedule I substance must remain in schedule I until it has been found to have a currently accepted medical use in treatment in the United States.

Moreover, the petitioners failed to review the indicators of abuse potential, as discussed in the legislative history of the CSA. The petitioners did not use data on marijuana usage, diversion, psychoactive properties, and dependence in their evaluation of marijuana abuse potential. The HHS and the DEA discuss those indicators above in this factor. HHS's evaluation of the full range of data led HHS and DEA to conclude that marijuana has a high potential for abuse.

The petitioners, based on their review of a survey by Gore and Earleywine (2007), concluded that marijuana has a low abuse potential. Gore and Earleywine surveyed 746 mental health professionals and asked them to rate the addictiveness (based on a seven-point scale) of several drugs (heroin, nicotine, cocaine/crack, oxycodone, methamphetamine, amphetamine, caffeine, alcohol, and marijuana). The petitioners stated that the health professionals rated marijuana as least addictive of the drugs surveyed. The DEA notes that the survey cited by the petitioners is based on subjective opinions from health professionals.

3) The petitioners mentioned that many of the cannabinoids in marijuana decrease the psychoactive effects of Δ^9-THC, and therefore marijuana lacks sufficient abuse potential for placement into schedule I. Further, the petitioners mentioned on page 4 in Exhibit B (lines 11-15), "*While the DEA considers cannabis a schedule I drug, it classifies dronabinol (Marinol) as schedule III. Dronabinol is 100 percent THC and is potentially very psychoactive. Natural cannabis typically would be no more than 15 percent THC by weight. Thus it is inconsistent that cannabis, with 15 percent*

[45] *See* Americans for Safe Access, 706 F.3d at 440.

weight THC, remains a [s]chedule I drug, while dronabinol, at 100 percent THC, is schedule III."

The HHS addressed this issue by indicating that the modulating effects of the other cannabinoids in marijuana on Δ^9-THC have not been demonstrated in controlled studies. The HHS and the DEA also note that the determination of the abuse potential of a substance considers not only psychoactive effects but also chemistry, pharmacology, pharmacokinetics, usage patterns, and diversion history among other measures.

Marinol (dronabinol in sesame oil) was rescheduled from schedule II to schedule III on July 2, 1999 (64 FR 35928, DEA 1999). In assessing Marinol, HHS compared Marinol to marijuana on several aspects of abuse potential and found that major differences between the two, such as formulation, availability, and usage, contribute to differences in abuse potential. The psychoactive effects from smoking are generally more rapid and intense than those that occur through oral administration (HHS, 2015; Wesson and Washburn, 1990; Hollister and Gillespie, 1973). Therefore, as concluded by both the HHS and the DEA, the delayed onset of action and longer duration of action from an oral dose of Marinol may contribute in limiting the abuse potential of Marinol relative to marijuana, which is most often smoked. The HHS also stated that the extraction and purification of dronabinol from the encapsulated sesame oil mixture of Marinol is highly complex and difficult, and that the presence of sesame oil mixture may preclude the smoking of Marinol-laced cigarettes.

Furthermore, marijuana and Marinol show significant differences in actual abuse and illicit trafficking. There have been no reports of abuse, diversion, or public health risks due to Marinol. In contrast, 22.2 million American adults report currently using marijuana (SAMHSA, 2015a). The DEA database, NFLIS, showed that marijuana was the most frequently identified drug in state and local forensic laboratories from January 2001 to December 2014 and indicates the high availability of marijuana. The differences in composition, actual abuse, and diversion contribute to the differences in scheduling between marijuana and Marinol.

Additionally, the FDA approved a New Drug Application (NDA) for Marinol, indicating a legitimate medical use for Marinol in the United States and allowing for Marinol to be rescheduled into schedule II and subsequently into schedule III of the CSA. The HHS mentioned that marijuana and Marinol differ on a wide variety of factors and these differences are major reasons for differential scheduling of marijuana and Marinol. Marijuana, as discussed more fully in Factors 3 and 6, does not have a currently accepted medical use in the United States, is highly abused, and has a lack of accepted safety.

FACTOR 2: SCIENTIFIC EVIDENCE OF THE DRUG'S PHARMACOLOGICAL EFFECTS, IF KNOWN

The HHS stated that there are large amounts of scientific data on the neurochemistry, mechanistic effects, toxicology, and pharmacology of marijuana. A scientific evaluation, as conducted by the HHS and the DEA, of marijuana's neurochemistry, human and

animal behavioral pharmacology, central nervous system effects, and other pharmacological effects (e.g. cardiovascular, immunological effects) is presented below.

Neurochemistry

Marijuana contains numerous constituents such as cannabinoids that have a variety of pharmacological actions. The petition defined marijuana as including all cannabis cultivated strains. The HHS stated that different marijuana samples derived from various cultivated strains may differ in their chemical constituents including Δ^9-THC and other cannabinoids. Therefore marijuana products from different strains will have different biological and pharmacological effects. The chemical constituents of marijuana are discussed further in Factor 3.

The primary site of action for cannabinoids such as Δ^9-THC is at the cannabinoid receptor. Two cannabinoid receptors, CB1 and CB2, have been identified and characterized (Battista et al., 2012; Piomelli, 2005) and are G-protein-coupled receptors. Activation of these inhibitory G-protein-coupled receptors inhibits adenylate cyclase activity, which prevents conversion of ATP to cyclic AMP. Cannabinoid receptor activation also results in inhibition of N- and P/Q-type calcium channels and activates inwardly rectifying potassium channels (Mackie et al., 1995; Twitchell et al., 1997). The HHS mentioned that inhibition of N-type calcium channels decreases neurotransmitter release and this may be the underlying mechanism in the ability of cannabinoids to inhibit acetylcholine, norepinephrine and glutamate from specific areas of the brain. These cellular actions may underlie the antinociceptive and psychoactive effects of cannabinoids. Δ^9-THC acts as an agonist at cannabinoid receptors.

CB1 receptors are primarily found in the central nervous system and are located mainly in the basal ganglia, hippocampus and cerebellum of the brain (Howlett et al., 2004). CB1 receptors are also located in peripheral tissues such as the immune system (De Petrocellis and Di Marzo, 2009), but the concentration of CB1 receptors there is considerably lower than in the central nervous system (Herkenham et al., 1990; 1992). CB2 receptors are found primarily in the immune system and predominantly in B lymphocytes and natural killer cells (Bouaboula et al., 1993). CB2 receptors are also found in the central nervous system, primarily in the cerebellum and hippocampus (Gong et al., 2006).

Two endogenous ligands to the cannabinoid receptors, anandamide and arachidonyl glycerol (2-AG), were identified in 1992 (Devane et al., 1992) and 1995 (Mechoulam et al., 1995), respectively. Anandamide is a low-efficacy agonist (Brievogel and Childers, 2000) and 2-AG is a high efficacy agonist (Gonsiorek et al., 2000) to the cannabinoid receptors. These endogenous ligands are present in both the central nervous system and in the periphery (HHS, 2015).

Δ^9-THC and cannabidiol (CBD) are two of the major cannabinoids in marijuana. Δ^9-THC is the major psychoactive cannabinoid (Wachtel et al., 2002). Δ^9-THC has similar affinity for CB1 and CB2 receptors and acts as a weak agonist at CB2 receptors. The

HHS indicated that activation of CB1 receptors mediates psychotropic effects of cannabinoids. CBD has low affinity for both CB1 and CB2 receptors. CBD has antagonistic effects at CB1 receptors, and some inverse agonistic properties at CB2 receptors.

Animal Behavioral Effects

Animal abuse potential studies (drug discrimination, self-administration, conditioned place preference) are discussed more fully in Factor 1. Briefly, it was consistently demonstrated that Δ^9-THC, the primary psychoactive component in marijuana, and other cannabinoids in marijuana have a distinct drug discriminative profile. In addition, animals self-administer Δ^9-THC, and Δ^9-THC in low doses produces conditioned place preference.

Central Nervous System Effects

Psychoactive Effects

The clinical psychoactive effects of marijuana are discussed more fully in Factor 1. Briefly, the psychoactive effects from marijuana use are considered pleasurable and associated with drug-seeking or drug-taking (HHS, 2015; Maldonado, 2002). Further, it was noted by HHS that marijuana users prefer higher concentrations of the principal psychoactive component (Δ^9-THC) over lower concentrations (HHS, 2015).

Studies have evaluated psychoactive effects of THC in the presence of high CBD, CBC, or CBN ratios. Even though some studies suggest that CBD may decrease some of Δ^9-THC's psychoactive effects, the HHS found that the ratios of CBD to Δ^9-THC administered in the studies were not comparable to the amounts found in marijuana used by most people (Dalton et al., 1976; Karniol et al., 1974; Zwardi et al., 1982). In fact, the CBD ratios in these studies are significantly higher than the CBD found in most marijuana currently found on the streets (Mehmedic et al., 2010). HHS indicated that most of the marijuana available on the street has a high THC and low CBD content and therefore any lessening of THC's psychoactive effects by CBD will not occur for most marijuana users (HHS, 2015). Dalton et al. (1976) reported that when volunteers smoked cigarettes with a ratio of 7 CBD to 1 Δ^9-THC (0.15 mg/kg CBD and 0.025 mg/kg Δ^9-THC), there was a significant decrease in ratings of acute subjective effects and achieving a "high" in comparison to smoking Δ^9-THC alone. In oral administration studies, the subjective effects and anxiety produced by combination of CBD and THC in a ratio of at least 1:2 CBD to Δ^9-THC (15, 30, 60 mg CBD to 30 mg Δ^9-THC; Karniol et al., 1974) or a ratio of 2:1 CBD to Δ^9-THC (1 mg/kg CBD to 0.5 mg/kg Δ^9-THC; Zuardi et al., 1982) are less than those produced by Δ^9-THC administered alone.

In one study (Ilan et al., 2005), the authors calculated the naturally occurring concentrations of CBC and CBD in marijuana cigarettes with either 1.8 or 3.6% Δ^9-THC by weight. The authors varied the concentrations of CBC and CBD for each concentration of Δ^9-THC in the marijuana cigarettes. Administrations in healthy

marijuana users (n=23) consisted of either: 1) low CBC (0.1% by weight) and low CBD (0.2% by weight); 2) high CBC (0.5% by weight) and low CBD; 3) low CBC and high CBD (1.0% by weight); or 4) high CBC and high CBD and the users were divided into low Δ^9-THC (1.8% by weight) and high Δ^9-THC (3.6% by weight) groups. Subjective psychoactive effects were significantly greater for all groups in comparison to placebo and there were no significant differences in effects among the treatments (Ilan et al., 2005).

The HHS also referred to a study with Δ^9-THC and cannabinol (CBN) (Karniol et al., 1975). In this study, oral administration of either 12.5, 25, or 50 mg CBN combined with 25 mg Δ^9-THC (ratio of at least 1:2 CBN to Δ^9-THC) significantly increased subjective psychoactive ratings of Δ^9-THC compared to Δ^9-THC alone (Karniol et al., 1975).

Behavioral Impairment

Several factors may influence marijuana's behavioral effects including the duration (chronic or short term), frequency (daily, weekly, or occasionally), and amount of use (heavy or moderate). Researchers have examined how long behavioral impairments persist following chronic marijuana use. These studies used self-reported histories of exposure duration, frequency, and amount of marijuana use, and administered several performance and cognitive tests at different time points following marijuana abstinence. According to HHS, behavioral impairments may persist for up to 28 days of abstinence in chronic marijuana users.

Psychoactive effects of marijuana can lead to behavioral impairment including cognitive decrements and decreased ability to operate motor vehicles (HHS, 2015). Block et al. (1992) evaluated cognitive measures in 48 healthy male subjects following smoking a marijuana cigarette that contained 2.57% or 19 mg Δ^9-THC by weight or placebo. Each subject participated in eight sessions (four sessions with marijuana; four sessions with placebo) and several cognitive and psychomotor tests were administered (e.g. verbal recall, facial recognition, text learning, reaction time). Marijuana significantly impaired performances in most of these cognitive and psychomotor tests (Block et al., 1992).

Ramaekers et al. (2006) reported that in 20 recreational users of marijuana, acute administration of 250 µg/kg and 500 µg/kg Δ^9-THC in smoked marijuana resulted in dose-dependent impairments in cognition, motor impulsivity, motor control (tracking impairments), and risk taking. In another study (Kurzthaler et al., 1999), when 290 µg/kg Δ^9-THC was administered via a smoked marijuana cigarette in 30 healthy volunteers with no history of substance abuse there were significant impairments of motor speed and accuracy. Furthermore, administration of 3.95% Δ^9-THC in a smoked marijuana cigarette increased the latency in a task of simulated braking in a vehicle (Liguori et al., 1998). The HHS noted that the motor impairments reported in these studies (Kurzthaler et al., 1999; Liguori et al., 1998) are critical skills needed for operating a vehicle.

As mentioned in the HHS document, some studies examined the persistence of the behavioral impairments immediately after marijuana administration. Some of

marijuana's acute effects may still be present for at least 24 hours after the acute psychoactive effects have subsided. In a brief communication, Heishmann et al. (1990) reported that there were cognitive impairments (digit recall and arithmetic tasks) in two out of three experienced marijuana smokers for 24 hours after smoking marijuana cigarettes containing 2.57% Δ^9-THC. However, Fant et al. (1998) evaluated subjective effects and performance measures for up to 25 hours in 10 healthy males after exposure to either 1.8% or 3.6% Δ^9-THC in marijuana cigarettes. Peak decrements in subjective and performance measures were noted within 2 hours of marijuana exposure but there were minimal residual alterations in subjective or performance measures at 23 – 25 hours after exposure.

Persistence of behavioral impairments following repeated and chronic use of marijuana has also been investigated and was reviewed in the HHS document (HHS, 2015). In particular, researchers examined how long behavioral impairments last following chronic marijuana use. In studies examining persistence of effects in chronic and heavy marijuana users, there were significant decrements in cognitive and motor function tasks in all studies of up to 27 days, and in most studies at 28 days (Solowij et al., 2002; Messinis et al., 2006; Lisdahl and Price, 2012; Pope et al., 2002; Bolla et al., 2002; Bolla et al., 2005). In studies that followed heavy marijuana users for longer than 28 days and up to 20 years of marijuana abstinence, cognitive and psychomotor impairments were no longer detected (Fried et al., 2005; Lyons et al., 2004; Tait et al., 2011). For example, Fried et al. (2005) reported that after 3 months of abstinence from marijuana, any deficits in intelligence (IQ), memory, and processing speeds following heavy marijuana use were no longer observed (Fried et al., 2005). In a meta-analysis that examined non-acute and long-lasting effects of marijuana, any deficits in neurocognitive performance that were observed within the first month were no longer apparent after approximately one month of abstinence (Schreiner and Dunn, 2012). HHS further notes that in moderate marijuana users deficits in decision-making skills were not observed after 25 days of abstinence and additionally IQ, immediate memory and delayed memory skills were not significantly impacted as observed with heavy and chronic marijuana users (Fried et al., 2005; HHS, 2015).

As mentioned in the HHS document (HHS, 2015), the intensity and persistence of neurological impairment from chronic marijuana use also may be dependent on the age of first use. In two separate smaller scale studies (less than 100 participants per exposure group), Fontes et al. (2011) and Gruber et al. (2012) compared neurological function in early onset (chronic marijuana use prior to age 15 or 16) and late onset (chronic marijuana use after age 15 or 16) heavy marijuana users and found that there were significant deficits in executive neurological function in early onset users which were not observed or were less apparent in late onset users. In a prospective longitudinal birth cohort study following 1,037 individuals (Meier et al., 2012), a significant decrease in IQ and neuropsychological performance was observed in adolescent-onset users and persisted even after abstinence from marijuana for at least one year. However, Meier et al (2012) reported in there was no significant change in IQ in adult-onset users.

The HHS noted that there is some evidence that the severity of the persistent neurological impairments may also be due in part to the amount of marijuana usage. In the study mentioned above, Gruber et al. (2012) found that the early onset users consumed three times as much marijuana per week and used it twice as often as late onset users. Meier et al. (2012) reported in their study, mentioned above, that there was a correlation between IQ deficits in adolescent onset users and the increased amount of marijuana used.

Behavioral Effects of Prenatal Exposure

In studies that examined effects of prenatal marijuana exposure, many of the pregnant women also used alcohol and tobacco in addition to marijuana. Even though other drugs were used in conjunction with marijuana, there is evidence of an association between heavy prenatal marijuana exposure and deficits in some cognitive function. There have been two prospective longitudinal birth cohort studies following individuals prenatally exposed to marijuana from birth until adulthood: the Ottawa Prenatal Prospective Study (OPPS; Fried et al., 1980), and the Maternal Health Practices and Child Development Project (MHPCD; Day et al., 1985). Both longitudinal studies report that heavy prenatal marijuana use is associated with decreased performance on tasks assessing memory, verbal and quantitative reasoning in 4-year-olds (Fried and Watkinson, 1990) and in 6 year olds (Goldschmidt et al., 2008). In subsequent studies with the OPPS cohort, deficits in sustained attention were reported in children ages 6 and 13 – 16 years (Fried et al., 1992; Fried, 2002) and deficits in executive neurological function were observed in 9- and 12-year-old children (Fried et al., 1998). DEA further notes that with the MHPCD cohort, follow-up studies reported an increased rate of delinquent behavior (Day et al., 2011) and decreased achievement test scores (Goldschmidt et al., 2012) at age 14. When the MHPCD cohort was followed to age 22, there was a marginal ($p = 0.06$) increase in psychosis with prenatal marijuana exposure and early onset of marijuana use (Day et al., 2015).

Association of Marijuana Use with Psychosis

There has been extensive research to determine whether marijuana usage is associated with development of schizophrenia or other psychoses, and the HHS indicated that the available data do not suggest a causative link between marijuana and the development of psychosis (HHS, 2015; Minozzi et al., 2010). As mentioned in the HHS review (HHS, 2015), numerous large scale longitudinal studies demonstrated that subjects who used marijuana do not have a greater incidence of psychotic diagnoses compared to non-marijuana users (van Os et al., 2002; Fergusson et al., 2005; Kuepper et al., 2011). Further, the HHS commented that when analyzing the available data examining the association between marijuana and psychosis, it is critical to differentiate whether the patients in a study are already diagnosed with psychosis or if the individuals have a limited number of symptoms associated with psychosis without qualifying for a diagnosis of the disorder.

As mentioned by the HHS, some of the studies examining the association between marijuana and psychosis utilized non-standard methods to categorize psychosis and these methods did not conform to the criteria in the Diagnostic and Statistical Manual (DSM-5) or the International Classification of Diseases (ICD-10) and would not be appropriate for use in evaluating the association between marijuana use and psychosis. For example, researchers characterized psychosis as "schizophrenic cluster" (Maremmani et al., 2004), "subclinical psychotic symptoms" (van Gastel et al., 2012), "pre-psychotic clinical high risk" (van der Meer et al., 2012), and symptoms related to "psychosis vulnerability" (Griffith-Lendering et al., 2012).

The HHS discussed an early epidemiological study conducted by Andreasson et al. (1987), which examined the link between psychosis and marijuana use. In this study, about 45,000 18- and 19-year-old male Swedish subjects provided detailed information on their drug-taking history and 274 of these subjects were diagnosed with schizophrenia over a 14-year period (1969 – 1983). Out of the 274 subjects diagnosed with psychosis, 21 individuals (7.7%) had used marijuana more than 50 times, while 197 individuals (72%) never used marijuana. As presented by the authors (Andreasson et al., 1987), individuals who claimed to take marijuana on more than 50 occasions were 6 times more likely to be diagnosed with schizophrenia than those who had never consumed the drug. The authors concluded that marijuana users who are vulnerable to developing psychoses are at the greatest risk for schizophrenia. In a 35 year follow up to the subjects evaluated in Andreasson et al. (1987), Manrique-Garcia et al. (2012) reported similar findings. In the follow up study, 354 individuals developed schizophrenia. Of those, 32 individuals (9%) had used marijuana more than 50 times and were 6.3 times more likely to develop schizophrenia. 255 of the 354 individuals (72%) never used marijuana.

The HHS also noted that many studies support the assertion that psychosis from marijuana usage may manifest only in individuals already predisposed to development of psychotic disorders. Marijuana use may precede diagnosis of psychosis (Schimmelmann et al., 2011), but most reports indicate that prodromal symptoms of schizophrenia are observed prior to marijuana use (Schiffman et al., 2005). In a review examining gene-environmental interaction between marijuana exposure and the development of psychosis, it was concluded that there is some evidence to support that marijuana use may influence the development of psychosis but only for susceptible individuals (Pelayo-Teran et al., 2012).

Degenhardt et al. (2003) modeled the prevalence of schizophrenia against marijuana use across eight birth cohorts in individuals born during 1940 to 1979 in Australia. Even though there was an increase in marijuana use in the adult subjects over this time period, there was not an increase in diagnoses of psychosis for these same subjects. The authors concluded that use of marijuana may increase schizophrenia only in persons vulnerable to developing psychosis.

Cardiovascular and Autonomic Effects

The HHS stated that acute use of marijuana causes an increase in heart rate (tachycardia) and may increase blood pressure (Capriotti et al., 1988; Benowitz and Jones, 1975). There is some evidence that associates the increased heart rate from Δ^9-THC exposure with excitation of the sympathetic and depression of the parasympathetic nervous systems (Malinowska et al., 2012). Tolerance to tachycardia develops with chronic exposure to marijuana (Jones, 2002; Sidney, 2002).

Prolonged exposure to Δ^9-THC results in a decrease in heart rate (bradycardia) and hypotension (Benowitz and Jones, 1975). These effects are thought to be mediated through peripherally located, presynaptic CB1 receptor inhibition of norepinephrine release with possible direct activation of vascular cannabinoid receptors (Wagner et al., 1998; Pacher et al., 2006).

As stated in the HHS recommendation (HHS, 2015), marijuana exposure causes orthostatic hypotension (fainting-like feeling; sudden drop in blood pressure upon standing up) and tolerance can develop to this effect upon repeated, chronic exposure (Jones, 2002). Tolerance to orthostatic hypotension is potentially related to plasma volume expansion, but tolerance does not develop to supine hypotensive effects (Benowitz and Jones, 1975).

Marijuana smoking, particularly by those with some degree of coronary artery or cerebrovascular disease, poses risks such as increased cardiac work, increased catecholamines and carboxyhemoglobin, myocardial infarction and postural hypotension (Benowitz and Jones, 1981; Hollister, 1988; Mittleman et al., 2001; Malinowska et al., 2012). However, electrocardiographic changes were minimal after administration of large cumulative doses of Δ^9-THC (Benowitz and Jones, 1975).

The DEA notes two recent reports that reviewed several case studies on marijuana and cardiovascular complications (Panayiotides, 2015; Hackam, 2015). Panayiotides (2015) reported that approximately 25.6% of the cardiovascular cases from marijuana use resulted in death from data provided by the French Addictovigilance Network during the period of 2006 – 2010. Several case studies on marijuana usage and cardiovascular events were discussed and it was concluded that although a causal link cannot be established due to not knowing exact amounts of marijuana used in the cases and confounding variables, the available evidence supports a link between marijuana and cardiotoxicity. Hackham (2015) reviewed 34 case reports or case series reports of marijuana and stroke/ischemia in 64 stroke patients and reported that in 81% of the cases there was a temporal relationship between marijuana usage and stroke or ischemic event. The author concluded that collective analysis of the case reports supports a causal link between marijuana use and stroke.

Respiratory Effects

The HHS stated that transient bronchodilation is the most typical respiratory effect of acute exposure to marijuana (Gong et al., 1984). In a recent longitudinal study, information on marijuana use and pulmonary data function were collected from 5,115

individuals over 20 years from 4 communities in the United States (Oakland, CA; Chicago, IL; Minneapolis, MN; Birmingham, AL) (Pletcher et al., 2012). Of the 5,115 individuals, 795 individuals reported use of only marijuana (without tobacco). The authors reported that occasional use of marijuana (7 joint-years for lifetime or 1 joint/day for 7 years or 1 joint/week for 49 years) does not adversely affect pulmonary function. Pletcher et al. (2012) further concluded that there is some preliminary evidence suggesting that heavy marijuana use may have a detrimental effect on pulmonary function, but the sample size of heavy marijuana users in the study was too small. Further, as mentioned in the HHS recommendation document (HHS, 2015), long-term use of marijuana may lead to chronic cough, increased sputum, as well as increased frequency of chronic bronchitis and pharyngitis (Adams and Martin, 1996; Hollister, 1986).

The HHS stated that the evidence that marijuana may lead to cancer of the respiratory system is inconsistent, with some studies suggesting a positive correlation while others do not (Lee and Hancox, 2011; Tashkin, 2005). The HHS noted a case series that reported lung cancer occurrences in three marijuana smokers (age range 31 – 37 years) with no history of tobacco smoking (Fung et al., 1999). Furthermore, in a case-control study (n = 173 individuals with squamous cell carcinoma of the head and neck; n = 176 controls; Zhang et al., 1999), prevalence of marijuana use was 9.7% in controls and 13.9% in cases and the authors reported that marijuana use may dose-dependently interact with mutagenic sensitivity, cigarette smoking, and alcohol use to increase risk associated with head and neck cancers (Zhang et al., 1999). However, in a large clinical study with 1,650 subjects, no positive correlation was found between marijuana use and lung cancer (Tashkin et al., 2006). This finding held true regardless of the extent of marijuana use when both tobacco use and other potential confounding factors were controlled. The HHS concluded that new evidence suggests that the effects of smoking marijuana on respiratory function and cancer are different from the effects of smoking tobacco (Lee and Hancox, 2011).

The DEA further notes the publication of recent review articles critically evaluating the association between marijuana and lung cancer. Most of the reviews agree that the association is weak or inconsistent (Huang et al., 2015; Zhang et al., 2015; Gates et al., 2014; Hall and Degenhardt, 2014). Huang et al. (2015) identified and reviewed six studies evaluating the association between marijuana use and lung cancer and the authors concluded that an association is not supported most likely due to the small amounts of marijuana smoked in comparison to tobacco. Zhang et al. (2015) examined six case control studies from the US, UK, New Zealand, and Canada within the International Lung Cancer Consortium and found that there was a weak association between smoking marijuana and lung cancer in individuals who never smoked tobacco, but precision of the association was low at high marijuana exposure levels. Hall and Degenhardt (2014) noted that even though marijuana smoke contains several of the same carcinogens and co-carcinogens as tobacco smoke (Roth et al., 1998) and has been found to be mutagenic and carcinogenic in the mouse skin test, epidemiological studies have been inconsistent, but more consistent positive associations have been reported in case control studies. Finally Gates et al. (2014), reviewed the studies evaluating marijuana use and lung cancer

and concluded that there is evidence that marijuana produces changes in the respiratory system (precursors to cancer) that could lead to lung cancer, but overall association is weak between marijuana use and lung cancer especially when controlling for tobacco use.

Endocrine System

Reproductive Hormones

The HHS stated that administration of marijuana to humans does not consistently alter the endocrine system. In a controlled human exposure study (n = 4 males), subjects were acutely administered smoked marijuana containing 2.8% Δ^9-THC or placebo and an immediate significant decrease in luteinizing hormone and an increase in cortisol was reported in the subjects that smoked marijuana (Cone et al., 1986). Furthermore, as cited by the HHS, two later studies (Dax et al., 1989; Block et al., 1991) reported no changes in hormone levels. Dax et al. (1989) recruited male volunteers (n = 17) that were occasional or heavy users of marijuana. Following exposure to smoked Δ^9-THC (18 mg/cigarette) or oral Δ^9-THC (10 mg three times per day for three days and on the morning of the fourth day), the subjects in that study showed no changes in plasma adrenocorticotropic hormone (ACTH), cortisol, prolactin, luteinizing hormone, or testosterone levels. Additionally, Block et al. (1991) compared plasma hormone levels amongst non-users as well as infrequent, moderate, and frequent users of marijuana (n = 93 men and 56 women) and found that chronic use of marijuana (infrequent, moderate, and frequent users) did not significantly alter concentrations of testosterone, luteinizing hormone, follicle stimulating hormone, prolactin, or cortisol.

The HHS noted that there is a discrepancy in the effect of marijuana on female reproductive system functionality between animals and humans (HHS, 2015). Female rhesus monkeys that were administered 2.5 mg/kg Δ^9-THC, i.m., during days 1 – 18 of the menstrual cycle had reduced progesterone levels and ovulation was suppressed (Asch et al., 1981). However, women who smoked marijuana (1 gram marijuana cigarette with 1.8% Δ^9-THC) during the periovulatory period (24 – 36 hours prior to ovulation) did not exhibit changes in reproductive hormone levels or their menstrual cycles (Mendelson and Mello, 1984). In a review article by Brown and Dobs (2002), the authors state that endocrine changes observed with marijuana are no longer observed with chronic administration and this may be due to drug tolerance.

Reproductive Cancers

The HHS stated that recent studies support a possible association between frequent, long-term marijuana use and increased risk of testicular germ cell tumors. In a hospital-based case-control study, the frequency of marijuana use was compared between testicular germ cell tumor (TGCT) patients (n = 187) and controls (n = 148) (Trabert et al., 2011). TGCT patients were more likely to be frequent marijuana users than controls with an odds ratio (OR) of 2.2 (95% confidence limits of 1.0 – 5.1) and were less likely to be infrequent or short-term users with odds ratios of 0.5 and 0.6, respectively in comparison

to controls (Trabert et al., 2011). The DEA further notes that in two population-based case-control studies (Daling et al., 2009; Lacson et al., 2012), marijuana use was compared between patients diagnosed with TGCT and matched controls in Washington State or Los Angeles County. In both studies, it was reported that TCGT patients were twice as likely as controls to use marijuana. Authors of both studies concluded that marijuana use is associated with an elevated risk of TGCT (Daling et al., 2009; Lacson et al., 2012).

The HHS cited a study (Sarfaraz et al., 2005) demonstrating that WIN 55,212-2 (a mixed CB1/CB2 agonist) induces apoptosis (one form of cell death) in prostate cancer cells and decreases expression of androgen receptors and prostate specific antigens, suggesting a potential therapeutic value for cannabinoid agonists in the treatment of prostate cancer, an androgen-stimulated type of carcinoma.

Other hormones (e.g. thyroid, appetite)

In more recent studies, as cited by the HHS, chronic marijuana use by subjects (n = 39) characterized as dependent on marijuana according to the ICD-10 criteria did not affect serum levels of thyroid hormones: TSH (thyrotropin), T4 (thyroxine), and T3 (triiodothyronine) (Bonnet, 2013). With respect to appetite hormones, in a pilot study with HIV-positive males, smoking marijuana dose-dependently increased plasma levels of ghrelin and leptin and decreased plasma levels of peptide YY (Riggs et al., 2012).

The HHS stated that Δ^9-THC reduces binding of the corticosteroid dexamethasone in hippocampal tissue from adrenalectomized rats and acute Δ^9-THC releases corticosterone, with tolerance developing to this effect with chronic administration (Eldridge et al., 1991). These data suggest that Δ^9-THC may interact with the glucocorticoid receptor system.

Immune System

The HHS stated that cannabinoids alter immune function but that there can be differences between the effects of synthetic, natural, and endogenous cannabinoids (Croxford and Yamamura, 2005; Tanasescu and Constantinescu, 2010).

The HHS noted that there are conflicting results in animal and human studies with respect to cannabinoid effects on immune functioning in subjects with compromised immune systems. Abrams et al. (2003) examined the effects of marijuana and Δ^9-THC in 62 HIV-1-infected patients. Subjects received one of three treatments, three times a day: smoked marijuana cigarette containing 3.95% Δ^9-THC, oral tablet containing Δ^9-THC (2.5 mg oral dronabinol), or oral placebo. There were no changes in CD4+ and CD8+ cell counts, HIV RNA levels, or protease inhibitor levels in any of the treatment groups (Abrams et al., 2003). Therefore, use of cannabinoids showed no short-term adverse virologic effects in individuals with compromised immune systems. Conversely, Roth et al. (2005) reported that in immunodeficient mice implanted with human blood cells

infected with HIV, exposure to Δ^9-THC *in vivo* suppresses immune function, increases HIV co-receptor expression, and acts as a cofactor to enhance HIV replication.

The DEA notes two recent clinical studies reporting a decrease in cytokine and interleukin levels following marijuana use. Keen et al. (2014) compared the differences in the levels of IL-6 (interleukin-6), a proinflammatory cytokine, amongst non-drug users (n = 78), marijuana only users (n = 46) and marijuana plus other drug users (n = 45) in a community-based sample of middle-aged African Americans (Keen et al., 2014). After adjusting for confounders, analyses revealed that lifetime marijuana only users had significantly lower IL-6 levels than the nonuser group. Further, Sexton et al. (2014) compared several immune parameters in healthy individuals and subjects with multiple sclerosis (MS) and found that the chronic use of marijuana resulted in reduced monocyte migration, and decreased levels of CCL2 and IL-17 in both healthy and MS groups.

The DEA also notes a review suggesting that Δ^9-THC suppresses the immune responses in experimental animal models and *in vitro* and that these changes may be primarily mediated through the CB2 cannabinoid receptor (Eisenstein and Meissler, 2015).

Petitioners' major comments in relation to Factor 2 and the Government's responses

1) The petitioners state that *"[m]edical use of cannabis is considered safe."* (Exhibit B, page 7); and that *"[t]here are adequate and well-controlled studies proving the medical efficacy of cannabis."* (Exhibit B, page 10). The petitioners also allege that *"Cannabis is safer than current, legal Schedule II opiate drugs"* and that it presents milder side effects (Exhibit B, page 9-10).

As detailed in the HHS review and as discussed later in this document (see Factor 3), there are neither adequate safety studies nor adequate, well-controlled studies proving marijuana's efficacy. The DEA notes that neither the CSA nor established scheduling criteria suggest that the HHS and DEA should consider the relative safety profiles of drugs when determining the proper schedule. To the extent that the petitioners were referring to abuse and dependence liability, this document discusses those effects in factors 1, 4, and 7.

2) The petitioners state that "*scientific evidence regarding the safety and efficacy of cannabis is readily available directly from the National Library of Medicine*." (Exhibit B, page 14).

The government agrees that many articles *discuss* marijuana and its constituents. Yet, these articles in no way demonstrate that marijuana is safe and effective for the treatment of any disease or condition. As mentioned in the HHS review and as discussed later in this document (see Factor 3), the current research does not provide adequate detailed scientific evidence regarding chemistry, pharmacology, toxicology, and effectiveness

derived from well-controlled clinical investigations to permit a conclusion that marijuana is safe and effective for treating a specific, recognized disorder.

3) The petitioners mentioned on page 9 of exhibit B that *"[t]here has never been a lethal overdose of marijuana reported in humans*" and that *"[t]here is no known LD50 for any form of cannabis*."

As more fully discussed in Factor 3 below, the HHS and DEA conclude that there are not adequate studies to determine the safety of marijuana. As discussed in the HHS document and below, the determination of safety is more complex than a mere determination of the rate or likelihood of death. Moreover, the lack of overdose deaths attributed to a drug is not evidence that the drug is safe for medical use.

FACTOR 3: THE STATE OF THE CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR SUBSTANCE

Chemistry

The HHS stated that marijuana, also known as *Cannabis sativa L.*, is part of the Cannabaceae plant family and is one of the oldest cultivated crops. The term "marijuana" is generally used to refer to a mixture of the dried flowering tops and leaves from *Cannabis*. Marijuana users primarily smoke the marijuana leaves, but individuals also ingest marijuana through food infused with marijuana and its extracts. *Cannabis sativa* is the primary species of *Cannabis* that is illegally marketed in the United States. Marijuana is one of three major derivatives sold as separate illicit products, the other two being hashish and hash oil. Hashish is composed of the dried and compressed cannabinoid-rich resinous material of *Cannabis* and is found as balls and cakes as well as other forms. Individuals may break off pieces and place them into a pipe to smoke. Hash oil, a viscous brown or amber colored liquid, is produced by solvent extraction of cannabinoids from *Cannabis* and contains approximately 50% cannabinoids. One to two drops of hash oil on a cigarette has been reported to produce the equivalent of a single marijuana cigarette (DEA, 2015).

The HHS indicated in its evaluation that the petitioners defined marijuana as including all *Cannabis* cultivated strains. However, different marijuana samples are derived from numerous cultivated strains and may have different chemical compositions including levels of Δ^9-THC and other cannabinoids (Appendino et al., 2011). A consequence of having different chemical compositions in the various marijuana samples is that there will be significant differences in safety, biological, pharmacological, and toxicological profiles and therefore, according to the HHS, all *Cannabis* strains cannot be considered collectively because of the variations in chemical composition. Furthermore, the concentration of Δ^9-THC and other cannabinoids present in marijuana may vary due to growing conditions and processing of the plant after harvesting. For example, the plant parts collected such as flowers, leaves and stems can influence marijuana's potency, quality, and purity (Adams and Martin, 1996; Agurell et al., 1984; Mechoulam, 1973). Variations in marijuana harvesting have resulted in potencies ranging from a low of 1 to

2% up to a high of 17% as indicated by cannabinoid content. The concentration of Δ^9-THC averages approximately 12% by weight in a typical marijuana mixture of leaves and stems. However, some specifically grown and selected marijuana samples can contain 15% or greater Δ^9-THC (Appendino et al., 2011). As a result, the Δ^9-THC content in a 1 gram marijuana cigarette can range from as little as 3 milligrams to 150 milligrams or more. In a systematic review conducted by Cascini et al. (2012), it was reported that marijuana's Δ^9-THC content has increased significantly from 1979 – 2009.

Since there is considerable variability in the cannabinoid concentrations and chemical constituency among marijuana samples, the interpretation of clinical data with marijuana is complicated. A primary issue is the lack of consistent concentrations of Δ^9-THC and other substances in marijuana which complicates the interpretation of the effects of different marijuana constituents. An added issue is that the non-cannabinoid components in marijuana may potentially modify the overall pharmacological and toxicological properties of various marijuana strains and products.

Various *Cannabis* strains contain more than 525 identified natural constituents including cannabinoids, 21 (or 22) carbon terpenoids found in the plant, as well as their carboxylic acids, analogues, and transformation products (Agurell et al., 1984; 1986; Mechoulam, 1973; Appendino et al., 2011). To date, more than 100 cannabinoids have been characterized (ElSohly and Slade, 2005; Radwan et al., 2009; Appendino et al., 2011), and most major cannabinoid compounds occurring naturally have been identified. There are still new and comparably more minor cannabinoids being characterized (Pollastro et al., 2011). The majority of the cannabinoids are found in *Cannabis*. One study reported accumulation of two cannabinoids, cannabigerol and its corresponding acid, in *Helichrysum* (*H. umbraculigerum*) which is a non-*Cannabis* source (Appendino et al., 2011).

Of the cannabinoids found in marijuana, Δ^9-THC (previously known as Δ^1-THC) and delta-8-tetrahydrocannabinol (Δ^8-THC, Δ^6-THC) have been demonstrated to produce marijuana's psychoactive effects. Psychoactive effects from marijuana usage have been mainly attributed to Δ^9-THC because Δ^9-THC is present in significantly more quantities than Δ^8-THC in most marijuana varieties. There are only a few marijuana strains that contain Δ^8-THC in significant amounts (Hively et al., 1966). Δ^9-THC is an optically active resinous substance that is extremely lipophilic. The chemical name for Δ^9-THC is (6a*R*-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo-[b,d]pyran-1-ol, or (-)-delta9-(trans)-tetrahydrocannabinol. The (-)-trans Δ^9-THC isomer is pharmacologically 6 to 100 times more potent than the (+)-trans isomer (Dewey et al., 1984).

Other relatively well-characterized cannabinoids present in marijuana include cannabidiol (CBD), cannabichromene (CBC), and cannabinol (CBN). CBD and CBC are major cannabinoids in marijuana and are both lipophilic. The chemical name for CBD is 2-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol and the chemical name for CBC is 2-methyl-2-(4-methylpent-3-enyl)-7-pentyl-5-chromenol. CBN is a minor naturally-occurring cannabinoid with weak psychoactivity and is also a

major metabolite of Δ^9-THC. The chemical name for CBN is 6,6,9-trimethyl-3-pentyl-benzo[c]chromen-1-ol.

In summary, marijuana has several strains with high variability in the concentrations of Δ^9-THC, the main psychoactive component, as well as other cannabinoids and compounds. Marijuana is not a single chemical and does not have a consistent and reproducible chemical profile with predictable or consistent clinical effects. In the HHS recommendation for marijuana scheduling (HHS, 2015), it was recommended that investigators consult a guidance for industry entitled, *Botanical Drug Products*,[46] which provides information on the approval of botanical drug products. Specifically, in order to investigate marijuana in support of a New Drug Application (NDA), clinical studies under an Investigational New Drug (IND) application should include "consistent batches of a particular marijuana product for [a] particular disease." (HHS, 2015). Furthermore, the HHS noted that investigators must provide data meeting the requirements for new drug approval as stipulated in 21 CFR 314.50 (HHS, 2015).

Human Pharmacokinetics

Pharmacokinetics of marijuana in humans is dependent on the route of administration and formulation (Adams and Martin, 1996; Agurell et al., 1984; Agurell et al., 1986). Individuals primarily smoke marijuana as a cigarette (weighing between 0.5 and 1 gram) or in a pipe. More recently, vaporizers have been used as another means for individuals to inhale marijuana. Marijuana may also be ingested orally in foods or as an extract in ethanol or other solvents. Pharmacokinetic studies with marijuana focused on evaluating the absorption, metabolism, and elimination profile of Δ^9-THC and other cannabinoids (Adams and Martin, 1996; Agurell et al., 1984; Agurell et al., 1986).

Absorption and Distribution of Inhaled Marijuana Smoke

There is high variability in the pharmacokinetics of Δ^9-THC and other cannabinoids from smoked marijuana due to differences in individual smoking behavior even under controlled experimental conditions (Agurell et al., 1986; Herning et al., 1986; Huestis et al., 1992a). Experienced marijuana users can titrate and regulate the dose by holding marijuana smoke in their lungs for an extended period of time resulting in increased psychoactive effects by prolonging absorption of the smoke. This property may also help explain why there is a poor correlation between venous levels of Δ^9-THC and the intensity of effects and intoxication (Agurell et al., 1986; Barnett et al., 1985; Huestis et al., 1992a). The HHS recommended that puff and inhalation volumes should be tracked in experimental studies because the concentration of cannabinoids can vary at different stages of smoking.

Δ^9-THC from smoked marijuana is rapidly absorbed within seconds. Psychoactive effects are observed immediately following absorption with measurable neurological and behavioral changes for up to 6 hours (Grotenhermen, 2003; Hollister, 1986; Hollister,

[46]Available at http://www.fda.gov/Drugs/default.htm under Guidance (Drugs).

1988). Δ^9-THC is distributed to the brain in a rapid and efficient manner. Bioavailability of Δ^9-THC from marijuana (from a cigarette or pipe) ranges from 1 to 24% with the fraction absorbed rarely exceeding 10 to 20% (Agurell et al., 1986; Hollister, 1988). The low and variable bioavailability of Δ^9-THC is due to loss in side-stream smoke, variation in individual smoking behaviors and experience, incomplete absorption of inhaled smoke, and metabolism in lungs (Herning et al., 1986; Johansson et al., 1989). After cessation of smoking, Δ^9-THC venous levels decline within minutes and continue to decline to about 5% to 10% of the peak level within an hour (Agurell et al., 1986; Huestis et al., 1992a; Huestis et al., 1992b).

Absorption and Distribution of Orally Administered Marijuana

Following oral administration of Δ^9-THC or marijuana, onset of effects start within 30 to 90 minutes, peak after 2 to 3 hours and effects remain for 4 to 12 hours (Grotenhermen, 2003; Adams and Martin, 1996; Agurell et al., 1984; Agurell et al., 1986). Dose titration of Δ^9-THC from orally ingested marijuana is difficult for users in comparison to smoked or inhaled marijuana due to the delay in the onset of effects. Oral bioavailability of Δ^9-THC, either in its pure form or in marijuana, is low and variable with a range from 5% to 20% (Agurell et al., 1984; Agurell et al., 1986). There is also inter- and intra-subject variability of orally administered Δ^9-THC under experimental conditions and even under repeated dosing experiments (HHS, 2015). The HHS noted that in bioavailability studies using radiolabeled Δ^9-THC, Δ^9-THC plasma levels following oral administration of Δ^9-THC were low relative to plasma levels after inhaled or intravenously administered Δ^9-THC. The low and variable bioavailability of orally administered Δ^9-THC is due to first pass hepatic elimination from blood and erratic absorption from stomach and bowel (HHS, 2015).

Metabolism and Excretion of Cannabinoids from Marijuana

Studies evaluating cannabinoid metabolism and excretion focused on Δ^9-THC because it is the primary psychoactive component in marijuana. Δ^9-THC is metabolized via microsomal hydroxylation and oxidation to both active and inactive metabolites (Lemberger et al., 1970; Lemberger et al., 1972a; Lemberger et al., 1972b; Agurell et al., 1986; Hollister, 1988). Metabolism of Δ^9-THC is consistent among frequent and infrequent marijuana users (Agurell et al., 1986). The primary active metabolite of Δ^9-THC following oral ingestion is 11-hydroxy-Δ^9-THC which is equipotent to Δ^9-THC in producing marijuana-like subjective effects (Agurell et al., 1986; Lemberger and Rubin, 1975). Metabolite levels following oral administration may be greater than that of Δ^9-THC and may contribute greatly to the pharmacological effects of oral Δ^9-THC or marijuana.

Plasma clearance of Δ^9-THC approximates hepatic blood flow at a rate of approximately 950 ml/min or greater. Rapid clearance of Δ^9-THC from blood is primarily due to redistribution to other tissues in the body rather than to metabolism (Agurell et al., 1984; Agurell et al., 1986). Outside of the liver, metabolism in most tissues is considerably slow or does not occur. The elimination half-life of Δ^9-THC ranges from 20 hours to

between 10 and 13 days (Hunt and Jones, 1980). Lemberger et al. (1970) reported that the half-life of Δ^9-THC ranged from 23 – 28 hours in heavy marijuana users and up to 60 to 70 hours in naïve users. The long elimination half-life of Δ^9-THC is due to slow release of Δ^9-THC and other cannabinoids from tissues and subsequent metabolism. Inactive carboxy metabolites of Δ^9-THC have terminal half-lives of 50 hours to 6 days or more and serve as long-term markers in urine tests for marijuana use.

Most of the absorbed Δ^9-THC dose is eliminated in the feces and about 33% in urine. The glucuronide metabolite of Δ^9-THC is excreted as the major urine metabolite along with 18 non-conjugated metabolites (Agurell et al., 1986).

Research Status and Test of Currently Accepted Medical Use for Marijuana

According to the HHS, there are numerous human clinical studies with marijuana in the United States under FDA-regulated IND applications. Results of small clinical exploratory studies have been published in the medical literature. Approval of a human drug for marketing, however, is contingent upon FDA approval of a New Drug Application (NDA) or a Biologics License Application (BLA). According to the HHS, the FDA has not approved any drug product containing marijuana for marketing.

The HHS noted that a drug may be found to have a medical use in treatment in the United States for purposes of the CSA if the drug meets the five elements described by the DEA in 1992. Those five elements "are both necessary and sufficient to establish a prima facie case of currently accepted medical use" in treatment in the United States." (57 FR 10499, 10504 (March 26, 1992)). This five-element test, which the HHS and DEA have utilized in all such analyses for more than two decades, has been upheld by the Court of Appeals. ACT, 15 F.3d at 1135. The five elements that characterize "currently accepted medical use" for a drug are summarized here and expanded upon in the discussion below:

1. *The drug's chemistry must be known and reproducible;*
2. *There must be adequate safety studies;*
3. *There must be adequate and well-controlled studies proving efficacy;*
4. *The drug must be accepted by qualified experts; and*
5. *Scientific evidence must be widely available.*

In its review (HHS, 2015), the HHS evaluated the five elements with respect to the currently available research for marijuana. The HHS concluded that marijuana does not meet any of the five elements – all of which must be demonstrated to find that a drug has a "currently accepted medical use." A brief summary of the HHS's evaluation is provided below.

Element #1: The drug's chemistry must be known and reproducible.

"The substance's chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of the Food,

Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient generally to meet this requirement." 57 Fed. Reg. 10499, 10506 (March 26, 1992).

Marijuana, as defined in the petition, includes all *Cannabis* strains. (For purposes of the CSA, marijuana includes all species of the genus *Cannabis*, including all strains therein[47]). Based on the definition of marijuana in the petition, the chemistry of marijuana is not reproducible such that a standardized dose can be created. Chemical constituents including Δ^9-THC and other cannabinoids vary significantly in marijuana samples derived from different strains (Appendino et al., 2011). As a result, there will be significant differences in safety, biological, pharmacological, and toxicological parameters amongst the various marijuana samples. Due to the variation of the chemical composition in marijuana samples, it is not possible to reproduce a standardized dose when considering all strains together. The HHS does advise that if a specific *Cannabis* strain is cultivated and processed under controlled conditions, the plant chemistry may be consistent enough to derive reproducible and standardized doses.

Element #2: There must be adequate safety studies.

"There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder." 57 Fed. Reg. 10499, 10506 (March 26, 1992).

The HHS stated that there are no adequate safety studies on marijuana. As indicated in their evaluation of Element #1, the considerable variation in the chemistry of marijuana complicates the safety evaluation. The HHS concluded that marijuana does not satisfy Element #2 for having adequate safety studies such that medical and scientific experts may conclude that it is safe for treating a specific ailment.

Element #3: There must be adequate and well-controlled studies of efficacy.

"There must be adequate, well-controlled, well-designed, well-conducted and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will

[47] Although the CSA definition of marijuana refers only to the species "*Cannabis sativa L.*," federal courts have consistently ruled that all species of the genus cannabis are included in this definition. *See United States v. Kelly*, 527 F.2d 961, 963-964 (9th Cir. 1976) (collecting and examining cases). The Single Convention (article 1, par. 1(c)) likewise defines the "cannabis plant" to mean "any plant of the genus Cannabis." As explained above in the attachment titled "Preliminary Note Regarding Treaty Considerations," 21 U.S.C. 811(d)(1) provides that, where a drug is subject to control under the Single Convention, the DEA Administrator must control the drug under the schedule he deems most appropriate to carry out such treaty obligations, without regard to the findings required by 21 U.S.C. 811(a) or 812(b) and without regard to the procedures prescribed by 21 U.S.C. 811(a) and (b).

have the intended effect in treating a specific, recognized disorder." 57 Fed. Reg. 10499, 10506 (March 26, 1992).

As indicated in the HHS's review of marijuana (HHS, 2015), there are no adequate or well-controlled studies that prove marijuana's efficacy. The FDA independently reviewed (FDA, 2015) publicly available clinical studies on marijuana published prior to February 2013 to determine if there were appropriate studies to determine marijuana's efficacy (please refer to FDA, 2015 and HHS, 2015 for more details). After review, the FDA determined that out of the identified articles, including those identified through a search of bibliographic references and 566 abstracts located on PubMed, 11 studies met the *a priori* selection criteria, including placebo control and double-blinding. FDA and HHS critically reviewed each of the 11 studies to determine if the studies met accepted scientific standards. FDA and HHS concluded that these studies do not "currently prove efficacy of marijuana" for any therapeutic indication due to limitations in the study designs. The HHS indicated that these studies could be used as proof of concept studies, providing preliminary evidence on a proposed hypothesis involving a drug's effect.

Element #4: The drug must be accepted by qualified experts.

"[A] consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus." 57 Fed. Reg. 10499, 10506 (March 26, 1992).

The HHS concluded that there is currently no evidence of a consensus among qualified experts that marijuana is safe and effective in treating a specific and recognized disorder. The HHS indicated that medical practitioners who are not experts in evaluating drugs cannot be considered qualified experts (HHS, 2015; 57 FR 10499, 10505). Further, the HHS noted that the 2009 American Medical Association (AMA) report entitled, "Use of Cannabis for Medicinal Purposes" does not conclude that there is a currently accepted medical use for marijuana. HHS also pointed out that state-level "medical marijuana" laws do not provide evidence of such a consensus among qualified experts.

Element #5: The scientific evidence must be widely available.

"In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder." 57 Fed. Reg. 10499, 10506 (March 26, 1992).

The HHS concluded that the currently available data and information on marijuana is not sufficient to allow scientific scrutiny of the chemistry, pharmacology, toxicology, and

effectiveness. In particular, scientific evidence demonstrating the chemistry of a specific *Cannabis* strain that could provide standardized and reproducible doses is not available.

Petitioners' major comments in relation to Factor 3 and the Government's responses

1) The petitioners indicate that there is medical support and acceptance for the medical use of marijuana and stated that "*[c]annabis has been accepted by the medical community as meeting the current, modern accepted standards for what constitutes medicine."* (Exhibit B, page 13). On page 3 of the cover letter of the petition, the petitioners stated, "*The American medical community supports rescheduling, and there are safe pharmacy-based methods to dispense medical cannabis."*

   Furthermore, they stated that *"[i]n 2009, the American Medical Association (AMA) reversed its earlier position that supported [s]chedule I classification of cannabis. The AMA now supports investigation and clinical research of cannabis for medicinal use, and urged the federal government to reassess the [s]chedule I classification. The American College of Physicians [ACP] recently expressed similar support."* In addition, they note that the Institute of Medicine (IOM) also documented the scientific basis and therapeutic effects of cannabis (Exhibit B, page 13).

The DEA notes that the statements by the cited organizations (AMA, ACP, IOM) support more research into the potential medical properties associated with marijuana. The HHS did not find that the statements by these organizations provide evidence supporting a conclusion that adequate safety studies and adequate, well-controlled efficacy studies demonstrate the safety and efficacy of marijuana (HHS, 2015). The AMA's official policy on medicinal use of marijuana is as follows: "*Our AMA urges that marijuana's status as a federal [s]chedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternative delivery methods. This should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product.*" (AMA, 2009).

The DEA further notes that the 2013 AMA House of Delegates report states that, "*cannabis is a dangerous drug and as such is a public health concern."* (AMA, 2013). In 2008, the ACP indicated that "*further research is needed to compare cannabinoids' efficacy and safety with current treatments."* (ACP, 2008). The ACP stated that, "*ACP urges an evidence-based review of marijuana's status as a [s]chedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana's safety and efficacy in some clinical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its crude smoked form*" (ACP, 2008). The IOM, consistent with others in the medical community, endorses further studies into the potential therapeutic uses of marijuana, but did not advocate for medicinal use without further testing (IOM, 2009).

As detailed in the HHS review, in order for a drug to be found to have a "currently accepted medical use," it must be accepted by qualified experts. There is no evidence that there is a consensus among qualified experts that marijuana is safe and effective for use in treating a specific, recognized disorder.

2) The petitioners claim that, "*The chemistry of cannabis is known and reproducible*" (Exhibit B, page 6) and "*newer medicinal strains of cannabis are lower in THC and higher in the non-psychoactive, more therapeutic cannabinoids, such as CBD, and CBN. These compounds further improved the efficacy of cannabis."* (Exhibit B, page 10).

As indicated by the HHS, the petitioners defined marijuana to include all *Cannabis* strains. As such, the chemistry of marijuana is not reproducible such that a standardized dose can be created. Chemical constituents including Δ^9-THC and other cannabinoids vary significantly in different marijuana samples (Appendino et al., 2011). Furthermore, the HHS cited a published report that indicates that new substances in marijuana are continually being characterized (Pollastro et al., 2011). If there is significant variance in the chemical composition of marijuana between samples, it is not possible for the chemistry to be reproducible.

Because the petition defines marijuana as including all cultivated strains, the DEA believes that the THC and CBD level of specific strains is not relevant to this consideration. In fact, the average Δ^9-THC content in marijuana has steadily risen from 1995 to 2014 as reported by the University of Mississippi Potency Monitoring Project, as presented in Factor 1. In 1995, the Δ^9-THC content was 4% on average and by 2015, the average content of THC had risen to 11.2% over a 20 year period. In the same time period, CBD and CBN percentages have ranged from 0.15% to 0.60% on average.

The DEA also notes statements in the petitioners' document that support the conclusion reached by DEA and HHS that the chemistry of marijuana as broadly defined by the petitioners is not reproducible or well-defined. For example, the petitioners acknowledge that "Cannabis is a complex plant, with several subtypes of cannabis." (Exhibit B, page 6). The petitioners also acknowledge that "the ratios of the various cannabinoids differ according to the plant strain, and, to some extent, how the plant is grown." (Exhibit B, page 12).

3) The petitioners stated in Exhibit B, page 8, that "*[o]verall, the 33 completed and published American controlled clinical trials with cannabis have studied its safety, routes of administration, and use in comparison with placebos, standard drugs, and in some cases dronabinol…,"* and further cited a systematic review by Wang et al. (2008), that evaluated 23 randomized controlled trials and 8 observational studies, stating that, "*[o]f all the adverse events reported, 97 percent were considered 'not serious,' with the most commonly reported 'dizziness.'"*

> The petitioners also cited in Exhibit B, page 8, "*There has been a long-term, prospective, federally funded cannabis clinical study jointly administered by National Institute on Drug Abuse (NIDA) and FDA. This study has been running for over 30 years without any demonstrable adverse outcomes related to chronic medicinal cannabis use."*

As cited in the HHS recommendation document (HHS, 2015), the FDA conducted its own evaluation of the published clinical studies on the medical application of marijuana prior to February 2013 (FDA, 2015). Further details on the FDA review can be found in the published report (FDA, 2015). Based on the analysis, 11 studies were evaluated further and the FDA concluded that none of these studies "meet the criteria required by the FDA to determine if marijuana is safe and effective in specific therapeutic areas." (page 6; FDA, 2015).

The DEA has reviewed the systematic review by Wang et al. (2008) and notes that most of the studies included in the review were synthetic cannabinoid medicines (e.g. dronabinol) or cannabinoid extracts (e.g. Sativex®); these types of studies were excluded in the FDA review as the analysis focused solely on natural forms of marijuana (FDA, 2015). Wang et al. (2008) concluded that "good safety and efficacy data on smoked cannabis are urgently needed."

With respect to the 30-year study cited by the petitioners (Russo et al., 2001) on page 8 of Exhibit B, it should be clarified that the referenced study was not jointly administered by NIDA and the FDA. As with other clinical studies, an IND application was approved by the FDA and marijuana was supplied by NIDA. The authors evaluated only 8 patients over this period, of which one patient died. While the findings cited by the petitioners and authors (e.g. no adverse outcomes with long term marijuana use) are informative, conclusions on long-term use of marijuana cannot be applied to the general population.

FACTOR 4: ITS HISTORY AND CURRENT PATTERN OF ABUSE

Marijuana continues to be the most widely used illicit drug. In 2013, an estimated 24.6 million Americans age 12 or older were current (past month) illicit drug users. Of those, 19.8 million were current (past month) marijuana users. As of 2013, an estimated 114.7 million Americans age 12 and older had used marijuana or hashish in their lifetime and 33.0 million had used it in the past year.

According to the NSDUH estimates, 3.0 million people age 12 or older used an illicit drug for the first time in 2014. Marijuana initiates totaled 2.6 million in 2014. Nearly half (46.8%) of the 2.6 million new users were less than 18 years of age. In 2014, marijuana was used by 82.2% of current (past month) illicit drug users. In 2014, among past year marijuana users age 12 or older, 18.5% used marijuana on 300 or more days within the previous 12 months. This translates into 6.5 million people using marijuana on a daily or almost daily basis over a 12-month period, a significant increase from the 3.1 million daily or almost daily users in 2006 and from the 5.7 million in just the previous year. In 2014, among past month marijuana users, 41.6% (9.2 million people) used the

drug on 20 or more days in the past month, a significant increase from the 8.1 million in 2013.

Marijuana is also the illicit drug with the highest numbers of past year dependence or abuse in the US population. According to the 2014 NSDUH report, of the 7.1 million persons aged 12 or older who were classified with illicit drug dependence or abuse, 4.2 million of them abused or were dependent on marijuana (representing 59.0% of all those classified with illicit drug dependence or abuse and 1.6% of the total U.S. non-institutionalized population aged 12 or older).

According to the 2015 Monitoring the Future (MTF) survey, marijuana is used by a large percentage of American youths, and is the most commonly used illicit drug among American youth. Among students surveyed in 2015, 15.5% of 8^{th} graders, 31.1% of 10^{th} graders, and 44.7% of 12^{th} graders reported that they had used marijuana in their lifetime. In addition, 11.8%, 25.4%, and 34.9% of 8^{th}, 10^{th}, and 12^{th} graders, respectively, reported using marijuana in the past year. A number of high school students reported daily use in the past month, including 1.1%, 3.0%, and 6.0% of 8^{th}, 10^{th}, and 12^{th} graders, respectively.

The prevalence of marijuana use and abuse is also indicated by criminal investigations for which drug evidence was analyzed in federal, state, and local forensic laboratories, as discussed above in Factor 1. The National Forensic Laboratory System (NFLIS), a DEA program, systematically collects drug identification results and associated information from drug cases submitted to and analyzed by federal, state, and local forensic laboratories. NFLIS data shows that marijuana was the most frequently identified drug from January 2001 through December 2014. In 2014, marijuana accounted for 29.3% (432,989) of all drug exhibits in NFLIS.

The high consumption of marijuana is being fueled by increasing amounts of domestically grown marijuana as well as increased amounts of foreign source marijuana being illicitly smuggled into the United States. In 2014, the Domestic Cannabis Eradication and Suppression Program (DCE/SP) reported that 3,904,213 plants were eradicated in outdoor cannabis cultivation areas compared to 2,597,798 in 2000, as shown above in Table 3. Significant quantities of marijuana were also eradicated from indoor cultivation operations. There were 396,620 indoor plants eradicated in 2014 compared to 217,105 eradicated in 2000. As shown in Table 2 above, in 2014, the National Seizure System (NSS) reported seizures of 1,767,741 kg of marijuana.

Petitioners' major comments in relation to Factor 4 and the Government's responses

1) The petitioners indicated that the history and current pattern of abuse is difficult to estimate since "*a large percentage of United States citizens*" have used marijuana at least once in their lifetime and some estimates have indicated that *"over 40 percent of the nation has tried the plant."* Further, the petitioners stated

that "*trying marijuana once should not be confused with a health problem, let alone a diagnosis of dependence or abuse."* (Exhibit B, page 26).

Marijuana usage numbers mentioned in both the HHS Recommendation and this DEA document include surveys from NSDUH and MTF. These surveys measure extent of use of marijuana. As mentioned in this Factor, according to the results of the 2013 NSDUH survey, 17.4% of past year marijuana users age 12 or older used marijuana on 300 or more days within the previous 12 months. This indicates that 5.7 million people used marijuana on a daily or almost daily basis over this 12-month period, which is a 1.8-fold increase from the 3.1 million daily or almost daily users in 2006. Furthermore, 6% of all twelfth graders in the United States reported daily use of marijuana in the 2015 MTF survey. These data strongly indicate that there is a significant portion of the U.S. population using marijuana on a daily basis.

2) As stated in Exhibit B on page 26, subpart A, "*Rates of dependence or abuse are remarkably low"* and further suggest that "*[i]nterviews for the National Longitudinal Alcohol Epidemiological Survey ([NLAES]* [sic] *and National Epidemiological Survey on Alcohol and Related Conditions ([NESARC]* [sic] *each confirm that rates of dependence or abuse of cannabis have never exceed (sic) two percent in a given year."*

The authors of study cited by the petitioners (Compton et al., 2004) concluded that a higher percentage of American adults had a marijuana use disorder in 2001 – 2002 (1.5%) than in 1991 – 1992 (1.2%). Compton et al. (2004) noted that the marijuana use disorder increase of 0.3% over the 10 year period would equate to an increase from 2.2 million people to 3 million people in the United States. The petitioners failed to explain the impact of 1.5% (or less than 2 percent) of the U.S. population having a marijuana use disorder. In order to put these numbers into perspective, the DEA reviewed the literature and found that non-medical prescription drug use and abuse rates were examined in the same NLAES and NESARC (1991 – 1992 and 2001 – 2002) populations (Blanco et al., 2007). Blanco et al (2007) examined non-medical prescription drug use and abuse rates from the periods of 1991 – 1992 and 2001 – 2002. In 1991 through 1992, the prevalence of non-medical prescription drug (opioid, stimulant, and tranquilizer) abuse and dependence was 0.1%. Non-medical prescription drug (primarily opioid-based drugs) abuse and dependence increased to 0.3% in 2001 through 2002. Therefore, in the same 2001 – 2002 NLAES and NESARC populations, the percentage of people with a marijuana use disorder was approximately five-fold higher (1.5% versus 0.3%) than those with opioid abuse and dependence resulting from non-medical prescription drug use.

Further, Volkow et al. (2014) reported that in long-term or heavy marijuana users, 9% of users become addicted to marijuana. This percentage increases to 17% when marijuana use starts in adolescence and it increases to 25 to 50% of those who are daily users.

FACTOR 5: THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

Abuse of marijuana is widespread and significant. As previously noted, according to the NSDUH, in 2014, an estimated 117.2 million Americans (44.2%) age 12 or older had used marijuana or hashish in their lifetime, 35.1 million (13.2%) had used it in the past year, and 22.2 million (8.4%) had used it in the past month. Past year and past month marijuana use has increased significantly since 2013. Past month marijuana use is highest among 18-21 year olds and it declines among those 22 years of age and older. In 2014, an estimated 18.5% of past year marijuana users age 12 or older used marijuana on 300 or more days within the past 12 months. This translates into 6.5 million persons using marijuana on a daily or almost daily basis over a 12-month period. In 2014, an estimated 41.6% (9.2 million) of past month marijuana users age 12 or older used the drug on 20 or more days in the past month (SAMHSA, NSDUH). Chronic use of marijuana is associated with a number of health risks (see Factors 2 and 6).

Furthermore, the average percentage of Δ^9-THC in seized marijuana has increased over the past two decades (The University of Mississippi Potency Monitoring Project). Additional studies are needed to clarify the impact of greater potency, but one study shows that higher levels of Δ^9-THC in the body are associated with greater psychoactive effects (Harder and Rietbrock, 1997), which can be correlated with higher abuse potential (Chait and Burke, 1994).

TEDS data show that in 2013, marijuana/hashish was the primary substance of abuse in 16.8% of all admissions to substance abuse treatment among patients age 12 and older. TEDS data also show that marijuana/hashish was the primary substance of abuse for 77.0% of all 12- to 14-year-olds admitted for drug treatment and 75.5% of all 15- to 17-year-olds admitted for drug treatment in 2013. Among the 281,991 admissions to drug treatment in 2013 in which marijuana/hashish was the primary drug, the average age at admission was 25 years and the peak age cohort was 15 to 17 years (22.5%). Thirty-nine percent of the 281,991 primary marijuana/hashish admissions (35.9%) were under the age of 20.

In summary, the recent statistics from these various surveys and databases (see Factor 1 for more details) demonstrate that marijuana continues to be the most commonly used illicit drug, with large incidences of heavy use and dependence in teenagers and young adults.

Petitioners' major comment in relation to Factor 5 and DEA's response

1) Petitioners' contend that, "*The prevalence and significance of potential abuse are limited for cannabis, especially in relation to other [s]chedule II substances."* The petitioners cited results from the 1990 NIDA Household Survey on Drug Abuse and indicated that, *"more than four out of five people who had used cannabis in the previous year reported no problems related to the drug."* (Exhibit B, page 28).

The prevalence of marijuana usage and marijuana dependence is significant in the United States. The 2014 NSDUH findings indicate that there are approximately 6.5 million Americans using marijuana on a daily or almost daily basis. Further,Volkow et al. (2014) reported that in long-term or heavy marijuana users, 9% of users become addicted to marijuana. Among those who began using marijuana in adolescence, marijuana dependence increases to 17%, and it further increases to 25 to 50% of daily users that started using marijuana during adolescence. These collective findings indicate that there is considerable significance associated with marijuana use and abuse since 9% of users become addicted to marijuana, 25 to 50% of daily marijuana users started during adolescence, and prevalence of usage is significantly high based on the data presented from Volkow et al (2014) and the 2014 NSDUH survey.

FACTOR 6: WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

In its recommendation, the HHS discussed public health risks associated with acute and chronic marijuana use in Factor 6. Public health risks as measured by emergency department visits and drug treatment admissions are discussed by HHS and DEA in Factors 1, 4, and 5. Similarly, Factor 2 discusses marijuana's pharmacology and presents some of the adverse health effects associated with use. Marijuana use may affect the physical and/or psychological functioning of an individual user, but may also have broader public impacts including driving impairments and fatalities from car accidents.

Risks from Acute Use of Marijuana

As discussed in the HHS review document (HHS, 2015), acute usage of marijuana impairs psychomotor performance including motor control and impulsivity, risk taking and executive function (Ramaekers et al., 2004; Ramaekers et al., 2006). In a minority of individuals using marijuana, dysphoria, prolonged anxiety, and psychological distress may be observed (Haney et al., 1999). The DEA further notes a recent review of acute marijuana effects (Wilkinson et al., 2014) that reported impaired neurological function including altered perception, paranoia, delayed response time, and memory deficits.

In its recommendation, HHS references a meta-analysis conducted by Li et al (2012) where the authors concluded that psychomotor impairments associated with acute marijuana usage have also been associated with increased risk of car accidents with individuals experiencing acute marijuana intoxication (Li et al., 2012; HHS, 2015). The DEA further notes more recent studies examining the risk associated with marijuana use and driving. Younger drivers (under 21) have been characterized as the highest risk group associated with marijuana use and driving (Whitehill et al., 2014). Furthermore, in 2013, marijuana was found in 13% of the drivers involved in automobile-related fatal accidents (McCartt, 2015). The potential risk of automobile accidents associated with marijuana use appears to be increasing since there has been a steady increase in individuals intoxicated with marijuana over the past 20 years (Wilson et al., 2014). However, a recent study commissioned by the National Highway Traffic Safety Administration (NHTSA) reported that when adjusted for confounders (e.g., alcohol use,

age, gender, ethnicity), there was not a significant increase in crash risk (fatal and nonfatal, n = 2,682) associated with marijuana use (Compton and Berning, 2015).

The DEA also notes recent studies examining unintentional exposures of children to marijuana (Wang et al., 2013; 2014). Wang et al. (2013) reviewed emergency department (ED) visits at a children's hospital in Colorado from January 1, 2005 to December 31, 2011. As stated by the authors, in 2000 Colorado passed Amendment 20 which allowed for the use of marijuana. Following the passage of "a new Justice Department policy" instructing "federal prosecutors not to seek arrest of medical marijuana users and suppliers as long as they conform to state laws" (as stated in Wang et al., 2013), 14 patients in Colorado under the age of 12 were admitted to the ED for the unintended use of marijuana over a 27 month period. Prior to the passage of this policy, from January 1, 2005 to September 30, 2009 (57 months), there were no pediatric ED visits due to unintentional marijuana exposure (Wang et al., 2013). The DEA also notes a larger scale evaluation of pediatric exposures using the National Poison Data System (Wang et al., 2014). That study reported that there were 985 unintentional marijuana exposures in children (9 years and younger) between January 1, 2005 to December 31, 2011. The authors stratified the ED visits by states with laws allowing medical use of marijuana, states transitioning to legalization for medical use, and states with no such laws. Out of the 985 exposures, 495 were in non-legal states (n=33 states), 93 in transitional states (n=8 states), and 396 in "legal" states (n=9 states). The authors reported that there was a twofold increase (OR = 2.1) in moderate or major effects in children with unintentional marijuana use and a threefold increase (OR = 3.4) in admissions to critical care units in states allowing medical use of marijuana, in comparison to non-legal states.

Risks Associated with Chronic Use of Marijuana

The HHS noted that a major risk from chronic marijuana use is a distinctive withdrawal syndrome, as described in the 2013 DSM-5. The HHS analysis also quoted the following description of risks associated with marijuana [cannabis] abuse from the DSM-5:

> *Individuals with cannabis use disorder may use cannabis throughout the day over a period of months or years, and thus may spend many hours a day under the influence. Others may use less frequently, but their use causes recurrent problems related to family, school, work, or other important activities (e.g., repeated absences at work; neglect of family obligations). Periodic cannabis use and intoxication can negatively affect behavioral and cognitive functioning and thus interfere with optimal performance at work or school, or place the individual at increased physical risk when performing activities that could be physically hazardous (e.g. driving a car; playing certain sports; performing manual work activities, including operating machinery). Arguments with spouses or parents over the use of cannabis in the home, or its use in the presence of children, can adversely impact family functioning and are common features of those with cannabis use disorder. Last, individuals with*

> *cannabis use disorder may continue using marijuana despite knowledge of physical problems (e.g. chronic cough related to smoking) or psychological problems (e.g. excessive sedation or exacerbation of other mental health problems) associated with its use.* (HHS 2015, page 34).

The HHS stated that chronic marijuana use produces acute and chronic adverse effects on the respiratory system, memory and learning. Regular marijuana smoking can produce a number of long-term pulmonary consequences, including chronic cough and increased sputum (Adams and Martin, 1996), and histopathologic abnormalities in bronchial epithelium (Adams and Martin, 1996).

Marijuana as a "Gateway Drug"

The HHS reviewed the clinical studies evaluating the gateway hypothesis in marijuana and found them to be limited. The primary reasons were: 1) recruited participants were influenced by social, biological, and economic factors that contribute to extensive drug abuse (Hall and Lynskey, 2005), and 2) most studies testing the gateway drug hypothesis for marijuana use the determinative measure *any use of an illicit drug* rather than applying DSM-5 criteria for drug abuse or dependence (DSM-5, 2013).

The HHS cited several studies where marijuana use did not lead to other illicit drug use (Kandel and Chen, 2000; von Sydow et al., 2002; Nace et al., 1975). Two separate longitudinal studies with adolescents using marijuana did not demonstrate an association with use of other illicit drugs (Kandel and Chen, 2000; von Sydow et al., 2002).

It was noted by the HHS that, when evaluating the gateway hypothesis, differences appear when examining use versus abuse or dependence of other illicit drugs. Van Gundy and Rebellon (2010) reported that there was a correlation between marijuana use in adolescence and other illicit drug use in early adulthood, but when examined in terms of drug abuse of other illicit drugs, age-linked stressors and social roles were confounders in the association. Degenhardt et al. (2009) reported that marijuana use often precedes use of other illicit drugs, but dependence involving drugs other than marijuana frequently correlated with higher levels of illicit drug abuse. Furthermore, Degenhardt et al. (2010) reported that in countries with lower prevalence of marijuana usage, use of other illicit drugs before marijuana was often documented.

Based on these studies among others, the HHS concluded that although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this does not mean that individuals initiated with marijuana inherently will go on to become regular users of other illicit drugs.

Petitioners' Major Comment in Relation to Factor 6 and the Government's Responses

1) The petitioners commented that marijuana does not significantly impact social behavior in domains such as motivation, driving, aggression, or hostility (Exhibit B, pages 30-41).

The HHS concluded that "Marijuana's acute effects can significantly interfere with a person's ability … to operate motor vehicles." (HHS, 2015) As mentioned in this factor, there is a significant risk with marijuana use and driving. Marijuana was found in 13% of drivers involved in automobile fatal accidents (McCartt, 2015). Furthermore, in a meta-analysis conducted by Li et al. (2011), an association was identified between marijuana use by the driver and an increased risk of getting into a car accident.

The DEA notes that the petitioners only considered whether marijuana creates social problems, and did not consider physiological changes and impacts that also should be evaluated in determining the risk to public health. The HHS and DEA considered the public health impacts of such physiological effects, as discussed in this factor and others above. Marijuana may result in acute cardiovascular toxicity as indicated by recent reviews examining these associations (Hackham, 2015; Panayiotides, 2015). There is a possible association between frequent, long-term marijuana use and increased risk of testicular germ cell cancers and some evidence that chronic marijuana use may lead to lung cancer although the evidence is inconsistent. Furthermore, a more recent risk is the increase in ED visits of children unintentionally exposed to marijuana with increased risk factors for major adverse effects or admission to critical care units in states that have legalized marijuana for medical purposes (Wang et al., 2014).

FACTOR 7: ITS PSYCHIC OR PHYSIOLOGICAL DEPENDENCE LIABILITY

Physiological (Physical) Dependence in Humans

The HHS stated that heavy and chronic use of marijuana can lead to physical dependence (DSM-5, 2013; Budney and Hughes, 2006; Haney et al., 1999). Tolerance is developed following repeated administration of marijuana and withdrawal symptoms are observed as following discontinuation of marijuana usage (HHS, 2015).

The HHS mentioned that tolerance can develop to some of marijuana's effects, but does not appear to develop with respect to the psychoactive effects. It is believed that lack of tolerance to psychoactive effects may relate to electrophysiological data demonstrating that chronic Δ^9-THC administration does not affect increased neuronal firing in the ventral tegmental area, a brain region that plays a critical role in drug reinforcement and reward (Wu and French, 2000). Humans can develop tolerance to marijuana's cardiovascular, autonomic, and behavioral effects (Jones et al., 1981). Tolerance to some behavioral effects appears to develop with heavy and chronic use, but not with occasional usage. Ramaekers et al. (2009) reported that following acute administration of marijuana, occasional marijuana users still exhibited impairments in tracking and attention tasks whereas performance of heavy users on the these tasks was not affected. In a follow-up study with the same subjects that participated in the study by Ramaekers et al. (2009), a neurophysiological assessment was conducted where event-related potentials

(ERPs) were measured using electroencephalography (EEG) (Theunissen et al., 2012). Similar to the earlier results, the heavy marijuana users (n = 11; average of 340 marijuana uses per year) had no changes in their ERPs with the acute marijuana exposure. However, occasional users (n = 10; average of 55 marijuana uses per year) had significant decreases in the amplitude of an ERP component (categorized as P100) on tracking and attention tasks and ERP amplitude change is indicative of a change in brain activity (Theunissen et al., 2012).

The HHS indicated that down-regulation of cannabinoid receptors may be a possible mechanism for tolerance to marijuana's effects (Hirvonen et al., 2012; Gonzalez et al., 2005; Rodriguez de Fonseca et al., 1994; Oviedo et al., 1993).

As indicated by the HHS, the most common withdrawal symptoms in heavy, chronic marijuana users are sleep difficulties, decreased appetite or weight loss, irritability, anger, anxiety or nervousness, and restlessness (Budney and Hughes, 2006; Haney et al., 1999). As reported by HHS, most marijuana withdrawal symptoms begin within 24 – 48 hours of discontinuation, peak within 4 – 6 days, and last for 1 – 3 weeks.

The HHS pointed out that the American Psychiatric Association's (APA's) Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) included a list of withdrawal symptoms following marijuana [cannabis] use (DSM-5, 2013). The DEA notes that a DSM-5 working group report indicated that marijuana withdrawal symptoms were added to DSM-5 (they were not previously included in DSM-IV) because marijuana withdrawal has now been reliably presented in several studies (Hasin et al., 2013). In short, marijuana withdrawal signs are reported in up to one-third of regular users and between 50% and 90% of heavy users (Hasin et al., 2013). According to DSM-5 criteria, in order to be characterized as having marijuana withdrawal, an individual must develop at least three of the seven symptoms within one week of decreasing or stopping the heavy and prolonged use (DSM-5, 2013). These seven symptoms are: 1) irritability; anger or aggression, 2) nervousness or anxiety, 3) sleep difficulty, 4) decreased appetite or weight loss, 5) restlessness, 6) decreased mood, 7) somatic symptoms causing significant discomfort (DSM-5, 2013).

Psychological (Psychic) Dependence in Humans

High levels of psychoactive effects such as positive reinforcement correlate with increased marijuana abuse and dependence (Scherrer et al., 2009; Zeiger et al., 2010). Epidemiological marijuana use data reported by NSDUH, MTF, and TEDS support this assertion as presented in the HHS 2015 review of marijuana and updated by the DEA. According to the findings in the 2014 NSDUH survey, an estimated 9.2 million individuals 12 years and older used marijuana daily or almost daily (20 or more days within the past month). In the 2015 MTF report, daily marijuana use (20 or more days within the past 30 days) in 8^{th}, 10^{th}, and 12^{th} graders is 1.1%, 3.0%, and 6.0%, respectively.

The 2014 NSDUH report stated that 4.2 million persons were classified with dependence on or abuse of marijuana in the past year (representing 1.6% of the total population age 12 or older, and 59.0% of those classified with illicit drug dependence or abuse) based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Furthermore, of the admissions to licensed substance abuse facilities, as presented in TEDS, marijuana/hashish was the primary substance of abuse for; 18.3% (352,297) of 2011 admissions; 17.5% (315,200) of 2012 admissions; and 16.8% (281,991) of 2013 admissions. Of the 281,991 admissions in 2013 for marijuana/hashish as the primary substance, 24.3% used marijuana/hashish daily. Among admissions to treatment for marijuana/hashish as the primary substance in 2013, 27.4% were ages 12 to 17 years and 29.7% were ages 20 to 24 years.

Petitioners' major comment in relation to Factor 7 and the Government's response

1) The petitioners stated, *"There is no severe physical withdrawal syndrome associated with cannabis. Cannabis addiction is amenable to treatment."* (Exhibit B, page 10). The petitioners further indicated that marijuana "*may be psychologically addictive, but much less so than other Scheduled* [sic] *II drugs*," (Exhibit B, page 10) and that there is a low risk of dependence associated with marijuana use. Petitioners further stated in Exhibit B, page 23, *"Cannabis has low relative dependence risk and does not reach the severity associated with other drugs."*

The HHS states that marijuana withdrawal syndrome "appears to be mild compared to classical alcohol and barbiturate withdrawal syndromes" and is similar in magnitude and time course to tobacco withdrawal syndrome.

DSM-5 now recognizes and describes a marijuana [cannabis] withdrawal syndrome. The lifetime risk of dependence to marijuana is approximately 9% among heavy or long-term users (Volkow et al., 2014). Marijuana results in tolerance and withdrawal as described earlier in this Factor 7. The data from NSDUH indicate that there is constant desire for marijuana as noted by the consistently high numbers of current daily users in adults and adolescents. Marijuana use also persists despite problems associated with the drug. Changes in IQ have been noted in adolescent-onset, chronic or dependent marijuana users, in addition to withdrawal symptoms. However, marijuana use has not declined in the time that usage of this drug has been monitored. Additionally, there has been an increase in content of the primary psychoactive chemical, Δ^9-THC, in marijuana samples analyzed by the University of Mississippi's Potency Monitoring Project, suggesting preference for marijuana strains with higher levels of Δ^9-THC.

FACTOR 8: WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THE CSA

Marijuana is not an immediate precursor of another controlled substance.

DETERMINATION

After consideration of the eight factors discussed above and of the HHS's Recommendation, the DEA 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):

1. Marijuana has a high potential for abuse.

The HHS concluded that marijuana has a high potential for abuse based on a large number of people regularly using marijuana, its widespread use, and the vast amount of marijuana that is available through illicit channels.

Marijuana is the most abused and trafficked illicit substance in the United States. Approximately 22.2 million individuals in the United States (8.4% of the United States population) were past month users of marijuana according to the 2014 NSDUH survey. A 2015 national survey (Monitoring the Future) that tracks drug use trends among high school students showed that by 12^{th} grade, 21.3% of students reported using marijuana in the past month, and 6.0% reported having used it daily in the past month. In 2011, SAMHSA's Drug Abuse Warning Network (DAWN) reported that marijuana was mentioned in 36.4% of illicit drug-related emergency department (ED) visits, corresponding to 455,668 out of approximately 1.25 million visits. The Treatment Episode Data Set (TEDS) showed that 16.8% of non-private substance-abuse treatment facility admissions in 2013 were for marijuana as the primary drug.

Marijuana has dose-dependent reinforcing effects that encourage its abuse. Both clinical and preclinical studies have demonstrated that marijuana and its principle psychoactive constituent, Δ^9-THC, possess the pharmacological attributes associated with drugs of abuse. They function as discriminative stimuli and as positive reinforcers to maintain drug use and drug-seeking behavior. Additionally, use of marijuana can result in psychological dependence.

2. Marijuana has no currently accepted medical use in treatment in the United States.

The HHS stated that the FDA has not approved an NDA for marijuana. The HHS noted that there are opportunities for scientists to conduct clinical research with marijuana and there are active INDs for marijuana, but marijuana does not have a currently accepted medical use in the United States, nor does it have an accepted medical use with severe restrictions.

FDA approval of an NDA is not the sole means through which a drug can be determined to have a "currently accepted medical use" under the CSA. Applying

the five-part test summarized below, a drug has a currently accepted medical use if all of the following five elements have been satisfied. As detailed in the HHS evaluation and as set forth below, none of these elements has been fulfilled for marijuana:

i. The drug's chemistry must be known and reproducible

Chemical constituents including Δ^9-THC and other cannabinoids in marijuana vary significantly in different marijuana strains. In addition, the concentration of Δ^9-THC and other cannabinoids may vary between strains. Therefore the chemical composition among different marijuana samples is not reproducible. Due to the variation of the chemical composition in marijuana strains, it is not possible to derive a standardized dose. The HHS does advise that if a specific *Cannabis* strain is cultivated and processed under controlled conditions, the plant chemistry may be consistent enough to derive standardized doses.

ii. There must be adequate safety studies

There are not adequate safety studies on marijuana for use in any specific, recognized medical condition. The considerable variation in the chemistry of marijuana results in differences in safety, biological, pharmacological, and toxicological parameters amongst the various marijuana samples.

iii. There must be adequate and well-controlled studies proving efficacy

There are no adequate and well-controlled studies that determine marijuana's efficacy. In an independent review performed by the FDA of publicly available clinical studies on marijuana (FDA, 2015), FDA concluded that these studies do not have enough information to "*currently prove efficacy of marijuana"* for any therapeutic indication.

iv. The drug must be accepted by qualified experts

At this time, there is no consensus of opinion among experts concerning the medical utility of marijuana for use in treating specific recognized disorders.

v. The scientific evidence must be widely available

The currently available data and information on marijuana is not sufficient to address the chemistry, pharmacology, toxicology, and effectiveness. The scientific evidence regarding marijuana's chemistry with regard to a

specific cannabis strain that could be formulated into standardized and reproducible doses is not currently available.

3. There is a lack of accepted safety for use of marijuana under medical supervision.

Currently, there are no FDA-approved marijuana products. The HHS also concluded that marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. According to the HHS, the FDA is unable to conclude that marijuana has an acceptable level of safety in relation to its effectiveness in treating a specific and recognized disorder due to lack of evidence with respect to a consistent and reproducible dose that is contamination free. The HHS indicated that marijuana research investigating potential medical use should include information on the chemistry, manufacturing, and specifications of marijuana. The HHS further indicated that a procedure for delivering a consistent dose of marijuana should also be developed. Therefore, the HHS concluded that marijuana does not have an acceptable level of safety for use under medical supervision.

REFERENCES

1. Abrams DI, Hilton JF, Reiser RJ, Shade SB, Elbeik TA, Aweeka FT, Benowitz NL, Bredt BM, Kosel B, Aberg JA, Deeks SG, Mitchell TF, Mulligan K, Bacchetti P, McCune JM, Schambelan M (2003). Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 139(4):258-266.

2. Adams IB, Martin BR (1996). Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 91:1585-1614.

3. Agurell S, Dewey WL, and Willetts RE (eds.) (1984). *The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects*. New York: Academic Press

4. Agurell S, Halldin M, Lindgren JE, Ohlsson A, Widman M, Gillespie H, Hollister L (1986). Pharmacokinetics and metabolism of delta-1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* 38(1):21-43.

5. American College of Physicians [ACP]. (2008). Supporting Research Into the Therapeutic Role of Marijuana. Philadelphia: American College of Physicians; 2008: Position Paper (Available from American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106).

6. American Medical Association [AMA]. (2009a). Use of Cannabis for Medical Purposes. *Report of the Council on Science and Public Health 3*.

7. American Medical Association [AMA]. (2009b). AMA Policy: Medical Marijuana. H-95-952 Medical Marijuana.

8. American Medical Association [AMA]. (2013). 2013 Interim Meeting. American Medical Association House of Delegates (I-13). Accessed at www.ama-assn.org/assets/meeting/2013i/i13-refcommk-annotated.pdf.

9. American Society of Addiction Medicine [ASAM]. (2014). *New York Times* calls for legalization of marijuana, ASAM strongly objects. Accessed at www.asam.org/docs/default-source/pressreleases/asam-press-release-nytimes-editorial-marijuana-2014-7-27.pdf?sfvrsn=2

10. Andreasson S, Allebeck P, Engström A, Rydberg U (1987). Cannabis and schizophrenia: A longitudinal study of Swedish conscripts. *Lancet* 1:483-1483.

11. Appendino G, Chianese G, Taglialatela-Scafati O (2011). Cannabinoids: occurrence and medicinal chemistry. *Curr Med Chem* 18(7):1085-1099.

12. Asch RH, Smith CG, Siler-Khodr TM, Pauerstein CJ (1981). Effects of delta 9-tetrahydrocannabinol during the follicular phase of the rhesus monkey (Macaca mulatta). *J Clin Endocrinol Metab* 52(1):50-55.

13. Balster RL (1991). Drug abuse potential evaluation in animals. *Br J Addict* 86(12):1549-1558.

14. Balster RL, Prescott WR (1992). Delta9-Tetrahydrocannabinol discrimination in rats as a model for cannabis intoxication. *Neurosci Biobehav Res* 16(1):55-62.

15. Balster RL, Bigelow GE (2003). Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug Alcohol Depend* 70:S13-S40.

16. Barnett G, Licko V, Thompson T (1985). Behavioral pharmacokinetics of marijuana. *Psychopharmacology* 85(1):51-56.

17. Benowitz NL, Jones RT (1975). Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clin Pharmacol Ther* 18(3):287-297.

18. Benowitz NL, Jones RT (1981). Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *J Clin Pharmacol* 21(8-9 Suppl):214S-223S.

19. Blanco C, Alderson D, Ogburn E, Grant BF, Nunes EV, Hatzenbuehler ML, Hasin DS (2007). Changes in the prevalence of non-medical prescription drug use and drug use disorders in the United States: 1991-1992 and 2001-2002. *Drug Alcohol Depend* 90(2-3):252-260.

20. Block RI, Farinpour R, Schlechte JA (1991). Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women. *Drug Alcohol Depend* 28(2):121-128.

21. Block RI, Farinpour R, Braverman K (1992). Acute effects of marijuana on cognition: relationships to chronic effects and smoking techniques. *Pharmacol Biochem Behav* 43(3):907-917.

22. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL (2002). Dose-related neurocognitive effects of marijuana use. *Neurology* 59:1337-1343.

23. Bolla KI, Eldreth DA, Matochik JA, Cadet JL (2005). Neural substrates of faulty decision-making in abstinent marijuana users. *NeuroImage* 26:480-492.

24. Bonnet U (2013). Chronic cannabis abuse, delta-9-tetrahydrocannabinol and thyroid function. *Pharmacopsychiatry* 46(1):35-36.

25. Bouaboula M, Rinaldi M, Carayon P, Carillon C, Delpech B, Shire D, Le Fur G, Casellas P (1993). Cannabinoid-receptor expression in human leukocytes. *Eur J Biochem* 214(1):173-180.

26. Braida D, Iosue S, Pegorini S, Sala M (2004). Delta9-tetrahydrocannabinol-induced conditioned place preference and intracerebroventricular self-administration in rats. *Eur J Pharmacol* 506(1):63-69.

27. Brievogel CS, Childers SR (2000). Cannabinoid agonist signal transduction in rat brain: comparison of cannabinoid agonists in receptor binding, G-protein activation, and adenylyl cyclase inhibition. *J Pharmacol Exp Ther* 295(1):328-336.

28. Brown TT, Dobs AS (2002). Endocrine effects of marijuana. *J Clin Pharmacol* 42(11 Suppl):90S-96S.

29. Browne RG, Weisman A (1981). Discriminative stimulus properties of delta 9-tetrahydrocannabinol: mechanistic studies. *J Clin Pharmacol* 21(8-9 Suppl):227S-234S.

30. Budney AJ, Hughes JR (2006). The cannabis withdrawal syndrome. *Curr Opin Psychiatry* 19(3):233-238.

31. Capriotti RM, Foltin RW, Brady JV, Fischman MW (1988). Effects of marijuana on the task-elicited physiological response. *Drug Alcohol Depend* 21(3):183-187.

32. Cascini F, Aiello C, Di Tanna G (2012). Increasing delta-9-tetrahydrocannabinol Δ-9-THC) content in herbal cannabis over time: systematic review and meta-analysis. *Curr Drug Abuse Rev* 5(1):32-40.

33. Chait LD, Burke KA (1994). Preference for "high" versus low-potency marijuana. *Pharmacol Biochem Behav* 7:357-364.

34. Cheer JF, Kendall DA, Marsden CA (2000). Cannabinoid receptors and reward in the rat: a conditioned place preference study. *Psychopharmacology (Berl)* 151(1):25-30.

35. Compton RP, Berning A (2015). Drug and Alcohol Crash Risk. *Traffic Safety Facts Research Note.* DOT HS 812 117. Washington, DC: National Highway Traffic Safety Administration.

36. Compton WM, Grant BF, Colliver JD, Glantz MD, Stinson FS (2004). Prevalence of marijuana use disorders in the United States: 1991-1992 and 2001-2002. *JAMA* 291(17):2114-2121.

37. Cone EJ, Johnson RE, Moore JD, Roache JD (1986). Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. *Pharmacol Biochem Behav* 24(6):1749-1754.

38. Croxford JL, Yamamura T (2005). Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? *J Neuroimmunol* 166(1-2):3-18.

39. Daling JR, Doody DR, Sun X, Trabert BL, Weiss NS, Chen C, Biggs ML, Starr JR, Dey SK, Schwartz SM (2009). Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer*. 115(6):1215-1223.

40. Dalton WS, Martz R, Lemberger L, Rodda BE, Forney RB (1976). Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. *Clin Pharmacol Ther* 19(3):300-309.

41. Dax EM, Pilotte NS, Adler WH, Nagel JE, Lange WR (1989). The effects of 9-enetetrahydrocannabinol on hormone release and immune function. *J Steroid Biochem* 34(1-6):263-270.

42. Day NL, Wagener DK, Taylor PM (1985). Measurement of substance use during pregnancy: methodologic issues. *NIDA Res Monogr* 59:36-47.

43. Day NL, Leech SL, Goldschmidt L (2011). The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. *Neurotoxicol Teratol* 33(1):129-136.

44. Day NL, Goldschmidt L, Day R, Larkby C, Richardson GA (2015). Prenatal marijuana exposure, age of marijuana initiation, and the development of psychotic symptoms in young adults. *Psychol Med* 45(8):1779-1787.

45. Degenhardt L, Hall W, Lynskey M (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend* 71(1):37-48.

46. Degenhardt L, Hall WD, Lynskey M, McGrath J, McLaren J, Calabria B, Whiteford H, Vos T (2009). Should burden of disease estimates include cannabis use as a risk factor for psychosis? *PLoS Medicine.* 6(9):e1000133.

47. Degenhardt L, Dierker L, Chiu WT, Medina-Mora ME, Neumark Y, Sampson N, Alonso J, Angermeyer M, Anthony JC, Bruffaerts R, et al (2010). Evaluating the drug use "gateway" theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. *Drug Alcohol Depend* 108(1-2):84-97.

48. De Petrocellis PL, Di Marzo V (2009). An introduction to the endocannabinoid system: from the early to the latest concepts. *Best Pract Res Clin Endocrinol Metab* 23(1):1-15.

49. Department of Health and Human Services [HHS] (2015). Basis for the recommendation for maintaining marijuana in Schedule I of the Controlled Substances Act.

50. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258(5090):1946-1949.

51. Dewey WL, Martin BR, May EL (1984). Cannabinoid stereoisomers: pharmacological effects. In Smith DF. (Ed.) *CRC Handbook of stereoisomers: drugs in psychopharmacology*, 317-26 (Boca Raton, FL, CRC Press).

52. Drug Enforcement Administration (2015). *Drugs of Abuse.*

53. DSM-5 (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association. Washington, DC: American Psychiatric Publishing.

54. Eisenstein TK, Meissler JJ (2015). Effects of cannabinoids on T-cell function and resistance to infection. *J Neuroimmune Pharmacol* 10(2):204-216.

55. Eldridge JC, Murphy LL, Landfield PW (1991). Cannabinoids and the hippocampal glucocorticoid receptor: recent findings and possible significance. *Steroids* 56(5):226-231.

56. ElSohly MA, Slade D (2005). Chemical constituents of marijuana: The complex mixture of natural cannabinoids. *Life Sci* 78:539-548.

57. Fant RV, Heishman SJ, Bunker EB, Pickworth WB (1998). Acute and residual effects of marijuana in humans. *Pharmacol Biochem Behav* 60(4):777-784.

58. Federal Register (1992). "Marijuana Scheduling Petition; Denial of Petition; Remand" – Drug Enforcement Administration, Final Order. *Fed Registr* 57(59):10499-10508.

59. Federal Register (1999). "Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [(-)-delta 9-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Capsules From Schedule II to Schedule III; Final Rule," *Fed Registr* 64(127):35928-35930.

60. Federal Register (2001). "Notice of Denial of Petition: Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act," *Fed Registr* 66(75):20038-20076.

61. Fergusson DM, Horwood LJ, Ridder EM (2005). Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction.* 100(3):354-366.

62. Fontes MA, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, Laranjeira RR, Bressan RA, Lacerda AL (2011). Cannabis use before age 15 and subsequent executive functioning. *Br J Psychiatry* 198(6):442-447.

63. Fried PA, Watkinson B, Grant A, Knights RM (1980). Changing patterns of soft drug use prior to and during pregnancy: a prospective study. *Drug Alcohol Depend* 6(5):323-343.

64. Fried PA, Watkinson B (1990). 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes and alcohol. *J Dev Behav Pediatr* 11:49-58.

65. Fried PA, Watkinson B, Gray R (1992). A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes and alcohol. *Neurotoxicol Teratol* 14:299-311.

66. Fried PA, Watkinson B, Gray R (1998). Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol* 20(3):293-306.

67. Fried PA (2002). Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. *J Clin Pharmacol* 42(11 Suppl):97S-102S.

68. Fried PA, Watkinson B, Gray R (2005). Neurocognitive consequences of marihuana—a comparison with pre-drug performance. *Neurotoxicol Teratol* 27(2):231-239.

69. Fung M, Gallagher C, Machtay M (1999). Lung and aero-digestive cancers in young marijuana smokers. *Tumori* 85(2):140-142.

70. Gates P, Jaffe A, Copeland J (2014). Cannabis smoking and respiratory health: consideration of the literature. *Respirology* 19(5):655-662.

71. Ghozland S, Matthes HW, Simonin F, Filliol D, Kieffer BL, Maldonado R (2002). Motivational effects of cannabinoids are mediated by mu-opioid and kappa-opioid receptors. *J Neurosci* 22(3):1146-1154.

72. Gold LH, Balster RL, Barrett RL, Britt DT, Martin BR (1992). A comparison of the discriminative stimulus properties of delta 9-tetrahydrocannabinol and CP 55,940 in rats and rhesus monkeys. *J Pharmacol Exp Ther* 262(2):479-486.

73. Goldschmidt L, Richardson GA, Willford JA, Day NL (2008). Prenatal marijuana exposure and intelligence test performance at age 6. *J Am Acad Child Adolesc Psychiatry* 47(3):254-263.

74. Goldschmidt L, Richardson GA, Willford JA, Severtson SG, Day NL (2012). School achievement in 14-year-old youths prenatally exposed to marijuana. *Neurotoxicol Teratol* 34(1):161-167.

75. Gong H Jr, Tashkin DP, Simmons MS, Calvarese B, Shapiro BJ (1984). Acute and subacute bronchial effects of oral cannabinoids. *Clin Pharmacol Ther* 35(1):26-32.

76. Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, Uhl GR (2006). Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. *Brain Res* 1071(1):10-23.

77. Gonsiorek W, Lunn C, Fan X, Narula S, Lundell D, Hipkin RW. Endocannabinoid 2-arachidonyl glycerol is a full agonist through human type 2 cannabinoid receptor: antagonism by anandamide. *Mol Pharmacol* 57(5):1045-1050.

78. Gonzalez R (2007). Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance. *Neuropsychol Rev* 17(3):347-361.

79. Gonzalez S, Cebeira M, Fernandez-Ruiz J (2005). Cannabinoid tolerance and dependence: a review of studies in laboratory animals. *Pharmacol Biochem Behav* 81(2):300-318.

80. Gore RL, Earleywine M (2007). Marijuana's perceived addictiveness: A survey of clinicians and researchers. In M. Earleywine, (Ed.) *Pot politics: The cost of prohibition*. New York: Oxford University Press.

81. Griffith-Lendering MF, Wigman JT, Prince van Leeuwen A, Huijbregts SC, Huizink AC, Ormel J, Verhulst FC, van Os J, Swaab H, Vollebergh WA (2013). Cannabis use and vulnerability for psychosis in early adolescence—a TRAILS study. *Addiction* 108(4):733-740.

82. Grotenhermen F (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 42(4):327-360.

83. Gruber SA, Sagar KA, Dahlgren MK, Racine M, Lukas SE (2012). Age of onset of marijuana use and executive function. *Psychol Addict Behav* 26(3):496-506.

84. Hackam DG (2015). Cannabis and stroke: systematic appraisal of case reports. *Stroke* 46(3):852-856.

85. Hall WD, Lynskey M (2005). Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs. *Drug Alcohol Rev* 24(1):39-48.

86. Hall W, Degenhardt L (2014). The adverse health effects of chronic cannabis use. *Drug Test Anal* 6(1-2):39-45.

87. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999). Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology (Berl)* 141(4):395-404.

88. Harder S, Rietbrock S (1997). Concentration-effect relationship of delta-9-tetrahydrocannabinol and prediction of psychotropic effects after smoking marijuana. *International Journal of Clinical Pharmacology and Therapeutics*. 35(4):155-159.

89. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, Compton WM, Crowley T, Ling W, Petry NM, Schuckit M, Grant BF (2013). DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* 170(8):834-851.

90. Heishman SJ, Huestis MA, Henningfield JE, Cone EJ (1990). Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacol Biochem Behav* 37(3):561-565.

91. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC (1990). Cannabinoid receptor localization in brain. *Proc Natl Acad Sci* 87:1932-1936.

92. Herkenham M (1992). Cannabinoid receptor localization in brain: relationship to motor and reward systems. *Ann N Y Acad Sci* 654:19-32.

93. Herning RI, Hooker WD, Jones RT (1986). Tetrahydrocannabinol content and differences in marijuana smoking behavior. *Psychopharmacology (Berl)* 90(2):160-162.

94. Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, Pike VW, Volkow ND, Huestis MA, Innis RB (2012). Reversible and regionally selective downregulation of brain cannabinoid CB 1 receptors in chronic daily cannabis smokers. *Mol Psychiatry* 17(6):643-649.

95. Hively RL, Mosher WA, Hoffman FW (1966). Isolation of trans-Δ9-tetrahydrocannabinol from marihuana. *J Am Chem Soc* 88:1832-1833.

96. Hollister LE, Gillespie HK (1973). Delta-8- and delta-9-tetrahydrocannabinol comparison in man by oral and intravenous administration. *Clin Pharmacol Ther* 14(3):353-357.

97. Hollister LE (1986). Health aspects of cannabis. *Pharmacological Rev* 3:1-20.

98. Hollister LE (1988). Cannabis (Literature review). *Acta Psychiatr Scand (Suppl)* 78:108-118.

99. Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ (2004). Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology* 47 Suppl:345-358.

100. Huang YH, Zhang ZF, Tashkin DP, Feng B, Straif K, Hashibe K (2015). An epidemiologic review of marijuana and cancer: an update. *Cancer Epidemiol Biomarkers Prev* 24(1):15-31.

101. Huestis MA, Sampson AH, Holicky BJ, Benningfield JE, Cone EJ (1992a). Characterization of the absorption phase of marijuana smoking. *Clin Pharmacol Ther* 52:31-41.

102. Huestis MA, Benningfield JE, Cone EJ (1992b). Blood Cannabinoids. 1. Absorption of THC and formation of 11-0H-THC and THC COOH during and after smoking marijuana. *J Anal Toxicol* 16(5):276-282.

103. Hunt CA, Jones RT (1980). Tolerance and disposition of tetrahydrocannabinol in man. *J Pharmacol Exp Ther* 215(1):35-44.

104. Ilan AB, Gevins A, Coleman M, ElSohly MA, de Wit H (2005). Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. *Behav Pharmacol* 16(5-6):487-496.

105. Institute of Medicine (1982). Division of Health Sciences Policy. Marijuana and Health: Report of a Study by a Committee of the Institute of Medicine, Division of Health Sciences Policy. Washington, DC: National Academy Press, 1982.

106. Institute of Medicine (1999). Division of Neuroscience and Behavioral Health. Marijuana and Medicine: Assessing the Science Base. Washington, DC: National Academy Press, 1999.

107. Johansson E, Halldin MM, Agurell S, Hollister LE, Gillespie HK (1989). Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana. *Eur J Clin Pharmacol* 37(3):273-277.

108. Jones RT, Benowitz NL, Heming RI (1981). Clinical relevance of cannabis tolerance and dependence. *J Clin Pharmacol* 21:143S-152S.

109. Jones RT (2002). Cardiovascular system effects of marijuana. *J Clin Pharmacol* 42(11Suppl):58S-63S.

110. Justinova Z, Tanda G, Redhi GH, Goldberg SR (2003). Self-administration of delta9-tetrahydrocannabinol (THC) by drug naïve squirrel monkeys. *Psychopharmacology (Berl)* 169(2):135-140.

111. Justinova Z, Tanda G, Munzar P, Goldberg SR (2004). The opioid antagonist naltrexone reduces the reinforcing effects of Delta 9 tetrahydrocannabinol (THC) in squirrel monkeys. *Psychopharmacology (Berl)* 173(1-2):186-194.

112. Kandel D (1975). Stages in adolescent involvement in drug use. *Science* 190:912-914.

113. Kandel DB, Chen K (2000). Types of marijuana users by longitudinal course. *J Stud Alcohol* 61(3):367-378.

114. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA (1974). Cannabidiol interferes with the effects of delta 9-tetrahydrocannabinol in man. *Eur J Pharmacol* 28(1):172-177.

115. Karniol IG, Shirakawa I, Takahashi RN, Knobel E, Musty RE (1975). Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacology* 13(6):502-512.

116. Keen L 2nd, Pereira D, Latimer W (2014). Self-reported lifetime marijuana use and interleukin-6 levels in middle-aged African Americans. *Drug Alcohol Depend* 140:156-160.

117. Kirk JM, de Wit H (1999). Responses to oral delta9-tetrahydrocannabinol in frequent and infrequent marijuana users. *Pharmacol Biochem Behav* 63(1):137-142.

118. Kuepper R, van Os J, Lieb R, Wittchen HU, Henquet C (2011). Do cannabis and urbanicity co-participate in causing psychosis? Evidence from a 10-year follow-up cohort study. *Psychol Med* 41(10):2121-2129.

119. Kurzthaler I, Hummer M, Miller C, Sperner-Unterweger B, Gunther V, Wechdorn H, Battista HJ, Fleischhacker WW (1999). Effects of cannabis use on cognitive functions and driving ability. *J Clin Psychiatry* 60(6):395-399.

120. Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK (2012). Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer* 118:5374-5383.

121. Lee MH, Hancox RJ (2011). Effects of smoking cannabis on lung function. *Exp Rev Resp Med* 5(4):537-546.

122. Lemberger L, Silberstein SD, Axelrod J, Kopin IJ (1970). Marihuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. *Science* 70:1320-1322.

123. Lemberger L, Weiss JL, Watanabe AM, Galanter IM, Wyatt RJ, Cardon PV (1972a). Delta-9-tetrahydrocannabinol: temporal correlation of the psychological effects and blood levels after various routes of administration. *New Eng J Med* 286(13):685-688.

124. Lemberger L, Crabtree RE, Rowe HM (1972b). 11-Hydroxy-Δ9-tetrahydrocannabinol: pharmacology, disposition and metabolism of a major metabolite of marihuana in man. *Science* 77:62-63.

125. Lemberger L, Rubin A (1975). The physiologic disposition of marihuana in man. *Life Sci* 17:1637-1642.

126. Li M-C, Brady JE, DiMaggio CJ, Lusardi AR, Tzong, KY, Li G (2012). Marijuana use and motor vehicle crashes. *Epidemiologic Rev* 34:65-72.

127. Liguori A, Gatto CP, Robinson JH (1998). Effects of marijuana on equilibrium, psychomotor performance, and simulated driving. *Behav Pharmacol* 9(7):599-609.

128. Lisdahl KM, Price JS (2012). Increased marijuana use and gender predict poorer cognitive functioning in adolescents and emerging adults. *J Int Neuropsychol Soc* 18(4):678-688.

129. Lyons MJ, Bar JL, Panizzon MS, Toomey R, Eisen S, Xian H, Tsuang MT (2004). Neuropsychological consequences of regular marijuana use: a twin study. *Psychol Med* 34(7):1239-1250.

130. Mackie K, Lai Y, Westenbroek R, Mitchell R (1995). Cannabinoids activate an inwardly rectifying potassium conductance and inhibit Q-type calcium currents in AtT20 cells transfected with rat brain cannabinoid receptor. *J Neurosci* 15(10):6552-6561.

131. Maldonado R (2002). Study of cannabinoid dependence in animals. *Pharmacol Ther* 95(2):153-164.

132. Malinowska B, Baranowska-Kuczko M, Schlicker E (2012). Triphasic blood pressure responses to cannabinoids: do we understand the mechanism? *Br J Pharmacol* 165(7):2073-2088.

133. Manrique-Garcia E, Zammit S, Dalman C, Hemmingson T, Andreasson S, Allebeck P (2012). Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. *Psychol Med* 42(6):1321-1328.

134. Maremmani I, Lazzeri A, Pacini M, Lovrecic M, Placidi GF, Perugi G (2004). Diagnostic and symptomatological features in chronic psychotic patients according to cannabis use status. *J Psychoactive Drugs* 36(2):235-241.

135. McCartt AT (2015). Marijuana and driving in the United States: prevalence, risks, and laws. Presented at the Casualty Actuarial Society Spring Meeting. Colorado Springs, CO. May 19, 2015.

136. McMahon LR, Ginsburg BC, Lamb RJ (2008). Cannabinoid agonists differentially substitute for the discriminative stimulus effects of Delta(9)-terahydrocannabinol in C57BL/6J mice. *Psychopharmacology (Berl)* 198(4):487-495.

137. McMahon LR (2009). Apparent affinity estimates of rimonabant in combination with anandamide and chemical analogs of anandamide in rhesus monkeys discriminating Delta9-tetrahydrocannabinol. *Psychopharmacology (Berl)* 203(2):219-228.

138. Mechoulam R (1973). Cannabinoid chemistry. In Mechoulam, R. (ed.) Marijuana, pp.2-88 (New York, NY, Academic Press, Inc.).

139. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR, Pertwee RG, Griffin G, Bayewitch M, Barg J, Vogel Z (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* 50(1):83-90.

140. Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, Ross SA, Khan IA, ElSohly MA (2010). Potency trends of Δ^9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci* 55(5):1209-1217.

141. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, Moffitt TE (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA* 109(40):E2657-E2664.

142. Mendelson JH, Mello NK (1984). Effects of marijuana on neuroendocrine hormones in human males and females. *NIDA Res Monogr* 44:97-114.

143. Messinis L, Kyprianidou A, Malefaki S, Papathanasopoulos P (2006). Neuropsychological deficits in long-term frequent cannabis users. *Neurology* 66:737-739.

144. Minozzi S, Davoli M, Bargagli AM, Amato L, Vecchi S, Perucci CA (2010). An overview of systematic reviews on cannabis and psychosis: discussing apparently conflicting results. *Drug Alcohol Rev* 29(3):304-317.

145. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE (2001). Triggering myocardial infarction by marijuana. *Circulation* 103:2805-2809.

146. Nace EP, Meyers AL, Rothberg JM, Maleson F (1975). Addicted and nonaddicted drug users. A comparison of drug usage patterns. *Arch Gen Psychiatry* 32(1):77-80.

147. Oviedo A, Glowa J, Herkenham M (1993). Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. *Brain Res* 616:293-302.

148. Pacher P, Batkai S, Kunos G (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 58(3):389-462.

149. Panayiotides IM (2015). What is the association between cannabis consumption and cardiovascular complications. *Subst Abuse* 9:1-3.

150. Pelayo-Teran JM, Suarez-Pinilla P, Chadi N, Crespo-Pacorro B (2012). Gene-environment interactions underlying the effect of cannabis in first episode psychosis. *Curr Pharm Des* 18(32):5024-5035.

151. Piomelli D (2005). The endocannabinoid system: a drug discovery perspective. *Curr Opin Investig* 6(7):672-679.

152. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, Lin F, Kertesz S (2012). Association between marijuana exposure and pulmonary function over 20 years. *Journal of the American Medical Association*. 307(2):173-181.

153. Pollastro F, Taglialatela-Scafati O, Allara M, Munoz E, Di Marzo V, De Petrocellis L, Appendino G (2011). Bioactive prenylogous cannabinoid from fiber hemp (Cannabis sativa). *J Nat Prod*. 74(9):2019-2022

154. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D (2002). Cognitive measures in long-term cannabis users. *J Clin Pharmacol* 42(11 Suppl):41S-47S.

155. Radwan MM, ElSohly MA, Slade D, Ahmed SA, Khan IA, Ross SA (2009). Biologically active cannabinoids from high-potency Cannabis sativa. *J Nat Prod* 72(5):906-911.

156. Ramaekers JG, Berghaus G, van Laar M, Drummer OH (2004). Dose related risk of motor vehicle crashes after cannabis use. *Drug and Alcohol Dependence*. 73(2):109-119.

157. Ramaekers JG, Kauert G, van Ruitenbeek P, Theunissen EL, Schneider E, Moeller MR (2006). High-potency marijuana impairs executive functions and inhibitory motor control. *Neuropsychopharmacology* 31(10):2296-2303.

158. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR (2009). Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol* 23(3):266-277.

159. Riggs PK, Vaida F, Rossi SS, Sorkin LS, Gouaux B, Grant I, Ellis RJ (2012). A pilot study of the effects of cannabis on appetite hormones in HIV-infected adult men. *Brain Res* 1431:46-52.

160. Rodriguez de Fonseca F, Gorriti MA, Fernandez-Ruiz JJ, Palomo T, Ramos JA (1994). Downregulation of rat brain cannabinoid binding sites after chronic delta 9-tetrahydrocannabinol treatment. *Pharmacol Biochem Behav* 47(1):33-40.

161. Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP (1998). Airway inflammation in young marijuana and tobacco smokers. *American Journal of Respiratory and Crit Care Med* 157:928-937.

162. Roth MD, Tashkin DP, Whittaker KM, Choi R, Baldwin GC (2005). Tetrahydrocannabinol suppresses immune function and enhances HIV replication in the huPBL-SCID mouse. *Life Sci* 77(14):1711-1722.

163. Russo E, Mathre ML, Byrne A, Velin R, Bach PJ, Sanchez-Ramos J, Kirlin KA (2001). Chronic cannabis use in the compassionate investigational new drug program: An examination of benefits and adverse effects of legal clinical cannabis. *J Cannabis Ther* 2:3-57.

164. Sarfaraz S, Afaq F, Adhami VM, Mukhtar H (2005). Cannabinoid receptor as a novel target for the treatment of prostate cancer. *Cancer Res* 65(5):1635-1641.

165. Scherrer JF, Grant JD, Duncan AE, Sartor CE, Haber JR, Jacob T, Bucholz KK (2009). Subjective effects to cannabis are associated with use, abuse and dependence after adjusting for genetic and environmental influences. *Drug Alcohol Depend* 105(1-2):76-82.

166. Schiffman J, Nakamura B, Earleywine MJ, LaBrie J (2005). Symptoms of schizotypy precede cannabis use. *Psychiatry Res* 134(1):37-42.

167. Schimmelmann BG, Conus P, Cotton SM, Kupferschmid S, Karow A, Schultze-Lutter F, McGorry PD, Lambert M (2011). Cannabis use disorder and age at onset of psychosis—a study in first episode patients. *Schizophr Res* 129(1):52-56.

168. Schreiner AM, Dunn ME (2012). Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol* 20(5):420-429.

169. Sexton M, Cudaback E, Abdullah RA, Finnell J, Mischley LJ, Rozga M, Lichtman AH, Stella N (2014). Cannabis use by individuals with multiple sclerosis: effects on specific immune parameters. *Inflammopharmacology* 22(5):295-303.

170. Sidney S (2002). Cardiovascular consequences of marijuana use. *J Clin Pharmacol* 42(11Suppl):64S-70S.

171. Solinas M, Panlilio LV, Justinova Z, Yasar S, Goldberg SR (2006). Using drug-discrimination techniques to study the abuse-related effects of psychoactive drugs in rats. *Nat Protoc* 1(3):1194-1206.

172. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Christiansen K, McRee B,Vendetti J (2002). Marijuana Treatment Project Research Group. Cognitive functioning of long-term heavy cannabis users seeking treatment. *Journal of the American Medical Association* 287(9):1123-1131.

173. Substance Abuse and Mental Health Services Administration (2013). *Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits.* HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD.

174. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality (2015a). Results from the 2014 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD.

175. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality (2015b). *Treatment Episode Data Set (TEDS): 2003-2013. National Admissions to Substance Abuse Treatment Services.* BHSIS Series S-75, HHS Publication No. (SMA) 15-4934. Rockville, MD.

176. Tait RJ, MacKinnon A, Christensen H (2011). Cannabis use and cognitive functioning: 8-year trajectory in a young adult cohort. *Addiction* 106(12):2195-2203.

177. Tanasescu R, Constantinescu CS (2010). Cannabinoids and the immune system: an overview. *Immunobiology* 215(8):588-597.

178. Tanda G, Munzar P, Goldberg SR (2000). Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nat Neurosci* 3(11):1073-1074.

179. Tanda G, Goldberg SR (2003). Cannabinoids: reward, dependence, and underlying neurochemical mechanisms—a review of recent preclinical data. *Psychopharmacology (Berl)* 169(2):115-134.

180. Tashkin DP (2005). Smoked marijuana as a cause of lung injury. *Monaldi Arch Chest Dis* 63(2):93-l00.

181. Tashkin DP, Zhang ZF, Greenland S, Cozen W, Mack TM, and Morgenstern H (2006). Marijuana use and lung cancer: results of a case-control study. *American Thoracic Society International Conference.* Abstract A777.

182. Theunissen EL, Kauert GF, Toennes SW, Moeller MR, Sambeth A, Blanchard MM, Ramaekers JG (2012). Neurophysiological functioning of occasional and heavy

cannabis users during THC intoxication. *Psychopharmacology (Berl)* 220(2):341-350.

183. Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA (2011). Marijuana use and testicular germ cell tumors. *Cancer* 117(4):848-853.

184. Twitchell W, Brown S, Mackie K (1997). Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. *J Neurophysiol* 78(1):43-50.

185. U.S. Food and Drug Administration (FDA), Center for Drug and Evaluation Research, Controlled Substances Staff (2015). The Medical Application of Marijuana: A Review of Published Clinical Studies. March 19, 2015.

186. van der Meer FJ, Velthorst E, Meijer CJ, Machielsen MW, de Haan L (2012). Cannabis use in patients at clinical high risk of psychosis: impact on prodromal symptoms and transition to psychosis. *Curr Pharm Des* 18(32):5036-5044.

187. van Gastel WA, Wigman JT, Monshouwer K, Kahn RS, van Os J, Boks MP, Volleburgh WA (2012). Cannabis use and subclinical positive psychotic experiences in early adolescence: findings from a Dutch survey. *Addiction* 107(2):381-387.

188. Van Gundy K, Rebellon CJ (2010). A Life-course Perspective on the "Gateway Hypothesis." *J Health Soc Behav* 51(3):244-259.

189. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. (2002). Cannabis use and psychosis: a longitudinal population-based study. *Am J Epi* 156(4):319-327.

190. Vann RE, Gamage TF, Warner JA, Marshall EM, Taylor NL, Martin BR, Wiley JL (2008). Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Delta(9)-tetrahydrocannabinol. *Drug Alcohol Depend* 94(1-3):191-198.

191. Volkow ND, Baler RD, Compton WM, Weiss SR (2014). Adverse health effects of marijuana use. *N Engl J Med* 370(23):2219-2227.

192. von Sydow K, Lieb R, Pfister H, Hofler M, Wittchen HU (2002).What predicts incident use of cannabis and progression to abuse and dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug Alcohol Depend* 68(1):49-64.

193. Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H (2002). Comparison of the subjective effects of Delta(9)-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology (Berl)* 161(4):331-339.

194. Wagner JA, Varga K, Kunos G (1998). Cardiovascular actions of cannabinoids and their generation during shock. *J Mol Med* 76(12):824-836.

195. Wang GS, Roosevelt G, Heard K (2013). Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatr* 167(7):630-633.

196. Wang GS, Roosevelt G, Le Lait MC, Martinez EM, Bucher-Bartelson B, Bronstein AC, Heard K (2014). Association of unintended pediatric exposures with decriminalization of marijuana in the United States. *Ann Emerg Med* 63(6):684-689.

197. Wang T, Collet JP, Shapiro S, Ware MA (2008). Adverse effects of medical cannabinoids: a systematic review. *CMAJ* 178(13):1669-1678.

198. Wesson DR, Washburn P (1990). Current patterns of drug abuse that involve smoking. *NIDA Res Monogr* 99:5-11.

199. Whitehill JM, Rivara FP, Moreno MA (2014). Marijuana-using drivers, alcohol-using drivers, and their passengers: prevalence and risk factors among underage college students. *JAMA Pediatr* 168(7):618-624.

200. Wiley JL, Barrett RL, Britt DL, Balster RL, Martin BR (1993). Discriminative stimulus effects of delta 9-tetrahydrocannabinol and delta 9-11-tetrahydrocannabinol in rats and rhesus monkeys. *Neuropharmacology* 32(4):359-365.

201. Wiley JL, Huffman JW, Balster RL, Martin BR (1995). Pharmacological specificity of the discriminative stimulus effects of delta 9-tetrahydrocannabinol in rhesus monkeys. *Drug Alcohol Depend* 40(1):81-86.

202. Wilkinson ST, Radhakrishnan R, D'Souza DC (2014). Impact of cannabis use on the development of psychotic disorders. *Curr Addict Rep* 1(2):115-128.

203. Wilson FA, Stimpson JP, Pagán JA (2014). Fatal crashes from drivers testing positive for drugs in the U.S., 1993-2010. *Public Health Rep* 129(4):342-350.

204. Wu X, French ED (2000). Effects of chronic delta9-tetrahydrocannabinol on rat midbrain dopamine neurons: an electrophysiological assessment. *Neuropharmacology* 39(3):391-398.

205. Zeiger JS, Haberstick BC, Corley RP, Ehringer MA, Crowley TJ, Hewitt JK, Hopfer CJ, Stallings MC, Young SE, Rhee SH (2010). Subjective effects to marijuana associated with marijuana use in community and clinical subjects. *Drug Alcohol Depend* 109(1-3):161-66.

206. Zhang ZF, Morgenstern H, Spitz MR, Tashkin DP, Yu GP, Marshall JR, Hsu TC, Schantz, SP (1999). Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiol Biomarkers Prev* 8(12):1071-1078.

207. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, Woll PJ, Orlow I, Cox B on behalf of the Cannabis and Respiratory Disease Research Group of New Zealand, Brhane Y, Liu G, Hung RJ (2015). Cannabis smoking and

lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *Int J Cancer* 136(4):894-903.

208. Zwardi AW, Shirakawa I, Finkelfarb E, Karniol IG (1982). Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subject. *Psychopharmcology (Berl)* 76(3):245-250.