PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF CANNABIS : REVIEW OF THE RESEARCH FINDINGS

PREPARED FOR THE SENATE SPECIAL COMMITTEE ON ILLEGAL DRUGS

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I. Cannabis and cannabinoids : Pharmacology and toxicology

An exhaustive and detailed approach was taken in this review, since an understanding of the complex effects of cannabis is vital for an objective discussion of the subject, and very little summarizing literature is available on the aspects portrayed here.

Introduction

Cannabis sativa is a dioecious (having male and female flowers in separate plants), green, leafy plant with characteristic opposite, usually seven-fingered, lance-shaped leaves; on dry, sandy, slightly alkaline soil it can grow to more than seven meters in height. Glandular hairs develop, usually on the female flower, which secrete a resin. The female plants are more important than the male plants for commercial purposes: their fibers are thicker, they form the nutritious seeds,
and they contain the psychoactive principle tetrahydrocannabinol (THC) which is much sought after by producers of marijuana and hashish.

Unlike most of the substances used in our western culture to induce an intoxication,
cannabis is not a single substance but contains a large number of different components;
over 420 have been identified to date. The cannabinoids, of which there are over 60, are the
most important class containing the active principle responsible for the psychotropic effects
of the plant, delta-9-tetrahydrocannabinol (referred to in the following as delta-9-THC, or THC).

Tetrahydrocannabinol is the main active ingredient in cannabis. The THC content usually varies between one and 15 percent in marijuana, and between 3 and 6 percent in hashish.

There are also hashish and marijuana oils. They contain a higher concentration of active ingredients, thus tetrahydrocannabinol, and the concentrations are usually between 30 and 50 percent. Cannabis is in the class of psychotropic substances, which are substances that act on an individual's psyche and cause different changes in his or her mental functioning. Cannabis is in the group of psychotropes known as psychodysleptic drugs or hallucinogens[1].

Basically all the parts of the cannabis sativa plant can contain cannabinoids, not just the seeds, but the quantity varies from one part to another. The resin secreted by the female glandular hairs contains up to 90 percent cannabinoids, the bracts of the flowers and fruits
contain an average of 3 to 6 percent, and the leaves contain only one to 3 percent[2].

The most important cannabis products in the drug trade are marijuana and hashish. Marijuana consists of all the dried parts of the plant; it is sold either loose or pressed and contains up to 2 percent THC. The THC content is increased (up to 6 percent) by using only
the flowering tops of the female plants. Hashish is a particularly resinous form of cannabis,
and good quality hashish contains between 10 and 20 percent THC[3]. The THC content of cannabis plants can be increased by selective breeding and optimal growing conditions. The ”Sinsemilla” type of marijuana, for example, had a THC content of one percent in the 1960s,
8.5 percent in the early 1980s, and as much as 17 to 22 percent in the 1990s[4].

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[1] M. Ben Amar, Pschodysleptic Drugs: Cannabis and Hallucinogens, University of Montreal, 2001
[2] Th. Geschwinde, Rauschdrogen: Marktformen und Wirkungsweisen, 3rd edition, Springer Verlag, Berlin, 1996.
[3] Th. Lehmann, Chemical Profile of Cannnabis Sativa, Innaugural Dissertation, University of Berne, Berne, 1995.
[4] I.B. Adams and B.R. Martin, Cannabis: Pharmacology and toxicology in animals and humans, Addiction 91 (11), 1585-1614; Geschwinde, 1996.

There are mainly two ways of ingesting cannabis: by inhalation, or through the lungs, and orally. Marijuana and hashish can be inhaled. Hashish can also be baked into biscuits or cake. The difference between these two modes of ingestion is observed during the onset of the drug's effects. The influence of this drug is felt more promptly when it is inhaled.

In the 1960s, Dr. Rafael Mechoulam isolated and identified the cannabinoids and the chief cannabinoid chemical in the marijuana plant: delta-9-THC[5]. The structure of tetrahydrocannabinol (THC), the major psychoactive constituent of cannabis, was ascertained and the pure compound was synthesized, making exact chemical and pharmacological studies possible for the first time. Approximately 20 years later, in the late 1980s, Allyn Howlett, a scientist in St. Louis, identified a receptor for THC that is a component of the cell surface of brain cells to which THC binds.

The drug works by inserting itself into a pre-existing structural and functional system. Thirty years after the identification of THC by Dr. Mechoulam, a scientist working with him, William Devane, identified a brain chemical, anandamide - a chemical we make - which binds to the cannabinoid receptor and causes changes which are qualitatively similar to those provoked by THC.

These studies, the identification of the particular cannabinoid chemical, and the identification and characterization of the receptor that binds that chemical, have led to a beginning understanding of the cannabinoid system in the mammalian brain. The discovery of this antagonist completes the basic requirements for a receptor system and provides a valuable tool for establishing the functional role of the cannabinoids in the central nervous system. Cannabinoid receptors are widely distributed in the brain and their activation provokes a number of effects.

The activation system might better be classified as a modulating system than as an effector system. In some cells, in the central nervous system, binding to the cannabinoid

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[5] R. Mechoulam, Marijuana chemistry: Recent advances open the area to more sophisticated biological research, Science 168: 1159-1166, 1970.

receptor modifies a pre-existing energy transmitting system in the cell so that the cell operates in a diminished or reduced response to the usual activation provoked by other neurotransmitters such as norepinephrine and acetylcholine. In other words, the cannabinoid system may quite often turn down cells. It is a down modulator, a modifier of cellular response, which often diminishes the response that cell has normally to other chemicals.

The cannabinoid system may modulate a large number of human physiological processes that may relate to formulation of memory; response to pain and other strong stimuli; modification of movement, particularly relative to its modification of muscular tone; and regulation of appetite. Future cannabinoid therapeutics, following the western pharmacological model, probably will reply upon delivery of THC in some fashion other than the smoking of crude marijuana. There is currently experimentation with pure THC inhalers.

I.2 Methodological issues in assessing cannabis use

There are difficulties in making causal inferences about the acute and chronic adverse health and psychological effects of cannabis use. Acute health effects are taken to be those that occur shortly after a single dose or after a small number of occasions of use. Chronic health effects are defined as those that occur after a period of years or decades. Wayne Hall, in his paper entitled A simplified logic of causal reference[6], has stated that the criteria for causal inference require that a number of conditions be met: that there is evidence of an association between cannabis use and an adverse health outcome; that chance is an unlikely explanation of the association; that it is clear that cannabis use preceded the health outcome; and that plausible alternative causal explanations of the association can be excluded. It is often difficult to satisfy all these criteria, especially concerning the effects of chronic cannabis use.

[6] W. Hall, A simplified logic of causal inference, Australian and New Zealand Journal of Psychiatry 21, 507-513, 1987.

Causal inferences about the adverse health effects of cannabis are complicated by: a lack of good studies of association between cannabis and use and health outcomes; difficulties in deciding between equally plausible explanations of associations because of ethical or practical obstacles to experimental studies; and, in the case of null findings, uncertainty as to whether they provide reasonable evidence of the absence of effects, or only constitute an absence of evidence.

Despite some sampling and response biases in surveys of drug use, most of which operate by underreporting or underestimating use, the evidence of validity of self-reported drug-use measures in carefully designed studies is quite strong[7]. Further, whatever biases there may be towards underestimation of cannabis use, they are probably fairly constant across time, making their impact on trend estimates of less concern[8].

In terms of the magnitude of the health risks of cannabis use, very few of the major potential effects of cannabis, including the effects of cannabis use on the immune and respiratory systems, have been the subject of epidemiological research to provide quantitative estimates of risks.

I.3 Cannabis in the body

Absorption, metabolism and excretion

Cannabis is usually smoked as a "joint," a variable mixture of hashish (or marijuana) and tobacco. The dosage depends on the desired effect (generally one cigarette containing 2 percent THC). The active principle is absorbed very rapidly via the respiratory tract and

[7] P.M. O'Malley, J.G. Bachman, L.D. Johnston, Reliability and consistency of self-reports of drug use, International Journal of the Addictions 18: 805-824, 1983.
[8] W. Hall, L. Johnston, N. Donnelly, Epidemiology of cannabis use and its consequences, The Health Effects of Cannabis, Addiction Research Foundation, 1999.

lungs, with an onset of action just a few minutes later. The effect peaks at fifteen minutes, subsides gradually after thirty to sixty minutes, and is largely finished after two to three hours[9]. The bioavailability (proportion of substance active in the body) depends greatly on the smoker's technique and varies between 10 and 25 percent (with a maximum of 56 percent).

THC is absorbed by the body much more slowly after oral intake (eating or drinking) and then has a lower bioavailability of 4 to 12 percent because of the poorer absorption, catabolism (breakdown into simpler substances) in the liver, and the fact that the inactive tetrahydrocannabinolidic acids in natural cannabis products cannot be transformed into psychoactive delta-9-THC unless they are heated first, as is the case when they are smoked[10]. In contrast to absorption through the respiratory tract, in which peak plasma concentrations of THC may be achieved while the product is being smoked, the plasma concentration increases constantly over a period of four to six hours when cannabis is ingested; a state of intoxication is reached later and is of a different quality.

The high solubility of delta-9-THC and its active metabolite 11-OH-delta-9-THC in fat mean that they are bound almost completely to protein in the plasma, cross the blood-brain barrier with ease, and are eliminated only slowly from lipid-containing tissue. This slow elimination gives the substances a biological half-life of one day[11]; other authors have reported half-lives of three to five days[12]. The substances are thought to be metabolized twice as quickly by chronic users of cannabis as by first-time users[13] [14].

The cannabinoids are metabolized rapidly in the liver. To date, some 80 different, mostly inactive metabolites have been identified[15]. No major metabolic differences between

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[9] Geschwinde 1996.
[10] Lehmann 1995.
[11] Ibid.
[12] Adams, Martin 1996.
[13] M.O. Maykut, Health Consequences of acute and chronic marijuana use, Prog. Neuro-Phychopharmacol, and Biol. Psychiat. 9 (3), 209-238, 1985.
[14] Adams, Martin 1996.
[15] S. Agurell, M. Halldin et al., Pharmacokinetics and metabolism of delta-9-THC and other cannabinoids with emphasis on man, Pharm. Rev. 38 (1), 21-43, 1986.

male and female users of cannabis have been observed[16].

There are several pharmacokinetic aspects of THC that have an impact on the effects of cannabis, but these are frequently misunderstood. THC is metabolized to the active metabolite 11-OH-delta-9-THC, but this is unlikely to contribute to THC's pharmacological effects because it is converted to the corresponding active metabolite, which is inactive. It is this latter metabolite that serves as the primary urinary marker for detecting cannabis use. It has been shown that THC can be deposited in fatty tissues for long periods of time after use[17] [18]. However, there is no evidence that THC exerts a deleterious effect when deposited in tissue or during its slow egress from these sites. Although the primary psychoactive effects of cannabis are attributed to THC, there is no linear relationship between blood levels and pharmacological effects with respect to time, a situation that hampers the prediction of cannabis-induced impairment based on THC blood levels.

Immediately following cannabis smoking, high concentrations of delta-9-THC are present in the blood and distributed to the tissues. The physiological and psychic effects of cannabis increase during this distribution phase, but may peak at times when blood concentrations of delta-9-THC are falling. Once equilibrium is established between brain and blood concentrations (approximately forty-five minutes after use), a linear relationship between blood concentrations and pharmacological effects appears. Recently developed mathematical models are useful in interpreting the relationship of delta-9-THC and metabolite concentrations in blood to drug-induced effects and in estimating time elapsed since cannabis use[19].

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[16] M.E. Wall, B.M. Sadler et al., Metabolism, disposition and kinetics of delta-9-THC in men and women, Clin. Pharmacol. Ther. 34 (3), 352-363, 1983.

[17] D.S. Kreuz and J. Axelrod, Delta-9-THC: Localization in body fat, Science, vol. 1979, 1973, 391and 392.

[18] E. Joansson and others, Prolonged apparent half-life of delta-9-THC in plasma of chronic marijuana users, Journal of Pharmacy and Pharmacology, vol. 40, 1988, 374 and 375.

[19] M.A. Huestis, J.E. Henningfield and E.J. Cone, Blood cannabinoids. II. Models for the prediction of time of marijuana exposure from plasma concentrations of delta-9-THC and 11 –nor-9-carboxy-delta-9-THC (THCCOOH), Journal of Analytical Toxicology, vol. 16, 1992, 283-290.

Pharmacodynamics

As mentioned above, specific research into the mode of action of cannabis was not possible until 1964[20], when delta-9-THC was isolated and its structure was elucidated. It then became possible to develop substances with an action similar to THC, some of them highly potent. During the 1980s, various scientific findings removed any lingering doubt about the existence of specific cannabis receptors[21 22 23 24 25].

A cannabinoid receptor (CB1) located predominantly in the cerebellum, the hippocampus and the cerebral cortex was finally discovered and cloned in 1990[26]. A further, peripheral, receptor (CB2) was found in certain parts of the immune system (e.g., the spleen) in 1993[27]. Investigations carried out to date would seem to confirm that these receptors are capable of affecting neurophysiological processes in the brain[28]. Future research will reveal the extent to which processes of this type involving cannabinoid receptors are linked to the complex effects of cannabis in humans.

In 1992, the endogenous ligand (linking substance) anandamide was discovered; it is thought to be synthesized and released on an ad hoc basis[29 30 31]. The discovery of the cannabinoid receptors, endogenous ligands, and the development of specific agonists and antagonists in the past and the future, are making a major contribution to scientific understanding of the effects of cannabis, of the neurophysiological role played by these

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[20] Agurell et al. 1986.
[21] M. Bidaut-Russel, W.A. Devane et al., Cannabinoid receptors and modulation of cyclic AMP accumulation in the rat brain, 55, 21-26, 1990.
[22] W.L. Dewey, B.R. Martin et al., Cannabinoid stereoisomers: Pharmacological effects, 317-326, 1984, in D.F. Smith (ed.), Handbook of Stereoisomers: Drugs in Psychopharmacology, CRC Press, Boca Raton.
[23] A.C. Howlett and R.M. Fleming, Cannabinoid inhibition of adenylate cyclase: pharmacology of the response in neuroblastoma cell membranes, Mol. Pharmacol. 26, 532-538, 1984.
[24] A.C. Howlett, J.M. Qualy et al., Involvement of Gi in the inhibition of adenylate cyclase by cannabimimetic drugs, Mol. Pharmacol. 29, 307-313, 1986.
[25] M.E. Abood and B.R. Martin, Molecular neurobiology of the cannabinoid receptor, Int. Rev. Neurobiol. 39, 1996.
[26] J. Axelrod and C.C. Felder, Cannabinoid receptors and their endogenous agonist, anandamide, Neurochem. Res. 23 (5), 575-581, 1998.
[27] Abood, Martin 1996; Lehmann 1995.
[28] Axelrod, Felder 1998.
[29] V. Di Marzo, A. Fontana et al., Formation and inactivation of endogenous cannabinoid anandamide in central neurons, Nature 372, 686-691, 1994.
[30] Abood, Martin 1996.

receptors, and of the possible effects on the human brain and its functions in the context of chronic cannabis use. New knowledge will perhaps enable the development of an active principle which is therapeutically highly active but has none of the psychoactive properties.

Acute effects of cannabis

The acute effects of cannabis use are an altered state of consciousness characterized by mild euphoria and relaxation, perceptual alterations, including time distortion, and the intensification of ordinary sensory experiences, such as those associated with eating, watching films and listening to music[32]. When used in a social setting its effects may include infectious laughter and loquacity. There are also pronounced cognitive effects, such as impaired short-term memory and a loosening of associations, enabling the user to become lost in pleasant reverie and fantasy. Motor skills and reaction time are also impaired so that skilled activity of various kinds is frequently disrupted [33].

Acute effects of cannabis on the central nervous system

The psychotropic (affecting the central nervous system and the mind) action of cannabis is

one of the reasons why cannabis products are used so widely. As mentioned above, cannabis starts to act more rapidly and more intensively when it is smoked, and the intoxication lasts a shorter time than when it is absorbed through the digestive system. The effect of cannabis depends not only on its composition, dosage and mode of consumption; much also depends on the mood of the individual, on the individual's expectations, and on the atmosphere and setting. These factors explain why the altered state

of consciousness, which may amount to pronounced intoxication, is experienced so differently by different people. At a low to moderate dose, cannabis produces a largely

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[31] Axelrod, Felder 1998.

[32] W. Hall, N. Solowij and J. Lemon, The Health and Psychological Consequences of Cannabis Use, National Drug Strategy Monograph Series No. 25 (Canberra, Australian Government Publication Service, 1994).

[33] Ibid.

pleasant feeling of relaxed euphoria, perhaps even with dreamy elements, which may be accompanied by heightening or alteration of the senses[34] . The sense of time shifts markedly, and the individual perceives periods of time as being considerably longer than they really are. Short-term memory is impaired[35], although recall of previously acquired knowledge is impaired only slightly if at all. It is uncertain whether other higher functions of the brain, such as the organization and integration of complex information, are affected[36].

Higher doses produce a general reduction in spontaneity, drive and involvement in the surroundings. Anxiety, confusion, aggressive feelings, (pseudo) hallucinations, nausea and
vomiting have all been reported but are not usually experienced. They may, however, develop even in experienced users[37] [38]. As the effects of THC subside, the individual often becomes drowsy and tired, but there is no "hangover" comparable to the effect experienced after heavy alcohol consumption.

Acute side effects and toxicity of cannabis

The physiological effects observed immediately after consumption are reddening of the conjunctivae of the eyes, a reduction in body temperature, a dry mouth and throat, hunger, a slightly elevated heart rate and blood pressure when lying down, and a drop in heart rate and blood pressure when standing[39] [40] [41] [42].

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[34] Hagers Handbuch der Pharmazeutischen Praxis, Cannabis Monograph, 5th edition, Springer, Berlin, 1992.
[35] Lehmann 1995.
[36] Adams, Martin 1996.
[37] Hagers Handbuch 1992.
[38] Lehmann 1995.
[39] Adams, Martin 1996.
[40] W.L. Dewey, Cannabinoid pharmacology, Pharmacol. Rev. 38 (2), 151-178, 1986.
[41] Hagers Handbuch 1992.
[42] M.O. Maykut, Health Consequences of Acute and Chronic Marijuana Use, Oxford, Pergamon Press, 1984.

Heart rate may increase 20 to 50 percent over baseline[43] [44]. This tachycardia occurs within a few minutes to a quarter of an hour and can last up to three hours. In healthy young users these cardiovascular effects are unlikely to be of any clinical significance because tolerance develops to the effects of THC, and young healthy hearts will be only mildly stressed[45].

The acute toxicity of cannabis is generally thought to be low. If the dose of cannabis lethal in rhesus monkeys is extrapolated to man, a human would have to smoke one hundred grams of hashish to achieve the same effect. No human fatality has ever been reported in the world medical literature in connection with acute cannabis intoxication.

The lethal dose also increases as one moves up the phylogenetic/evolutionary tree, suggesting by extrapolation that the lethal dose in humans could not be easily achieved by smoking or ingesting the drug[46]. This feature distinguishes cannabis from other drugs of abuse in that almost all can produce lethality at high doses. Unfortunately, this fact is often used to portray cannabis as a safe drug, an implication that cannabis can be used without adverse effects. In actual fact, most problems stemming from cannabis abuse can be attributed to disruption of a normal productive life rather than death.

Use of high-dose cannabis products can lead to psychotic states which manifest as a combination of emotional symptoms, such as fluctuating mood, disorientation and schizophrenia-like states, as well as depression, anxiety, visual and auditory hallucinations, and
paranoid persecution mania. Panic reactions are often due to the individual's fear of losing

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[43] G.L. Huber, D.L. Griffith and P.M. Langsjoen, The effects of marijuana on the respiratory and cardiovascular systems, in Marijuana: An International Research Report, G. Chesher, P. Consroe and R. Musty (eds.), National Campaign Against Drug Abuse Monograph No. 7, Canberra, Australian Publishing Service, 3-18, 1988.
[44] R.T. Jones, Drug abuse profile: Cannabis, Clinical Chemistry, vol. 33, 72B-81B, 1987.
[45] W. Hall et al. 1994.
[46] H. Rosenkrantz, Cannabis, marijuana, and cannabinoid toxicological manifestations in man and animals, in Cannabis and Health Hazards: Proceedings of an ARF/WHO Scientific Meeting on Adverse Health and

control or his/her mind[47] [48]. The treatment of such states often involves nothing more than reassuring the person. Drug therapy is generally unnecessary because the calming effect of the drug in any case comes to the fore as the intoxication subsides[49] [50].

When evaluating the significance of the potential negative effects of cannabis consumption mentioned above, it should not be forgotten that similar effects may also occur in patients using many of the psychoactive medications prescribed today.

Relationship between plasma concentration and degree of intoxication

A number of studies have attempted to correlate plasma concentrations of delta-9-THC and its metabolites with the psychoactive effects of cannabis in order to deduce the extent of the intoxicated state currently being experienced by an individual, or to determine when cannabis was last used. However, this is far more difficult than with alcohol because of the many factors that affect the pharmacological action of cannabis. Peak plasma concentrations do not correspond to the point of maximum intoxication when cannabis is inhaled (smoked), injected intravenously or ingested (eaten or drunk)[51]. More recent mathematical models are thought to permit more accurate assessment of the time that has elapsed since cannabis was last consumed[52].

Effects of chronic cannabis use

As the Swiss Federal Commission for Drug Issues (EKDF) points out in its 1999 Cannabis Report, opinions differ, in some cases widely, on the effects of chronic

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Behaviour Consequences of Cannabis Use, K.O. Fehr and H. Kalant (eds.), Toronto, Addiction Research Foundation, 91-176, 1983.

[47] C. Tart, Marijuana intoxication: Common experiences, Nature, vol. 226, 1970, 701-704.

[48] A. Weil, Adverse reactions to marijuana, New England Journal of Medicine, vol. 282, 1970, 997-1000.

[49] Hagers Handbuch 1992.

[50] L.E. Hollister, Health aspects of cannabis, Pharmacol. Rev. 38 (1), 1-20, 1986.

[51] D.M. Cochetto, S.M. Owens et al., Relationship between plasma delta-9-THC concentration and pharmacological effects in man, Psychpharmacology 75, 158-164, 1981.

[52] World Health Organization (WHO), Cannabis: A Health Perspective and Research Agenda, 1997.

cannabis use, and the results obtained from research to date leave room for assumptions and speculation. It appears to be practically impossible to demonstrate effects due solely to cannabis. It is difficult to extrapolate from animal experiments, some of which use high doses of pure substance and whose duration is too short to be comparable with chronic use of cannabis, to man. Even in clinical trials with chronic cannabis users, the results will be falsified, for example if the individuals studied have been consuming alcohol and tobacco for the same length of time. For this reason, it is not possible to attribute the results solely to the use of cannabis with any degree of certainty. Moreover, the number of other possible causes of the effects observed grows as the duration of use gets longer[53].

The United Nations Office for Drug Control and Crime Prevention (ODCCP) noted in a 1999 paper on the health effects of cannabis[54] that the main physiological and psychological effects of chronic heavy cannabis use, especially daily use over many years, remain uncertain. The main potential adverse effects are respiratory disease, cannabis dependence, and subtle cognitive impairment. Respiratory diseases are those associated with smoking as the method of administration, such as chronic bronchitis. There is also some evidence that cannabis smokers show histopathological (diseased tissue) changes that may be precursors to the development of malignancy. The cannabis dependence syndrome is characterized by an inability to abstain from or to control cannabis use. The subtle forms of cognitive impairment affect attention and memory, persist while the user remains chronically intoxicated, and may or may not be reversible after prolonged abstinence from cannabis.

II. Physiological Effects of Cannabis

[53] WHO 1997.
[54] B.R. Martin and W. Hall, The Health Effects of Cannabis: Key Issues of Policy Relevance, 1999.

II.1 Cannabis Effects on the Respiratory System

Cannabis smoke – cellular, bronchial and pulmonary effects

Studies of the chronic effects of cannabis are difficult to perform, and much less is understood regarding long-term effects of cannabis than is known about acute exposure. When cannabis is smoked by non-tolerant individuals, physiological and behavioural effects appear rapidly. Huestis and colleagues[55] found that subjects displayed mean heart rate increases of 46.0 ± 18.6 and 55.8 ± 22.2 beats per minute over baseline levels following the smoking of a single 1.75 percent or 3.55 percent THC cigarette, respectively. Peak effects occurred at 17.4 ± 4.8 and 13.8 ± 4.2 minutes after initiation of smoking of the low- or high-dose cigarette. Maximum effects were recorded within four to six minutes after the last puff of cannabis smoke.

Although cannabis contains over sixty cannabinoids, the major active ingredient, delta-9-THC, appears to be primarily responsible for its psychoactive effects[56]. The THC molecule is a neutral, lipophilic (having an affinity for fat) substance that readily crosses alveolar membranes when cannabis is smoked, resulting in near instantaneous appearance in blood and distribution to tissues.

In their review of the scientific evidence, authors John P. Morgan and Lynn Zimmer state that current research indicates that moderate smoking of cannabis appears to pose minimal danger to the lungs[57]. Like tobacco smoke, cannabis smoke contains a number of irritants and carcinogens. Because cannabis users typically smoke much less often than tobacco smokers and, over time, inhale much less smoke, the risk of serious lung damage should be lower in cannabis smokers[58]. The authors note there have been no reports of

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[55] M.A. Huestis, A.H. Sampson, B.J. Holicky, J.E. Henningheld, E.J. Cone, Characterization of the absorption phase of marijuana smoking, Clinical Pharmacology and Therapeutics 52, 31-41, 1992.

[56] B.R. Martin and E.J. Cone, Chemistry and pharmacology of cannabis, in H. Kalant, W. Corrigall, W. Hall,
R. Smart (eds.), The Health Effects of Cannabis, Addiction Research Foundation, Toronto, 1999.

[57] J.P. Morgan and L. Zimmer, Marijuana Myths, Marijuana Facts: A review of the scientific evidence, 1997.

[58] T. Wu et al., Pulmonary hazards of smoking marijuana as compared with tobacco, New England Journal of Medicine 318,347-51, 1988.

lung cancer related solely to cannabis. However, because researchers have found precancerous changes in cells taken from the lungs of heavy cannabis smokers, the possibility of lung cancer from cannabis cannot be ruled out[59]. Unlike heavy tobacco smokers, heavy cannabis smokers exhibit no obstruction of the lung's small airways, indicating that people might not develop emphysema from smoking cannabis.

Except for their active ingredients – nicotine in tobacco and over 60 cannabinoids in cannabis tobacco smoke and cannabis smoke are similar[60]. However, cannabis smoke contains substantially more particulate matter and may contain more of some carcinogens (e.g., benzopyrene) than does tobacco smoke[61 62]. The tar phase of the smoke of cannabis has about 50 percent more of some of the carcinogens than a comparable quantity of unfiltered tobacco[63]. Adverse respiratory symptoms include chronic cough, phlegm, wheezing, and episodes of bronchitis. However, cannabis-only smokers report fewer of these symptoms than tobacco smokers[64 65]. In a review of records from the Kaiser Permanente Medical Care Program, researchers found that people who smoked cannabis daily, and did not smoke tobacco, were only slightly more likely than nonsmokers to make outpatient visits for respiratory illnesses. During a six-year period, 36 percent of daily cannabis smokers sought treatment for colds, flu and bronchitis. The rate among nonsmokers was slightly lower at 33 percent[66].

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[59] S.H. Barsky, M.D. Roth, E.C. Kleerup, M. Simmons, D.P. Tashkin, Histiopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco, Journal of the National Cancer Institute 90, 1198-1205, 1998.

[60] G.I. Huber et al., Marijuana and tobacco smoke: Gas-phase cytoxins, Pharmacology Biochemistry and Behaviour 40, 629-36, 1991.

[61] Institute of Medicine, Marijuana and Health, Washington DC, National Academy Press, 1982.

[62] C. Leuchtenberger, Effects of marijuana (cannabis) smoke on cellular biochemistry of in vitro test systems, in K.O. Fehr and H. Kalant (eds.), Cannabis and Health Hazards, 127-223, Addiction Research Foundation, Toronto, 1983.

[63] D.P. Tashkin, Cannabis effects on the respiratory system, in H. Kalant, et al. (eds), The Health Effects of Cannabis, Addiction Research Foundation, 1999, for Cannabis: A Health Perspective and Research Agenda, World Health Organization, 1997.

[64] D.P. Tashkin et al., Effects of habitual use of marijuana and/or cocaine on the lung, 63-87, in N. Chiang and
R.L. Hawkins (eds.), Research Findings on Smoking of Abused Substances, Rockville MD, National Institute on Drug Abuse, 1990.

[65] D.L. Sherrill et al., Respiratory effects of non-tobacco cigarettes: A longitudinal study in the general population, International Journal of Epidemiology 20, 132-37, 1991.

[66] M.R. Polen, Health care use by frequent marijuana smokers who do not smoke tobacco, Western Journal of Medicine 158, 596-601, 1993.

Despite the reasonableness of the hypothesis, it has been difficult to investigate the contribution of heavy cannabis smoking to diseases of the respiratory system[67]. Tobacco smoking is known to cause diseases such as bronchitis, emphysema, and various forms of cancer affecting the lung, oral cavity, trachea, and esophagus[68]. Not only is it difficult to disentangle the effects of cannabis from those of tobacco smoking in those who smoke both, but in terms of current and lifetime exposure, variations in the quality and potency make it difficult to examine the long-term risk of developing various respiratory diseases. As well, the long latency period between exposure and development of the disease actually exceeds the length of time since cannabis smoking became widespread in western societies.

Bronchitis and airways obstruction

The most convincing evidence that chronic cannabis use may contribute to impaired lung function and symptoms of respiratory disease comes from a series of prospective controlled studies conducted by D.P. Tashkin and his colleagues since the mid-1970s.

These studies found that the prevalence of bronchitis symptoms of cough, sputum and wheeze is higher among all types of smokers than among nonsmokers, and that there was an additive adverse effect of cannabis and tobacco smoking on these symptoms. They have also shown that subjects who smoked had more prevalent and severe histopathological (diseased tissue) abnormalities than nonsmokers.

Bloom et al.[69] have reported a cross-sectional epidemiological study that broadly confirmed the findings of Tashkin and his colleagues. There were mean differences in forced respiratory volume and forced vital capacity, with those who had never smoked

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[67] G.I. Huber, D.E. Griffith, P.M. Langsjoen, The effects of marijuana on the respiratory and cardiovascular systems, in G. Chesher, P Consroe and R. Musty (eds.), Marijuana: An International Research Report, Canberra, 1988.

[68] D. English, C.J.D. Holman, et al., The Quantification of Drug-Caused Morbidity and Mortality in Australia, Canberra, Commonwealth Department of Human Services and Health, 1995.

[69] J.W. Bloom, W.T. Kaltenborn, P. Paoletti, A. Camilli and M.D. Leibowitz, Respiratory effects of non-tobacco cigarettes, British Medical Journal 295, 1516-1518, 1987.

having the best functioning, followed by current tobacco smokers, current non-tobacco smokers, and current smokers of both tobacco and non-tobacco cigarettes. Non-tobacco smoking alone had a larger effect on all flow indices than tobacco smoking alone, and the effect of both types of smoking was additive.

In 1997, Tashkin et al., reporting on rates of decline in respiratory function over eight years among cannabis and tobacco smokers, found that tobacco smokers showed the greatest rate of decline in respiratory function. The rate of decline in cannabis-only smokers did not differ from that of nonsmokers. This was in contrast to a follow-up study of the Tucson cohort[70] which found a greater rate of decline in respiratory function among cannabis-only smokers than among tobacco smokers, and additive effects of tobacco and cannabis smoking. The studies of Tashkin et al. and Bloom et al. are consistent in showing that chronic cannabis smoking increases the prevalence of bronchitis symptoms, but they disagree in their findings on the rate of decline in respiratory function with cannabis smoking.

For all smoking-related diseases, what matters most is the dose of smoke inhaled over time[71].

Researchers at UCLA have detected precancerous changes in bronchial cells taken from heavy long-term cannabis smokers[72]. Other researchers have found greater cell pathology in people who smoke both cannabis and tobacco than in people who smoke only one or the other[73]. It is possible that people who smoke both cannabis and tobacco heavily have an increased risk of lung cancer.

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[70] D.L. Sherrill, M. Krzyzanowski, J.W. Bloom and M.D. Leibowitz, Respiratory effects of non-tobacco cigarettes: A longitudinal study in general population, International Journal of Epidemiology 20, 132-137, 1991.

[71] G.L. Huber et al., The effects of marijuana on the respiratory and cardiovascular systems, 3-18, in G. Chesher et al. (eds.), Marijuana: An International Research Report, Canberra, Australian Government Publishing Service, 1988.

[72] S.E.G. Fligiel et al., Bronchial pathology in chronic marijuana smokers: A light electron microscope study, Journal of Psychoactive Drugs 20, 33-42, 1988.

[73] S.E.G. Fligiel et al., Pulmonary pathology in marijuana smokers, 43-47, in G. Chesher et al. (eds.), Marijuana: An International Research Report, Canberra, Australian Government Publishing Service, 1988.

Most people who smoke cannabis smoke far less than the cannabis smokers studied at UCLA, and probably do not ingest enough smoke to cause serious lung damage. In 1994, of adults in the United States who said they had used cannabis during the previous year, nearly one-half said they had not used it at all during the previous month. Among past-month cannabis users, 55 percent said they had used it on four or fewer occasions. Only 0.8 percent of Americans reported using cannabis on a daily or near daily basis[74].

Heavy frequent cannabis users might reduce the pulmonary risk by smoking higher-potency cannabis, which can produce desired psychoactive effects with less smoking. A study to determine if inhaling cannabis smoke through a water pipe would result in the delivery of less tar and particulate matter concluded this was untrue[75]. Heavy smokers will also often inhale cannabis deeply and hold their breath, rituals which increase the deposit of dangerous materials in the lungs, but increase psychoactive effects marginally, if at all[76].

The Institute of Medicine, in its 1999 report for the U.S. White House Office of National Drug Control Policy, conducted a review of the scientific evidence to assess the potential health benefits and risks of cannabis and its constituent cannabinoids. On the issue of cannabis smoke, the report entitled Marijuana and Medicine: Assessing the Science Base concluded that chronic cannabis smoking might lead to acute and chronic bronchitis and extensive microscopic abnormalities in the cells lining the bronchial passageways, some of which may be premalignant[77]. These respiratory symptoms are similar to those of tobacco smokers, and the combination of cannabis and tobacco smoking augments these

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[74] Substance Abuse and Mental Health Services Administration, National Household Survey on Drug Abuse: Main Findings 1994, Rockville MD, US Department of Health and Human Services, 46 and 49, 1996.

[75] R. Doblin, The MAPS / California NORML Marijuana Waterpipe / Vaporizer Study, Newsletter of the Multidisciplinary Association for Psychedelic Studies 5, 1,19-22, 1994.

[76] S. Agurell and K. Leander, Stability, transfer and absorption of cannabinoid constituents of cannabis (hashish) smoking, Acta Pharmaceutica Suecica 8, 391-402, 1971; J.P. Zacny and L.D. Chait, Breathold duration and response to marijuana smoke, Pharmacology, Biochemistry and Behaviour 33, 481-84, 1989; J. Zorilosa et al., Marijuana smoking: Effects of varying puff volumes and breatholding duration, Journal of Pharmacology and Experimental Therapeutics 272, 560-69, 1995.

[77] S.H. Barsky et al., Histopathologic and molecular alterations in bronchiol epithelium in habitual smokers of marijuana, cocaine, and/or tobacco, Journal of the National Cancer Institute 90, 1198-1205, 1998.

effects. The report noted that at that time it had not been established whether chronic smoking of cannabis caused chronic obstructive pulmonary disease (COPD), but there was probably an association[78].

Macrophages. Alveoli macrophages are the principal immune-effector cells in the lung and are primarily responsible for protecting the lung against infectious microorganisms, inhaled foreign substances, and tumour cells. They are increased during tissue inflammation. In a large sample of volunteers, habitual cannabis smokers had twice as many alveolar macrophages as nonsmokers, and smokers of both cannabis and tobacco had twice as many again[79]. Cannabis smoking also reduced the ability of alveoli macrophages to kill fungi, pathogenic bacteria, and tumour target cells. Furthermore, cannabis smoking depressed production of proinflammatory cytokines, which are important regulators of macrophage function. This cannabis-related decrease in inflammatory cytokine production might be a mechanism whereby cannabis smokers are less able to destroy fungal and bacteria organisms, as well as tumour cells.

The inability of alveolar macrophages from habitual cannabis smokers without apparent disease to destroy fungi, bacteria, and tumour cells, and to release proinflammatory cytokines, suggests that cannabis might be an immunosuppressant with clinically significant effects on host defense.

Studies by Tashkin et al. suggested that regular cannabis consumption reduces the respiratory immune response to invading organisms. Further, serious invasive fungal infections as a result of cannabis contamination have been reported among individuals who are immuno-compromised, including patients who were infected by AIDS. These findings suggest that frequent heavy cannabis consumption over prolonged periods can cause airway injury, lung inflammation, and impaired pulmonary defence against infection. Epidemiological studies that have adjusted for sex, age, race, education, and

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[78] J.E. Joy, S. Watson Jr. and J.A. Benson Jr. (eds.), Marijuana and Medicine: Assessing the Science Base, 111, 1999.

[79] R.G. Barbers et al., Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers, American Review of Respiratory Disease 135, 1271-1275.

alcohol consumption suggest that daily cannabis smokers have a slightly elevated risk of respiratory illness compared to nonsmokers. Other epidemiological studies in HIV-positive individuals have identified cannabis use as a significant risk factor for acquisition of opportunist and/or Kaposi's sarcoma.

Bronchial tissue changes. Habitual cannabis smoking is associated with changes in the lining of the human respiratory tract. Many cannabis or tobacco smokers have increased redness (erythema) and swelling (edema) of the airway tissues and increased mucous secretions[80]. In cannabis smokers the number and size of small blood vessels in the bronchial wall are increased, tissue edema is present, and the normal ciliated cells – which transport mucous toward the mouth by rapid wave-like motion – lining the inner surface of the bronchial wall are largely replaced by mucous-secreting goblet cells. Overproduction of mucous by the increased numbers of mucous-secreting cells in the presence of decreased numbers of ciliated cells tends to leave coughing as the only major mechanism to remove mucous from the airways; this might explain the relatively high proportion of cannabis smokers who complain of chronic cough and phlegm production[81].

Chronic Obstructive Pulmonary Disease (COPD). Researchers at UCLA report that "marijuana smokers probably will not develop emphysema[82]." All of the cannabis-only smokers in the sample are heavy users, smoking an average of three to four cannabis cigarettes per day for about fifteen years. Researchers looked for small airway obstruction by measuring the volume of air that people can expel from their lungs in one second. Over time, most tobacco smokers have shown increasing obstruction of the lung's small airways. Heavy cannabis smokers have not. In a 1997 paper reporting their latest findings, the researchers conclude that "in contrast to the accelerated annual rate of decline in lung function that occurs in regular tobacco smokers of comparable age …

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[80] S.E.G. Fligiel et al., Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco, Chest 112, 319-326, 1997.

[81] D. Tashkin, Effects of marijuana on the lung and its defenses against infection and cancer, School Psychology International 20, 23-37, 1999.

[82] D. Tashkin, quoted in L. Gagnon, Marijuana less harmful to lungs than cigarettes, Medical Post, Quebec,

findings in the present study do not support an association between even heavy, regular marijuana smoking and the development of chronic obstructive lung disease." In this paper, Tashkin et al. also report that in smokers of both tobacco and cannabis, there was no additive effect on airway obstruction. Indeed, smokers of both substances had less obstruction, probably because they smoked fewer tobacco cigarettes than tobacco-only smokers[83]. A recent study of 268 cannabis smokers in Australia supports the UCLA finding. After smoking cannabis on a daily or weekly basis for an average of nineteen years, the cannabis users had a lower prevalence of emphysema and asthma than the general population[84].

Still, there is conflicting evidence on whether regular cannabis use harms the small airways of the lungs. Bloom and co-workers[85] found that an average of one joint smoked per day significantly impaired the function of small airways. But Tashkin and co-workers [86] did not observe such damage among heavier cannabis users (three to four joints per day for at least ten years), although they noted a narrowing of large central airways. Lung function test results from the 1987 study by Tashkin et al. indicated an association between the smoking of cannabis, but not tobacco, and an obstructive abnormality in the large, central airways, as indicated by abnormal increases in airway resistance and decreases in specific airway conductance.

Tashkin and co-workers' long-term study, which adjusted for age-related decline in lung function (associated with an increased risk for developing COPD), showed an accelerated

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6 September 1994.

[83] D.P. Tashkin, Heavy habitual marijuana smoking does not cause an accelerated decline in FEVI with age, American Journal of Respiratory and Critical Care Medicine 155, 141-48, 1997.

[84] P. Didcott et al., Long-Term Cannabis Users on the New South Wales North Coast, Canberra, Australian Government Publishing Service, 1997.

[85] J.W. Bloom et al., Respiratory effects of non-tobacco cigarettes, British Medical Journal 295, 516-518, 1987.

[86] D.P. Tashkin et al., Respiratory symptoms and lung function in habitual, heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers, American Review of Respiratory Disease 135, 209-216, 1987.

rate of decline in tobacco smokers but not in cannabis smokers[87]. Thus, the question of whether usual cannabis smoking habits are enough to cause COPD remains open.

Carcinogenic effect

THC does not appear to be carcinogenic. There are no epidemiological or aggregate clinical data showing higher rates of lung cancer in people who smoke cannabis. In laboratory petri dishes, THC does not cause cellular changes of the sort associated with cancer[88]. However, cannabis smoke – like tobacco smoke – does[89]. Some chemists reported in the 1970s that, compared to tobacco, cannabis had higher levels of one cancer-causing chemical, benzopyrene[90]. However, other chemists have found more benzopyrene in tobacco[91]. Neither form of smoke may be inherently safer or more dangerous than the other.

The work of Fligiel et al.[92] has indicated that histopathological changes of the type that are believed to be precursors of carcinoma can be observed in the lung tissue of chronic cannabis smokers. These observations have received support from case reports of cancers of the upper aerodigestive tract in young adults who have been chronic cannabis smokers. The case reports include:

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[87] D.P. Tashkin et al., Heavy habitual marijuana smoking does not cause an accelerated decline in FEV with age, American Journal of Respiratory and Critical Care Medicine 155, 141-148, 1997.

[88] H. Glatt et al., elta-1-Tetrahydrocannabinol and i Alpha, 2-Alpha-Epoxyhexahydrocannabinol: Mutagenicity Investigation in the Ames Test, Mutation Research 66, 329-35, 1979; S. Zimmerman and A.M. Zimmerman, Genetic effects of marijuana, International Journal of the Addictions 25, 19-33, 1990-91.

[89] C. Leuchtenberger, Effects of marijuana (cannabis) smoke on cellular biochemistry of in vitro test systems, 177-224, in K.O. Fehr and H. Kalant (eds.), Cannabis and Health Hazards, Toronto, Addiction Research Foundation, 1983.

[90] M. Novotny et al., Possible basis for the higher mutagenicity of marijuana smoke as compared to tobacco smoke, Experientia 32, 280-82, 1975; D. Hoffman et al., On the carcinogenicity of marijuana smoke, Recent Advances in Phytochemistry 9, 63-81, 1975.

[91] R.G. Harvey, Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity, Cambridge, Oxford University Press, 1991.

[92] S.E.G. Fligiel et al., Pulmonary pathology in marijuana smokers, in G. Chesher et al. (eds), Marijuana: An International Research Report, National Campaign Against Drug Abuse, Monograph 7, 43-48, Canberra, Australian Government Publishing Service, 1988.

- thirteen cases of advanced head and neck cancer occurring in young adults under forty years of age, eleven of whom had been daily cannabis smokers[93];
- ten cases of upper respiratory tract cancer occurring in adults under the age of forty years over a four-year period, seven of whom were probable regular cannabis smokers[94]; and
- two cases of squamous cell carcinoma of the tongue in men aged thirty-seven to fifty-two years, whose only shared risk factor was a history of long-term daily cannabis use[95].

These case reports provide limited support for the hypothesis that cannabis use is a cause of upper respiratory cancers. None of them compare the prevalence of cancer in cases with that in a control sample, and cannabis exposure was not assessed in a standardized way or in ignorance of case or control status - all standard controls to minimize bias in case-control studies of cancer etiology[96]. Interpretation is complicated by the fact that many of these patients also smoked tobacco, and were alcohol consumers, both risk factors for cancers of the upper aerodigestive tract, although the average age of onset in smokers and drinkers is over sixty, rather than under forty years.

Nonetheless, there is a consistency about these reports that bears further study to compare the proportions of cannabis smokers among patients with cancers of the upper aerodigestive tract and appropriate controls. Chronic cannabis smokers who began their use in the early 1970s are now entering the period of risk for such cancers.

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[93] P.J. Donald, Marijuana and upper aerodigestive tract malignancy in young patients, in G. Nahas and C. Latour (eds.), Physiopathology of Illicit Drugs: Cannabis, Cocaine, Opiates, 39-54, Oxford, 1991; Advanced malignancy in the young marijuana smoker, in H. Friedman et al. (eds.), Drugs of Abuse, Immunity and Immunodeficiency, 33-36, London, 1991.

[94] F.M. Taylor, Marijuana as a potential respiratory tract carcinogen: A retrospective analysis of a community hospital population, Southern Medical Journal 81, 1213-1216, 1988.

[95] G.A. Caplan and B.A. Brigham, Marijuana smoking and carcinoma of the tongue: Is there an association?, Cancer 66, 1005-1006, 1990.

[96] W. Hall et al., Epidemiology of cannabis use and its consequences, in H. Kalant et al. (eds.), The Health Effects of Cannabis, Toronto, Addiction Research Foundation, 1999.

From the evidence to date, the most likely long-term consequences of prolonged heavy cannabis use would appear to be not too different from the risks associated with long-term tobacco use, namely, cancers of the respiratory tract and also certain other sites (including the bladder, esophagus, mouth and tongue) following distribution of individual pyrolysis (chemical decomposition) products via the bloodstream to all parts of the body[97].

In the Cannabis Report released in 1999 by the Swiss Federal Commission for Drug Issues (EKDF), it was noted that cannabis is probably the most widely smoked substance in the world after tobacco. In addition to the nicotine in tobacco and the cannabinoids in cannabis, the matter inhaled from both substances contains a large number of other compounds which irritate the respiratory tract and may have carcinogenic (cancer-causing) properties[98].

The effects of tobacco and cannabis on the respiratory system are very probably not additive[99],
or in other words they cannot simply be added together. However, the cannabis smoker inhales more deeply than the tobacco smoker, allowing four times the quantity of tar to enter the lungs[100]. Bronchial irritation and inflammation, reduced macrophage and cilia activity (making the removal of particles from the lungs more difficult), and changes to the mucous lining of the respiratory tract have been observed in heavy users of hashish. In general, studies of longstanding cannabis smokers have demonstrated damage to the mucosa in the trachea and bronchial tubes[101].

Smoking cannabis products is therefore assumed to be associated with an increased risk of

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[97] D. MacPhee, Effects of marijuana on cell nuclei, in H. Kalant et al. (eds.), The Health Effects of Cannabis, Toronto, Addiction Research Foundation, 1999.
[98] R.M. Julien, Drugs and Pharmacology, Spektrum Verlag, Heidelberg, 1997.
[99] World Health Organization, Cannabis: A Health Perspective and Research Agenda, 1997.
[100] Hagers Handbuch der Pharmazeutischen Praxis, Cannabis Monograph, 5th edition, Springer, Berlin, 1992.
[101] World Health Organization, Cannabis: A Health Perspective and Research Agenda, 1997.

lung and bronchial cancers. However, it is difficult to consider the carcinogenicity of cannabis
in the lung in isolation because hashish and marijuana smokers are usually also cigarette smokers as well – quite apart from the fact that these two cannabis products are generally smoked in a mixture with tobacco anyway[102].

According to Tashkin et al., biochemical, cellular, immunologic, genetic, tissue, and animal studies provide a biologically plausible basis for the concern that cannabis may play a role in the development of respiratory cancer.

It is now clear that THC modulates the function of immune cells including lymphocytes, macrophages, and polymorphonuclear cells (PMNs)[103]. Virtually every function examined from antibody production to phagocytosis (destruction of harmful material), is affected in some way by the drug, especially when *in vitro* (in an artificial environment of glass, such as a test tube) models are employed.

The health impact of cannabis-induced immunomodulation is still unclear. Few studies exist employing animal paradigms or human trials assessing the effects of cannabis exposure on host resistance to bacteria, viruses, and tumours. The studies that have been done in this area employed rather high cannabinoid doses and therefore have limited relation to the cannabis smoking experience.

II.2 Psychomotor Effects and Driving

The main potential adverse acute effects of cannabis use arise from its effects on psychomotor performance. Intoxication produces dose-related impairments in a wide range of cognitive and behavioural functions that are relevant to a skilled performance

[102] Hagers Handbuch der Pharmazeutischen Praxis, Cannabis Monograph, 5th edition, Springer, Berlin, 1992.
[103] T.W. Klein, Cannabis and immunity, in H. Kalant et al., The Health Effects of Cannabis, Toronto, Addiction Research Foundation, 1999.

such as driving an automobile or operating machinery[104]. These include slowed reaction time and information processing, impaired perceptual/motor coordination and motor performance, impaired short-term memory, attention, signal detection and tracking behaviour, and slowed time perception[105].

The negative effects of cannabis on the performance of psychomotor tasks are almost always related to dose[106]. The effects are generally greater, more consistent and more persistent in the case of difficult tasks requiring sustained attention. The acute effects of cannabis doses that are subjectively equivalent to or higher than the usual recreational doses on driving performance in laboratory simulators and over standardized driving courses resemble those of doses of alcohol that produce blood alcohol concentrations between 0.07 and 0.10 percent[107] [108] [109].

The most important aspect is how long cannabis is likely to affect the ability to drive after it

has been taken. Some studies have noted that effects on driving behaviour are present up to an hour after smoking, but do not continue for extended periods[110]. Other studies conclude that the reduced reaction speed and altered perception, alertness and ability to process information mean that cannabis is likely to impair the ability to drive as much as two to four hours after being smoked (up to a maximum of eight hours)[111] [112] [113] [114].

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[104] B.E. Belgrave and others, The Effect of –trans-delta-9-THC, alone and in combination with ethanol, on human performance, Psychopharmacology, 53-60, 1979.

[105] L.D. Chait and J. Pierri, Effects of smoked marijuana on human performance: A critical review, in Marijuana/Cannabinoids: Neurobiology and Neurophysiology, L. Murphy and A. Bartke (eds.), CRC Press, Boca Raton, 387-423, 1992.

[106] Ibid.

[107] R. Hansteen and others, Effects of cannabis and alcohol on automobile driving and psychomotor tracking, Annals of the New York Academy of Sciences, vol.282, 240-256, 1976.

[108] R.C. Peck and others, The effects of marijuana and alcohol on actual driving performance, in Alcohol, Drugs and Driving, vol.2, 135-154, 1986.

[109] A. Smiley, Marijuana: On-road and driving simulator studies, in Alcohol, Drugs and Driving, vol.2, 121-134, 1986.

[110] A.M. Smiley, Y.I. Noy and W. Tostowaryk, The effects of marijuana, alone and in combination with alcohol, on driving an instrumented car, Proceedings of the 10th International Conference on Alcohol, Drugs and Traffic Safety, Amsterdam, 203-206, 1983.

[111] Adams, Martin 1996.

[112] Hollister 1986.

[113] P.X. Iten, Fahren unter Drogen – oder Medikamenteneinfluss, Institute for Forensic Medicine, University of Zurich, 1994.

While cannabis impairs performance in laboratory and simulated driving settings[115], there is no clear evidence that these impairments increase the risk of involvement in traffic accidents. Studies of the effects of cannabis on actual on-road driving performance have found slight impairments[116 117]. It has been proposed that cannabis-intoxicated persons drive more slowly, perhaps because they are more aware of their level of psychomotor impairment than alcohol-intoxicated drinkers, who generally drive at faster speeds[118 119].

This failure to prove a direct role for cannabis in traffic accidents does not exonerate it. Although no controlled epidemiological studies have established that cannabis users are at increased risk of traffic accidents, the role of cannabis in such accidents is likely to remain uncertain because the issue is difficult to research. Cannabis use has been detected in surveys of truck drivers[120], drivers in Australia[121], motor vehicle collision victims[122], homicide victims and vehicular fatalities[123 124], and trauma patients[125]. The frequency of detection of cannabinoids ranged from 6 to 34 percent. Blood levels of cannabinoids do not indicate whether a driver or pedestrian was intoxicated with cannabis at the time of an

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[114] WHO 1997.
[115] G. Chesher, Cannabis and road safety: An outline of research studies to examine the effects of cannabis on driving skills and actual driving performance, in The Effects of Drugs (Other than Alcohol) on Road Safety, Melbourne, Road Safety Committee, Parliament of Victoria, 1995, 67-96.
[116] L. Sutton, The effects of alcohol, marijuana and their combination on driving ability, Journal of Studies on Alcohol, vol.44, 438-445, 1983.
[117] H.W.J. Robbe, Influence of Marijuana on Driving, Masstricht, University of Limberg, Institute for Human Psychopharmacology, 1994.
[118] Smiley 1986.
[119] Robbe 1994.
[120] A.K. Lund and others, Drug use by tractor-trailer drivers, Journal of Forensic Sciences, vol. 33, 648-661, 1988.
[121] S. McLean and others, Drugs, alcohol and road accidents in Tasmania, Medical Journal of Australia, vol. 147, 6-11, 1987.
[122] G. Stoduto and others, Alcohol and drug use among motor vehicle collision victims admitted to a regional trauma unit: Demographic, injury, and crash characteristics, Accident Analysis and Prevention, vol. 25, 411-420, 1993.
[123] J.C. Garriott, M.V.J. Di and R.G. Rodriguez, Detection of cannabinoids in homicide victims and motor vehicle fatalities, Journal of Forensic Sciences, vol. 31, 1274-1282, 1986.
[124] C. Soderstrom and S. Carson, Update: Alcohol and other drug use among vehicular crash victims, vol. 37, 541-545, 1988.
[125] Ibid.

accident, and many drivers with cannabinoids in their blood were found to be also intoxicated with alcohol at the time of the accident[126].

Factors other than psychomotor performance also contribute to the danger of drug use when driving. Foremost among these is the user's readiness to take risks when intoxicated, which the available evidence suggests is reduced by cannabis intoxication, in contrast with alcohol intoxication which consistently increases risk-taking[127] [128] [129]. The fact that cannabis is rarely found on its own in fatalities is consistent with the epidemiological evidence that cannabis is most often used in combination with alcohol[130] [131] [132]. The separate effects of alcohol and cannabis on psychomotor impairment and driving performance are approximately additive[133] [134], a fact that should be emphasized in health education about cannabis use and driving.

II.3 Genetic Effects and Effects on Reproduction and Pregnancy

An increased rate of chromosomal abnormalities, mainly chromosome breaks and translocations, has been observed among marijuana smokers[135]. Changes at the cellular level were
reversible in clinical trials[136]. The clinical significance of these observations is disputed, not
least because similar changes can occur in individuals taking commonly prescribed drugs

[126] Smiley 1986.
[127] Ibid.
[128] Chesher 1995.
[129] Robbe 1994.
[130] A.S. Carlin and R.D. Post, Patterns of drug use among marijuana smokers, Journal of the American Medical Association, vol. 218, 867-868, 1971.
[131] M. Hochhauser, Alcohol and marijuana consumption among undergraduate polydrug users, American Journal of Drug and Alcohol Abuse, vol. 4, 65-76, 1977.
[132] W. McGlohlin, K. Jamison and S. Rosenblatt, Marijuana and the use of other drugs, Nature, vol. 228, 1227-1228, 1970.
[133] Smiley 1986.
[134] Chesher 1995.
[135] Hollister 1986.
[136] WHO 1997.

on a daily basis[137] [138]. The 1997 World Health Organization study on cannabis notes that the effects on the concentration of testosterone, estrogen and prolactin in plasma observed in animal experiments have not been reproduced unequivocally in clinical trials with humans. In
women, cannabis consumption leads to lower levels of follicle-stimulating hormone (FSH) and
luteinizing hormone (LH), and may affect the menstrual cycle, although these effects are evidently reversible and disappear once the drug is discontinued[139] [140].

Pregnancy

The good lipid solubility of the cannabinoids allows them to cross the placenta with ease, and they can be recovered from the fetus after just a few minutes. Animal experiments investigating the effects of cannabis consumption during pregnancy have produced varying
results. A major study of 12 000 women, 11 percent of whom used marijuana, found shorter
gestation periods, longer deliveries, lower birth weights and a higher rate of deformities[141] [142]. However, the impact of cannabis on birth weight is minor compared to the effect of cigarette smoking during pregnancy. Apart from these physical aspects, the possibility cannot be excluded that cannabis may affect the behaviour and cognitive functions (e.g., learning ability) of the child. Accordingly, the use of cannabis during pregnancy should be restricted as systematically as the consumption of alcohol and smoking[143] [144].

The United Nations ODCCP 1999 study on the health effects of cannabis concludes that the findings of epidemiological studies of the effects of cannabis use on human

[137] Hollister 1986.
[138] Maykut 1985.
[139] Hollister 1986.
[140] Maykut 1985.
[141] Hollister 1986.
[142] WHO 1997.
[143] Hagers Handbuch 1992.

development have been mixed for a number of reasons, firstly, because adverse reproductive outcomes and heavy cannabis use during pregnancy are both relatively rare, large sample sizes are required in order to detect adverse effects of cannabis use on fetal development, and many of the studies undertaken have been too small.

Secondly, the stigma associated with illicit drug use, especially during pregnancy, may discourage honest reporting, compounding the usual problem of the stage at which women are asked about their drug use being disregarded, that is, whether it is during early pregnancy, late in their pregnancy or even after the birth[145] If a substantial proportion of cannabis users are misclassified as non-users, any relationship between cannabis use and adverse outcomes will be attenuated, requiring even larger samples for its detection[146].

Thirdly, even with large samples, difficulties arise in interpreting any associations found between adverse pregnancy outcomes and cannabis use because cannabis users are more likely to use tobacco, alcohol and other illicit drugs during their pregnancy. They also differ from non-users in other ways (e.g., social class, education, nutrition) that contribute to an increased risk of adverse outcome of pregnancy[147]. Despite these difficulties, there is reasonable consistency in the findings that cannabis use in pregnancy is associated with reduced birth weight[148] and length at birth. This relationship has been found in the best controlled studies and has persisted after statistically controlling for potential confounding variables[149]. The effect is small, however, and cannot be unequivocally attributed to cannabis as against tobacco smoking or alcohol use during pregnancy.

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[144] Hollister 1986.
[145] N.L. Day, D.K. Wagener and P.M. Taylor, Measurement of substance use during pregnancy: Methodologic issues, in Current Research on the Consequences of Maternal Drug Abuse, 36-47.
[146] B. Zuckerman and others, Effects of maternal marijuana and cocaine use on fetal growth, New England Journal of Medicine, vol. 320, 762-768, 1989.
[147] K. Tennes and others, Marijuana: prenatal and postnatal exposure in the human, in Current Research on the Consequences of Maternal Drug Abuse, 48-60.
[148] G.T. Gibson, P.A. Baghurst and D.P. Colley, Maternal alcohol, tobacco and cannabis consumption and the outcome of pregnancy, Australian and New Zealand Journal of Obstetrics and Gynaecology, vol. 23, 15-19, 1983.
[149] E.E. Hatch and M.B. Bracken, Effect of marijuana use in pregnancy on fetal growth, American Journal of Epidemiology, vol. 124, 986-993, 1986.

The findings on the relationship between cannabis use and birth abnormalities are more mixed. Four studies have reported no increased rate of major congenital abnormalities among children born to women who use cannabis[150] [151] [152] [153]. One study has reported a fivefold increased risk of children with features resembling those found in fetal alcohol syndrome being born to women who reported using cannabis[154], but the study also found no relationship between self-reported alcohol use and features of fetal alcohol syndrome. This is doubly surprising because of other evidence on the adverse effects of alcohol and because the epidemiological data indicates that cannabis and alcohol use are associated[155]. The study by Zuckerman et al. provides the most convincing failure to find an increased risk of birth defects among women who used cannabis during pregnancy. It included a large sample of women with a substantial prevalence of cannabis use verified by urinalysis. There was a low rate of birth abnormalities among the cannabis users and no suggestion of an increase by comparison with the controls. But given the uncertainty, it would be unwise to exonerate cannabis as a cause of birth defects until larger, better controlled studies have been conducted.

Generally, there is uncertainty about whether cannabis smoking during pregnancy produces a small increase in the risk of birth defects. There is some animal evidence of such effects although these studies have usually involved very high doses by the oral route. The limited studies in humans have generally but not consistently produced null results[156] [157]. There is suggestive evidence that infants exposed *in utero* to cannabis may experience transient behavioural and developmental effects during the first few months

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[150] Zuckerman et al. 1989.
[151] Tennes et al.
[152] Gibson et al. 1983.
[153] R. Hingson and others, Effects of maternal drinking and marijuana use on fetal growth and development, Pediatrics, vol. 70, 539-546, 1982.
[154] Ibid.
[155] R. Norton and J. Colliver, Prevalence and patterns of combined alcohol and marijuana use, Journal of Studies on Alcohol, vol. 49, 378-380, 1988.
[156] Zuckerman et al. 1989.
[157] Hatch, Bracken 1986.

after birth[158] [159]. There are three studies that suggest an increased risk of certain types of childhood cancer (leukaemia, rhabdosarcoma and astrocytomas) in children born to women who reported using cannabis during their pregnancies[160]. None of the studies was a planned investigation of the association between these cancers and cannabis use, which in each case was one of a large number of the possible confounding variables measured. Their replication would indeed be advisable.

Dozens of studies have compared the newborn babies of women who used cannabis during pregnancy with the babies of women who did not. They have looked for differences in birth weight, birth length, head circumference, chest circumference, gestational age, neurological development, and physical abnormalities. Most of these studies have found no differences between babies exposed to cannabis prenatally and babies not exposed[161].

In examining older children for the effects of prenatal exposure to cannabis, a study of one-year-olds found no differences between cannabis-exposed and non-exposed babies on measures of health, temperament, personality, sleeping patterns, eating habits, psychomotor ability, physical development, or mental functioning[162]. In two studies, one of three-year-olds[163], the other of four-year-olds[164], there was no effect of prenatal cannabis exposure on children's overall IQ test scores.

Since 1978, psychologist Peter Fried and his colleagues have collected longitudinal data on prenatal cannabis exposure as part of the Ottawa Prenatal Prospective Study (OPPS).

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[158] P.A. Fried, Postnatal consequences of maternal marijuana use, in Current Research on the Consequences of Maternal Drug Abuse.
[159] P.A. Fried, Postnatal consequences of maternal marijuana use in humans, Annals of the New York Academy of Sciences, vol. 562, 123-132, 1989.
[160] L.I. Robinson and others, Maternal drug use and the risk of childhood nonlymphoblastic leukemia among offspring: An epidemiologic investigation implicating marijuana, Cancer, vol. 63, 1904-1911, 1989.
[161] F.R. Witter and J.R. Niebyl, Marijuana use in pregnancy and pregnancy outcome, American Journal of Perinatology 7, 1990.
[162] Tennes et al. 1985.
[163] N.L. Day et al., Effect of prenatal marijuana exposure on the cognitive development of offspring at age three, Neurotoxicology and Teratology 16, 1994.
[164] A.P. Streissguth et al., IQ at age four in relation to maternal alcohol use and smoking during pregnancy, Developmental Psychology 25, 1989.

Over the years, these researchers have administered hundreds of tests to the same group of children, assessing their physical development, psychomotor ability, emotional and psychological adjustment, cognitive functioning, intellectual capacity, and behaviour. Out of all the OPPS studies and all the tests given, researchers have found very few differences between cannabis-exposed and non-exposed children[165]. John P. Morgan and Lynn Zimmer, in their book entitled Marijuana Myths, Marijuana Facts: A review of the scientific evidence, suggest that despite the overwhelming similarities in the children of cannabis users and non-users, in their published reports OPPS researchers consistently highlight the occasional negative finding. Fried believes that these findings underestimate the harms of prenatal cannabis exposure, and he suggests that "more sensitive measures" are needed. Additional reports of harm based on the OPPS sample, which now includes fewer that thirty cannabis-exposed children, may be forthcoming, despite the fact that, according to Fried, the consequences of prenatal drug exposure typically diminish as children get older[166].

Fried estimates that prenatal drug exposure accounts for 8 percent or less of variance in children's scores on developmental and cognitive tests – and this estimate is for alcohol, tobacco and cannabis combined[167]. In essentially all studies, cannabis contributes less than alcohol or tobacco[168]. In addition, the findings differ from one study to another, and show no consistent relationship of fetal harm to either the timing or degree of cannabis exposure.

Sex hormones

In 1974, Robert Kolodny and his associates reported that frequent cannabis users had lower testosterone levels than occasional cannabis users[169]. Later, these researchers

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[165] P.A. Fried, Prenatal exposure to marijuana and tobacco during infancy, early and middle childhood: Effects and attempts at a synthesis, Archives of Toxicology 17, 1995.
[166] P.A. Fried, Prenatal exposure to tobacco and marijuana: Effects during pregnancy, infancy and early childhood, Clinical Obstetrics and Gynecology 36, 319-337, 1993.
[167] Ibid.
[168] N. Day et al., The effects of prenatal tobacco and marijuana use on offspring growth from birth through three years of age, Neurotoxicology and Teratology 14, 407-414, 1992.
[169] R.C. Kolodny et al., Depression of plasma testosterone levels after chronic intensive marijuana use, New England Journal of Medicine 290, 872-874, 1974.

reported temporary reductions in testosterone immediately after men smoked cannabis[170]. In numerous other studies, however, researchers have found no reduction in testosterone after men smoked cannabis, even very high doses[171]. Studies of men in the general population have also failed to find differences in the testosterone levels of cannabis users and non-users[172].

In examining cannabis' impact on the quantity and quality of sperm, Kolodny reported in his 1974 study that frequent cannabis users had lower sperm counts that occasional users; however, this study failed to control for sexual activity in the days prior to examination, a factor known to affect sperm concentrations[173]. In another study, men spent thirty days in a closed laboratory where they smoked up to twenty cannabis cigarettes per day. Although some decrease in sperm concentrations and sperm motility was detected, the values were not outside normal ranges. The slight differences that did occur were reversed when the experiment was ended[174].

In a laboratory study measuring female sex hormones following cannabis administration, some subjects displayed lowered prolactin levels, but the effect was of short duration and concentrations were never below normal[175]. More recently, a study of women in the general population found no effect of cannabis on any hormones, even among high-dose frequent users[176].

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[170] R.C. Kolodny et al., Depression of plasma testosterone with acute marijuana administration, in M.C. Braude and S. Szara (eds.), Pharmacology of Marijuana, New York, Raven Press, 217-225, 1976.
[171] E.J. Cone et al., Acute effects of marijuana on hormones, subjective effects and performance in male human subjects, Pharmacology, Biochemistry and Behaviour 24, 1749-1754, 1986.
[172] R.I. Block et al., Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women, Drug and Alcohol Dependence 28, 121-128, 1991.
[173] A.M. Chauson and B. Safer, Marijuana and sex, New England Journal of Medicine 291, 1974.
[174] W.C. Hembree et al., Changes in human spermatozoa associated with high dose marijuana smoking, in G.G. Nahas and W.D.M. Paton (eds.), Marijuana: Biological Effects, Oxford, Pergamon Press, 429-439, 1979.
[175] J.H. Mendelson et al., Acute effects of marijuana smoking on prolactin levels in human females, Journal of Pharmacology and Experimental Therapeutics 232, 220-222, 1985.
[176] Block et al. 1991.

In both male and female animals, a single large dose of THC has more impact on sex hormones than repeated administration. When animals are exposed to THC for weeks or months, tolerance develops, and cannabis loses its impact. In one study of female primates, hormone levels and ovulation cycles were suppressed initially, but after continual daily dosing with THC, they returned to normal[177].

There is no convincing evidence of infertility related to cannabis consumption in humans. In one survey, women who were seeking professional help for infertility reported higher rates of cannabis use than a matched sample of fertile women. However, the difference was slight (61 percent versus 53 percent), and was even lower when researchers controlled for lifestyle factors associated with infertility[178]. In a recent study, researchers found no association between cannabis use and early pregnancy loss[179].

There are no epidemiological studies showing that men who use cannabis have higher rates of infertility than men who do not. Nor is there evidence of diminished reproductive capacity among men in countries where cannabis use is common[180] [181]. It is possible that cannabis could cause infertility in men who already have low sperm counts. However, it is likely that regular cannabis users develop tolerance to cannabis' hormonal effects.

II.4 Effects on the Immune System

Animal experiments and cell cultures have shown cannabinoids to affect B- and T-lymphocytes (e.g., increased susceptibility to infection), although these effects were not

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[177] C.G. Smith et al., Tolerance develops to the disruptive effects of THC on the primate menstrual cycle, Science 219, 1453-1455, 1983.
[178] B.A. Mueller et al., Recreational drug use and the risk of primary infertility, Epidemiology 1, 195-200, 1990.
[179] A.J. Wilcox et al., Risk factors for early pregnancy loss, Epidemiology 1, 382-385, 1990.
[180] E.L. Abel, Marijuana and sex: A critical survey, Drug and Alcohol Dependence 8, 1-22, 1981.
[181] J.R.L. Ehrenkranz and W.C. Hembree, Effects of marijuana on male reproductive function, Psychiatric Annals 16, 243-249, 1986.

pronounced, were fully reversible, and were induced only by very high concentrations in excess of those used by individuals to achieve psychotropic effects[182] [183] [184]. The human immune system is relatively resistant to the immunosuppressive effects of the cannabinoids, and the research carried out so far supports the therapeutic use of delta-9-THC even in patients whose immune system has been compromised by other diseases (AIDS, cancer).

The 1999 United Nations ODCCP study on the health effects of cannabis notes that THC can produce alterations in cell metabolism and DNA synthesis *in vitro*[185], and cannabis smoke is mutagenic *in vitro* and *in vivo*, and is therefore potentially carcinogenic[186]. These facts suggest that a likely health risk of smoking cannabis is the development of cancer after long-term exposure to cannabis smoke at the sites that receive maximum exposure, namely, the lung and upper aerodigestive tract. There is also evidence that cannabinoids impair the cell-mediated and humoral (body fluid) immune systems in rodents, decreasing resistance to infection by bacteria and viruses. Further evidence indicates that the non-cannabinoid components of cannabis smoke impair the functioning of alveolar macrophages, the first line of the body's defence system in the lungs. The relevance of these findings to human health is uncertain: high doses of THC have often been used in animal studies and the problem of extrapolating from the effects of such doses to those used by humans is complicated by the possibility that tolerance may develop to these effects[187].

The limited experimental and clinical evidence on immune effects in humans is mixed, the adverse effects suggested by a small number of early studies remaining unreplicated

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[182] Adams, Martin 1996.
[183] Hollister 1986.
[184] WHO 1997.
[185] E. Bloch, Effects of marijuana and cannabinoids on reproduction, endocrine function, development, and chromosomes, in Cannabis and Health Hazards: Proceedings of an ARF/WHO Scientific Meeting, 355-432.
[186] C. Leuchtenberger, Effects of marijuana (cannabis) smoke on cellular biochemistry of in vitro test systems, in Cannabis and Health Hazards: Proceedings of an ARF/WHO Scientific Meeting.
[187] L.E. Hollister, Marijuana and immunity, Journal of Psychoactive Drugs, vol. 24, 159-164, 1992.

by later research[188]. At present, there is no conclusive evidence that consumption of cannabinoids predisposes humans to immune dysfunction, as measured by reduced numbers or impaired functioning of T-lymphocytes, B-lymphocytes or macrophages, or reduced immunoglobulin levels.

There is no epidemiological evidence of increased rates of infectious disease among chronic heavy cannabis users analogous to that seen among healthy young homosexual men in the early 1980s when AIDS was first recognized. Two prospective studies of human immunodeficiency virus (HIV)-positive homosexual men have found that cannabis use was not associated with an increased risk of progression to AIDS[189]. Given the long history of large-scale cannabis use by young adults in western societies, the absence of any epidemics of infectious disease makes it unlikely that cannabis smoking produces major impairments in the immune system.

More difficult to exclude is the possibility that chronic heavy cannabis use produces minor impairments in immunity. Such effects would produce small increases in the incidence of common bacterial and viral illnesses among chronic cannabis users. A recent epidemiological study by Polen et al.[190], which compared health service utilization by "nonsmokers" and "daily cannabis-only smokers," suggested a small increase among cannabis smokers in the rate of presentation of respiratory conditions. This finding remains suggestive, however, because infectious and non-infectious respiratory conditions were considered together. The finding that cannabinoids produce minor impairments in immunity would therefore cast doubt on the therapeutic value of cannabinoids in immunologically compromised patients, such as those undergoing cancer chemotherapy or those with AIDS. AIDS patients who use cannabis do face an increased risk of contracting the pulmonary disease aspergillosis. This disease, caused by fungal

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[188] Ibid.
[189] R.A. Coates and others, Cofactors of progression to acquired immunodeficiency syndrome in a cohort of male sexual contacts of men with human immunodeficiency virus disease, American Journal of Epidemiology, vol. 132, 717-722, 1990.
[190] M. Polen and others, Health care use by frequent marijuana smokers who do not smoke tobacco, Western Journal of Medicine, vol. 158, 596-601, 1993.

spores that sometimes contaminate improperly stored cannabis[191], has only been reported in smokers with immune-suppression disorders. Careful screening of cannabis supplies for aspergillus spores and other contaminants would make cannabis safer for AIDS patients.

III. Psychological Effects of Cannabis

III.1 Effects on Human Behaviour and Central Nervous System Functions

Cannabis and the Brain

Employing modern brain imaging technologies, such as the CAT scan, researchers have found no evidence of brain damage in human cannabis users[192] [193], even in subjects smoking an average of nine cannabis cigarettes per day. Brain wave patterns of chronic cannabis users and non-users, produced by standard electroencephalographic (EEG) tests, cannot be distinguished by visual examination[194]. Using computer-generated quantitative analysis, however, one group found differences in the distribution of certain brainwave frequencies between heavy cannabis users and occasional users[195] - differences of unknown significance. Using a specialized EEG technique, researchers have also measured the amplitude of a particular brain wave (the P300) in response to auditory and visual stimuli. One study found minor abnormalities in this "event-related potential" (ERP) of chronic cannabis users[196]. However, in the only ERP study to use medically and

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[191] M.J. Chusid et al., Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease, Annals of Internal Medicine 82, 1975.
[192] J. Kuehnle et al., Computed tomographic examination of heavy marijuana smokers, Journal of American Medical Association 237, 1977.
[193] J. Hannerz and T. Hindmarsh, Neurological and Neuroradiological Examination of Chronic Cannabis Smokers, Annals of Neurology 13, 207-210, 1983.
[194] F.A Struve and J.J. Straumanis, Electroencephalographic and evoked potential methods in human marijuana research: Historical review and future trends, Drug Development Research 20, 369-388, 1990.
[195] F.A. Struve et al., Persistent topographic quantitative EEG sequelae of chronic marijuana use: A replication study and initial discriminant function analysis, Clinical Electroencephalography 25, 63-73, 1994.
[196] N. Solowij et al., Effects of long-term cannabis use on selective attention: An event-related potential study, Pharmacology, Biochemistry and Behaviour 40, 683-688, 1991.

psychiatrically healthy subjects, and to institute controls for age, researchers found no difference in the ERP responses on chronic cannabis users and non-users[197].

Cognitive Effects

The available evidence suggests that even long-term heavy use of cannabis produces no severe or grossly debilitating impairment of cognitive function[198] [199]. There is no evidence, for example, that it produces anything comparable to the cognitive impairments found in chronic heavy alcohol drinkers; if it did, research to date should have detected it[200]. There is some clinical and experimental evidence, however, that the long-term use of cannabis may produce more subtle cognitive impairment in the higher cognitive functions of memory, attention and organization, and the integration of complex information[201] [202]. The evidence suggests that the longer the period of cannabis use, the more pronounced the cognitive impairment [203]. It remains to be determined how significant these impairments are for everyday functioning and whether they are reversed after an extended period of abstinence from cannabis.

A suspicion that chronic heavy cannabis use may cause gross structural brain damage was raised by a single poorly controlled study which reported that cannabis users had enlarged cerebral ventricles[204]. Since then a number of better controlled studies using more sophisticated methods of investigation have consistently failed to provide evidence of structural change in the brains of heavy long-term cannabis users[205] [206] [207]. These

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[197] G. Patrick et al., Auditory and visual P-300 event-related potentials are not altered in medically and psychiatrically normal chronic marijuana users, Life Sciences 56, 2135-2140, 1995.
[198] W.E. Carter, W. Coggins and P.L. Doughty, Cannabis in Costa Rica: a study of chronic marijuana use, Philadelphia, Institute for the Study of Human Issues, 1980.
[199] K.O. Fehr and H. Kalant, Long-term effects of cannabis on cerebral function: A review of the clinical and experimental literature, in Cannabis and Health Hazards, K.O. Fehr and H. Kalant (eds.), Toronto, Addiction Research Foundation, 501-576, 1983.
[200] Hall et al. 1994.
[201] H. Pope and D. Yurgelun-Todd, The residual cognitive effects of heavy marijuana use in college students, Journal of Psychoactive Drugs, vol. 20, 57-65, 1996.
[202] N. Solowij, P.T. Michie and A.M. Fox, Differential impairments of selective attention due to frequency and duration of cannabis use, Biological Psychiatry, vol. 37, 731-739, 1995.
[203] Ibid.
[204] A.M.G. Campbell and others, Cerebral atrophy in young cannabis smokers, The Lancet, vol. 2, 1219-1224, 1971.
[205] Hall et al. 1994.

negative results are consistent with the evidence that any cognitive effects of chronic cannabis use are subtle and hence unlikely to be manifested as gross structural changes in the brain.

Although experimental studies have identified many effects of cannabis administration, it is difficult to predict how and to what degree these effects could disrupt real-life functioning, especially in naive users. Previous experience with cannabis could possibly attenuate its acute effects through a variety of tolerance mechanisms, or might even result in an exaggerated response, relative to a naive user, through accumulated toxicity. Although the use of cannabis-naive subjects is experimentally desirable, it often may not be allowed for ethical reasons.

A variety of non-pharmacological factors can modulate the effects of cannabis and these factors are often uncontrolled, unreported or non-standardized across experimental studies. The subject's personality and attitude toward cannabis, experience with tasks similar to the experimental tasks, variations in the physical environment, and the consequences (e.g., rewards) for completing the experimental tasks correctly vary from study to study.

The existence of a naturally occurring cannabinoid-like substance in the human brain (anandamide) signifies that this substance plays some role in our normal functioning[208]. It has been suggested that anandamide may play a role in movement or motor control[209], in sleep[210], and in the modulation of attention[211].

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[206] B.T. Co and others, Absence of cerebral atrophy in chronic cannabis users: Evaluation by computerized transaxial tomography, Journal of the American Medical Association, vol. 237, 1229-1230, 1977.
[207] J. Kuehnle, J.H. Mendelson and K.R. David, Computed tomographic examination of heavy marijuana users, Journal of the American Medical Association, vol. 237, 1231-1232, 1977.
[208] N. Solowij, Long-term effects of cannabis on the central nervous system, H. Kalant et al. (eds.), The Health Effects of Cannabis,Toronto, Addiction Research Foundation, 1999.
[209] R. Mechoulam, L. Hanus and B.R. Martin, The search for endogenous ligands of the cannabinoid receptor, Biochemical Pharmacology 48, 1537-1544, 1994.
[210] R. Mechoulam et al., Anandamide may mediate sleep induction, Nature 389, 25-26, 1997.

Although substantial research on the psychomotor and cognitive effects of cannabis has resulted in a greater awareness of the functional effects of cannabis consumption, the mechanisms through which these functional effects are produced remain largely obscure. Additional research on the mechanisms through which cannabis alters behaviour is necessary.

Effects of Cannabis on Memory

Although several studies before and after 1981[212] have documented that cannabis can affect memory, the effects are typically modest, at least in comparison to effects reported with other behaviourally active drugs[213]. Free recall, where items-to-be-learned and their recall occur with cannabis present, is often impaired, and the major impairment is often in intrusions of new items. The few studies evaluating the recall of prose material have generally reported deleterious effects induced by cannabis. Effects of cannabis on recognition and paired-associate tasks have, however, been inconsistent.

Typically, once something is learned, recall is little impaired by cannabis if cannabis is present only during recall. Although the effects of cannabis on memory appear to be modest, it is unclear to what degree the level of difficulty of the memory task determines the magnitude of the effect imposed by cannabis. Few studies have been conducted to manipulate this variable across cannabis-dosing conditions.

It is also unclear how the consequences of performance could modulate the effects of cannabis on performance, e.g., could increased monetary reward produce corresponding

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[211] N. Solowij, Cannabis and Cognitive Functioning, Cambridge, Cambridge University Press, 1998.
[212] L. Miller, Marijuana: Acute effects on human memory, in S. Agurell, W.L. Dewey and R.E. Willette (eds.), The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects, New York, Academic Press, 21-46, 1984.
[213] P.M. Beardsley and T.H. Kelly, Acute Effects of Cannabis on Human Behaviour and Central Nervous System Functions, in The Health Effects of Cannabis, H. Kalant et al. (eds.), Toronto, Addiction Research Foundation, 1999.

decreases in detriments imposed by cannabis? Earlier reviews[214] have suggested that the consequences of performance can indeed modulate the effects of cannabis, but this variable seems to have been largely ignored in recent years.

During the past thirty years, researchers have found, at most, minor cognitive differences between chronic cannabis users and non-users, and the results differ substantially from one study to another[215]. Based on this evidence, it does not appear that long-term cannabis use causes any significant permanent harm to intellectual ability. Even animal studies, which show short-term memory and learning impairment with high doses of THC, have not produced evidence of permanent damage[216] [217].

It has been suggested by S.A. Deadwyler[218] that endogenous cannabinoids (those originating within the brain) are involved in the selective forgetting or elimination of certain information at the encoding stage of short-term memory, and that exogenous cannabinoids (e.g., THC) override the normal function of the endogenous cannabinoids by disrupting the encoding of information when it is not appropriate or advantageous to do so. The neurotransmitters and peptides that govern our behaviour are finely balanced, and any surplus or depletion generally results in dysfunction. With long-term use of cannabis, prolonged or continual binding to the cannabinoid receptor may alter its properties also in the long term[219]. These physiological mechanisms and the interactions between ingested cannabis, ananamide and the cannabinoid receptor need to be elucidated.

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[214] D.P. Ferraro, Acute effects of marijuana on human memory and cognition, in R.C. Petersen (ed.), Marijuana Research Findings, 1980, NIDA Research Monograph 31, 98-119, Washington, DC, US Government Printing Office, 1980.
[215] L. Zimmer and J.P. Morgan, Marijuana Myths, Marijuana Facts: A review of the scientific evidence, Lindesmith Center, 1997.
[216] S.A. Deadwyler et al., The Effects of delta-9-THC on mechanisms of learning and memory, in L. Erinoff (ed.), Neurobiology of Drug Abuse: Learning and Memory, Rockville, MD, National Institute on Drug Abuse, 1990.
[217] A.H. Lichtman et al., Systemic or intrahippocampal cannabinoid administration impairs spatial memory in rats, Psychpharmacology 119, 282-290, 1995.
[218] Deadwyler et al. 1990.
[219] Solowij 1999.

There is converging evidence that dysfunction due to chronic cannabis use lies in the realm of the higher cognitive functions that appear to be subserved by the frontal lobes; these are important in organizing, manipulating and integrating a variety of information, and in structuring and segregating events in memory[220].

Until better measures have been developed to investigate the subtleties of dysfunction produced by chronic cannabis use, cannabis may be viewed as posing a lower level threat to cognitive function than other psychoactive substances such as alcohol.

Effects of Cannabis on Appetite

In preliminary studies by Foltrin and colleagues on the effects of smoking cannabis on food intake, where subjects lived in a residential laboratory and engaged in structured work activities as well as social activities, analysis of the data indicated that increases in food intake were attributable to increases in eating occasions and were confined to the social-access periods and to the consumption of snacks. The authors speculated that the interactive social effects may have played a part in the food consumption increases observed.

In a follow-up study by Foltrin and colleagues[221], subjects smoked placebo or active cannabis twice a day in their private rooms and twice a day in their social areas. Smoking active cannabis cigarettes increased food intake during both the private and social periods. The greatest rate of change in caloric intake occurred during the social periods for most subjects. Smoking cannabis cigarettes nearly doubled the number of snack occasions during both the private and social periods without affecting the number of meal occasions, and the increases in caloric intake were mainly attributable to these snack occasions. The authors concluded that it was most likely a dose effect rather than a social effect that restricted the increases of food consumption to the social periods of their original study.

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[220] Ibid.

[221] R.W. Foltrin, M.W. Fischman and M.F. Byrne, Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory, Appetite 11, 1-14, 1988.

Although there have been several studies reporting that cannabis increases the intake of food, there have been fewer and less consistent reports that have documented that "appetite," the individual's self-report of the current level of hunger is similarly increased. It is difficult to determine whether there is truly a dissociation between cannabis-increased consumption of food and levels of self-reported hunger ratings because few studies have explicitly assessed both variables[222].

Amotivational Syndrome

Acute, reversible psychotic states have been documented in exceptional cases following cannabis use, but the existence of "amotivational syndrome," first described in the literature in 1968, has never been confirmed. The term was used to describe the changes in attitude and personality, the neglect of appearance, and general disinterest displayed by chronic users of cannabis, although nowadays it is considered to be obsolete and not typical of cannabis consumption[223] [224].

It is exceptionally difficult – if not impossible – to establish a direct and exclusive causality between speculative consequences of chronic cannabis use and the drug itself. For example, studies attempting to link dropping out of school at an early age with cannabis use have tended to show that it was in fact the family background, the child's relationship with parents during the school years, social values, etc. which led the child to stop going to school[225].

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[222] Beardsley, Kelly1999.
[223] T. Huw, Psychiatric symptoms in cannabis users, British Journal of Psychiatry 163, 141-149, 1993.
[224] WHO 1997.
[225] Hollister 1986.

The evidence for "amotivational syndrome" among adults consists largely of case histories and observational reports (e.g., [226] [227]). The few controlled field and laboratory studies have not found compelling evidence for such a syndrome[228] [229]. The value of the negative field studies is limited by their small sample sizes and the limited socio-demographic characteristics of their samples, while the evidential value of the laboratory studies is limited by the short periods of drug use, the youth and good health of the volunteers, and the minimal demands made on the motivation of volunteers in the laboratory[230].

There has been limited supportive evidence for the occurrence of an amotivational syndrome among adolescents. Cannabis use appears to increase the risk of discontinuing a high-school education and of experiencing job instability in young adulthood[231]. The apparent strength of these relationships in cross-sectional studies[232] may have been exaggerated because those adolescents who are most likely to use cannabis have lower academic aspirations and poorer high school performance prior to using cannabis than their peers who do not[233].

There is suggestive evidence that heavy cannabis use has adverse effects upon family formation, mental health and involvement in drug-related crime[234]. In each case, however, the apparently strong associations revealed in cross-sectional data are much

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[226] H. Kolansky and W.T. Moore, Effects of marijuana on adolescents and young adults, Journal of the American Medical Association, vol. 216, 486-492, 1971.
[227] R.B. Millman and R. Sbriglio, Patterns of use and psychpathology in chronic marijuana users, Psychiatric Clinics of North America, vol.9, 533-545, 1986.
[228] R.L. Dornbush, The long-term effects of cannabis use, in Marijuana: Effects on Behaviour, L.L. Miller (ed.), New York, Academic Press, 1974.
[229] J.C. Negrete, Psychiatric aspects of cannabis use, in cannabis and Health Hazards: Proceedings of an ARF/WHO Scientific Meeting, 577-616.
[230] S. Cohen, Cannabis effects upon adolescent motivation, in Marijuana and Youth: Clinical Observations on Motivation and Learning, Rockville, MD, National Institute on Drug Abuse, US Department of Health and Human Services, 2-11, 1982.
[231] T. Newcome and P. Bentler, Consequences of Adolescent Drug Use: Impact on the Lives of Young Adults, Newbury Park, California, Sage Publications, 1988.
[232] D.B. Kandel and J.A. Logan, Patterns of drug use from adolescence to young adulthood: I. Periods of risk for initiation, continued use and discontinuation, American Journal of Public Health, vol. 74, 660-666, 1984.
[233] Newcome, Bentler 1988.
[234] Ibid.

more modest in longitudinal studies after statistically controlling for associations between cannabis use and other pre-existing characteristics that independently predict these adverse outcomes.

Canadian researchers designed a token-economy study (where subjects worked for tokens which could be exchanged for cannabis) to evaluate cannabis' impact on motivation. They found that subjects worked less efficiently in the period immediately after they were allowed to smoke cannabis. However, productivity quickly increased and surpassed levels achieved during the abstinence period. Although subjects consuming the most cannabis spent the least amount of time working, overall, they were no less productive. This was because when they worked, they worked harder. In addition, during the period of highest cannabis consumption, subjects organized a strike and successfully negotiated with researchers for increased wages. After that, they worked even harder[235] [236].

III.2 Dependence and Tolerance

Cannabis consumption can lead to psychological dependence; it is estimated that around half of heavy users develop dependence of this type[237]. In a German study, one in five respondents admitted to frequently or very frequently consuming more cannabis than they had intended[238]. The tendency to develop physical dependence is only weak. It has been demonstrated in animal experiments by administering an antidote (the receptor antagonist
SR 141716A) following chronic administration of cannabis and observing withdrawal symptoms[239]. Abrupt withdrawal in humans following heavy daily consumption

[235] C.G. Miles et al., An Experimental Study of the Effects of Daily Cannabis Smoking on Behavioural Patterns, Addiction Research Foundation, Toronto, 1974.
[236] I. Campbell, The Amotivational Syndrome and Cannabis Use With Emphasis on the Canadian Scene, Annals of the New York Academy of Sciences 282, 33-36, 1976.
[237] WHO 1997.
[238] D. Kleiber, R. Soellner et al., Cannabiskonsum in der Bundesrepublik Deutschland, Entwicklungsfaktorem, Konsmmuster und Einflussfaktoren, Berlin, 1997.
[239] M.D. Aceto, S.M. Scates et al., Cannabinoid-precipitated withdrawal by the selective cannabinoid receptor antagonist SR 141716A, European Journal of Pharmacology 282, R1-R2, 1995.

produces autonomic withdrawal symptoms such as nausea, perspiration, trembling, insomnia, and loss of
appetite[240] [241]. These symptoms regress following renewed administration of cannabis, an observation that corroborates the development of dependence[242].

The dependence profile is classified by the World Health Organization as a distinctive type of dependence, known as cannabis-type dependence. The development of tolerance is associated with pharmacodynamic changes. Chronic administration of THC has been shown to reduce the number of receptor binding sites[243], although this appears to be reversible[244]. The tolerance to the functional and psychological effects of THC observed in animal experiments has also been demonstrated in man, but does not lead the individual to increase the dose of cannabis[245] [246].

Clear tolerance development has been demonstrated with respect to mood swings, elevated heart rate, and impairment of psychomotor functions. The conditions under which tolerance and dependence develop – high doses of THC over a long period – do not correspond to the widespread recreational use of cannabis, and this is why these properties of cannabis may not necessarily constitute a serious problem.

The existence of a cannabis dependence syndrome among some heavy and long-term cannabis users can be inferred from data on the prevalence and characteristics of persons seeking professional help to stop using cannabis, from observational studies of problems

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[240] Hollister 1986.
[241] G.A. Wiesbeck, M.A. Schuckit et al., An evaluation of the history of a marijuana withdrawal syndrome in a large population, Addiction 91 (10), 1469-1478, 1996.
[242] Adams, Martin 1996.
[243] F. Rodriguez de Fonseca, M.A. Gorriti et al., Downregulation of rat brain cannabinol binding sites after chronic delta-9-THC treatment, Pharm. Biochem. Behav. 47, 33-40, 1994.
[244] T.M. Westlake, A.C. Howlett et al., Chronic exposure to delta-9-THC fails to irreversibly alter brain cannabinoid receptors, Brain Res. 544, 145-149, 1996.
[245] P.M. Beardsley, R.L. Balster et al., Dependence on THC in rhesus monkeys, Journal Pharmacol. Exp. Ther.
239 (2), 311-319, 1986.
[246] Hollister 1986.

reported by non-treatment samples of long-term cannabis users, and from clinical research on the validity of the cannabis dependence syndrome as embodied in the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, (DSM-III-R) (American Psychiatric Association 1987) and other classification systems.

Direct support for the validity of a cannabis dependence syndrome comes from studies of diagnostic criteria for substance dependence. Kosten et al.[247] tested the extent to which the DSM-III-R psychoactive substance dependence disorders for alcohol, cannabis, cocaine, hallucinogens, opiods, sedatives, and stimulants constituted syndromes. There was consistent support for a unidimensional dependence syndrome for alcohol, cocaine and opiates. The results were more equivocal in the case of cannabis. A Principal Components Analysis (PCA) suggested that there were three dimensions of cannabis dependence: (1) compulsion – indicated by impaired social activity attributable to drug use, preoccupation with drug use, giving up other interests, and using more than intended; (2) inability to stop – indicated by inability to cut down, rapid reinstatement after abstinence, and tolerance to drug effects; and (3) withdrawal – identified by withdrawal symptoms, use of cannabis to relieve withdrawal symptoms, and continued use despite problems.

Persons who use cannabis on a daily basis over periods of weeks to months are at greatest risk of becoming dependent[248]. In the Epidemiological Catchment Area (ECA) study involving face-to-face interviews with 20 000 Americans in five cities[249], approximately one-half of those who used any illicit drug on a daily basis satisfied DSM-III criteria for abuse or dependence[250]. Kandel and Davis[251] estimated the risk of dependence among near-daily cannabis users (according to approximated DSM-III criteria) at one in three.

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[247] T.R. Kosten et al., Substance-use disorders in DSM-III-R, British Journal of Psychiatry 151, 8-19, 1987.
[248] S.M. Channabasavanna, M. Paes and W. Hall, Mental and behavioural disorders due to cannabis use, in The Health Effects of Cannabis, H. Kalant et al. (eds.), Toronto, Addiction Research Foundation, 1999.
[249] L.N. Robbins and D.A. Regier (eds.), Psychiatric Disorders in America, New York, Free Press, 1991.
[250] J.C. Anthony and J.E. Helzer, Syndromes of drug abuse and dependence, in L.N. Robins and D.A. Regier (eds.), Psychiatric Disorders in America, 116-154, New York, Free Press, 1991.
[251] D.B. Kandel and M. Davies, Progression to regular marijuana involvement: Phenomenology and risk factors for near daily use, in M. Glantz and R. Pickens (eds.), Vulnerability to Drug Abuse, 211-253, Washington DC, American Psychological Association, 1992.

The risk of developing dependence among less frequent users is substantially less. In the ECA study, 20 percent of those who used any illicit drug more than five times met criteria for drug abuse and dependence at some time in their lives. The National Comorbidity Survey (NCS), a population survey undertaken between 1990 and 1992 to estimate comorbidity (relation to disease) between substance use and non-substance use disorders, and other formal comparisons of the dependence potential of cannabis with that of other drugs[252], suggest that the dependence risks of cannabis use are probably more like those of alcohol than those of tobacco and opiates.

III.3 Psychotic Disorders

There is suggestive evidence that large doses of THC can produce an acute psychosis in which confusion, amnesia, delusions, hallucinations, anxiety, agitation, and hypomanic (mild mania without much change in behaviour) symptoms predominate. The main evidence comes from clinical observations of psychotic symptoms in heavy cannabis users that occur after unusually heavy cannabis use, appear to comprise a syndrome, and remit rapidly after abstinence from cannabis[253]. Epidemiological research has produced reasonably consistent evidence from case-control, cross-sectional and prospective studies that there is an association between cannabis use and schizophrenia. The prospective study of Andreasson et al.[254] showed a dose-response relationship between the frequency with which cannabis had been used by age eighteen and the risks over the subsequent fifteen years of being diagnosed as schizophrenic. This relationship has been interpreted by some as evidence that chronic cannabis use may precipitate schizophrenia in vulnerable individuals[255] [256].

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[252] G.E. Woody, L.B. Cottler and J. Caciola, Severity of dependence: Data from the DSM-IV field trials, Addiction 88, 1573-1579, 1993.
[253] G. Edwards, Cannabis and the psychiatric position, in Cannabis and Health, J.D.P. Graham (ed.), London, Academic Press, 1976.
[254] S. Andeasson and others, Cannabis and schizophrenia: A longitudinal study of Swedish conscripts, The Lancet, vol. 1, 1483-1485, 1987.
[255] Ibid.

Others are more sceptical. They note that in the only prospective study conducted to date[257], the use of cannabis was not documented at the time of diagnosis, there was a possibility that cannabis use was confounded by amphetamine and other drug use, and there were doubts about whether the study could reliably distinguish between schizophrenia and acute psychoses induced by cannabis or other drugs[258]. Even if this relationship is a causal one, its public health significance should not be overstated. The findings of Andreasson et al. indicate that fewer than 10 percent of cases of schizophrenia are attributable to cannabis use[259]. On the grounds of biological plausibility it is probable that cannabis use exacerbates the symptoms of schizophrenia and precipitates schizophrenic disorders[260]. However, the declining incidence of treated cases makes it unlikely that cannabis use has caused schizophrenia that would not otherwise have occurred[261].

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[256] F.R. Schneier and S.G. Siris, A review of psychoactive substance use and abuse in schizophrenia: Patterns of drug use, Journal of Nervous and Mental Disorders, vol.175, 641-652, 1987.
[257] Andreasson et al. 1987.
[258] J.C. Negrete, Cannabis and schizophrenia, British Journal of Addiction, vol. 84, 349-351, 1989.
[259] Hall et al. 1984.
[260] Ibid.
[261] G. Der, S. Gupta and R.M. Murray, Is schizophrenia disappearing?, The Lancet, vol. 1, 513-516, 1990.