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June 8, 2010

TO: Each Supervisor

FROM: Jonathan E. Fielding, M.D., M.P.H. *J. Fielding*  
Director and Health Officer

SUBJECT: **HEALTH EFFECTS OF MARIJUANA**

As the public debate continues to unfold over policies surrounding the legal use of marijuana (cannabis), this and related issues will likely continue to come to your attention. As one of the primary concerns about marijuana use is the health effects, I want to provide you a brief analysis of those impacts.

While scientific evidence of the health benefits of marijuana based on well-designed clinical studies is quite limited, the overall effects of marijuana are well known. Smoked cannabis causes immediate effects on the cardiovascular system including an increase in the heart rate and the possibility that blood pressure may decrease when an individual stands. Marijuana intoxication is associated with impairment of short-term memory, attention, motor skills, and reaction time, as well as an impaired ability to organize and integrate complex information. Smoked marijuana can cause relaxation and enhance mood, but these effects are dependent on the setting. Some individuals experience acute anxiety or panic reactions, confusion, mood disorders, paranoia, and psychotic symptoms (e.g., delusions, hallucinations). Additional side effects are listed below in the section on the medical uses of marijuana.

Marijuana contains over 400 chemicals whose levels vary widely from batch-to-batch. Some substances absorbed into the human body as a result of smoking marijuana (called "cannabinoids") are closely related to substances produced normally in the human body (called "endocannabinoids"). The normal brain and many other organs use endocannabinoids to regulate many functions, including appetite, pain sensation, mood, and memory. The pharmacologic doses of cannabinoids achieved through smoking marijuana produce the marked psychoactive effects described above. In addition, smoking marijuana creates additional potentially harmful, combustion products. From a medical standpoint, the lack of a full understanding of the health effects of all of the components in marijuana smoke as well as the high variability of the doses achieved make the clinical effects difficult to assess and predict.\*

In general, the health effects of marijuana may be considered in two broad categories: medical use and recreational use.

\*FDA-approved cannabinoids in the form of prescription medications are available, but not the subject of this document.

### Medical Uses of Marijuana

While marijuana has been used for many reasons, only limited information from high quality medical studies is available. A recent systematic review from the American Medical Association found that smoking marijuana may be effective in treating a small number of conditions including:

- Neuropathic pain (nerve pain)
- Severe weight loss (improves appetite and caloric intake)
- Spasticity, pain, and sleep problems in patients with multiple sclerosis
- Nausea and vomiting from chemotherapy
- High internal eye pressure in adults with glaucoma

In clinical use, the side effects typically attributable to marijuana (e.g., anxiety, sedation, confusion, dizziness, fatigue, tachycardia, and dry mouth) are generally tolerable and do not limit the amount of marijuana that can be consumed.

The Institute of Medicine (IOM) of the National Academy of Sciences recommends that long-term use of marijuana for medical treatment be limited to persons who are terminally ill or those with debilitating symptoms for whom the long-term risks are not of great concern. The IOM also says that for short-term use, marijuana should only be used in patients with debilitating symptoms who meet the following criteria:

- Documented failure of all approved drugs to provide relief
- Expectation that symptoms can be relieved by marijuana
- Administration under medical supervision with assessment of effectiveness
- Oversight comparable to a clinical research study

### Adverse Health Effects of Marijuana in Recreational Use

#### *Substance Abuse and Dependence*

- Over thirty percent of people aged 18 and over who used marijuana in the past year are classified as dependent based on national surveys of users.
- Four to nine percent of marijuana users fulfill diagnostic criteria for substance dependence. Although some users develop dependence, they are considerably less likely to do so than users of alcohol and nicotine, and withdrawal symptoms are less severe. Addiction rates are higher among those under 18. The younger the age, the greater the risk. For example, 17% of users at age 13 become addicted.
- The Institute of Medicine concluded that cannabis use is not the cause or even the most serious predictor of hard drug abuse.

#### *Cognitive Deficits and Mental Health*

- Long-term studies found that marijuana use was consistently associated with lower ability to learn and to remember new information, lower test scores, and lower educational attainment; marijuana use also increased use of other drugs, but it was not consistently associated with other measures of mental and psychological harm (e.g., personality factors, antisocial behavior, and social integration).

- Acute intoxication with marijuana causes marked changes in subjective mental status, brain functioning, and neuropsychological performance.
- Recent clinical trial was ended prematurely because some subjects developed suicidal ideation, demonstrating that substances produced by smoking marijuana affect normal body substances that regulate mood.
- The association of marijuana with psychosis has been somewhat controversial. Recent studies suggest that there is an increased risk of psychosis associated with marijuana use, but marijuana accounts for only a small proportion of psychoses.

#### *Respiratory Illness and Cancer*

- The composition of tobacco and marijuana smoke is similar. Marijuana smoking is associated with markers of lung damage and symptoms of chronic bronchitis. While studies have not demonstrated an increased risk for lung cancer or other cancers affecting the oral cavity and airway, it is premature to suggest that marijuana does not cause these cancers as the long-term follow-up studies that are needed to adequately look at these outcomes have not been performed.

#### *Impairments of the Immune System*

- Cannabinoids can affect the immune system, but the clinical importance is unclear.

#### *Health Care Utilization*

- Nationally, 110,000 people a year who voluntarily participate at treatment facilities report marijuana as their primary substance of abuse.
- In Los Angeles County, one-in-three persons admitted for treatment at facilities under contract with Substance Abuse Prevention and Control reported marijuana as either a primary or secondary drug of choice.
- In 2008, marijuana was involved in 375,000 emergency room visits nationwide.

Please let me know if you have any questions concerning this information.

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#### Attachments

c: Chief Executive Office  
County Counsel  
Executive Officer, Board of Supervisors

#### **Primary References Describing the Health Effects of Marijuana:**

American Medical Association. Report 3 of the Council on Science and Public Health (I-09). Use of Cannabis for Medicinal Purposes. 2009  
Institute of Medicine. Marijuana and Medicine: Assessing the Science Base. Washington, DC. National Academy Press (1999).  
Institute of Medicine, Marijuana and Health, Washington, D.C. National Academy Press, 1988  
Kerlikowske RG. Statement from the Office of the National Drug Control Policy Direct. Why marijuana legalization would compromise public health and public safety. 3/4/2010

The following provide more detailed information on the results of clinical trials and harms of marijuana.

Table 1 is from the American Medical Association. Report 3 of the Council on Science and Public Health (I-09). Use of Cannabis for Medicinal Purposes. 2009. Detailed references cited in the table can be found in that report.

Table 1. Randomized, Placebo-Controlled Trials of Smoked Cannabis					
Study	N	Design	Product and dosage	Efficacy	Adverse Effects
<i>Antiemetic effects in patients receiving cancer chemotherapy</i>					
Chang et al <sup>17</sup>	15 patients with osteogenic sarcoma undergoing high dose methotrexate chemotherapy (median age 24 years)	R, DB, CR, PC	Oral THC 10 mg/m <sup>2</sup> 5 times daily or smoked cannabis (1.93% THC) cigarette substituted if vomiting occurred	Oral THC alone or the combination of oral and smoked cannabis had an antiemetic effect > placebo. THC reduced the number of retching and vomiting episodes, the degree and duration of nausea, and the volume of emesis. Clinical responses appeared to correlate with plasma THC values. Smoked THC yielded plasma concentrations more than 5 ng/mL on 70% of occasions compared with 44% of the time with oral THC.	Sedation in 80% of patients, most of whom had prior experience with smoked cannabis
Chang et al <sup>18</sup>	8 patients with various tumors undergoing adjuvant therapy with doxorubicin and cyclophosphamide (median age 41 years)	R, DB, CR, PC	Oral THC 10 mg/m <sup>2</sup> 5 times daily or smoked cannabis (1.93% THC) cigarette substituted if vomiting occurred	No antiemetic effect. Seven of eight patients inexperienced in the use of cannabis.	Mood alteration and episodes of tachycardia
Levitt et al <sup>19</sup>	20 patients with various tumors	R, DB, CR, PC	One cannabis cigarette + placebo oral THC x 4; oral THC 15 mg + placebo cannabis cigarette x 4	Treatments were effective in only in 25% of patients; 35% preferred oral THC; 20% preferred smoked cannabis; 45% had no preference.	Seven individuals exhibited distortions of time perception or hallucinations; four that had received THC; two with cannabis, and one with both

*Appetite stimulation*

Abrams et al <sup>41</sup>	67 adults with HIV infection	R, DB for oral THC or P, PL	One to three cannabis cigarettes/day (3.95% THC) or oral THC 2.5 mg tid for 21 days	Smoked cannabis and oral THC equivalent on weight gain and superior to placebo; viral load and pharmacokinetics of protease inhibitors unaffected	Generally well tolerated; one cannabis recipient discontinued due to emergence of neuropsychiatric symptoms; two oral THC recipients dropped out due to side effects (paranoia; headache)
Haney et al <sup>42</sup>	30 HIV+ experienced cannabis smokers, half with less than 90% ideal body mass	R, DB, PC	Dronabinol zero to 30 mg or cannabis cigarettes zero to 3.9% THC, administered in eight 7 hour sessions over three to four weeks	Cannabis and dronabinol significantly increased caloric intake in the low body mass group	Few adverse effects reports, except intolerance of high (30 mg) dronabinol dose
Haney et al <sup>43</sup>	10 HIV+ experienced cannabis smokers	R, DB, PC	Dronabinol 5 or 10 mg, or cannabis cigarettes 2% or 3.9% THC each four times daily for four days	Cannabis and dronabinol increased caloric intake in a dose dependent fashion, and body weight at the highest doses	Relative absence of cognitive impairment. Improved mood and objective and subjective sleep measures.

*Pain Management/Analgesia*

Abrams et al <sup>44</sup>	55 patients with HIV-associated neuropathic pain	R, DB, PC, PL	Up to three cannabis (3.95% THC) cigarettes daily for 5 days	Smoked cannabis relieved chronic neuropathic pain (34% reduction), and more than 50% of patients experienced at least a 30% reduction in pain intensity. Smoked cannabis also reduced experimentally induced hyperalgesia	All patients had prior cannabis smoking experience. Anxiety, sedation, disorientation, confusion, and dizziness occurred more often in cannabis recipients, but were rated as between "none" and mild.
Ellis et al <sup>47</sup>	34 adult patients with HIV-associated neuropathic pain	R, DB, CR, PC	Cannabis cigarettes of varying THC concentration (1-8%) administered 4 times daily for 5 days	46% more patients achieved at least a 30% reduction in pain relief with cannabis vs placebo	All patients were taking additional analgesics. Concentration difficulties, fatigue, sedation, dry mouth, tachycardia more frequent but not dose limiting. Two dropouts for "psychosis" and "cough"
Wilsey et al <sup>46</sup>	38 adult patients experienced cannabis smokers with central and peripheral neuropathic pain	R, DB, CR, PC	Cannabis cigarettes zero, 3.5% or 7% THC administered in graded puffs over 2 hours	Smoked cannabis reduced pain intensity at 4 hours compared with placebo; no difference was noted between the 2 doses. No effects observed on evoked pain responses. Most patients had complex regional pain syndrome.	Cannabis recipients were more likely to report subjective and psychoactive drug effects including impairment and sedation. General cognitive decline on psychological testing.

### Multiple sclerosis

Greenberg et al <sup>15</sup>	10 adult patients with multiple sclerosis and spasticity	R, DB, PC	One cannabis cigarette (1.54% THC) smoked over 10 minutes	Subjective feeling of clinical improvement in some patients	Impairment of posture and balance as measured by dynamic posturography
Cory-Bloom et al <sup>16</sup>	30 adult patients with multiple sclerosis and spasticity	R, DB, CR, PC	One cannabis cigarette (3.95%) daily for 3 days	Reduced pain (~50%) and spasticity (~30%) scores.	Cognitive impairment; dizziness; fatigue, "too high." 80% had prior cannabis use

### Glaucoma

Merritt et al <sup>16</sup>	18 adults with glaucoma ages 28-71)	R, DB, CR, PC	One cannabis cigarette containing 2% THC	Significant reduction in intraocular pressure	Alteration in sensory perception (100%); tachycardia and palpitations (44%), postural hypotension (28%)
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R = randomized; DB = double-blind; CR = crossover trials, PL = parallel group study; PC = placebo-controlled

**Table 2. Marijuana Adverse Effects**

Study	n	Design	Product Dosage	Efficacy	Adverse Effect
Moore, et al <sup>i</sup> searched Medline, Embase, CINAHL, PsycINFO, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, and MEDCARIB from inception through September, 2006	N/A	35 Population based longitudinal or Case Control studies, combined "using DerSimonian & Laird random effects model"	Not Specified	Increased risk of psychosis-independent of confounders, if ever used cannabis (combined adjusted odds ratio=1.41, 95% CI 1.20-1.65). Suggestive of a dose-response relationship, with greater risk among more frequent users (2.09, 1.54-2.84).	Clinically relevant Psychosis Depression, suicidal thoughts, and anxiety examined separately. Considerable confounding effect for both psychotic and affective outcomes.
McGrath et al <sup>ii</sup>	3801	Prospective birth cohort, with a subset of 228 sibling pairs. ( 3801 young adults born 1981-1984 (Mater-University Study of Pregnancy).	Smoked Cannabis, THC not specified	Time from first cannabis use was associated with "psychosis-related outcomes". If time since first cannabis use was 6 or more years, "significantly increased risk of (1) non-affective psychosis (adjusted odds ratio, 2.2; 95% confidence interval, 1.1-4.5), (2) being in the highest quartile of Peters et al Delusions Inventory score (adjusted odds ratio, 4.2; 95% confidence interval, 4.2-5.8), and (3) hallucinations (adjusted odds ratio, 2.8; 95% confidence interval, 1.9-4.1)" Within sibling pairs, significant association between time from first cannabis use & higher scores on Delusions Inventory (Peters et al).	Psychosis-related outcomes among young adults, with early cannabis use. Reduced likelihood of confounding effects by using sibling pairs.
Henquet C, et al <sup>iii</sup>	N/A	Reviewing 104 articles	THC amount not specified	Cannabis-Psychosis association, possible mechanism: gene-environment interaction. "Multiple variations within multiple genes--rather than single genetic polymorphisms--together with other environmental factors (e.g., stress) may interact with cannabis to increase the risk of psychosis". Cannabis-Mania association independent of the prevalence/incidence of psychosis. Cannabis use may increase the "expression of manic symptoms (and subsequent risk to develop bipolar disorder)" Suggestive of possible decrements in learning and remembering new information, without affecting other cognitive abilities, among chronic cannabis users.	Psychosis
Henquet C, et al <sup>iv</sup>	N/A	N/A	N/A		Mania Bipolar Disorder, risk of.
Grant, I et al <sup>v</sup>	1,188 (i.e., 704 cannabis users and 484 non-users)	Meta analysis	N/A		Reduced capacity to learn and remember new information

Study	n	Design	Product Dosage	Efficacy	Adverse Effect
Jager G, et al <sup>vi</sup>	N/A	Review	N/A	Both human and animal studies suggest that severity of the adverse effects on cognitive development depends on the age of first cannabis use. Possible interference with educational and vocational training. An overall 4779 adverse events were reported: 4615 [96.6%] were not serious. <ul style="list-style-type: none"> <li>Dizziness (714 events [15.5%])</li> </ul> 164 serious adverse events; the most common events included: <ul style="list-style-type: none"> <li>relapse of multiple sclerosis (21 events [12.8%])</li> <li>vomiting (16 events [9.8%])</li> <li>Urinary tract infection (15 events [9.1%])</li> </ul>	<p>"Use of cannabis during critical developmental periods in the still maturing brain may induce persistent alterations in brain structure and brain function."</p> <p>MS relapse, vomiting, UTI (Serious) dizziness (non-serious)</p> <p>Medical cannabis: Short-term use was associated with higher non-serious adverse events; long term use was "poorly characterized in published clinical trials and observational studies".</p>
Wang T, et al <sup>vii</sup>	31 studies (23 randomized controlled trials and 8 observational studies)	Review: 31 studies (23 randomized controlled trials and 8 observational studies)	Dose (N/A) "In the 23 randomized controlled trials, the median duration of cannabinoid exposure was 2 weeks". (range: 8 hours-12 months)	<p>"The rate of non-serious adverse events: higher among participants assigned to medical cannabinoids (rate ratio [RR] 1.86, 95% confidence interval [CI] 1.57-2.21)</p> <p>No significant difference in the rate of serious events between the 2 groups (RR 1.04, 95% CI 0.78-1.39).</p>	
Hall W, et al <sup>viii</sup>	N/A	Review Articles: Searched PubMed & Thompson Reuters Web of Science citation indexes for epidemiologic studies (past 10 years on adverse health effects of cannabis) plus additional articles/books	In the USA, THC content of cannabis increased from less than 2% in 1980 to 4-5% in 1997 and 8-9% in 2006.	<p>"Acute and chronic adverse effects of cannabis use:</p> <ul style="list-style-type: none"> <li>Anxiety and panic, especially in naive users</li> <li>Psychotic symptoms (at high doses)</li> <li>Road crashes if a person drives while intoxicated</li> </ul> <p>Chronic adverse effects</p> <ul style="list-style-type: none"> <li>Cannabis dependence syndrome (in around one in ten users)</li> <li>Chronic bronchitis and impaired respiratory function in regular smokers</li> <li>Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders</li> <li>Impaired educational attainment in adolescents who are regular users</li> <li>Subtle cognitive impairment in those who are daily</li> </ul>	<p>Emphasis on assessing "adverse health effects of greatest potential public health interest":</p> <ul style="list-style-type: none"> <li>Dependence syndrome</li> <li>Increased risk of motor vehicle crashes</li> <li>Impaired respiratory function</li> <li>Cardiovascular disease</li> </ul>



Study	n	Design	Product Dosage	Efficacy	Adverse Effect
Tetraault JM, et al <sup>x</sup>	N/A	Two independent reviews of Medline, PsychInfo, & Embase evaluating MJ smoking effects on pulmonary function and respiratory complications (January 1, 1966- October 28, 2005).	N/A	users for 10 years or more"	<ul style="list-style-type: none"> <li>Adverse effects of regular use on adolescent psychosocial development and mental health.</li> <li>Short-term exposure associated with bronchodilation.</li> <li>Long-term marijuana smoking, associated with increased respiratory symptoms:</li> </ul> <p>Inconclusive physiological data about long term exposure marijuana smoking and airflow obstruction measures.</p>
Hanchi, A, et al <sup>x</sup>	48 subjects (31 men and 17 women), including 14 NS (mean age SEM, 30.1_5.8 years), 12 TS (37.0_8.7 years), 12 MS (37.2_9.3 years), and 10 CS (46.5_5.5 years).	Experimental	<p>On average, smokers (TS) were current heavy smokers of tobacco (18.2_13.7 pack-years); 7-30 cigarettes per day.</p> <p>Marijuana Smokers (MS) (116.4_111 joint-years) 3-70 joints/week, Cocaine (CS) (1.5_1.5 g/week) 0.3 and 5 g/week.</p>	<p>11/12 challenge studies found an association between short-term marijuana administration and bronchodilation (eg, increases of 0.15-0.25 L in forced expiratory volume in 1 second). No consistent association was found between long-term marijuana smoking and airflow obstruction measures. All 14 studies that assessed long-term marijuana smoking and respiratory complications noted an association with increased respiratory symptoms, including cough, phlegm, and wheeze (eg, odds ratio, 2.00; 95% confidence interval, 1.32-3.01, for the association between marijuana smoking and cough). Studies were variable in their overall quality (eg, controlling for confounders, including tobacco smoking).</p> <p>Human alveolar macrophages (AMs) from the lungs of healthy nonsmokers (NS) or tobacco smokers (TS), marijuana (MS), or crack cocaine (CS) were recovered and "challenged in vitro with Staphylococcus aureus. AMs from NS and TS exhibited potent antibacterial activity that correlated with the production of nitric oxide (NO) and induction of NO synthase without the requirement for priming with exogenous cytokines".</p> <p>AMs from MS and CS "exhibited minimal antibacterial activity and failed to produce NO unless primed with additional cytokines".</p>	<p>Nitrite production was considerably lower (<math>P &lt; .01</math>) among MS and CS cultures, compared with alveolar "macrophages from NS and TS, at the same time points"</p>

- <sup>i</sup> Moore T H M, Zammit S, Lingford-Hughes A, Barnes T, Jones P B, Burke M, Lewis G. Cannabis Use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007; 370: 319-28.
- <sup>ii</sup> McGrath, J et al. Association Between Cannabis Use and Psychosis-Related Outcomes Using Sibling Pair: Analysis in a Cohort of Young Adults. *ArchGenPsychiatry*. 2010;67(5):(doi:10.1001/archgenpsychiatry.2010.6)
- <sup>iii</sup> **Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene-environment interplay between cannabis and psychosis. *Schizophrenia Bull*. 2008 Nov;34(6):1111-21. Epub 2008 Aug 22.**
- <sup>iv</sup> The association between cannabis use and mania was independent of the prevalence and the incidence of psychotic symptoms. cannabis use may affect population expression of manic symptoms (and subsequent risk to develop bipolar disorder
- <sup>v</sup> Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc*. 2003 Jul;9(5):679-89.
- <sup>vi</sup> Jager G, Ramsey NF. Long-term consequences of adolescent cannabis exposure on the development of cognition, brain structure and function: an overview of animal and human research. *Curr Drug Abuse Rev*. 2008 Jun;1(2):114-23.
- <sup>vii</sup> Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *CMAJ*. 2008 Jun 17;178(13):1669-78.
- <sup>viii</sup> Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009 Oct 17;374(9698):1383-91.
- <sup>ix</sup> Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *Arch Intern Med*. 2007 Feb 12;167(3):221-8.
- <sup>x</sup> **Hanchi Shay, A et al. Impairment of Antimicrobial Activity and Nitric Oxide Production in Alveolar Macrophages from Smokers of Marijuana and Cocaine. *JID* 2003:187 (15 February) : 700-704.**