Chapter
Marijuana-Impaired, or, Just Cannabinoid Positive ?

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INTRODUCTION--

The Title of this publication as "Drug Injury", allows a wide range of sub-topics and an almost endless level of health-related information. Thus, the inclusion of this Chapter is a de facto statement that Marijuana/Cannabinoids are an integral part of our Drug Lexicon. Historically, the Medical/Drug aspect of Marijuana is well documented in the On-Line entity at ProCon.org as recently as 08/13/2013. And, lest the reader retain some skepticism as to the Drug categorization of Marijuana/Cannabinoids, our U.S. Government was issued a Patent # 6630507 in Oct. 2003 for Marinol. This synthetic Cannabinoid Drug had a recommendation as "cannabinoids as antioxidants and neuroprotectants". This Patent stands not withstanding the statement of "no medical use" for Marijuana in the 1970 placement as a Schedule 1 substance in the Controlled Substance Act. And, even more incredulous, given the 1937 Marijuana Stamp Act that established Marijuana as an Illegal Substance.

Perhaps having learned the lessons of Alcohol Prohibition with the consequent establishment of Domestic Crime Families, and, the War-On-Drugs with the establishment of Foreign Drug Cartels, our U.S. Government created the "Pot Farm" in Mississippi in 1969. That University-based facility produces Marijuana Cigarettes allegedly to this day for at least one smoker in Florida. The "Farm" initially also afforded material for researchers at Research Triangle Park in North Carolina for ground-breaking research by Dr. Wall, et al., on the Pharmacokinetic and Pharmacodynamic aspects of Marijuana/Cannabinoids. That New Beginning of research studies on Marijuana was then turned Clinical with the National Cancer Institute studies in 1980; but even more-so after the New Mexico Legislature in 1978 concluded that Marijuana has Medicinal Value.

To recapitulate briefly, I note that the U.S. Government had/has Marijuana as an "illegal substance"; being grown for distribution to individuals and Institutions; which has "no medical use"; which has/had a Patent with health recommendations. These apparent internal Governmental inconsistencies are matched by the overarching competing Societal efforts. Thus, we have over 20 National Political entities (States) with Medical Marijuana Facilities; we have a West Coast block of 4 States with, or, soon to have recreational Marijuana use; we have Official Marijuana growers, and, unofficial growers. The topic of Marijuana may be a classic case of States' Rights v. Federal Duties v. Personal Freedoms. This truly Democratic Conundrum was recently documented In "Medicolegal Aspects of Marijuana- Colorado Edition" from Lawyers and Judges Pub. Co, 2015.

As noted in the foregoing, as-well-as well documented in the general press, and On-Line outlets, Marijuana and the derived Cannabinoids have moved to straddle the fence/divide/chasm between Prescription Drugs, and, Drugs of Abuse. These Individual, State, and, Federal Efforts toward effective movement of Marijuana-related products as available for the Common Good is now about 50 years young. And, given the recent pace of change in Society and Legislatures, Marijuana Is moving to be a commercially marketed Integral part of our Societal Spectrum of Substances-of-Abuse which include Alcohol, Tobacco Products, Foods, and Prescription Drugs.

Now, given that Marijuana and related Cannabinoids are variously still on the Illegal/Legal fence in some sections of the U.S., the following presentations evaluate Smoking, and, Ingestion as routes of assimilation of Marijuana-related products. It is anticipated that this afforded level of Information will prepare the Patient, and, Recreational User as to expectations which are the Marijuana Experience.

Synopsis

12.1 Cannabinoid Disposition: After Smoking

A. Introductory Summary

In the 20 years from about 1993 until 2013, the marijuana testing program at the University of Mississippi has demonstrated that the average THC (Tetrahydrocannabinol) concentration of the generally available marijuana has increased from about 3.1 percent.[1] Recent testing has shown average values between 25 and 28 percent, and values of 36–40 percent THC. Also, during about the time frame since the 1970s, some states have decriminalized marijuana possession, and about 20 states and the District of Columbia have permitted the dispensing of medical marijuana.[2,3] Thus, we now have hundreds of sources of marijuana on the "street," and such clinics and dispensaries compete with the unregulated marijuana sources. Furthermore, both Colorado and Washington have legalized recreational marijuana. This broadening of the market for marijuana use may increase the number of users.

The challenge of this new and possibly increasing prevalence of marijuana use requires effective evaluation by businesses, governments, legal entities, and scientists to position marijuana use into a positive functional societal role. Thus, the authors having expertise as small businesses, laboratory scientists, and consultants, afford this brief review of some of the scientific studies in the marijuana arena. In so doing, we evaluate the logic of a five nanograms per milliliter (ng/mL) level of blood THC in assessing the psychomotor functionality of a marijuana user when, in fact, the marijuana smoker attains a plasma THC level up to about 250 ng/mL that decreases to less than ten ng/mL in the one hour from the beginning of a ten to 15 minute smoking session. Even more confounding are the results of two seven-day abstinence studies in which THC-positive plasma test results even after the seven-day washout period show THC up to 5.5 ng/mL.[4,5] Even more absurd is the 2006 report which recommended a THC level of 0.5 ng/mL as the cut-off for psychomotor functionality.[6] We thus propose, based upon the following, a plasma THC level of 30 ng/mL as an objective value toward assessing impairment related to marijuana smoking in accident/incident conditions.

B. Questions in Search of Answers

1. Blood THC v. brain THC: Any relationships?
2. How does the percent THC in the smoked marijuana cigarette relate to blood levels of THC in the user?
3. How does the blood level of THC relate to the perception of "high" in the user?
4. Is the practiced/heavy marijuana user just one end of the scale for dose-response effects?
5. Is the blood level of THC the only cannabinoid[1] of interest in evaluating behavioral effects in the

[1] The general term for chemicals related to THC is cannabinoids.

user?

6. Is urine testing for cannabinoids of any either clinical or evidentiary value?
7. Impairment & marijuana: laboratory and on-road considerations.

C. Scientific Data Relating to THC

1. Blood THC v. brain THC: any relationships?

Given that the use of marijuana is fostered by the effects of the cannabinoids upon the brain of the smoker, it is appropriate that some early studies attempted to measure the concentrations of cannabinoids in the brain.[7,8,9] Animals were of necessity in those quantitative studies, such as mice, rats, and pigs, which afforded consistent comparable results. Thus, a 1972 study with radioactive THC found brain levels were at their maximum 15 minutes after intravenous administration.[7] The noted two cannabinoids were THC and Hydroxy-THC, and the effects paralleled the brain cannabinoid levels over 1.5 to four hours.[10] A similar study with mice noted relative cannabinoid levels in the smoke were the same as relative levels in the brain for three Cannabinoids.[11] They further showed that no Hydroxy-THC was in the smoke condensate, but was found in the brain. Other studies have proposed that THC is metabolized in the lung and liver but no definitive data is available as to metabolism in either brain tissue or brain blood vessels. The evidence is that both THC and Hydroxy-THC easily penetrate into brain tissue, with Hydroxy-THC most easily accumulating in the brain. Likewise, a study with eight cannabinoids noted that all showed effects correlated with their brain/plasma level ratios.[9]

2. Relationships between percent plant-THC and plasma-THC

As noted in the foregoing, the THC in available marijuana can be as high as 36 percent. However, the science is a bit behind these numbers in that most of the available studies are with marijuana in the range from 1.3 to about 13 percent THC per cigarette. Moreover, the free molecules of THC in the marijuana plant are not the defining number as to the potential blood level of THC in the user. New molecules of THC are created during smoking, while some THC is destroyed during smoking.[12] Thus, only ten to perhaps 60 percent of the potential THC in the plant is actually delivered to the user. Further of note is the use of the word “blood” in some of the studies. Blood is normally used to denote whole blood, rather than the derived fractions known as plasma and serum. And, given that plasma is about 55 percent of the whole blood and THC, and other cannabinoids are about 90 percent bound to proteins in the plasma, the specimen of choice for marijuana studies is plasma from the living humans.[13]

Now, following up on the question, “is there a relationship between percent THC in the smoked cigarette and plasma THC?” the following edited tabulation from two articles in 1990 and 2006 allows an initial answer.[14,15]

Just looking at the numbers in the two columns of plasma levels, there seems to be no direct relationship of increasing levels with increasing the percent of THC. In fact, the average value for the maxima of the ranges is 171.8 with a standard deviation of 44.3. That is only a variation of 26 percent in the high plasma levels for about a 1,200 percent increase in the plant-THC level. A similar evaluation of the column of "Ave. Plasma THC" data affords an average value of 109.02 +- 31.5 with a Standard Error of 29 %. Clearly, there is no relationship between the dose (amount of THC) and one’s response (which is the plasma level of THC). The true variable herein is likely the user, whereby a level of effect is personally attained by adjustments in smoking to obviate the variable amount of THC in the cigarette.[16] A next logical conclusion could be that even with marijuana at 25 percent THC or higher, users will *not* increase their maximum plasma THC levels. In fact with more THC per puff, one *could* expect total smoking will not increase.

3. Relation between degree of “High” and plasma THC

One learns to smoke, and to get to a “high” that is likely unique to the person as suggested in the above

data analysis. And, as suggested in the following tabulation, with no dose-response relationship, some persons report a perception of a "high" from marijuana cigarettes with little-to-no THC.[17] The "personalization" of this phenomenon, "the high," seems to be well illustrated in the following tabulation.[11,12,18,20]

An analysis of the tabulated results above allows one to conclude as per the previous tabulation of percent plant THC v. plasma THC, that there is no direct relationship between the degree of "high" and plasma THC level. In addition, an analysis of the range of the maxima for the range of plasma levels, affords an average of 214.1 with a Standard Deviation of 55.9. Again, similarly as for the percent THC, we note only a variation of 26 percent when the "degree of high" changed by more than 1,000 percent. Thus, the first entry in the table shows that the "high" was experienced by no one, even at a plasma level of 190, and, some noted a maximum "high" of ten with a Plasma THC of only five. Once again, it seems that the true variable is the user.

As reported by Heustis, *et al*., the peak plasma level can occur in five minutes while smoking, or up to about 15 minutes post smoking even after the intravenous administration of THC.[18] And, the peak level is usually found before the perception of the "high." It has also been shown by Heustis, *et al*., that the plasma level of THC decreased from about 150 ng/mL to less than ten ng/mL within about 50 minutes after starting to smoke.[19] Moreover, the practiced user will usually experience the "high" earlier than the occasional user under the same conditions, as does the alcohol drinker at low blood alcohol levels.[20]

4. Occasional marijuana users v. practiced users

As noted in the foregoing, the practiced marijuana user is additionally distinguishable from the occasional user by at least the following:

1. Achieves a "high" about 5 minutes earlier than the occasional user;[21]
2. Achieves a plasma THC level about twice as high as the occasional user when smoking equal cigarettes as shown in the following at five minutes post smoking at a dose of 500 micrograms (µg) THC per kilogram body mass;[16,21]

Table 12.3
Plasma THC Levels in Occasional v. Practiced Users

Occasional Users	(Plasma Levels)	Practiced Users
1.9–134 ng/mL	Range	7.9–244.8 ng/mL

After Smoking 13% THC at the Two Doses:[15]

250 µg/mL	500 µg/mL
57.3 +- 48.9 ng/mL	93.6 +- 63.9 ng/mL
58.0 +- 47.7 ng/mL	95.1 +- 63.2 ng/mL

These two groups, thus, showed a dose-response of about two when the amount of THC was doubled from 250 to 500 μg/mL. This seeming dose-response relationship was not seen in population studies noted in the foregoing tabulations of "percent THC" and "degree of high" relative to plasma levels of THC.

3. On the first day of a seven-day forced abstinence study, heavy users had residual plasma-THC levels of from 7.0 to 9.0 ng/mL.
4. Even after a seven-day forced abstinence, heavy/practiced users can have plasma THC levels of 1.2 to 5.5 ng/mL. More importantly, the change over time of the THC level was not continuously decreasing; but, some days showed an increased level from the previous day's level.[4,5]
5. At five to 15 minutes post smoking of a single marijuana cigarette, as shown above, the heavy user can achieve a plasma THC of up to 250 ng/mL.
6. One study with 6.8 percent plant-THC found no adverse behavioral effects in heavy users at 15 minutes post smoking with plasma levels of THC of 13 to 63 ng/mL.[22]

5. Is THC the only psycho-active cannabinoid?

One of the earliest studies with carbon-14-labeled (radioactive) THC concluded that the peak of the "high" was between ten to 140 minutes.[8] The other finding was that the peak effects coincided with peak levels of THC-metabolites. The study further identified two of these metabolites as 11-hydroxy-THC and 8,11-Dihydroxy-THC, just a portion of the hundred-or-so known cannabinoids. The study's author, R. Mechoulam, debatedly the father of marijuana chemistry, states that THC has no odor, but that it is the burning of the marijuana plant that affords the unique pyrolized terpene-based smell.[23] In fact, both of these early studies concluded that the whole marijuana experience is due to the diverse cannabinoids formed in the plant, the smoke, and the user. And, consistent with these early observations, more recent analytical reports show how rapidly the metabolites are found in the blood either after smoking or intravenous administration of THC.[8] For example, after having smoked a cigarette with 15.8 milligrams of THC, a peak THC plasma level occurred at 8.4 minutes during smoking. And, a peak level of 11-Hydroxy-THC occurred at 15 minutes post smoking.[19] A further study after I.V. injection of 4 to 5 mg THC afforded the following: [12]

- THC peak level at 20 minutes with 63.0 ng/mL;
- 11-Hydroxy-THC peak level at 25 minutes with 3.0 ng/mL;
- Beta-hydroxy-THC peak level at 25 minutes with 4.0 ng/mL.

All three of the above are noted to be psychoactive. In addition, in one study with heavy-users at a dose of 400 μg/kg, the following were found (see also 24.):

e (min.)	THC (ng/mL)	11-Hydroxy-THC
0	7.1	2.9
15	101.0*	17.5
30	47.4*	15.2
60	22.1	10.8

From this tabulation, it should be noted that the heavy user was back to about the pre-smoking THC-level after four hours (7.1 v. 8.0) but not the metabolite level (2.9 v. 4.7). And, as noted in the seven-day abstinence study, one can tentatively conclude that the heavy user will have an elevated level of THC and at least one active metabolite at some time even if not having recently smoked. One other point to be made is that the metabolite did not decrease in concentration in the blood as rapidly as did the THC, which delay is likely due to time of metabolism from THC to the 11-hydroxy-THC metabolite. This property of the half-time (half-life) for elimination is likely an individual characteristic for redistribution to tissues and metabolic efficiency, and is a measure of the time for the level to decrease by 50%. And, different studies, as would be expected, afford different half-lives. In fact, there is an initial half-life of about 15 to 30 minutes and a terminal half-life of hours to weeks at levels below ten ng/mL as noted above. THC is reported to decrease by about 50 percent in about 0.3 to 1.6 hours, and 11-hydroxy-THC in two to 3.1 hrs. This infers that after a single cigarette, a typical occasional user would likely have a plasma THC less than 1.0 ng/mL at six hours post smoking.[7,11,12,25]

Perhaps noteworthy, in contrast to the above numbers for the living patient, the post-mortem values have been noted to have much higher 11-hydroxy-THC values of 2.5 to 85, with THC levels of 1.4 to 20.0.[13,26] The conclusion here could be that the user involved in an auto accident had smoked some hours prior to an accident. The autopsy condition affords another complication in the impairment question in that post-mortem redistribution of THC from the lung has been demonstrated affording higher blood levels than pre-mortem.[27]

6. Urine testing for cannabinoids: clinical or evidentiary value?

To try to coin a phrase, smoking marijuana produces Psychoactive THC which is converted (metabolized) into non-Psychoactive THC-COOH, also referred to as THC-ACID in the body. Current laws/statutes of some states note that any amount of a marijuana-related substance (THC-COOH) in urine affords that “You Are Dead Meat!” What is a different science-based reality for tomorrow’s laws/statutes?

a. Two studies of 18 and 25 person groups of “long-term heavy cannabis users” maintained in a research unit for a seven-day period of cannabis absence reported that all 43 had measurable plasma THC-COOH at day seven. The amounts were between 2.8 and 45.6 ng/mL. Although limited urinary data were collected, it is well recognized that urine has the effect of affording concentrated solutions of some chemicals relative to their blood levels. THC-COOH is used as the abbreviation for the principal non-psychoactive metabolite of THC that is found in blood, urine, and elsewhere after THC is assimilated in some form.[6,28]

b. More to the point of this section is the conclusion of a 1992 study: “No correlation was found between blood THC and blood or urine THC- Acid concentrations.”[29]

c. A 2001 article that focused upon urine THC for an eight-hour period after smoking concluded that urine-THC peaked after about two hours post smoking.[21,30] They then positively concluded that a urine THC value greater than 1.5 ng/mL “suggests” use in previous eight-hour period. These authors also positively concluded for THC-COOH that ”this metabolite cannot be employed as a chemical marker in urine for recent use.” And, passive inhalation or false positive test results further complicate the interpretation of the urine test data for THC-COOH.

d. Ellis, *et al*., in 1985 found that one person had a positive test for urine THC-COOH up to day 77 post use before the test became negative at the 20 ng/mL cut-off level.[31]

e. Concurring with the manufacturer of the Emit II screening test kit statement relative to a positive result, "does NOT indicate or measure intoxication." And, Leiken and Paloucek assert that, "urine drug levels are NOT directly related to toxic symptoms seen clinically."[30,32,33]

f. A positive urine test result for THC-COOH after a single smoking event does not repeatedly re-test as positive on consecutive days and does not relate to a body level of any psycho-active cannabinoid. Furthermore a positive test result for urinary THC-COOH should *not* be used to predict either the time-of-use of marijuana, or, the condition of the user at the time of presentation of the specimen.[34]

7. Impairment & marijuana: laboratory and on-road data

This section deals principally with the alleged impairment effects of marijuana use, and, may be better described as behavioral effects noted in marijuana users. These marijuana-associated effects include: forgetfulness, distractibility, attention, concentration, transient awareness lapses (getting stuck), short-term memory, tympanic awareness of cardiac effects, heightened senses, anxiety/panic, sleepiness, munchies (hunger), giggles, uncontrolled (collective) laughter, increased sociability, need for physical activity, and relaxation, among others.

Thus, we begin with a quote from O'Kane, *et al*., in 2002[35]: "The purpose of measuring active THC levels can only be to detect recent use, or estimate the time of use, rather than directly measure the degree of intoxication." They further note that after a single cigarette, the perceived effects last about 45 minutes; and, a meta-analysis indicated that THC-related impairment is concentrated in the first two hours after smoking. Likewise, Kurzthaler, *et al*., in 1999 noted, "very important parameters of driving ability seem to be impaired immediately after cannabis consumption," with, "physiological, emotional and perceptual changes rarely last longer than 2–3 hours after consumption of a single cigarette."[36] More specifically, the report by Solowij in 1998 notes that laboratory tasks and flight simulators may not be realistic in trying to relate to actual driving.[37] And, a review by Iverson in 2000 states, "marijuana users, however, seem to be aware that their driving skills may be impaired and they tend to compensate by driving more slowly, keeping some distance away from the vehicle ahead and in general taking less risks."[38] These authors also note in a statement by Weil, *et al*., in 1986, that some drug-experienced subjects show no deficits in cognitive and motor functions at all with heavy marijuana use, whereas naïve users were very much affected.[39] Further to this point, a study by Klonoff, *et al*., in 1974 with on-road driving, noted that 23 percent of subjects showed comparative improvement, and 14 percent significant improvement in a high dose condition.[40] Solowij also quoted Smiley (1986) that under an emergency situation the seeming ability of the marijuana user to compensate is decreased.[37,41] And, finally in 2002, Heustis states, "the results of open- and closed-road driving studies and of culpability studies do not consistently document increased driving risk."[11]

1. A most recent study (2012) by Schwope, *et al*., evaluated performance and observable signs of ten chronic, heavy marijuana users for six hours after having smoked a 6.8 percent cigarette (58 mg THC). A summary of their findings is as follows: [22,32]

   a. Peak "High" and heart rate were noted at about 15 minutes from the beginning of the ten-minute smoking period. Blood pressure and respiration were not affected.
   b. At five minutes post smoking with plasma THC levels of 13 to 63 ng/mL, "little psychomotor impairment was observed, although there were robust cardiovascular and subjective responses."
   c. Blood THC concentrations decreased rapidly during the hour after smoking; but, subjective effects persisted, and, decreased linearly for one to six hours post smoking. Good subjective effects included: good drug effect; stoned; high; stimulated; and sedated.

2. Bosker, *et al*., in 2012 studied the possibility of using Standardized Field Sobriety Testing (SFST) for evaluating the effect on performance in 20 heavy users. They concluded that SFSTs were mildly sensitive to impairment from cannabis in heavy users as was the result of a similar study by Papafotiou, *et*

al., in 2005. Both of these studies showed a 30 to 50 percent probability of indicating impairment. These results are about as ineffective as the breath test to blood test relationship and FSTs at alcohol levels below about 0.125.[42,43,44]

3. Likewise, a study by Bramness, *et al*., in 2010 employed the Norwegian Clinical Test for Impairment (CTI) consisting of some 20 sub-tests.[44] They apparently concluded from a study of 589 drivers, "No relationship was found between blood THC and most of the CTI tests." The study seemed to allow between a five to 53 percent probability of indicating impairment using CTI data. They did conclude that blood THC was related to conjunctival injection, pupil dilation, pupil reaction to light, and the overall risk of being judged impaired. Clearly, the results seem to come from the eye of the beholder as with FSTs of DUI-related suspects.[44]

4. A 2006 study by Ramaekers, *et al*., tried three performance test protocols with 20 marijuana users. Only at serum THC levels greater than 30 ng/mL did they find impairments for about the first hour.[24] They noted that suggestions of impairment were noted between two to five ng/mL. The dose-response plots of performance v. THC afforded correlations of three to 14 percent; thus, not supporting their conclusions. A similar study by Barnett, *et al*., indicated impairment at about 25 ng/mL also; but no linear plots were afforded, thus no statistical analysis was possible.[46] More to the point of THC-level and impairment, six of the following seven references show THC-levels less than 30 ng/mL within 30 minutes of peak plasma THC-levels.[2,11,16,19,20,35,48] These results seriously argue against the five ng/mL level at the time of testing as defining "statutory impairment" as argued in refs. 2 and 15 by Ramaekers, *et al*., based upon the referenced articles by Hunter, *et al*., and Drummer, *et al*.[49] The Data in the Drummer, et al;, article also do NOT support the 5 ng/ml limit as follows :: Their data were from autopsies, thus not plasma: A direct pre=mortem comparison would have their value as above 5 to be above 15 ng/ml (13.); their OddsRatio (OR) data for THC did not correlate with Crash-Risk Data; their OR data for Alcohol were also not correlated with Alcohol Crash-Risk data.

5. A 2000 on-the-road study reported by NHTSA noted that a dose of 100 μg/kg: "significantly impaired performance" and "performance deficits were minor."[46]

6. The 2006 study by Ramaekers, et al., with 20 "light users" and 13 percent plant-THC cigarettes at 250 and 500 μg/kg showed a serum THC of 93.6 ng/mL at five minutes, and 10.61 ng/mL at 60 minutes post smoking. However, they reported major impairments from 15 to 90 minutes for cognition, impulse control, and psychomotor function.[24]

7. A similar study by Heishman, *et al*., in 1989 with a lesser THC concentration in moderate users, found no significant impairment in a circular lights task, a tracking task, and DSST at times up to 135 minutes post smoking.[47,48]

8. In 1998, N. Solowij stated, "a clear relation between blood levels of THC or its metabolites and degree of either impairment or subjective intoxication has not been demonstrated."[37]

D. Conclusions

1. Scientific literature reports on practiced marijuana users afford analytical and clinical data that totally disallow the definitive estimation of time since last use, and, any degree of any impairment based upon current drug testing methods.

2. THC-COOH has no part to play in any attempt to determine time-of-use of marijuana since the half-lives in plasma or urine are in the ranges of days to weeks respectively.

3. Given that THC-COOH is not psychoactive, neither plasma nor urine THC-COOH levels have any utility in assessing "degree of impairment."

4. Urine THC levels have been found to peak at about two hours post smoking, and urine 11-Hydroxy-THC peaks at about three hours post smoking. Thus, a ratio of 11-Hydroxy-THC to THC levels of greater than two allows that the time-of-use was less than about three hours.

5. Higher percentage amounts of THC in the available marijuana have not significantly increased plasma THC-levels in users, and, therefore, cause no probable change in currently acknowledged

marijuana-associated behaviors. It remains to be seen if increased levels of THC in the available marijuana will, in fact, lead to less total marijuana-smoking as is suggested by anecdotal evidence.

6. The perception of the "degree-of-high" is not directly related to a plasma level of THC.

7. The signs and symptoms associated with marijuana use are unique to the individual user, and are not defined/determined by blood levels of any cannabinoids.

8. When cognitive and/or psychomotor impairment was reported to have occurred, such effects were usually found within one hour of beginning the individual marijuana-smoking event.

9. So-called standardized field sobriety tests (SFSTs) in alleged marijuana-exposed individuals have, at best, a 30 to 50 percent probability of indicating some degree of impairment, and are a function of set and setting.

10. Plasma THC levels of above 30 ng/ml would allow that the occasional smoker could have been exposed to marijuana smoke within about the previous hour and the practiced smoker within about two hours.

11. The above afforded data and available comparative considerations of psychomotor functionality allow that the practiced/heavy-marijuana smoker is no more impaired, and either a danger to self or society than that of the committed social drinker and may be similar to the practiced coffee drinker, committed aspirin, valium, and/or non-steroidal anti-inflammatory drug-treated patients.

12. The sum and substance of the foregoing is that no blood level of any cannabinoid is objectively defensible as a measure of any degree of impairment in the individual smoker.

13. The proposed blood THC level of five ng/ml as the legal/illegal marker for the probable marijuana-related criminalization of the individual has *no scientific legs*.

12.2 Cannabinoid Disposition : After Ingestion

A. Introductory Summary

During thousands of years of cannabis/marijuana use by humans for both pleasure and alleged health/medical benefits, the almost exclusive method of assimilation was by smoking the cannabis plant in one form or another.[50] However, after the identification of the cannabinoids[2] as the principle unique chemicals in cannabis,[51] objective scientific studies related to cannabis became a reality. And, ultimately in the last 60 years, extraction and identification methodologies for very small amounts of chemicals in diverse specimens have been developed.[52] The published reports of such efforts have afforded tentative dose-response information relative to drugs in-general, and, cannabinoids in particular. Even given that most interest in marijuana/cannabis use has seemingly focused upon the recreational/illegal aspect of marijuana, some early studies in the 1970s referred to human health conditions such as epilepsy as possible therapeutic avenues for cannabis and cannabinoids. More recently,[53] a listing of such therapeutic opportunities included: neuropathic pain; spasticity from multiple sclerosis; urinary incontinence; increased intraocular pressure; pain from rheumatoid arthritis; cancers; and, with proven efficacy, in chemotherapy-induced nausea, and emesis and anorexia with AIDS. Even in consideration of the foregoing positive avenues for cannabinoid-related therapies, the primary difficulty was that smoking was not usually the desired route for administration. Thus, for about 50 years, the literature on the oral route for the administration of cannabinoids has been accumulating.[54] More robustly, however, given the legalization interventions in Alaska, Colorado, Washington, and Uruguay, the reality of the oral ingestion of very diverse cannabinoid-based products exists. This actual and perceived growing use of the ingestion and oromucosal routes of cannabis-based products for recreational and therapeutic health/medical effects provided an impetus for the preparation of this report.

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[2] Delta-9-tetrahydrocannabinol (a cannabinoid chemical) is denoted as THC. Please see Figure 12.1. below.

B. Some Comparative Data on Smoking and Ingesting Cannabis

The respiratory and gastro-intestinal routes for assimilation of chemicals into the human body offer dramatic contrasts. Small molecules in the air are generally known to pass into the blood stream very quickly. Breathing is the best example of such a chemical exchange. Absorption from the G-I tract, however, is quite another scenario. Time of transport seems to be first to come to mind. Thus, inhalation will afford blood levels of volatile chemicals within seconds to minutes. In fact, the blood in the lungs only has to pass through the left heart and up to the brain in seconds. Since the output from the heart affords about 20 percent of the blood to the brain, rapid onset is the norm after inhalation exposures. Continued smoking of a marijuana cigarette thus affords the brain first choice of inhaled cannabinoids with about 50 percent of the blood first going to the liver (27 percent) and kidney (23 percent). Then the re-circulating blood affords more THC and new cannabinoids formed in the liver or other tissue sites. However, absorption in the G-I tract may require hours to afford effective blood levels of many chemicals. The reasons for this may include time of emptying the stomach perhaps due to food or other aspects. The digestion processes in the stomach and intestines may also alter the rate and amount of absorption. Even then the chemicals must pass through the liver after entering the blood stream. The liver does a great amount of normal creating and destroying of chemicals. The absorbed THC is thus subject to destruction (metabolism) in the liver. The new products of this metabolism are new cannabinoids such as 11-Hydroxy-THC and other Hydroxy-THCs that may have effects on the brain (psychoactivity) as shown in Figure 12.1.

This figure offers the chemical structures of the principle cannabinoids considered as acting directly in/on the brain and other structures. Also, these and other cannabinoids may show additive and/or inhibitory effects by interacting at the diverse psychologic, physiologic, metabolic, and excretory processes. Of special note in this Figure 12.1 is that only the addition of one atom of oxygen changes THC into 11-hydroxy-THC, both of which are considered to be equally psychoactive. However, given the differences in plasma levels for perceived psychoactivity, the 11-hydroxy-THC may be the more potent of the two. The further addition of oxygen to the 11-hydroxy-THC produces the THC-COOH, which has no known psychoactivity and is the molecule most found in the urine. In summary, after smoking marijuana for a few minutes, the brain is accumulating only THC for about five minutes, and then THC and 11-Hydroxy-THC plus other cannabinoids for minutes to hours during the experiencing of the "high" as shown in Table 12.5.

Take for example the time of 15 minutes and note the levels of each chemical in Table 12.5. Clearly, the THC value seems to have peaked at about 50 ng/ml. None of the other hydroxylated metabolites of the THC molecule have reached their peak values. Thus, it seems quite logical that the feeling of some aspects of the "high" even during the first deep inhalation must be ascribed almost exclusively to the THC molecules affecting the brain. A more detailed evaluation of the above tabulations affords a molecular view of the effects of cannabis via smoking and I.V. routes versus the ingestion route. Thus, at five minutes, the THC level was at 33 whereas the other four cannabinoids were at a total of 2.16. Then at 60 minutes the levels were THC at 12 v. 5.2 for smoking/I.V. and 3.8 v. 5.4 for ingestion; however, even at 90 minutes, the THC is highest after the I.V. route. Then, at 90 minutes the metabolites of THC were about equal to or higher than the THC levels after ingestion. These data comparisons allow relative changes whereby the molecules become more concentrated in the blood than the original THC. And several authors have stated that it is the metabolites with psycho-activity that are the agents of the "high" at about one to three hours post cannabis use.[57]

About two hours after ingestion of THC-products, the brain will be almost equally exposed to three or four cannabinoids due to metabolism of the ingested THC (as noted above and in Table 12.6 below). Most importantly, this exposure may not begin for one to three hours after ingestion as noted in the time versus effects and plasma levels in Table 12.6. This summary tabulation clearly shows the distinguishing characteristics between the timing of the "high" after inhalation versus ingestion. Moreover the tabulation affords some blood testing data that allow a better appreciation of the user's cannabis-effect scenario. In this regard, the seemingly seminal data are for the plasma levels of the cannabinoids near the plateau phase,

which may be described as the desired level of "high" for many persons. Thus, it is shown that the total of the plasma levels after both routes of assimilation are very nearly identical at one hour. Namely 13–18 ng/mL for inhalation and 22.3 for ingestion. In neither of these conditions would the users be objectively considered impaired even with the plasma levels above 5 ng/mL but less that 30 ng/mL as noted in the previous article.

From this confluence of time-of-onset of effects and different cannabinoids in the blood during the perception of cannabis' effects, as one source intimates, "it may be useful to think of oral cannabis as a different drug than smoked cannabis."[56] Most noteworthy in regard to this comparison of smoking versus ingestion is that the smoker can attain levels of THC up to 200 ng/mL within minutes of starting to smoke, but levels less than 30 ng/mL appear to be attainable via the oral route as noted in this above tabulation.

This difference in the cannabinoid levels while "high" is shown with the THC/11-hydroxy-THC ratio. Thus, only after a few minutes of smoking, the THC-level is 10 to 20 times the level of 11-hydroxy-THC. However, after ingestion the THC is less than one-half that of the 11-hydroxy-THC metabolite. Perhaps after reading this chapter, the perceptive reader will conclude that the specifics of assimilation via the different routes do have different objective behavioral consequences.[60]

1. How do bioavailability measures relate to ingestion?

The bioavailability concept regarding ingestion of cannabis products is most complicated by the fact of the distance that the psychoactive cannabinoids must travel to enter the blood. This travel time of about 0.5 to 1.5 hours must be contrasted with that of smoking with a travel time of seconds to minutes. Furthermore, given the known facts that the cannabinoids bind very strongly to proteins and are highly selective for fatty tissues, the very biology of the gastro-intestinal tract interferes with the passage of the cannabinoids into the blood. This propensity for fatty tissue distribution is relatable to a measurement known as the Volume of Distribution (V_d). Thus, alcohol which is water soluble has a V_d of 0.6 relating to the water content of the body of about 60 percent. The V_d for THC is about ten. Well known in this regard is the fact that drugs with a high V_d are not usually well understood in terms of their effects when plasma level data are used in therapeutic drug monitoring situations.[11] This V_d-related effect thus well explains the general lack of dose-response relationships with cannabis-related products noted in the previous section (12.1).

Even in consideration of the concerns of the type of cannabis product, effects of food on gastric emptying time and state of mind of the person, a major determinant of bioavailability via the ingestion route focuses upon the liver. The liver is where much of the chemical formation and destruction (metabolism) occurs in the body. Thus, THC is just another chemical when introduced into the metabolism process. And, as noted in the foregoing tabulations, metabolites of THC occur in the blood within minutes.

2. Is Dronabinol administration a good model for cannabis ingestion?

This dosage form (Dronabinol, Marinol) may be the most researched of the drug-products listed in the bioavailability comparison noted above. And, even with an absorption of 90 to 95 percent of the administered dose of THC, only about ten to 20 percent eventually reaches the circulating blood. Furthermore, the diverse effects of this therapeutically available drug (THC, Marinol, Dronabinol) have been well documented as both psychological and physiological. One source lists increased heart rate, reddening of the eyes, dry mouth and throat, increased appetite, and vasodilation as most frequently noted.[58] A somewhat complete listing of noted adverse effects is in Table 12.8.

This listing of 35 "events" may seem excessive and/or prejudicial, but similar listings are as follows: Xanax-46; Paxil- 35; Cymbalta-30. And, most critically, one must consider that with *all drugs*, the concept of *side-effects* is *obfuscation* since they *all have multiple effects*. Another very good listing of these effects as positive, neutral, and negative is at EROWID.com as of Feb. 28, 1998 and updated on March 24, 2014.[58] One special precautionary event is described as the abstinence syndrome after dronabinol. This phenomenon was noted in a seemingly unique study at a dose of 210 mg/d for 12 to 16 consecutive days.[61] Then, within about 12 hours of discontinuation of dosing, some of the volunteers exhibited irritability,

insomnia, restlessness, hot flashes, sweating, rhinorrhea, loose stools, hiccoughs, and anorexia for up to 48 hours.

As a prescription medication uniquely formulated with THC as the active ingredient, to ask as to whether Dronabinol is a good model of ingestion seems like a moot question. And, in fact, the PDR (Physician's Desk Reference)[61], affords quite unique details of dose and response; but, more importantly plasma levels of THC with accompanying text in Table 12.9.

To be specifically noted in this tabulation are the apparent therapeutic levels after 10 and 20 mg twice a day. And, as noted above, the generally stated level is five ng/mL for impairment relative to the operation of a motor vehicle in several states. Noted under *warnings*: "Patients… should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it established that they are able to tolerate the drug and to perform such tasks safely." One may be tempted here to ask, "how do I do this safety analysis?"

The most definitive quantitative study with Dronabinol available to these writers was that of Lile, *et al*.[63] They reported plasma levels of THC and 11-hydroxy-THC as-well-as diverse effects for 12 hours following the ingestion of up to 90 mg of THC in fixed doses from 15 to 90 mg. Thus, at doses of 60, 75, and 90 mg, the plasma THC levels were above 30 ng/mL (25 to 75 ng) for three to five hours. But, the 11-hydroxy-THC levels never reached 30 ng/mL. Only at the lowest doses of 15 & 30 mg were the levels of THC and 11-hydroxy-THC about equal at between five and 15 ng/mL. Previous reports at lower doses have reported about equal levels of both of these cannabinoids after the administration of THC. These higher levels of THC at the highest doses suggests that the metabolic machinery can be saturated by excess THC. The question then becomes, "what are the behavioral effects of any ratio differences of the levels of cannabinoids with unequal efficacy?"

The studies noted in the PDR above had an analysis of the drug's effects between 30 and 60 minutes with the "high" at two to four hours and some psycho stimulation from four to six hours with the plasma levels at or below 20 ng/mL. In the report by Lile, *et al*.[63], they reported *no* significant dose-dependent effects on "good drug effect, high, and, tired sedated" up to 90 mg doses with blood levels of THC in the ten to 20 ng/mL range in the first one to two hours, and levels between 30 and 75 ng/mL during hours three to five in the regular cannabis users. This comparison of two sets of data suggests, and is a well known conundrum that, set-and-setting are prime factors in physiological and psychological effects during cannabis use. Also documented and discussed in the report was the phenomenon of individual variability. Thus, the highest THC value was 130 ng/mL with an average of about 75; and the highest 11-hydroxy-THC value was 50 with an average value of about 25 ng/mL.

As discussed earlier, the route of assimilation of THC affords a different ratio of cannabinoids in the blood of the users over time from the earliest minutes until about one hour post inhalation. The work of Lile, *et al*. even after ingestion of THC noted different amounts of the cannabinoids over the three to five hours post use. This quantitative comparison further suggests that the effects after cannabis use cannot be completely described as the direct effect of only THC.[64.65]

3. Any overall advantages of the oromucosal route?

Sativex will be described herein as the prototypical agent in this category. Most interesting is the fact that Sativex has been introduced as a therapeutic agent in Canada and the United Kingdom in the treatment of spasticity with multiple sclerosis. The Sativex product is represented as an extract of cannabis. Up to 13 cannabinoids and related chemicals have been detected in some samples. In this regard Sativex can be considered as a mixture not unlike the smoke from a burning reefer. Actually a sample studied by Karschner, *et al*.[53], had a composition of about equal amounts of THC and Cannabidiol (CBD) that was administered to 9 (six male, three female) marijuana smokers. They reported that absorption was 92 to 98 percent with bioavailability of 11 and 13 percent, about that which is noted for Dronabinol. They also interpreted their data to show that there was no significant interference in the disposition of THC in the body due to the presence of CBN. This finding suggests that absorption, distribution, metabolism, and

excretion were not integral to any drug-drug interactions of these two cannabinoids. Their data were presented as comparisons of plasma levels of THC after oral THC versus oromucosal (buccal) administration as follows:

As can be noted from this tabulation, the levels of both the THC and CBD were about equal from both dosage forms. Also, the times to maximum levels were about equal. This data suggests that the two cannabinoids were apparently not competing at any level. They further noted that the times until detectable effects was 2.0 to 2.5 hours for the two doses, which is not significantly different. The maximum levels for CBD were 1.6 and 6.7 and for THC 5.1 and 15.3 ng/mL between the two doses. The highest level for CBD was 20.5 ng/mL. The 11-hydroxy-THC levels after the spray administration were 4.2 and 8.4 ng/mL for the doses respectively. Also noted was the great individual variability among the participants as with the Dronabinol reports. Again, note that these therapeutically-directed blood levels were above the legal/illegal value of 5 ng/mL.

Given the ability to spray as desired would seem to offer as much control as smoking until one notes the times of effect of an hour or so. That delay would argue that smoking allows the most control toward eliciting the desired effects of cannabis use. The oromucosal route may be second best, with the ingestion route and all of the diverse dosage forms already on the market the least likely to be effectively mastered. One additional caveat needs be kept in mind regarding the buccal route of administration is that some to much of the material is swallowed. Thus, one has two routes contributing to the blood levels.

4. Can the effects after ingestion of cannabis be made more objective?

The cannabis smoker has almost total control of the process of assimilation of cannabinoids into the blood stream. Given the spray of Sativex with the oromucosal route, one would think that one would have quite good control of the effects as well. But the buccal route is not as efficient as was originally postulated as detailed above. This process of controlled application/administration of several prescription medications such as morphine and Xanax is known as titration. And, in general one starts with a lowest dose which is readily/rapidly acting, and, depending upon the perceived effect, one can the change the dose or not. In this manner one can arrive at a dose and time process to afford optimal drug effectiveness. And, in contrast to the smoking and oromucosal routes, one has the tedious ingestion route of assimilation. In fact, emesis may be the only method to intervene with the effects of the ingestion of the cannabis products.

Unlikely as the probability for effectively interrupting the effects following the ingestion of cannabis seems, a very reasoned process for effective ingestion of cannabis-containing products has been published on the EROWID web site which they have entitled “L.E.S.S.“ Perhaps, this is one instance where LESS is likely *more*! We further afford an interpretation of this “L.E.S.S.” process as follows : A *low* percent-THC cannabis product is ingested regularly (about every 30 minutes) to *establish* effects for at least two hours, then *supplemented slowly*. A further note on the EROWID site states that cannabis products are *drugs* and *not food*.[58] These comestibles are “*drug delivery devices*“, or, *dosage forms*, and *not food*.

Another listing may be more effective for novices:

- Start low (% THC);
- Establish potency (30 to 60-minute intervals for four to six hours);
- Slow, be patient (haste makes wasted);
- Supplement as determined from effects at interval ingestions;
- Start sober;
- Larger batches provide consistency (unless Rx-perientialism is the philosophy).

Another quite natural product that has been utilized by humans and other organisms for thousands of years is alcohol. Clearly, the histories of both cannabis and alcohol have many similarities. But, contrary to

the ingestion of alcohol, only recently has the ingestion of cannabis-infused products come to the fore. And, a web search of medical marijuana infused products shows the colorful items and apparent THC concentrations as per item pictured (unit doses). Now, again similarly but way out front, is unit dose information for alcohol-infused products.[66,67] Thus, except for the most recent imported and craft beers, a beer contains about ten to 12 grams of alcohol. A four-ounce glass of "average" wine and a shot of "average" whiskey each also have about ten to 12 grams of alcohol. And, again similar to the afforded suggestion for cannabis ingestion, a routine for drinking alcohol is available. As reported in 1963,[68] a person of average weight of 150 pounds who drinks one shot per hour will not attain a blood alcohol concentration (BAC) of 0.08 percent, with 0.08 percent being the legal limit in the United States. The average drinker, consuming the average beverage, will likely have a BAC between 0.04 and 0.07 percent even after five to seven hours of drinking. However, at two drinks per hour, this average person is more likely to have a BAC above 0.08 percent after two hours of drinking.

Thus, the answer to this question 4 is *yes*. But, like much else in this good life, it will not be easy.

C. Conclusions

1. The ingestion of cannabis products affords a banquet of cannabinoids that differ from those rapidly available after smoking.
2. All routes of cannabis assimilation afford some cannabis-derived chemicals for gastro-intestinal absorption.
3. Two therapeutically available cannabis-derived drugs prescribe doses that afford THC plasma levels below 30 ng/mL.
4. Dronabinol (Marinol) is reportedly considered safe and effective with cannabinoid blood levels above five ng/mL with one Dronabinol study at 90 mg THC per day reporting a level of 75 ng/mL.
5. The psychological and physiological effects evidenced after cannabis use cannot be explained based only upon plasma levels of lipoidal-THC.
6. As Sativex is being evaluated for therapeutic use, the plasma THC levels apparently considered as safe and effective will have some patients above the level of five ng/mL as with some Dronabinol patients.
7. Ingestion of cannabis-containing products even without unit-dose concentrations data for THC/ Cannabinoids could be safely carried out via the EROWID-noted "L.E.S.S." process.
8. Controlled effective ingestion of unit-dose cannabis-containing products can be effected with these products with known levels of cannabinoids as with the known unit-dose alcohol-based products.
9. The available therapeutic cannabis formulations and cannabis-infused products also with identified concentrations of THC can afford plasma levels of THC routinely up to about 20 to 30 ng/mL.
10. The known statutory "per se" limits of one to five ng/mL for plasma THC levels in suspects in some states are not scientifically reliable relative to any statistically significant degree of impairment.

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Table 12.1
Percent Plant THC and Plasma THC Relationship

No. of subjects	Plant-THC(%)	Ave. Plasma THC (ng/ml)	Range*
6	1.0	90.4	45.6–187.8
4	1.3	71.3	18.7–99.6
6	1.32	100.0	62.8–125.3
6	1.92	119.8	44.5–180.9
18	2.40	63.0	11.7–137.0
6	2.46	119.0	81.0–203.0
6	2.54	162.6	107.4–204.7
4	4.60	146.3	63.5–227.6
12	4.84	124.2	44.8–218.0
11	13.0	93.6	25.0–134

* Modified Table I. from reference 14, where the percent Plant THC/plasma-THC correlation was 0.269, or 7.2 percent.

Table 12.2
Degree of "HIGH" and Plasma THC

Degree of "High"	Plasma THC (ng/mL)*
0 = least "high"	2–190
1	2–6
2	2–317
3	3–240
4	2–251
5	2–250
6	3–210
7	4–112
8	4–215
9	7–196
10	5–160

* The correlation for degree of high and plasma THC was only 12.2 percent.

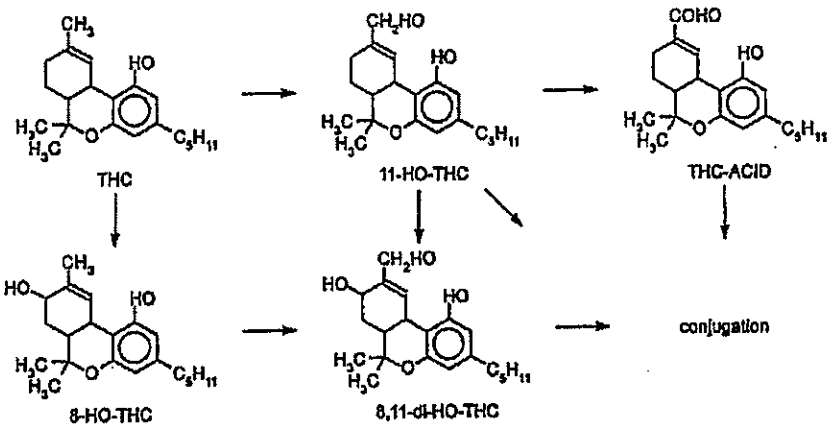

Figure 12.1 Cannabis-derived cannabinoids found in humans.
** Modified from Baselt[55]*

Table 12.5
Time Course of Plasma Cannabinoids #

After 4–5 mg I.V.

Time	THC	11-hydroxy-	8-alpha-hydr-	8-beta-hydr-	8,11-dihydroxy
5 min.	33	0.8	0.26	0.8	0.3
15 min.	51	2.3	0.34	1.8	0.6
30 min.	36	2.8	0.79	2.2	1.0
60 min.	12	1.7	0.70	1.8	1.0
90 min.	8.6	1.4	0.68	1.3	1.0

After 20 mg Orally

60 min.	3.8	3.4	—	—	2.0
90 min.	5.7	4.7	—	—	3.8
120 min.	4.3	7.2	—	—	6.0
180 min.	7.1	8.5	—	—	6.7

#Plasma levels are as nanograms per milliliter(ng/ml).[56,57]

Table 12.6
Psychometrics After Cannabis Ingestion*

"HIGH"	SMOKING#	INGESTION#
Onset	0–10 min.	30–120 min.
Increasing	5–20 min.	30–90 min.
Plateau	15–30 min.	130–300 min.
Decreasing	45–180 min.	60–240 min.
Duration	60–240 min.	240–600 min.

Blood Testing Data

THC/11-Hydroxy-THC Ratio at Onset :	10–20 times	1.0–0.45 times
Cannabinoids found in plasma at Onset :	THC 11-Hydroxy-THC	THC 11-Hydroxy-THC 8-Hydroxy-THC's 8,11-Dihydroxy-THC
Plasma levels at Plateau (nanograms per ml.) :	THC : 100–200 11-Hydroxy-THC : 5–10	THC : 7.1 11-Hydroxy-THC : 8.5 Dihydroxy-THC : 6.7
Plasma levels at 1 hr.	THC : 10–15 11-Hydroxy-THC : 3–5	Variable to none

*Modified from EROWID March 24, 2014[58]
#Average values from products containing about 20 mg THC[56,59]

Table 12.7
Bioavailibility Data on THC from Dosage Forms

The bioavailability is a measure of the amount of a chemical found-in versus the amount administered-to the person.

1.	Smoking	2–56 %
2.	Ingestion	4–20 %
3.	Dronabinol(Marinol)	10–20 %
4.	Sativex(40 % THC & 35 % Cannabidiol)	11–13 %
5.	Volcanos	36–61 %

Table 12.8
Adverse Events After Dronabinol Ingestion*

Incidence greater than 10%		Incidence less than 1%
Asthenia	Aberrant thoughts	Conjunctivitis
Facial flush	Nervousness	Hypotension
Palpitations	Ataxia	Myalgias
Tachycardia	Confusion	Diarrhea
Vasodilation	Depersonalization	Fecal Incontinence
Abdominal Pain	Dizziness	Depression
Nausea	Euphoria	Nightmares
Vomiting	Hallucinations	Speech Difficulty
Amnesia		Tinnitis
Paranoia		Flushing of Skin/Limbs
Somnolence		Vision Difficulties

Overdose is Indicated by the Following

Decreased Motor Coordination	Lethargy
Slurred Speech	Postural Hypotension
Panic	Seizures

* PDR-2007 and [61,62]...

follows:

Table 12.10
Pharmacokinetics of Sativex

DOSAGE FORMS	CBD	THC	T_{max} (hours)*
	ng/mL (std. dev.)		
Oral capsule (10 mg each THC & CBD)	2.5 (2.3)	6.4 (3.1)	1.0–2.4 (THC)
Buccal spray (10 mg each THC & CBD)	3.0 (3.1)	6.1 (5.4)	1.3–2.8 (CBD)

*The plasma data are for one dose only; but the time to max, levels was low v. high dose (low was 5.4 mg THC and 5.0 mg CBD v. 16.2 and 15.0 respectively). Dosing via six actuations within one to two minutes by study physician.[53]

Table 12.9
Pharmacokinetics: Dronabinol In Fasted Persons*

TWICE DAILY DOSE (milligrams)	PLASMA LEVELS (ng/mL, (Std. Dev.))	EFFECT (hours)
2.5	1.32 (0.62)	0.5–4.0
5.0	2.96 (1.81)	0.5–4.0
10	7.88 (4.54)	0.5–3.5
20 (extrapolated data)	17.0 (9.0 est.)	unknown

*Modified from PDR as per above.