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# Evaluating the Broadening Use of Prescription Marijuana Related to Workers' Compensation Claims

## I. The Legal Status of Medical Marijuana

Marijuana is mentioned in historical texts dating back at least 5,000 years, and its recreational and medicinal uses have been well documented for centuries (Bostwick 2012; Littlebury, 1737). In the United States, marijuana was officially listed as an illegal substance in 1937, and its lawfulness has been debated ever since. The recreational use of marijuana in the United States emerged most notably in the 1960s as part of a counter-culture movement. At that time, its use evoked a negative connotation and was associated closely with the use of other illicit drugs such as cocaine and heroin. Over the years, the public and scientific view of marijuana use has softened as researchers have found beneficial uses of the drug for medicinal purposes. In 2013, the U.S. federal government allowed legalization and oversight at the state level (NCSL 2016). As of early 2016, 25 states had legalized medical marijuana, and 17 others had passed limited access marijuana product (low THC/high CBD- cannabidiol) laws (NCSL 2016). However, one may argue that complete legalization of this very complex and understudied drug is a bit premature.

Many positive research studies have given marijuana a legitimate reason for acceptance in the medical field. Many of these patients (specifically, chronic pain) attribute the origin of their disease or suffering from a work-related incident that is covered by a worker's compensation claim. The insurance industry has been struggling with how to legally and fairly handle such claims when marijuana (a Federally illegal, Schedule 1 drug) has been recommended to treat the patient. In addition, there are at least 10 drugs on the market that are based on the main psychoactive components of marijuana and the research in this field is exploding. The future of marijuana use in medical issues is only going to increase.

## II. Definition of Marijuana

Many marijuana advocates boast that it is a "natural" product that has been used safely for millennia; however, today's marijuana is not the same as that of the Greeks (Littlebury 1737; Wargo 2013). Over the years, marijuana aficionados, kitchen chemists, and backyard cultivators have developed ways to elevate their "high" through breeding, extraction, and further concentrating the psychoactive components of marijuana. This has resulted in marijuana that is as much as 22 times more potent than

that of the 1960s (Greydanus et al. 2013; Volkow et al. 2014). Resinous secretions from the plant can be collected, dried, compressed, and smoked as hashish. Hashish oil is extracted using a solvent and can also be smoked, eaten, or vaporized (NHTSA 2004). Each of these techniques effectively concentrates the main psychoactive compound, delta- 9- tetrahydrocannabinol (THC), thus creating a more potent "high". This process results in the unintended concentration of many other chemicals as well, including pesticides (Raber et al. 2015).
THC is one of many naturally occur-ring cannabinoids in marijuana and is the most significant and potent psycho-active cannabinoid in the plant. The average THC concentration in marijuana can range between 1–22 percent, with concentrations in hashish ranging between 5–15 percent and concentrations in hashish oil raging between 3–20 percent (Greydanus et al. 2013; NHTSA 2004). Marijuana cannabinoids have also used for medicinal purposes. For example, Dronabinol (Marinol) is a synthetic THC that has several clinical uses, such as an appetite stimulant and an antiemetic to treat or prevent nausea and vomiting caused by cancer medications or to increase the appetite in AIDS patients.

**Acute Health Effects of Marijuana**

Once inhaled, THC blood concentration peaks between 3–10 minutes, quickly followed by psychological effects within 5–30 minutes (Huestis 2007; Neavyn et al. 2014). Marijuana induces acute effects in multiple organ systems, including cardiovascular, respiratory, immune, gastrointestinal, and neurological (Sachs et al. 2015). Acute, dose- dependent cardiovascular effects of marijuana exposure includes tachycardia, increased cardiac labor, systemic vasodilation, and increased blood pressure (Sachs et al. 2015). The acute respiratory effects include increased airway resistance, inflammation of large airways, and damaged lung tissue (Sachs et al. 2015). It is clear that marijuana affects cognitive behavior, and there is strong evidence that short-term cannabis use can affect a user's ability to have free recall, acquisition of information, working memory, and procedural memory (Sachs et al. 2015). Other cognitive abilities that are impaired by short-term use include attention, impulsivity, inhibition, sensory perception, and executive function (Sachs et al. 2015). Additional acute effects include increased total sleep at the cost of poor sleep quality, impairments of gross motor tasks, and decrements in decision making (Sachs et al. 2015). Notably, all of these abilities that marijuana affects are essential to navigating a vehicle properly (Sachs et al. 2015).

The many types of cognitive impairments that are effected by short-term cannabis use are transient and diminish over time upon cessation of marijuana use (Sachs et al. 2015). Yet, there are some studies that indicate functional alterations in the brain can be found in adolescents shortly after using this drug, suggesting the younger brain may be uniquely susceptible to long-term damage even after short-term exposure (Sachs, 2015).

**Chronic Health Effects of Marijuana**

There is some evidence of persistent neurophysiological impairments after chronic use of marijuana; however, the risk of developing these impairments is related to the age of initial use and the frequency and duration of use (Sachs et al. 2015). Essentially serious deficits of IQ, visual attention, verbal fluency, inhibition, short-term recall, impulsivity, and executive functions have been associated with early (young adult) and prolonged use of marijuana (Sachs et al. 2015). Importantly, with early and chronic use, these conditions are not transient, and cognitive deficits may remain after cessation (Sachs et al. 2015). Chronic use since adolescence is also associated with structural abnormalities in the brain of the adult and has been shown to cause a reduction in the size of specific regions of the brain, including the para-hippocampal, hippocampal, and thalamic volumes (Sachs et al. 2015).

Immune disorders associated with marijuana use are complex and not fully understood and there is evidence that marijuana is immunosuppressive and has been shown to have anti-inflammatory properties (Sachs et al. 2015). Based on limited information, researchers speculate that naturally-occurring cannabinoids (endocannabinoids) generally enhance the immune response, whereas exogenous cannabinoids, such as those in marijuana, play a role in immunosuppression (Sachs et al. 2015).

**Pharmacokinetics of Marijuana**

The very complicated pharmacokinetics (absorption, distribution, metabolism, excretion, ADME) of marijuana (THC and other metabolites) has been studied for decades. The early studies focused on the effects of the drug on behavior and less on the toxicity or complex pharmacological properties of the drug. The recent interest in legalizing the drug has driven a four-fold increase in scientific studies over the past 15 years, and these studies have shown that marijuana is a complex mixture of chemicals that have both beneficial and detrimental health effects. Other than THC, there are more than 100 different cannabinoids in marijuana, many of which can be metabolized to other reactive compounds. While scientific studies on the effects of marijuana have increased, the full effects are still unknown. One complicating factor in understanding its metabolism is that there are 100 currently known metabolites of THC (Huestis 2007).

Once ingested or inhaled, THC is quickly absorbed into the blood stream and systemically distributed throughout the body. The general order of organ deposition over time for THC is first in the blood-brain-high profusion tissues (heart, lung, liver), secondly in the low perfusion tissues (adrenal glands, skin), and then it is ultimately stored in fat (Kreutz and Axelrod 1973). With prolonged use, THC will concentrate in fat, suggesting that THC forms stable fatty acid conjugates. Fat deposition is an important factor in the interpretation of testing results, especially for chronic marijuana users. Over time and during abstinence, THC redistributes from the fat tissue to the blood stream, and then systemically. THC is primarily metabolized in the liver to two primary metabolites, 11-hydroxytetrahydrocannabinol (11-OH-THC) and 11-nor-9- carboxytetrahydrocannabinol (THC COOH), which are eliminated in the urine (Huestis 2007). THC COOH in the urine is used as an indirect indicator for THC exposure or past marijuana use. Chronic users may have detectable THC COOH in their urine for weeks or months after cessation due to the slow release of THC from fat tissues, which is then metabolized to THC COOH. However, for acute or occasional users, detectable THC COOH in the urine may be present for less than 24 hours (Battistella et al. 2013; Huestis et al. 2006). It is suggested that prolonged retention of THC in heavy cannabis users is responsible for the prolonged detection of THC COOH in urine, cannabis-related flashbacks, and cognitive deficits (Huestis 2007).

In contrast to alcohol impairment effects, which are driven by one primary component (ethanol), marijuana is a mixture of different components that contribute to multiple (positive and negative) effects in individuals. Smoking or eating marijuana has been shown to induce psychoactive, pain- killing, appetite stimulation, anti-nausea, and many other effects, many of which are currently under study. It is well known that marijuana has diverse and individual psychoactive effects in humans; however, it is the individual- specific nature of these effects that makes it very difficult to determine the dose- response associated with the use of marijuana and impaired driving for the general public.

## III. Marijuana in Medicine

**Early medicinal use of marijuana**

Early uses of marijuana and hemp seed include anesthetic for surgery, treatments for measles, chicken pox, inflammation, gonorrhea, cough, jaundice, worms, rheumatism, rabies, cholera, tetanus, cramps, delirium tremens. At the time, there were very few early alternatives for many of these illnesses (especially cholera), so it is not surprising that they would turn to herbal remedies. It was not until the mid-20th century did the "medical development" or its use slow. Some of the main responds for this reduction include pharmaceutical development of similar-affect drugs, its well-known pharmaceutical instability (i.e. a wide variety of efficacy and effects) and legal/economic aspects, including restriction of transport and use. One could argue that it's reemergence in the US was instigated by the state of California legalizing its medicinal use.

More recent studies have provided insight into the components of Marijuana. Specifically that it's a mixture of chemicals that may have diverse effects, including 489 naturally-formed chemicals, which include 70 cannabinoids.

**Current, promising animal studies**

Recent studies have shown that Cannabis derivatives may have a role in treating multiple medical issues, including acute, visceral and cancer pain, neuro-inflammatory, neurodegenerative disorders, appetite, weight gain, cancer, seizure disorder, and inflammatory bowel disease. The research community is gaining confidence in the future use of cannabis as well. In 2015, the National Institutes of Health (NIH) spent $111 million on 281 projects involving cannabinoid research, including $21 million on therapeutic properties.

**Future projects**

The cannabis-related projects that the NIH is projecting to fund in the next few years include those related to stress (both physical and anxiety), schizophrenia, inflammation, atherosclerosis, viral persistence in treated HIV/SIV, using it to treat opioid addiction, those involving alcohol + marijuana – driving, genetics related to use and abuse,  and gender differences. NIH projects related to worker injuries can include those related to stress (physical – carpal tunnel; psychological – anxiety), inflammation – repetitive action, HIV – occupationally acquired, cancer (appetite, nutritional uptake), pain management.

**Complications after use**

Delineating the complications of marijuana use is as complex and controversial as the drug itself. Some studies have indicated there is a fast progression to dependence and a greater likelihood of engaging in other risky behaviors. Some studies indicate that prolonged use can cause a specific physiological issues, namely cannabis use disorder (CUD). There are also case studies that indicate excess intake, specifically through eating THC-containing food may trigger of an undiagnosed psychotic behavior. These studies are on-going and caution should be taken when interpreting the ramifications of this drug on such psychological behavior. It is expected that, as legalization spreads to other states, so will its use. Over a period of time and as research studies progress, more and higher quality information will emerge regarding the how acute and chronic use impacts ones behavior.

**Clinical Testing for Marijuana**

Obtaining a representative cannabinoid concentration (THC or THC COOH) from a person is essential to understanding the effects of smoking or ingesting marijuana on driving behavior. For marijuana, four types of biological samples can be collected and examined for cannabinoid concentration; blood, urine, saliva, or hair. There are advantages and disadvantages to each.

Blood samples represent the most accurate account of THC concentration, and THC correlates well with psychomotor deficiencies (Huestis 2007), especially after acute exposure. THC is rapidly metabolized within 30 minutes of inhalation exposure and blood concentrations can drop to below 5 micrograms per liter (μg/L) within 3 hours of exposure for non- chronic users (Battistella et al. 2013). Thus, to corre-late behavior such as impaired driving to THC blood concentrations, samples should be taken and analyzed as soon as possible. Additionally, taking blood samples is considerably more invasive and requires a skilled technician. These factors pose significant challenges to using blood as the testing media to indicate driving impairment. Blood samples may be beneficial in legal cases because generally an accurate concentration is required to determine an exceedance of a legal threshold. THC concentration in saliva correlates well with blood concentrations, and saliva testing is less invasive, provides rapid results, and is currently being used for road-side testing (Lee and Huestis 2014). However, the concentration of THC in saliva that directly corresponds to deficiencies in psychoactive behavior has not been fully elucidated, and there is considerable variability among testing populations. Urine testing offers an opportunity to test only for the presence of THC COOH. This methodology is even less invasive, but it provides little information regarding recent marijuana use because THC COOH can be detected in the urine for weeks to months after drug use (Huestis 2007). Hair testing is the least invasive and has been used extensively, especially for marijuana-related cases involving employment and child protection (Moosmann 2015; Pichini 2014). However, interpretation of hair-test results for THC, THC COOH, or THCA-A (Δ 9- tetrahydrocannabinolic acid A, the non- psychoactive precursor of THC), is limited to past use or passive secondhand exposure. Studies have shown that these three cannabinoids can be detected in hair of non- consuming individuals due to transfer through the cannabis consumer via touch, sebum/sweat, or smoke (Moosmann 2015; Pichini 2014). It is generally accepted that hair is not an appropriate medium to illustrate impairment or recent use (Moosmann 2015).

There are a few studies that have shown that storage conditions and containers used for the biological sample can affect THC testing results (McCurdy et al. 1989; Schwope et al. 2011; Stout et al. 2000). Collection of whole blood in plastic containers and stored at room temperature (20–25°C), followed by being frozen for four weeks can result in a 0–40 percent decrease of THC in the samples. No change in THC concentration was found in those samples collected in glass vials (McCurdy et al. 1989). Another study of THC COOH in urine collected in plastic containers reported a 14–17 percent decrease in THC COOH when samples were stored at 4°C. Samples stored at 25°C, a higher temperature, indicate <5 percent decrease in THC COOH levels (Stout et al. 2000). This presents yet another layer of uncertainty with interpreting testing results relative to impairment at the time that the biological sample was collected.

**Mathematical Models to Predict Past Exposure and Impairment**

Clinical data (e.g., blood, breath) taken after an accident are commonly used to determine blood alcohol content and level of impairment before, or at the time of an accident. As previously discussed, the way that the body responds to and metabolizes alcohol easily permits the use of predictive models. Those models provide scientifically valid and practical estimates for interpreting the level of impairment due to

alcohol at the time of an accident. Unfortunately, cannabinoid metabolism is considerably more complicated. This is due to possible psychoactive effects from multiple cannabinoids that can contribute to impairment. In addition, THC can be stored in fat tissues and later released in chronic marijuana users; it is metabolized by enzymes that are known to have a varying rate of activity, and the pharmacokinetics and pharmacodynamics depend on the individual (Huestis 2007). Early studies in the development of pharmacokinetic models for marijuana were promising and may be considered in some cases (Huestis et al. 1992). However, the application and interpretation of these models should be performed with caution, and limitations should be clearly stated.

Furthermore, it is hard for a marijuana smoker to predict his or her own psychological responses to different types of marijuana. There is no standard concentration labeling for a joint or a marijuana-containing food product as there is for alcohol products, such as a bottle of beer, which would have labeling indicating the beer's alcohol concentration. Thus, even if someone self-reports marijuana use, the dose would be unknown and can be very difficult to determine.

There are several important weaknesses in the body of literature regarding the metabolism of cannabinoids and how cannabinoids affect psychomotor skills, as well as driving skills. The most striking limitation is an almost global lack of pre- study testing for THC or THC COOH to determine baseline levels, which may be present in the case of chronic users, especially in the early studies. In addition, most studies rely on questionnaires to self-report prior cannabis use, which may bias the study results. Without understanding the pre-study cannabinoid concentrations, the attribution of the test substance versus that from previous exposures to the testing endpoint (e.g. blood concentrations, urine concentrations, psychomotor testing, among others) would be in question (Sachs et al. 2015). This limits the application of these studies for determining the contribution of the drug to a level of measured impairment.

Global variation in smoking behavior is also a significant factor to consider when applying study data to forensic analysis for marijuana. In one small study, the authors attribute reported cannabinoid concentrations in clinical samples to differences in smoking behaviors, including side-stream inhalation, smoking retention, and depth of inhalation (Schwope et al. 2011). Another problem with many of these studies is the lack of appropriate control groups (Neavyn et al. 2014; Sachs et al. 2015).

## IV. How Toxicology Can Help

A toxicologist can help understand how, or to what extent, the clinical data indicates impairment, if other contributing factors were involved, including other prescription drugs or alcohol. The can also evaluate the blood or urine sample for the presence of other substances (e.g., legal or illegal drugs) at levels that may be associated with impairment, help you understand the limitations in the use of mathematical models to predict past exposure to marijuana, and understand and elucidate the complexity of this drug regarding dose-responses associated with various levels and forms of impairment. Finally, toxicology is what drives the justification for legal and illegal use. Understanding the limitations of this data that is the bases of decision making is essential in ensuring the rules and regulations pertaining to this drug are fair for all stakeholders.

**Reference lists for bases of document**

- Battistella G, Fornari E, Thomas A, Mall JF, Chtioui H, Appenzeller M, Annoni JM, Favrat B, Maeder P, Giroud C. Weed or wheel! Behavioral and toxicological investigations of how cannabis smoking affects skills necessary for driving. PLoS One. 2013; 8(1): e52545.
- Bostwick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. Mayo Clin Proc. 2012 Feb;87(2):172-86.
- Greydanus DE, Hawver EK, Greydanus MM, Merrick J. Marijuana: current concepts. Front Public Health. 2013 Oct 10;1:42.
- Hels T. Bernhoft IM, Lyckegaard A. Risk of Injury by Driving with Alcohol and other Drugs. Driving under the Influence of Drugs, Alcohol and Medicines (DRIUD) Integrated Project. 2011. Available at: http://www.druid-project.eu/Druid/EN/deliverales-list/downloads/ Deliverable_2_3_5.pdf?__blob= publicationFile
- Huestis MA, Elsohly M, Nebro W, Barnes A, Gustafson RA, Smith ML. Estimating time of last oral ingestion of cannabis from plasma THC and THC COOH concentrations. Ther Drug Monit. 2006 Aug ;28(4) :540-4.
- Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. II. Models for the prediction of time of marijuana exposure from plasma con-centrations of delta 9- tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta 9- tetrahydrocannabinol (THC COOH). J Anal Toxicol. 1992 Sep-Oct;16(5):283-90.
- Huestis MA. Human Cannabinoid Phar-macokinetics. Chemistry & biodiversity. 2007;4(8):1770-1804.
- Kreuz DS, Axelrod J. Delta- 9-tetrahydrocannabinol: localization in body fat. Science. 1973 Jan 26;179(4071):391-3.
- Lee D and Huestis MA. Current knowledge on Cannaboids in Oral Fluid. Drug Test Anal. 2014, 6(0):88-11.
- Littlebury I. The history of Herodotus: Trans-lated from the Greek: 1737. London, Volume 1, Third Edition: 381.
- McCurdy HH, Callahan LS, Williams RD. Studies on the stability and detection of cocaine, benzoylecgonine, and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid in whole blood using Abuscreen radioimmunoassay. J Forensic Sci. 1989 Jul;34(4):858-70.
- Moosmann B, Roth, N, Auwärtera V. Finding cannabinoids in hair does not prove cannabis consumption. Sci Rep. 2015; 5: 14906.
- National Conference of State Legislatures (NCSL). State Medical Marijuana Laws. 2016. Available at: http://www.ncsl.org/ research/health/state-medical-marijuana-laws. aspx
- National Highway Traffic Safety Admin-istration (NHTSA). Drugs and Human Performance Fact Sheets, Cannabis / Mar-ijuana (r9 - Tetrahydrocannabinol, THC) 2004. Available at: http://www.nhtsa.gov/ PEOPLE/INJURY/research/job185drugs/can-nabis.htm
- National Highway Traffic Safety Administra-tion (NHTSA). Marijuana & Alcohol Combined Increase Impairment, No. 201. 1999. Available at: http://www.nhtsa.gov/About+NHTSA/ Traffic+Techs/current/Marijuana+&+Alcohol+C ombined+Increase+Impairment
- National Highway Traffic Safety Administra-tion (NHTSA). Research Report. Drug and Alcohol Crash risk. 2015. U.S. Department of Transportation NHTSA. DOT HS 812 117.
- National Transportation Safety Board (NTSB). 2013. Reaching Zero: Actions to Eliminate Substance-Impaired Driving. Washington, D.C. Available at: http://www. ntsb.gov/Pages/default.aspx
- Neavyn MJ, Blohm E, Babu KM, Bird SB. Medical marijuana and driving: a review. J Med Toxicol. 2014 Sep;10(3): 269-79.

- Pichini S, Garcia-Algar O, Alvarez A, Got-tardi M, Marchei E, Svaizer F, Pellegrini M, Rotolo MC, Pacifici R. Assessment of unsus-pected exposure to drugs of abuse in chil-dren from a Mediterranean city by hair testing. Int J Environ Res Public Health. 2014 Feb 21;11(2):2288-98.
- Raber JC, Elzinga S, Kaplan C. Understand-ing dabs: contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. J Toxicol Sci. 2015; 40 (6) :797-803.
- Ramaekers JG, Berghaus G, van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend. 2004 Feb 7;73(2):109-19.
- Repp KK and Raich AL. Marijuana and Health: A comprehensive Review of 20 Years of Research. Washington County, Oregon Department of Health and Human Services. 2014. Available at: http://learn-aboutmarijuanawa.org/Reports/Marijuana_ review_ReppRaich_Oct2014.pdf
- Sachs J, McGlade E, Yurgelun- Todd D. Safety and Toxicology of Cannabinoids. Neurother-apeutics. 2015 Oct;12(4):735-46.
- Sagan C. 1969. As relayed by Grinspoon L, Marijuana Reconsidered. Harvard Medical School Harvard University Press, 1971.
- Schwope DM, Karschner EL, Gorelick DA, Huestis MA. Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharma-cokinetics following controlled smoked cannabis administration. Clin Chem. 2011 Oct;57(10):1406-14
- Sewell RA. Poling G, Sofuoglu M. The effect of cannabis compared with alcohol on driving. Am. J. Addict. 2009 18(3):185-193.
- Stout PR, Horn CK, Lesser DR. Loss of THC COOH from urine specimens stored in poly-propylene and polyethylene containers at different temperatures. J Anal Toxicol. 2000 Oct;24(7):567-71.
- Transportation Research Board, 2010 - http://onlinepubs.trb.org/onlinepubs/circulars/ec146.pdf
- USDOT 2015. Procedures for Transportation Workplace Drug and Alcohol Testing Pro-grams. DOT Rule 49, CFR Part 40, Section 40.87, Subpart F – Drug Testing laborato-ries, What are the cutoff concentrations for drug tests? Available at: https://www.trans-portation.gov/odapc/part40/40_87
- Volkow ND, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014 Aug 28;371(9):879
- Wargo E. 2013. Drugs and Health Blog: Can it be Bad If It's Natural? From the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH). https://teens.dru-gabuse.gov/blog/post/can-it-be-bad-if-its-natural