Should Per Se Limits Be Imposed For Cannabis? Equating Cannabinoid Blood Concentrations with Actual Driver Impairment: Practical Limitations and Concerns

Paul Armentano

National Organization for the Reform of Marijuana Laws

paul@norml.org

Abstract

Fourteen US states have amended their longstanding, effect-based DUI drug laws to *per se* or zero tolerant *per se* statutes in regard to cannabis. Other states are considering enacting similar legislation. Under these amended traffic safety laws, it is a criminal violation for one to operate a motor vehicle with trace levels of cannabinoids or their metabolites in his or her blood or urine. Opponents of *per se* cannabinoid limits argue that neither the presence of cannabinoids nor their metabolites are appropriate or consistent predictors of behavioral or psychomotor impairment. They further argue that the imposition of such *per se* limits may result in the criminal conviction of individuals who may have previously consumed cannabis at some unspecified point in time, but were no longer under its influence. As more states enact statutory changes allowing for the legal use of cannabis under certain circumstances, there is a growing need to re-examine the appropriateness of these proposed *per se* standards for cannabinoids and their metabolites because the imposition of such limits may, in some instances, inadvertently criminalize behavior that poses no threat to traffic safety, such as the state-sanctioned private consumption of cannabis by adults.

Keywords: marijuana, cannabis, cannabinoids, driving, psychomotor skills, per se, medical marijuana, impairment, carboxy THC, THC

Introduction

Since 1996, 18 states and the District of Columbia have enacted legislation regulating the physician-authorized use of cannabis by patients diagnosed with specific qualifying diagnoses (NORMLa, n.d.). In November 2012, voters in two states – Colorado and Washington – decided in favor of ballot initiatives legalizing the private consumption of cannabis by those over the age of 21. These two latter state laws took effect in December 2012. Separate statewide legislative proposals to allow for the limited therapeutic use of cannabis and/or the substance's social consumption by adults are pending in the various state legislatures and are increasingly gaining support among the public (Silver, 2011).

The ongoing political debate regarding the legal status of cannabis for adults, along with the recent relaxation of cannabis laws in certain jurisdictions in the United States, has coincided with renewed concerns among politicians, law enforcement personnel, and some members of the public regarding the substance's potential impact on driving performance and accident risk. These concerns have provoked some state legislatures to amend their traffic safety laws in regard to cannabis.

Presently, the criminal laws in all 50 states prohibit the operation of a motor vehicle by a person who is proven to be under the influence of cannabis. These types of traffic safety laws are referred to as "effect-based DUI laws" because they mandate prosecutors establish that a motorist recently ingested cannabis and that doing so prohibited him or her from safely operating a motor vehicle. (In other words, the state must prove that a subject's psychomotor impairment was a direct effect of the substance consumed.)

Recently, however, some states have begun to enact additional *per se* or zero tolerant *per se* statutes to their criminal traffic safety codes specific to cannabis. These *per se* laws create a new traffic safety violation based solely on whether or not specific quantities of cannabinoids or their inert metabolites are present in a subject's blood or urine above a specific, state-imposed threshold. By definition, a zero tolerance *per se* limit for cannabinoids means that the presence of any amount of cannabinoids in the body above zero is a traffic safety violation. Under such statutes, prosecutors do not need to establish in court that the presence of these compounds caused a subject's psychomotor impairment (or even that a subject was, in fact, impaired). As a matter of law, the only issue before the court is whether or not a defendant engaged in the act of driving with a detectable level of cannabinoids or cannabinoid metabolites in his or her bodily fluids. Proof that the defendant was behaviorally impaired is not required under the law for a prosecutor to gain a criminal conviction.

The imposition of *per se* traffic safety laws is not an altogether new legal development. Notably, *per se* blood alcohol limits already exist and are legally enforced in all 50 states. That is because a scientific consensus exists regarding the presence of specific blood alcohol levels and impairment of performance. However, until recently, such *per se* standards were not imposed upon other psychoactive substances, such as illicit drugs or prescription pharmaceuticals, despite the fact the ingestion of these substances may adversely impact psychomotor performance.

In recent years, lawmakers in several states have expanded *per se* limits to include cannabinoids. To date, *per se* or zero tolerant *per se* laws exist for cannabis in 14 states. Prosecutors in four of these states (Nevada, Ohio, Pennsylvania, and Washington) enforce *per*

se levels for THC and/or its [1]metabolites, while the other 10 states (Arizona, Delaware, Georgia, Illinois, Indiana, Iowa, Michigan, Rhode Island, Utah, and Wisconsin) impose zero tolerant *per se* thresholds (NORMLb, n.d.). The 2012 National Drug Control Strategy Report called for the imposition of zero tolerant *per se* standards for cannabis in every state, including in those states that allow for its legal consumption (Executive Office of the President, 2012).

This federal recommendation has elicited significant debate. At present there is limited and, at times, conflicting research available regarding the complex relationship between cannabis intoxication, driving behavior, and traffic accident risk (Grant et al., 2012). Further, cannabis' unique pharmacokinetics and its varying effects on human performance raise questions regarding whether the imposition of such a one-size-fits-all *per se* limit is applicable for cannabinoids or their metabolites. Finally, the changing legal status of cannabis under various states' laws also begs the question of whether the imposition of these statutes may be scientifically validated or whether they are legally justifiable, particularly in those jurisdictions that allow for the substance's legal use in private.

To clarify this ongoing political and public safety debate, the following paper reviews the pharmacokinetics of cannabinoids and assesses whether the available science substantiates the presumption that psychomotor impairment may be consistently inferred from the presence of THC or its metabolites in a single blood sample and, thus, whether the enactment of legal *per se* limits for cannabis are appropriate.

Cannabinoid Pharmacokinetics

Cannabis possesses a distinctive absorption pattern following ingestion. The term pharmacokinetics refers to the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body. The term cannabinoids refer to the biologically active (though, depending on the specific cannabinoid in question, not necessarily psychoactive) constituents in cannabis. Cannabinoids possess relatively unconventional pharmacokinetics, particularly compared to alcohol (Chesher et al., 2002).

Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive constituent in cannabis. Maximum levels of THC are typically present in the blood in human subjects within three to ten minutes following cannabis inhalation (Grotenhermen, 2003). However, unlike in the case of alcohol, these peak THC/blood levels do not typically correspond with a subject's maximum levels of behavioral impairment. In a clinical setting, it has been documented that subjects exhibit "little psychomotor impairment" during the initial fifteen minutes immediately following cannabis inhalation, despite maximum concentrations of THC occurring in the participants' blood during this time period (Schwope et al., 2012). This phenomenon is defined as "counter-clockwise hysteresis," meaning that the effects of the psychoactive substance lag behind observed, maximal drug concentrations. This phenomenon is contrary to the pharmacokinetic profile of alcohol, whereby as peak blood alcohol levels positively correspond with a subject's peak level of drug-impaired performance.

[1]The *per se* limits in these states are as follows: Nevada: 2ng/ml THC in blood or 15 ng/ml of carboxy THC in blood or urine; Ohio: 2ng/ml THC in blood or 35 ng/ml of carboxy THC in blood or urine; Pennsylvania: 1ng/ml THC in blood or 1 ng/ml carboxy THC in blood or urine; Washington: 5ng/ml THC in blood.

Cannabis' maximum influence on performance typically manifests in subjects some 20 to 40 minutes following inhalation (Sewell et al., 2009), during a time period when the subject's THC/blood levels are rapidly falling. The substance's influence on behavior then diminishes relatively rapidly some 60 minutes (National Highway Traffic Safety Administration, 2003) to 2.5 hours (Sewell et al., 2009) after inhalation. During this period of time, subjects' blood/THC levels continue to decline. Because of this relatively confined duration of drug effect, it has been suggested that cannabis consumers who wish to avoid driving impaired wait a minimum of 3 to 4 hours after dosing before attempting to operate a motor vehicle (Fischer et al., 2011).

In addition to THC, blood analyses for cannabinoids also typically screen for the additional presence of two distinct THC metabolites: hydroxy THC and carboxy THC (THC-COOH). Hydroxy THC is psychoactive and is considered to be at least equipotent to THC (National Highway Traffic Safety Administration, n.d.). It is present in blood at low levels almost immediately following cannabis inhalation. Peak concentrations of hydroxy THC in blood are typically present some 20 to 30 minutes following inhalation (Huestis et al., 1992). This metabolite possesses a relatively short detection period in blood, typically not exceeding six hours (National Highway Traffic Safety Administration, 1999), though the detection of hydroxy THC at trace levels for longer periods of time has been reported (Huestis et al., 1992). Because of this fairly short detection window, it may be argued that the presence of hydroxy THC, particularly when present in substantial quantities, may be an indicator of recent cannabis ingestion and, possibly, behavioral impairment.

The more commonly detected cannabis metabolite in blood screens is carboxy THC. Unlike hydroxy THC, carboxy THC is not psychoactive (National Highway Traffic Safety Administration, 1999). Contrary to hydroxy THC, carboxy THC typically remains present in blood plasma for several days in occasional users and weeks in more chronic consumers (Musshoff et al., 2006). It is also readily detectable in urine for extensive periods of time, such as several months, in formerly heavy consumers of cannabis (Musshoff et al., 2006). Because this metabolite is non-psychotropic and possesses a relatively long half-life in both blood and urine, it has been concluded, "[Q]uantitation of THC-COOH can neither accurately predict the time of last cannabis use nor suggest any relationship between urine drug concentrations and psychomotor performance" (Musshoff et al., 2006, p. 159)." Ramaekers and colleagues similarly state, "[P]ast use of cannabis as determined by the presence of THC–COOH in drivers does not (increase crash risk)" (Ramaekers et al., 2004, p. 116). The website of the National Highway Transportation Safety Association (NHTSA) also affirms, "It is … impossible to predict specific effects based on THC-COOH (blood) concentrations" (National Highway Traffic Safety Administration, n.d.). Consequently, *per se* and zero tolerant *per se* laws that define a traffic safety violation solely based upon the presence of this commonly identified metabolite lack scientific validity and risk inappropriately convicting non-impaired individuals simply because they previously consumed cannabis several days or even weeks earlier.

THC Absorption Patterns: Variances Between Naive and Experienced Users

As previously acknowledged, peak concentrations of THC in blood are typically present in subjects prior to their cessation of smoking or immediately thereafter (National Highway Traffic Safety Administration, n.d.). These maximum concentrations decline rapidly after inhalation, often falling below 5ng/ml in non-chronic users within 1 to 4 hours (Huestis et al.,

1992, Musshoff et al., 2006, National Highway Traffic Safety Administration, n.d.). Subjects' consumption of higher potency THC will result in slightly higher THC blood concentrations for more persistent lengths of time (Huestis et al., 1992). Concentrations of THC in the blood of infrequent cannabis consumers generally fall below limits of quantitation within 8 to 12 hours following inhalation (Huestis et al., 1992, National Highway Traffic Safety Administration, n.d.).

The oral ingestion of THC results in a different pharmacokinetic profile. Following oral ingestion, THC/blood concentrations rise slowly over time, resulting in maximal concentrations some 60 to 120 minutes after dosing (Grotenhermen, 2003). The onset of drug effects is also significantly delayed. THC/blood concentrations then decline slowly over a period of several hours. Unlike the case with cannabis inhalation, counter-clockwise hysteresis is less apparent following the oral ingestion of cannabis.

Following consumption, THC accumulates rapidly in body fat, where it is stored in various tissues and then slowly redistributed to the blood. While occasional consumers of cannabis will likely test negative for the presence of THC in blood within 12 hours following inhalation, THC's lipid solubility may cause some chronic users – such as those legally authorized under state law to consume cannabis therapeutically for the treatment of a chronic medical condition – to potentially test positive for residual concentrations of THC even after several days of abstinence[2] (Karschner et al., 2009), long after any behavioral influence of the substance has worn off[3] (Skopp et al., 2008). Chronic consumers may also experience intermittent spikes (Karschner et al., 2009, Musshoff et al., 2006) in THC/blood levels in the absence of new use during this terminal elimination phase. The potential presence of residual, low levels of THC in the blood, combined with the possibility of periodic increases in THC/ blood levels absent concomitant use, arguably confounds the ability of toxicologists or prosecutors to interpret whether the presence of THC in the blood in a single sample is evidence of new cannabis consumption by an occasional consumer or, instead, is indicative of past consumption by a more frequent cannabis user. (Toennes et al., 2008).

Because cannabinoids' pharmacokinetic profile may be influenced by the subjects' prior pattern of use, as well as by the specific route of cannabis administration, rather than solely by the single use of cannabis itself, the website of the US National Highway Traffic Safety Administration (n.d.) acknowledges, "It is difficult to establish a relationship between a person's THC blood or plasma concentration and performance impairing effects." Nonetheless, under the cannabis-specific *per se* and zero tolerant *per se* standards now imposed in 14 US states, the detection of virtually any concentration of THC or its metabolites will result in a criminal conviction, regardless of whether the defendant has recently consumed cannabis or whether the state can establish that a person was behaviorally impaired by cannabis. In those states that now allow for the legal use of cannabis by specific segments of the population under statute, it is arguable that the traffic safety laws – in order to be equitable and impartial – should

[2]A study by Karshner et al. (2009) of 25 frequent, long-term cannabis users residing in a clinical research unit reported, "On day 7, six full days after entering the unit, six participants still displayed detectable THC concentrations (in whole blood)" (p. 1).

[3]A study by Skopp et al. (2008) concluded THC's extended presence was not accompanied by the presence of cognitive or behavioral impairment. Investigators concluded: "[D]etection of psychoactive cannabinoids seems possible over a time period of more than 24-48 hours after abstaining from cannabis smoking. … Impairment could not be assessed … in any subject at the time of blood sampling" (pp. 161, 163).

mandate sufficient evidence of a subject's cannabis use immediately prior to driving as well as objective evidence of behavioral impairment as a legal requirement. Such requirements would assure that the traffic safety laws are not inadvertently punishing unimpaired individuals who have engage in the legally protected behavior of having consuming cannabis in private.

Inferring Psychomotor Impairment from a Single THC Blood Sample: Additional Limitations

Cannabinoids' influence on psychomotor skills is complex and, at this time, not well understood. While it is well established that alcohol consumption increases accident risk, evidence of cannabis' culpability in on-road driving accidents and injury is far less robust (Armentano, 2013). Some studies identify an association between the presence of THC the blood of drivers and an increased risk of motor vehicle crashes (Paula et al., 2012, Asbridge et al., 2012, Laumon et al., 2005,) while others do not (Sewell et al., 2009, Chesher et al., 2002). It has been suggested by Sewell (2009) and others (Ronen et al., 2008) that subjects under the influence cannabis are hyperaware of their perceived impairment and attempt to compensate for it accordingly by driving more cautiously, such as by engaging in fewer lane changes, driving more slowly, and leaving greater headway between their car and the vehicle in front of them. One recent meta-analysis (Elvik, 2012) assessing the risk of road accident associated with drivers' use of licit and illicit drugs concluded that although cannabis consumption was nominally associated with greater accident risk, this risk was comparable to that associated with motorists' consumption of penicillin or anti-histamines – neither of which are subject to *per se* limits. By contrast, studies are fairly consistent in their conclusion that the combined ingestion of cannabis and alcohol, even at low doses, poses an additive adverse impact on psychomotor performance (Ramaekers et al., 2004) and is associated with an increased crash risk (Paula et al., 2012).

To further assess the potential role that cannabis consumption may or may not play in on-road accidents, a limited number of papers have evaluated whether there exists a concentration-dependent relationship between the presence of specific amounts of THC in a driver's blood and an elevated risk of accident. A 2004 multi-center case-control study of 3398 fatally-injured drivers reported: "Drivers with THC in their blood had a significantly higher likelihood of being culpable than drug-free drivers. For drivers with blood THC concentrations of 5 ng/ml or higher the odds ratio was greater and more statistically significant" (Drummer et al., 2004. p. 239). A double-blind, placebo-controlled study by Stough et. al. (2006) evaluating the performance of 80 participants following the inhalation of either cannabis cigarettes or placebo reported that psychomotor impairment appeared to occur in subjects with THC/blood levels above 3.1ng/ml but not in subjects with THC/blood levels below this threshold. It concluded, "As a result, in cases where only blood samples are available from drivers, low THC levels may not give rise to concern about driver impairment" (Monograph, p. 1, Key Findings) A cross-sectional assessment by Khiabani and colleagues of blood samples from Norwegian drivers suspected of driving under the influence of non-alcoholic drugs similarly reported, "Drivers with blood THC concentrations above 3 ng/ml had an increased risk for THC concentrations in blood above 2ng/ml (Paula et al., 2012). By contrast, other studies – including a series of trials commissioned by the United States government during which subjects inhaled cannabis drove in high intensity urban traffic– have reported no consistent

association between elevated THC concentrations in blood and significant psychomotor being judged impaired compared to drivers with lower concentration ranges" (Khiabani et al., 2006, p. 111). Most recently, a population-based case-control study of European motorists by Paula and colleagues reported a significantly increased risk of accident among drivers with impairment (National Highway Traffic Safety Administration 1993). Specifically, the National Highway Traffic Safety Administration (1993), concluded:

> One of the program's objectives was to determine whether it is possible to predict driving impairment by plasma concentrations of THC and/or its metabolite, THC-COOH, in single samples. The answer is very clear: it is not. Plasma of drivers showing substantial impairment in these studies contained both high and low THC concentrations; and drivers with high plasma concentrations showed substantial, but also no impairment, and even some improvement. (p. 107)

At this time, the literature attempting to associate dose-dependent blood THC concentrations with psychomotor impairment or accident risk remains limited and inconclusive. Among the available studies, most employ different methodologies and yield divergent results. Moreover, among the experts who have evaluated this potential relationship, there is no consensus as to what specific blood THC thresholds, if any, may be designated as evidence of impairment[4] (National Highway Traffic Safety Administration, 2003). A review of this literature identifies a fairly wide range of estimates, with some papers suggesting an association between THC blood concentrations and crash risk at levels as low as 1ngml in blood (Ramaekers et al., 2009) while others suggest that an elevated risk does not occur until THC blood concentrations exceed 10ng/ml (Grotenhermen et al., 2005). Other papers have suggested that THC concentrations in blood between 3.5 to 5ng/ml (Grotenhermen et al., 2007) or between 4 and 6ng/ml (Ramaekers, 2006) may offer "a reasonable separation of unimpaired drivers from impaired drivers" (Ramaekers 2006, p. 66). A review by Sewell et al. (2009) acknowledged, "Case-control studies are inconsistent, but suggest that while low concentrations of THC do not increase the rate of accidents, and may even decrease them, serum concentrations of THC higher than 5 ng/mL are associated with an increased risk of accidents" (p. 190).

The existence of these wide range of estimates make it apparent that experts have yet to achieve consensus regarding what, if any, specific concentrations of THC in blood may be considered as definitive predictors of psychomotor impairment. Further, variance in THC absorption patterns and in drug effects often differ significantly from person to person. Some subjects may exhibit behavioral impairment at low THC/blood levels while other subjects may exhibit limited or no behavioral impairment at relatively high THC/blood levels. This fact therefore makes it difficult, if not impossible, to apply proposed THC impairment levels equitably to individual subjects. Ramaekers et al. (2009) affirm, "It should be stressed however that the predictive validity of any *per se* limit is confined to the driving population at large, and not necessarily applicable to each and every driver as an individual" (p. 494).

[4]Statement of Gil Kerlikowske, "I'll be dead — and so will lots of other people — from old age, before we know the impairment levels [for marijuana]" (Associated Press, 2012).

Attempting to establish a consistent relationship between THC blood concentrations and psychomotor impairment is additionally complicated by the fact that experienced cannabis consumers become tolerant to many of the substance's behavioral effects. A study by Schwope et al. (2012) reported, "No significant differences were observed for critical-tracking or divided-attention task performance in (a) cohort of heavy, chronic cannabis smokers" (p. 405). A separate review by Sewell et al. (2009) also affirmed that experienced cannabis consumers who drive on a set course show almost no functional impairment under the influence of marijuana. Separate experimental trials (D'Souza et al., 2008, Ramaekers et al., 2009, Hart et al., 2010, Ramaekersb, et al., 2010) further confirm that experienced cannabis consumers become tolerant to cannabis' behavioral effects. These findings "emphasize the importance of taking into account the drug-use histories of research participants and examining multiple measures when investigating marijuana-related effects on cognitive functioning" (Hart et al. 2010, p. 333). Most recently, a review by Grotenhermen et al. (2012) concluded that subjects "who take cannabinoids at a consistent dosage over an extensive period of time often develop tolerance to the impairment of psychomotor performance, so that they can drive vehicles safely" (p. 499). Nonetheless, *per se* cannabinoid standards, as presently enforced in 14 states, do not allow arbiters of the law to take into account any of these factors, including some subjects' behavioral tolerance to the drug. Nor does the imposition of such standards reflect the reality that there exists little if any scientific basis or support for such legal limits. As more states debate the merits of depenalizing cannabis consumption and/or enact laws legalizing and regulating this behavior, further discussion and criticism regarding the scientific merits and equity of these laws would appear warranted.

Conclusion

The sole presence of THC and/or its metabolites in blood, particularly at low levels, is an inconsistent and largely inappropriate indicator of psychomotor impairment in cannabis consuming subjects. While some studies have suggested that an elevated crash risk is associated with increased THC concentrations in blood, others have not. Experts have also failed to agree on what specific THC concentrations, if any, may be consistently linked with impairment.

Further complicating such calculations is that cannabinoids' absorption patters and effects on performance vary widely from subject to subject, raising concerns that proposed estimates are unlikely to be consistently applicable to individual subjects. In particular, experienced cannabis consumers become tolerant to the substance's behavioral effects. They also retaining trace concentrations of THC in blood for extended periods of time well beyond the duration of impairment, in some cases several days following last use, while occasional users do not. THC's metabolites, in particular carboxy THC, may also be detectable in blood for several days, even in less frequent users, making them especially poor indicators of recent cannabis use or impaired performance. As a result, recently adopted statewide *per se* limits and zero tolerant per se thresholds in the United States criminally prohibiting the operation of a motor vehicle by persons with the trace presence of cannabinoids or cannabinoid metabolites in their blood or urine are not based upon scientific evidence or consensus. Further, the enforcement of these strict liability standards risks inappropriately convicting unimpaired subjects of traffic safety violations, including those persons who are consuming cannabis legally in accordance with other state statutes. As additional states consider amending their

cannabis consumption laws, lawmakers would be advised to consider alternative legislative approaches to address concerns over DUI cannabis behavior that do not rely on solely on the presence of THC or its metabolites in blood or urine as determinants of guilt in a court of law. Otherwise, the imposition of traffic safety laws may inadvertently become a criminal mechanism for law enforcement and prosecutors to punish those who have engage in legally protected behavior and who have not posed any actionable traffic safety threat.

References

Armentano, P. (2013). Cannabis and psychomotor performance: A rational review of the evidence and implications for public policy. *Drug Testing and Analysis*, 5, 52-56.

Asbridge, M, Hayden JA, Cartwright JL. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *British Medical Journal* 344: e536.

Associated Press. (March 18, 2012). *Stoned driving epidemic puts wrinkle in marijuana debate*.

Chesher G., Longo M. (2002). Cannabis and Alcohol in Motor Vehicle Accidents. In *Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential*, (Eds: Grotenhermen, F, Russo, E.). Haworth Integrative Healing Press, New York, pp. 313-323.

Drummer, OH, Gerostamoulos, J, Batziris, H, Chu, M, Caplehorn, J, Robertson, MD, Swann, P. (2004). The involvement of drugs in drivers killed in Australian road traffic crashes. *Accident Analysis & Prevention*, 36: 239-48.

D'Souza DC, Ranganathan M, Braley G, Gueorguieva R, Zimolo Z, Copper T, Perry E, Krystal J. (2008). Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology* 33: 2505-16.

Elvik R. (2012). Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accident Analysis and Prevention*, doi.org/10.1016/j. aap.2012.06.017.

Executive Office of the President of the United States. *National Drug Control Strategy, 2012*. Washington, DC. 2012.

Fischer B, Jeffries V, Hall W, Room R, Goldner E, Rehm J (2011). Lower risk cannabis use guidelines for Canada: A narrative review of evidence and recommendations. *Canadian Journal of Public Health*, 102: 324-7.

Grant I, Atkinson JH, Gouaux B, Wilsey B (2012). Medical marijuana: clearing away the smoke. *The Open Neurology Journal*, 6: 18-25.

Grotenhermen F (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmocokinetics*, 42: 327-60.

Grotenhermen F, Leson G, Berhaus G, Drummer OH, Kruger HP, Longo M, Moskowitz H, Perrine B, Ramaekers JG, Smiley A, Turnbridge R (2005). *Developing Science-Based Per Se Limits for Driving Under the Influence of Cannabis (DUIC): Findings and Recommendations by an Expert Panel.* Marijuana Policy Project, Washington, DC.

Grotenhermen F, Leson G, Berhaus G, Drummer OH, Kruger HP, Longo M, Moskowitz H, Perrine B, Ramaekers JG, Smiley A, Turnbridge R (2007). Developing per se limits for driving under cannabis. *Addiction*, 102: 1910-7.

Grotenhermen F, Muller-Vahl K (2012). The therapeutic potential of cannabis and cannabinoids. *Deutsches Arzteblatt International*, 109: 29-30.

Hart CL, Ilan EB, Gevins A, Gunderson EW, Role K, Colley J, Foltin RW (2010). Neurophysiological and cognitive effects of marijuana in frequent users. *Pharmacology Biochemistry and Behavior,* 96: 333-41.

Huestis MA, Henningfield JE, Cone EJ (1992). Blood cannabinoids. 1. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *Journal of Analytical Toxicology*, 16: 276-82.

Karschner EL, Schwilke EW, Lowe RH, Darwin WD, Pope HG, Herning R, Cadet JL, Huestis MA (2009). Do Delta- 9-tetrahydrocannabinol concentrations indicate recent use in chronic cannabis users? *Addiction*, 104: 2041-48.

Khiabani HZ, Bramness JG, Bjorneboe A, Morland J (2006). Relationship between THC concentration in blood and impairment in apprehended drivers. *Traffic Injury and Prevention*, 7: 111-6.

Laumon B, Gadegbeku B, Martin JL, Biecheler, MB, SAM Group (2005). Cannabis intoxication and fatal road crashes in France: a population base case-control study. *British Medical Journal*, 331: 1371-77.

Musshoff F, Madea B (2006). Review of biological matrices (urine, blood, and hair) as indicators of recent or ongoing cannabis use. *Therapeutic Drug Monitoring*, 28: 155-63.

National Highway Traffic Safety Administration. (1993). *Marijuana and Actual Driving Performance.* Washington, DC.

National Highway Traffic Safety Administration. (1999). *Drug Evaluation and Classification Training "The Drug Recognition Expert School" Student Manual*. Washington, DC..

National Highway Traffic Safety Administration. (2003). *State of Knowledge of Drug-Impaired Driving: Final Report.* Department of Transportation report HS 809 642. Washington, DC..

National Highway Traffic Safety Administration. (n.d.). Drugs and Human Performance Fact Sheets: Cannabis/Marijuana (Delta-9-tetrahydrocannabinol) <http://www.nhtsa.gov/people/injury/research/job185drugs/cannabis.htm> Webpage accessed on September 3, 2012.

National Organization for the Reform of Marijuana Laws (NORML). (n.d.). Active State Medical Marijuana Programs <http://norml.org/legal/medical-marijuana-2> Webpage accessed on January 13, 2013.

National Organization for the Reform of Marijuana Laws (NORML). (n.d.). State DUID Laws <http://norml.org/legal/drugged-driving> Webpage accessed on January 13, 2013.

Paula K, Kuypers C, Legrand SA, Ramaekers JG, Verstraete AG (2012). A case-control study estimating accident risk for alcohol, medicines, and illegal drugs. *PLoS ONE,* 7(8): e43496

Ramaekers JG, Berghaus G, van Laar M, Drummer OH (2004). Dose related risk of motor vehicle crashes after cannabis use. *Drug and Alcohol Dependence*, 7: 109-19.

Ramaekers JG (2006) "Commentary of Cannabis and Crash Risk: Concentration Effect Relations." In *Transportation Research Circular: Number E-C096* (Eds Transportation Research Board of the National Academies) Woods Hole, Massachusetts, pp. 65-66.

Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR (2009). Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *Journal of Psychopharmacology*, 23: 266-77.

Ramaekers JG, Berhaus G, van Laar MW, Drummer OH (2010). "Dose related risk of motor vehicle crashes after cannabis use: an update." in *Drugs, Driving, and Traffic Safety* (Eds: J.C. Verster, D.R. Pandi-Perumai, J.G. Raemakers, J.J. de Gier) Birkhauser, Basel, Switzerland, pp: 501-518.

Ramaekers JG, Theunissen EL, de Bower M, Toennes SW, Moeller MR, Kauert G (2010) Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users. *Psychopharmacology* (Berl*),* 214: 391-401.

Ronen A, Gershon P, Drobiner H, Rabinovich A, Bar-Hamburger R, Mechoulam R, Cassuto Y, Shinar D (2008). Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. *Accident Analysis and Prevention*, 40: 926-934.

Schwope DM, Bosker WM, Ramaekers JG, Goerlick DA, Huestis, MA (2012). Psychomotor performance, subjective and physiological effects of whole blood delta-9-THC concentrations in heavy, chronic cannabis smokers following acute smoked cannabis. *Journal of Analytical Toxicology*, 36: 405-12.

Sewell RA, Polling J, Sofuoglu M (2009). The effect of cannabis compared to alcohol on driving. *American Journal on Addictions*, 18: 185-93.

Silver, N (October 18, 2011). "Gallup poll is first to find plurality support for marijuana legalization." The New York Times.

Skopp G, Potsch L (2008). Cannabinoid concentrations in spot serum samples 24-48 hours after discontinuation of cannabis smoking. *Journal of Analytical Toxicology*, 32: 160-4.

Stough, C., Boorman, M., Odgen, E., Papafotiou, K. *An Evaluation of the Standardised Field Sobriety Test for the Detection of Impairment Associated With Cannabis With and Without Alcohol.* Australian Government Department of Health and Aging, Canberra, 2006.

Toennes SW, Ramaekers JG, Theunissen EL, Moeller MR, Kauert GF (2008). Comparison of cannabinoid pharmacokinetic properties in occasional and heavy users smoking a marijuana or placebo joint. *Journal of Analytical Toxicology*, 32: 470-77.