Report on Drug *Per Se* Limits

Canadian Society of Forensic Sciences
Drugs and Driving Committee

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Executive Summary

- Establishing a drug *per se* limit does not imply all drivers below this limit are not impaired and all drivers above this limit are impaired.
- Impairment can be defined as a decreased ability to perform a certain task; this differs from intoxication which can be described as the observable signs of drug use.
- The primary psychoactive compound in cannabis products is tetrahydrocannabinol (THC).
- THC impairs the ability to operate a motor vehicle.
- THC is the most frequently encountered drug in Canadian drivers, after alcohol.
- THC and alcohol are frequently detected in combination in drivers.
- Although the scientific literature varies, several well-controlled studies with sufficient discriminating power have demonstrated an increased crash risk in THC-positive drivers. Risks were increased for fatal collisions and with elevated THC concentrations.
- Available evidence suggests significantly increased risks for drivers positive for alcohol and THC in combination.
- Unlike alcohol, the effects of THC do not correlate well with THC blood concentrations.
- Impairment due to THC is related to the amount, the route of administration, the time elapsed since use, and inter-individual variability.
- Existing *per se* limits for THC vary widely between jurisdictions.
- The THC *per se* limits considered by this committee are 5 ng/mL and 2 ng/mL in blood.
- The 5 ng/mL THC *per se* limit is based upon impairment considerations, while the 2 ng/mL THC *per se* limit is based upon public safety considerations.
- This committee recommends the use of distinct but corresponding *per se* limits for plasma[i].
- This committee recommends a combined offence of 50 mg of alcohol in 100 mL of blood when detected in combination with THC at a concentration less than the limit for the THC alone offence.
- Minimizing time delays in sample collection is critical to implementation of an effective THC *per se* limit.
- Consideration of THC *per se* limits is complicated by the potential for prolonged THC blood concentrations in chronic users although there is evidence of residual impairment in this population.
- The potential for passive exposure to THC resulting in concentrations at or above a *per se* limit is not a practical concern in the context of the conditions that would be required, the levels discussed and the inevitable time delay to sample collection.
- Cocaine is a central nervous system stimulant which impairs the ability to operate a motor vehicle. Cocaine is susceptible to degradation in the body and in a collection tube; therefore, timely collection, preservative and proper storage conditions, and timely analysis are important. This committee recommends a cocaine *per se* limit of 30 ng/mL in the blood. No limit is recommended for benzoylecgonine, the inactive breakdown product of cocaine.

- Gammahydroxybutyrate (GHB) is a drug which demonstrates central nervous system depressant activity in a dose dependent manner. GHB impairs the ability to operate a motor vehicle. GHB is also a compound that occurs naturally in the body at low levels, and as such, the *per se* limit must reflect a concentration above endogenous levels. This committee recommends a GHB *per se* level of 10 mg/L in the blood.
- Heroin is an opioid analgesic which has central nervous system depressant properties. Heroin impairs the ability to operate a motor vehicle. Given the extremely short time frame for heroin detection in the body due to the rapid metabolism of heroin to its active metabolite, 6-monoacetylmorphine (6-MAM), this committee recommends zero tolerance for 6-MAM detection in the blood.
- Ketamine is a dissociative anaesthetic which impairs the ability to operate a motor vehicle. This committee recommends zero tolerance for ketamine detection in the blood.
- Lysergic Acid Diethylamide (LSD) is a potent hallucinogen which impairs the ability to operate a motor vehicle. This committee recommends zero tolerance for LSD detection in the blood. LSD is susceptible to degradation in a collection tube as it is light and heat labile; therefore, proper storage conditions and timely analysis are important.
- Methamphetamine is a central nervous system stimulant which impairs the ability to operate a motor vehicle. This committee recommends a methamphetamine *per se* limit of 50 ng/mL in the blood.
- Phencyclidine (PCP) is a dissociative anaesthetic which impairs the ability to operate a motor vehicle. This committee recommends zero tolerance for PCP detection in the blood.
- Psilocybin is the compound present in 'magic' mushrooms which are used for hallucinogenic purposes; psilocin is the primary psychoactive metabolite of psilocybin. Psilocybin/psilocin impairs the ability to operate a motor vehicle. This committee recommends zero tolerance for psilocybin and/or psilocin in the blood.
- Any drug recommended for zero tolerance in a blood sample is also recommended for zero tolerance in a serum or plasma sample.
- Since zero tolerance will be related to the limits of the methodology employed, this committee recommends that the provincial and federal government forensic laboratory systems develop a common limit of detection for the aforementioned drugs so as to ensure the criminal code offence will not vary between jurisdictions.

Introduction

Traditionally the approach to drug-impaired driving investigations has involved three components: (i) observation of driving impairment, (ii) evidence of drug use, which varies in nature but may include evidence of drugs or drug paraphernalia in the motor vehicle, signs and symptoms of drug use, and/or drug findings from a biological sample collected from the accused driver, and (iii) connection of the drug findings to driving impairment, typically provided by a toxicologist. Even with the legislative changes implemented on July 2, 2008 which provided for the Drug Evaluation and Classification Program (DECP) within Canada, the approach to drug-impaired driving investigations has largely continued to incorporate these same components. Since that time, several issues have become apparent with use of the DECP as the primary means by which to address drug-impaired driving in Canada. These include the substantial cost and time commitments required to train an officer to become a Drug Recognition Expert (DRE), the difficulty in providing the requisite number of DRE officers in a geographically diverse and relatively unpopulated country such as Canada, and the strain placed on police services and forensic laboratories to meet the increasing demand for testimony by both DRE officers and toxicologists. As such, the utility of additional tools to help address drug-impaired driving in Canada needs to be considered.

While many jurisdictions have introduced *per se* limits to help with drug-impaired driving enforcement, to date there has not been a consistent approach used in the development of this type of legislation. *Per se* limits specify the concentration of a particular drug in the blood or other bodily fluid at or above which it is an offence to operate a motor vehicle, irrespective of any observed driving impairment. As such, the court needs only to determine if the individual's drug concentration was at or above the specified threshold to determine guilt. In Canada, a *per se* limit of over 80 mg of alcohol in 100 mL of blood has been in place since 1969. This *per se* limit is supported by the epidemiological relationship between blood alcohol concentration (BAC) and crash risk, experimental closed-course driving studies, and laboratory studies of alcohol-induced impairment on specific driving-related tasks and functions. Unlike alcohol, one of the challenges for many potentially impairing drugs is that there is not currently substantive and consistent scientific evidence upon which to base *per se* limits.

The interest in utilizing a *per se* approach is an attempt to simplify the adjudication process, facilitate enforcement, and enhance deterrence. Together, these factors can have a positive impact on traffic safety. Research has determined that alcohol *per se* laws are associated with a 14%-15% reduction in alcohol-related fatal crashes (Tippetts *et al*., 2005; Villaveces *et al*., 2003). The relative simplicity of *per se* laws, their widespread acceptance, and the demonstrated effectiveness of alcohol *per se* laws, have bolstered the call that similar limits be established for other drugs in Canada.

In 1985, a National Institute on Drug Abuse (NIDA) sponsored consensus development panel (Consensus Report, 1985) stated “In order to establish that use of a drug results in impairment of driving skills and to justify a testing program to respond to this hazard, certain facts must be available.

1) The drug can be demonstrated in laboratory studies to produce a dose-related impairment of skills associated either with driving or with related psychomotor functions.
2) Concentrations of the drug and/or its metabolites in body fluids can be accurately and quantitatively measured and related to the degree of impairment produced.
3) Such impairment is confirmed by actual highway experience.
4) Simple behavioral tests, such as can be done at the roadside by police officers with modest training, can indicate the presence of such impairment to the satisfaction of courts.
5) A range of concentrations of the drug can be incorporated in laws relating to impaired driving as ipso facto evidence.

These criteria have been met for ethanol. It is not certain that they can be met for other drugs that are now of concern to highway safety."

It remains challenging to fulfill all five aforementioned criteria for many drugs for several reasons: relevant laboratory studies are limited in part due to the medical and ethical issues with administering illicit drugs and/or prescription drugs to subjects at the elevated levels detected in impaired driving populations; interpretation of crash and fatality data is complicated by the prevalence of poly-drug use in such cases. Further complications with these data include: the potential for drug concentrations to alter due to variable timeliness of sample collection and, for fatalities, postmortem redistribution, choice of sample collection area, and/or putrefactive changes may result in altered drug concentrations between the time of death and the time of sample collection.

There are numerous other factors that complicate the consideration of *per se* limits for drugs. Many drugs form one or more active metabolites which may remain present in the body for periods of time beyond that of the parent compound, thereby extending the duration of action of the drug. For example, diazepam metabolizes into nordiazepam, temazepam, and oxazepam, all of which have similar central nervous system depressant effects to diazepam, and which effectively prolongs the duration of action despite the continued metabolism and declining concentration of diazepam. Although most drug concentrations remain unchanged once a blood sample has been collected, some drugs break down in blood samples despite attempts to minimize this degradation through addition of preservatives and optimized storage conditions. For example, cocaine breaks down into an inactive metabolite known as benzoylecgonine both in the body and in the test tube after sample collection, and as such, it can impede determination of the cocaine concentration present at the time of sample collection. An additional complication to the development of *per se* limits is the tolerance which can develop to the effects of certain drugs. In such situations, the impairment produced in an individual at the start of use of that drug diminishes with regular use over time. Conversely, if that individual increases their dosage, does not maintain a regular dosage, or recommences drug use after a period of abstinence, their

tolerance to particular effects of the drug may be lessened. Disease or significant health alterations may also impact an individual's drug tolerance. To further complicate matters, an individual who is tolerant to the impairing effects of a given drug may experience a certain degree of cross-tolerance to the impairing effects of related drugs, even at commencement of their use. The extent of any such cross-tolerance cannot reliably be predicted and can vary widely between individuals. Further complications in the relationship between drug concentrations and impairment include that impairment of an individual at a given blood concentration is dependent upon whether they are in the acute or withdrawal phase of drug action and, for those drugs to which tolerance can develop, that tolerance may be altered by the administration of other compounds that can interact with the drug or which can alter its metabolism. This latter complication is of concern given the high incidence of multi-drug use in the population, including the concomitant use of over-the-counter drugs, prescription drugs, alcohol and/or illicit compounds.

Despite the complications inherent in determining *per se* limits for drugs, there are certain drugs for which such limits can be reasonably considered. This document outlines, along with the relevant issues for consideration, specific drugs that are being proposed for new legislation to assist with drug-impaired driving investigations.

Tetrahydrocannabinol (THC)

THC is the primary psychoactive component of cannabis products. Cannabis products are available in many forms for administration including, but not limited to, marijuana, hashish, and concentrates ('butter', 'shatter', 'oil') which can be smoked, ingested, and vapourized. Setting a *per se* limit for this drug is a controversial exercise for many reasons which will be examined. As legalization of cannabis in Canada is impending, THC *per se* limits are of particular importance. THC impairs an individual's ability to operate a motor vehicle; however, setting a *per se* limit does not mean that all drivers below that concentration are not impaired and all drivers above that concentration are impaired. Determination of a *per se* limit which addresses both public safety concerns and minimizes the potential for an individual to be "wrongly" convicted of a drugged-driving related offence can be considered an exercise in selecting the least objectionable alternative. Ultimately, there are options for future legislation: continued support and enhancement of Standardized Field Sobriety Tests (SFST) and the DECP, possible inclusion of Advance Roadside Impaired Driving Enforcement (ARIDE), adoption of a *per se* limit based on concerns for road safety, or adoption a *per se* limit based on impairment.

Epidemiology

Roadside Surveys – Drivers at Risk

Roadside surveys provide a unique source of information on alcohol and drug use among the general driving population. Participating drivers are not selected based on their driving behaviour, vehicle type or condition, or personal characteristics. Rather, roadside surveys are intended to provide a representative sample of drivers on the road in an area, at a particular time of day, day of the week, and, potentially, time of the year. Although roadside surveys have been conducted for many years to collect information on alcohol use by drivers, recent surveys have been able to gather information on drug use through the collection of oral fluid samples from drivers at the roadside.

In the United States, a National Roadside Survey of alcohol and drug use was conducted in 2013-2014 (Berning *et al*., 2015). Drivers were selected randomly at 300 locations across the contiguous United States and asked to provide breath, oral fluid and blood samples. Data collection occurred primarily on Friday and Saturday nights between 10 p.m. and 3 a.m. In total, 7,881 drivers provided an oral fluid sample, and 4,686 agreed to provide a blood sample. Based on oral fluid samples, 19.8% of night-time drivers tested positive for psychoactive drugs. Based on blood samples, 21.2% of night-time drivers tested positive for at least one drug. Overall, 22.5% of night-time drivers were positive for drugs in oral fluid and/or blood. Cannabis was the most commonly detected substance, accounting for over half of all drug-positive cases (11.3% of drivers who provided an oral fluid sample); a 48% increase was documented for THC positive weekend nighttime drivers when compared to previous data collection in 2007.

In a study conducted in British Columbia, Canada, breath and oral fluid samples were collected from a total of 4,711 randomly selected drivers on Wednesday through Saturday nights in June of 2008, 2010 and 2012 (Beasley *et al*., 2013). Of these drivers, 8.1% were positive for drugs only, 6.8% were positive for alcohol only, and 1.7% were positive for both drugs and alcohol. Cannabis, the most common drug finding, was detected in 5.5% of drivers. A similar survey conducted in Ontario in 2014 found 10.2% of drivers to be positive for drugs whereas only 4.0% tested positive for alcohol. Cannabis was detected in 8.0% of drivers, representing 69.1% of all drug-positive drivers (Beirness *et al*., 2015).

Drug Use by Drivers involved in Road Crashes

Numerous studies from around the world have examined the incidence of drugs and alcohol among drivers injured or killed in crashes. In reviewing these studies, it is important to recognize that they use a variety of methods, populations, sample sizes, and case selection methods, which can affect the results of the study. For example, low testing rates among injured and deceased drivers in motor vehicle collisions continues to confound the search for a valid estimate of the prevalence of drug use among crash-involved drivers. In jurisdictions where such testing is not required, drivers who are injured in crashes are rarely tested without at least suspicion of drug or alcohol use. This restricts the ability to

reliably determine the overall prevalence of drug use by drivers involved in crashes. In Canada, Stoduto *et al*. (1993) collected drug and alcohol data from 339 drivers treated at a trauma centre for injuries sustained in a motor vehicle crash. Overall, 35.5% of these drivers tested positive for alcohol and 41.3% tested positive for at least one drug other than alcohol. Cannabinoids were the most common drug finding (14%) in these injured drivers. In 2012, 33% of fatally injured drivers in Canada (excluding BC) tested positive for alcohol and 40% were positive for drugs (Brown *et al*., 2015). Cannabis was the most frequently detected drug accounting for 18.2% of all cases and 45.5% of drug-positive cases (Brown *et al*., 2015). For a one-year period between February 1, 2011 and January 31, 2012, standardized comprehensive testing was performed for all fatal motor vehicle collisions drivers, who died within hours of the collision, in the province of Ontario (Woodall *et al*., 2015). Of the 252 cases that qualified for the study, 12.2% were positive for alcohol only, 28.4% were positive for drugs only and 15.3% were positive for both; the most common drug finding was cannabis which represented 27% of the drug positive cases.

Risks Associated with Drug Use by Drivers

Epidemiological studies attempt to quantify the extent to which drugs are disproportionately represented in road crashes. Cases are defined as drivers involved, injured, or killed in road crashes. The frequency of alcohol or other drugs detected in the cases is compared to the frequency of drugs and/or alcohol detected in a comparable control group of drivers who have either not been involved in crashes or were deemed not responsible for a crash. The extent to which alcohol and/or drugs are more frequently detected in crash populations than in control populations is an indication of the degree to which the use of psychoactive substances presents an elevated risk for drivers. This method has been instrumental in understanding the risks associated with alcohol use by drivers. In addition, by comparing the concentration of alcohol among cases and controls, it is possible to determine the relative likelihood of crash involvement at different BACs (Blomberg *et al*., 2009; Borkenstein *et al*., 1974). Comparable information would be beneficial to a discussion of drug *per se* limits.

The application of such case-control methods to the study of crash risks for drivers using drugs is somewhat more complex than for alcohol. In comparison to alcohol, the testing for drugs, both among the cases and the controls, is more difficult. Analysis for drugs occurs in a laboratory setting rather than at roadside or at a police station. Ideally, blood for drug analysis should be obtained from both cases and controls, but obtaining the needed compliance from controls can be difficult and, consequently, testing rates are often low and attributing meaning to the data is problematic. Among cases, similar problems are experienced unless the individual has been taken to hospital where a blood sample has been taken or in fatalities in which postmortem blood is available. The net result is that the estimates of risk are often of questionable validity and reliability.

The sample medium used to test for drugs is also an important consideration. For alcohol, BACs can be easily and reliably determined from breath samples which can be readily and unobtrusively obtained

from control populations. This is not the case with other types of psychoactive substances, which typically require that toxicological testing be conducted on other bodily fluids. Blood samples are considered to be the most relevant and reliable sample medium for determining the concentration of active drug in the driver's blood. However, due to the inherent difficulties in obtaining blood samples from drivers at roadside, other fluids are often used instead. Although overall estimates of risk associated with drug use can be calculated from these data, quantifying the risk associated with various drug concentrations in samples other than blood is not recommended.

Should a substance be found to be overrepresented in crashes, it is often assumed that the mere presence of the substance was sufficient to have contributed to the crash. In fact, the case-control approach simply provides evidence of an association between drugs and crashes and does not directly provide evidence that the substance induced a degree of impairment sufficient to have contributed to the crash. Other factors associated with drug use, e.g., characteristics of the person, their driving style, their comfort level with risk, could also explain the observed association. This also applies to case-control studies concerning the role of alcohol in crashes; however, for alcohol the repeated demonstration of a dose-dependent increase in crash risk combined with a corresponding dose-response relationship in experimental studies of impairment provides convincing evidence of the contributory role of alcohol in crashes. To date, many epidemiological studies of the role of drugs in crashes have simply determined the presence or absence of particular drugs as compared with those few studies that have attempted to determine the extent of increased risk according to the concentration of THC detected (Drummer *et al*., 2004; Laumon *et al*., 2005). In a recent review and meta-analysis of studies assessing the relative collision risk associated with the use of cannabis, Asbridge *et al*. (2012) identified nine studies of sufficient quality to be included. In seven of these studies, an increased risk of motor vehicle collision was found when drivers had consumed cannabis within a few hours prior to the collision. The pooled results indicated that drivers positive for cannabis use were almost twice as likely (Odds Ratio=1.92, 95% confidence interval = 1.35-2.73) as drug negative drivers to be involved in a collision. This risk was increased in studies of fatal collisions. Studies of crash risk associated with drug use were also conducted in several countries in Europe as part of the DRUID (Driving Under the Influence of Drugs, Alcohol and Medicines) project (Gadegbeku *et al*., 2011; Thorsteinsdóttir *et al*., 2011; Hels *et al*., 2011). These studies varied considerably in terms of the approach and methods employed. Drivers were sampled from different populations, drug and alcohol analyses differed as did the samples analyzed, and compliance rates and sample sizes varied. Consequently, the risk estimates had large confidence intervals and only two of the three estimates were statistically significant.

Among the studies that have examined the role of cannabis in crashes, there are several studies (Drummer *et al*., 2004; Laumon *et al*., 2005; Longo *et al*., 2000; Mura *et al*., 2003) that are methodologically stronger than the others because they all used blood samples to specifically test for the presence of the active ingredient in cannabis (THC) rather than its inactive metabolite (carboxy-THC). This is important because individuals found to have a positive THC blood concentration are most

likely to be under the influence of cannabis. Three of these studies reported a significant increase in risk associated with cannabis use; the Longo study, which specifically examined crash culpability, determined no statistical difference in culpability rates for THC-positive and drug-free drivers. Nevertheless, Longo *et al*., did note that most THC-positive drivers in their study were at extremely low THC concentrations, and did not exclude the possibility of adverse effects at THC concentrations greater than 2 ng/mL in blood. Mura *et al*. (2003) employed a case-control approach, comparing a sample of injured drivers with a sample of other patients also attending hospital in France and found drivers with THC blood concentrations greater than 1 ng/mL were 2.5 times more likely to have been injured in a crash than controls. The significant increase in risk associated with cannabis use, however, was restricted to those under 27 years of age. Over the age of 27, there were relatively few drivers and controls positive for THC in this study. Among the available studies, those using both large sample sizes and rigorous methodology provide the strongest evidence of increased crash risk associated with THC. These studies are among those included in the meta-analysis by Asbridge *et al*. (2012) referred to previously. Using responsibility analysis with samples of fatally injured drivers in Australia, Drummer *et al*. (2004) reported drivers with THC levels greater than 5 ng/mL were 6.6 times more likely to be responsible for the crash than drivers who had not used drugs or alcohol. Laumon *et al*. (2005) reported that the risk of drivers being responsible for a fatal motor vehicle collision increased with increasing blood THC concentrations; THC positive drivers with blood concentrations less than 1 ng/mL were 2.18 times more likely than drug-free drivers to be responsible for fatal motor vehicle collisions, with that likelihood increasing to 4.72 times for drivers with THC blood concentrations in excess of 5 ng/mL. In an analysis of data from 32,543 drivers between the ages of 20 and 49 involved in fatal crashes in the United States who were tested for cannabis, Bédard *et al*. (2007) found drivers positive for cannabis were significantly more likely than controls to have at least one potentially unsafe driving action recorded in relation to the crash, such as speeding.

Among the limited number of recent epidemiological studies that have measured THC in blood samples, there remains a degree of inconsistency in the evidence. However, the weight of the evidence shows that cannabis use is associated with increased risk of crash involvement. In addition, studies that demonstrate a dose-related increase in risk provide strong evidence implicating cannabis as a causal factor in crashes (Drummer *et al*., 2004; Laumon *et al*., 2005).

The apparent inconsistency of the available epidemiological results may be attributable, in part, to the variability of the studies in terms of the approach (case-control, responsibility analysis), severity of crash (injury, fatality), fluid tested (urine, oral fluid, blood), component of cannabis tested (THC, carboxy-THC), and sample size. Although the total number of drivers included in any study may appear large, the actual number who test positive for THC is typically small. The relatively low incidence of cannabis detection among drivers renders the results sensitive to even small variations in sampling and case selection. Large scale studies using rigorous and consistent methods are necessary to provide clear and unambiguous evidence of the increased risk of crashes associated with cannabis use by drivers.

The concomitant use of alcohol and cannabis has also been studied in the context of relative risk. The available evidence indicates that the use of cannabis in combination with alcohol is associated with higher risk of crash involvement. Among the small number of studies that specifically investigate drivers positive for both cannabis and alcohol, significantly increased risks are reported relative to drivers who are drug-free (Laumon *et al*., 2005; Longo *et al*., 2000), or relative to those who are positive for alcohol alone (Drummer *et al*., 2004).

Pharmacological Considerations

Pharmacology, the study of drugs, can be divided into pharmacokinetics and pharmacodynamics. Pharmacokinetics simply defined is what happens to the drug in the body (absorption, distribution and elimination); pharmacodynamics simply defined is how the drug affects the body (impairment and intoxication). The challenge in determining a *per se* concentration for THC arises from the unique pharmacokinetics of this compound, as well as the variability in pharmacodynamics. THC causes impairment in various faculties required for the operation of a motor vehicle including divided and concentrated attention, vigilance, tracking, and executive functioning. Impairment is a decreased ability to perform a task, whereas intoxication is the observable signs associated with drug use. The effects of THC are related to the route of administration, amount administered, pattern of administration, the time elapsed since last use, and inter-individual variability.

Cannabis is commonly administered by smoking. During cannabis smoking, THC is rapidly absorbed through the lungs and distributed in the body, resulting in peak THC concentrations during active smoking. Upon cessation of smoking, THC concentrations either have already started to decline or begin to decline shortly thereafter, with the rapid removal of THC from the blood via redistribution into fatty tissues of the body. This intense THC peak and rapid decline was demonstrated in 6 individuals smoking a marijuana cigarette, with either 1.75% or 3.55% THC, in whom maximum plasma concentrations were reached around the end of smoking at a mean of 8.4 min from the start of smoking (Huestis *et al*., 1992). A dramatic decrease in THC concentration was observed in the first hour post-smoking and by 4 hours the blood THC concentrations ranged from not detected to 1.7 ng/mL[ii] (Huestis *et al*., 1992). Note the cigarettes in this study contained relatively low percentages of THC as compared to the current products that are available. An important concept with respect to the effects of THC on the brain and, therefore, cognitive functioning is that THC demonstrates counter-clockwise hysteresis, which means that the subjective effects of the drug do not correlate with the blood drug concentration (as they do with alcohol). The rapid redistribution from the blood into fatty tissues results in low THC blood concentrations despite persisting effects on the brain. Therefore, individuals may be impaired at what appears to be low blood concentrations. The peak impairing effects generally occur within the first hour after smoking a cannabis product, and may last up to 6 hours after use.

In conjunction with the legalization of cannabis in many states, the availability of different products containing cannabis has led to increased oral administration. Commercially-available products

containing THC are available for ingestion; alternately, cannabis can be added to baked goods or other food stuffs for consumption. As compared to smoking cannabis, ingestion results in slower absorption of THC through the gastro-intestinal tract and into the blood stream. The impact will be a potentially lower THC concentration, a greater contribution of a THC metabolite, hydroxy-THC, to the psychoactive effects, a slower onset of effects, and an increase in the duration of action when compared to smoking cannabis. The effects of oral THC generally occur within the first hour after consumption but may take longer to peak effects and may persist for 6 hours or more after ingestion.

The THC content of cannabis products has increased dramatically over the years. Cannabis products that have been subject to extraction techniques such as 'wax', 'butter', 'shatter', 'concentrates' or whatever terminology is employed may be of such a high potency that 70% or greater is possible. Currently, research papers deal with THC concentrations much lower than those available for recreational use. There is a paucity of literature on the impact of this high THC content on individuals; although logically the effects would be dose dependent and the impact would be to intensify the established effects of THC, but also to possibly give rise to new symptomology that has not generally been associated with low potency cannabis use.

Proposed Legal Limits

Legal limits for THC are used in other jurisdictions. The concentrations for these limits range from detection (essentially the limit of detection of the method used) up to 5 ng/mL in a blood sample (Jones, 2005; Vindenes *et al*., 2012; Wolff and Johnston, 2014; Wong *et al*., 2014). Table 1 illustrates possible THC *per se* limits that have been discussed and considered by this committee for use within Canada. There are advantages and disadvantages to each of the concentrations being considered, namely THC concentrations of 2 and 5 ng/mL in blood. Based on the smoking route of administration, the rapid decline in THC blood concentrations and the inevitable time delay to sample collection, many individuals would be expected to have blood THC concentrations above 5 ng/mL at the time of the incident but for those concentrations to be much lower by the time their blood is drawn. Lowering the THC *per se* limit would result in more individuals being in violation of this traffic safety measure; for example, a *per se* limit of 2 ng/mL would result in a larger number of charges. However, this is problematic as heavy users of cannabis may have residual blood THC levels beyond a time frame typically associated with the duration of action for the acute psychoactive effects and resultant driving impairment. The inevitable issue of the time delay in sample collection, passive exposure, and the implications of chronic use will be discussed. Furthermore, sample type and inclusion of a combined THC and alcohol offence will be addressed.

Table 1. Potential Canadian *per se* limits for THC (ng/mL) and the combined offence of alcohol (mg/100 mL) and THC.

Sample Type	THC-only Concentration	THC Concentration in Combination with Alcohol	Alcohol Concentration in Combination with THC
Blood[a]	5	<5	50
Blood[b]	2	<2	50
Plasma[a]	10	<10	60[c]
Plasma[b]	4	<4	60[c]

[a]Corresponding blood and plasma THC concentrations; that is if a blood THC limit of 5 ng/mL is selected the corresponding plasma level would be 10 ng/mL

[b]Corresponding blood and plasma THC concentrations; that is if a blood THC limit of 2 ng/mL is selected the corresponding plasma level would be 4 ng/mL

[c]Would not require a conversion to blood since the sample type would be plasma; therefore, it would be plasma alcohol concentration. Note serum and plasma would be considered the same matrix for the purposes of THC and alcohol concentrations.

Time Delay in Sample Collection

In impaired driving investigations, the time elapsed from the roadside event and subsequent arrest to collection of a blood sample is likely to be in the range of hours. Collection of a blood sample thus effectively constitutes a race against the potential for lost evidence due to drug metabolism and re-distribution following recent use. The higher the *per se* limit, the less likely an individual would meet that limit as time passes. With implementation of a THC *per se* limit of 5 ng/mL, many individuals initially above that limit would fall below that concentration after an hour or more of procedural requirements involved in their arrest. In a study of *ad libitum* cannabis smoking, less than 61% of the subjects had a blood THC concentration[ii] at or above 5 ng/mL beyond 2 hours post-smoking. This percentage decreased to 30% at 4.1 to 8 hours post-smoking (Lee *et al*., 2015). Therefore, a lower legal limit, i.e., 2 ng/mL would reflect the decrease in blood concentrations to levels likely to be present at the time of sample collection. It is important to note that back extrapolations of blood concentrations, routinely performed with alcohol, are not possible with THC. There is too much variability in the absorption, distribution and elimination kinetics of THC within the population. This means the concentration detected at the time of the analysis is the totality of the information that will be available

from an analytical perspective. The higher the THC concentration, the more likely there was recent administration, and time of use is an important factor when considering impairment due to THC. However, due to the relationship of the pharmacokinetics and pharmacodynamics of THC an individual could be impaired below both 2 and 5 ng/mL. Therefore, in the interest of public safety, a legal limit of 2 ng/mL THC in blood would be the more prudent measure. However, if the approach is to focus on the increased likelihood of impairment due to cannabis use, then 5 ng/mL THC in blood would be a more appropriate *per se* limit.

Drivers who come to the attention of the police as a result of their driving behaviour provide an example of the potential challenges associated with proposed THC *per se* limits. In a study of 602 drivers arrested for impaired driving and who had positive THC blood concentrations in the absence of any other drugs or alcohol findings, THC concentrations ranged from 1 to 47 ng/mL with a median of 5 ng/mL (Logan *et al*., 2016). The time delay between arrest and blood drawn, where this information was available, was a mean, median, and maximum of 74 minutes, 61 minutes, and 3 hours and 45 minutes, respectively. Furthermore, the DRE evaluations performed on these drivers were unable to distinguish between the clinical observations and psychomotor indicators of impairment for drivers whose THC blood concentrations would later be determined to be either above or below 5 ng/mL. In the year following the implementation of a THC legal limit and graded sanctions in Norway of 1.3, 3, and 9 ng/mL, the percentage of drivers apprehended on suspicion of drugged driving cases with THC blood concentrations above these limits were 31.5%, 19.0%, and 5.4%, respectively (Vindenes *et al*., 2014).

Chronic Use

THC is a lipophilic compound which means that blood concentrations rapidly decline as THC preferentially distributes to lipid-rich tissues. This same proclivity results in a slow release of THC from these tissues and resultant low levels of THC detectable within the blood of chronic users for prolonged periods of time; this would be further exacerbated by the intensity of the exposure. Individuals who use cannabis products daily or multiple times throughout the day may have THC blood concentrations above the *per se* limit despite having had a period of cessation for hours or possibly days. In a study of 11 occasional and 12 heavy cannabis users, none of the occasional users tested positive at the beginning of the study prior to smoking, and at 8 hours after smoking a cannabis product, all had THC concentrations less than 1 ng/mL in blood[ii]. In contrast, one individual who was a chronic user had a THC concentration greater than 5 ng/mL in blood[ii] both at the beginning of the study prior to smoking, and 8 hours after smoking a placebo cigarette (Toennes *et al*., 2008). In this same study, 3 of the chronic users had THC blood concentrations[ii] of 2 ng/mL or greater 8 hours after smoking a cannabis product due to, at least in part, the residual THC present prior to smoking. In a study of daily cannabis users, blood THC concentrations approximately 6 days since last use ranged from not detectable to 4.2 ng/mL; additionally, 7 of 11 subjects had concentrations of 2 ng/mL or greater at this time (Odell *et al*., 2015). In this same study, 9 of 21 subjects had THC concentrations above 5 ng/mL on the second day which was at least 24 hours since reported last use. Thus, these individuals would have blood THC concentrations

above potential *per se* limits well beyond the period during which they would be expected to experience the acute intoxication and impairing effects of cannabis administration. However, the potential for development of cognitive deficits due to chronic cannabis use becomes a relevant discussion point in this driving population.

There is evidence to suggest that repeated administration of cannabis may result in impairment past the expected duration of action. This may be due to residual THC in the brain having a continued impact, withdrawal effects due to abrupt discontinuation of use, or alterations in brain functioning associated with years of cumulative cannabis exposure. The mechanism is difficult to determine considering the confounding issues that are inherent in retrospective studies and the ethical issues that are inherent in prospective studies. Regardless, these deficits are possibly related to duration of use, the age that the individual started cannabis use, and/or frequency of use (Bolla *et al*., 2002; Pope *et al*., 2003). Deficits in memory, learning, attention, and manual dexterity have been postulated to be attributable to regular cannabis use (Bolla *et al*., 2002; Pope and Yurgelun-Todd, 1996). Whereas acute effects have been previously defined as 0-6 hours after smoking cannabis, residual effects are considered to be those occurring 7 hours to 20 days after last use, and long term effects as 3 weeks or longer after last use (Crean *et al*., 2011). Chronic, heavy use by individuals can result in enduring deficits for both the residual and long-term categories (Crean *et al*., 2011). Days to weeks of decreased performance are possible with chronic heavy cannabis users (Bolla *et al*., 2002; Bosker *et al*., 2013; Pope *et al*., 2001). Baseline THC levels in chronic users within a placebo group were determined to be as high as approximately 5.4 ng/mL in blood equivalents[ii] (Ramaekers *et al*., 2016). These users still perceived a subjective high despite not being given active THC in the study. During the cannabis administration part of this study, the subjects, all cannabis users but of varying frequency, demonstrated decreased abilities in executive functioning, impulse control, attention, and psychomotor functioning. Furthermore, it was considered possible that impairment of neurocognitive functioning of chronic users could persist beyond the initial phase of intoxication (Ramaekers *et al*., 2016). This cognitive decline is less likely as the frequency of cannabis use declines and improvements are possible after a period of abstinence from cannabis products suggesting these deficits are reversible (Pope *et al*., 2002). Theories that these deficits could be permanent are likely attributed to those individuals who began chronic cannabis use at early ages and may have experienced deleterious effects of cannabis on the developing brain.

Chronic users also achieve higher THC concentrations from smoking the same THC content in a cigarette as compared to occasional users, likely due to the more efficient smoking technique that they have acquired with experience. For example, in a study of 12 heavy (use more than 4 times per week) and 12 occasional (less than 2 times per week) users, the mean peak THC concentration after smoking was approximately 2.5 times higher in heavy users compared to the occasional users (Theunissen *et al*., 2012). Even accounting for the residual THC concentrations present prior to smoking that would contribute to the final resulting THC level, chronic users are able to capture more of the active ingredient through the inhalation process.

Passive Inhalation/Exposure

Another issue which needs to be considered is whether passive inhalation of cannabis smoke could result in THC concentrations in the blood that would be over the *per se* limit. Some early work (Mørland *et al*., 1985) suggested that THC blood concentrations achieved through passive inhalation could reach up to 6.3 ng/mL at the cessation of smoking and then dropped to close to 0.5 ng/mL by 2 hours from the start of smoking. In more recent research, THC blood equivalent[ii] levels in eight volunteers passively exposed to cannabis smoke for 3 hours in a busy Dutch "coffee shop" were all less than 0.5 ng/mL (Röhrich *et al*., 2010). Peak THC blood concentrations ranged from 1.2 to 5.6 ng/mL in 6 individuals passively inhaling THC (11.3%) smoke for 1 hour from 6 smokers (*ad libitum*); all individuals had blood concentrations less than 2 ng/mL by 1 hour after the end of exposure (Cone *et al*., 2015). A subjective drug effect was reported for these non-smoking subjects that mimicked active THC smoking, although to a lesser effect (Cone *et al*., 2015). The passive exposure studies tend to be extreme conditions where subjects are surrounded by many individuals smoking cannabis in a small space with a lack of ventilation; smoke is inhaled through proximity and lack of fresh air, and the subjects are sometimes offered goggles due to the intensity of the smoke and the potential for eye irritation to be experienced. These are not conditions typically associated with passive exposure and were considered extreme or noxious smoke conditions that are unlikely to be casual encounters or unnoticed. The risk of achieving a THC concentration above a selected *per se* limit from passive inhalation is low considering the conditions required to achieve such blood concentrations and the time delay to sample collection. Furthermore, if the exposure conditions are so extreme that a resultant THC concentration occurs, the administration is arguably no longer passive, but rather active.

Sample Type

The distribution of THC into the red blood cells is limited, and therefore, blood and plasma THC concentrations will be different. For the purposes of THC concentrations, plasma and serum are considered to be an equivalent matrix and the term plasma is used for simplicity. Blood levels of THC are typically lower than plasma levels and there are ranges associated with the ratios of these sample types. In a study of 25 subjects smoking *ad libitum* a 6.8% THC containing cigarette for up to 10 minutes, blood and plasma samples were compared and blood-to-plasma ratios ranging from 0.31 to 1.1 were determined, with a median of 0.68 (Desrosiers *et al*., 2014); in another study of oral THC administration in chronic users over an 8 day period, blood-to-plasma ratios ranged from 0.3 to 1.7, with a median of 0.63 when all participants (n=196) and time points were combined (Karschner *et al*., 2012). The Netherlands Advisory Committee recommended the use of separate *per se* limits in blood and serum for THC (Wong *et al*., 2014). This approach would make the most sense rather than trying to determine an appropriate conversion factor for serum or plasma samples commonly obtained from a hospital by warrant. Table 1 outlines the recommended plasma concentrations which correspond to selected *per se* blood concentrations. For simplicity and as a conservative conversion, a blood-to-plasma conversion of 0.5 was used to determine a plasma equivalency from the blood *per se* level.

THC and Alcohol

In a study of male drivers, the combined detection of cannabis and alcohol in drivers was more common than cannabis as the sole intoxicant, and similar in occurrence to alcohol alone (Williams *et al*., 1985). This observation is a current concern as poly-drug use is common amongst drug-impaired drivers. The combined use of THC and alcohol is expected to produce at least additive impairment of the faculties required for the operation of a motor vehicle. Consideration of a combined offence of alcohol and THC *per se* limits would depend on the *per se* limit selected for THC. Table 1 outlines the proposed limits for the combined presence of THC and alcohol. As the technology exists to quickly determine a BAC (or within a range of BACs) at the roadside, and with the possible implementation of oral fluid screening technology, a BAC within a specified range and evidence of recent cannabis administration through a positive oral fluid screen, and/or other observations such as smell of burnt cannabis, paraphernalia or other evidence of cannabis use, could be used to demand a blood sample for the purposes of the dual level offence. Furthermore, if a blood sample was obtained for THC and the concentration was below the *per se* limit for the single drug offence, further examination at the forensic laboratory could be performed for alcohol and the possibility of the dual limit offence investigated. The combination of THC and alcohol could also be used as an aggravating factor if a dual offence is not implemented.

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Cocaine

Cocaine is a potent central nervous system (CNS) stimulant drug commonly used for its euphoric effects. Typical routes of administration for cocaine and related compounds (e.g., crack) include insufflation (snorting), smoking, and injection. The onset of effects is dependent on the route of administration but is rapid, from seconds to minutes. The initial desirable stimulant effects of cocaine include euphoria, excitation, talkativeness, reduced fatigue, and a heightened sense of well-being. Some early physical signs include pupil dilation, increases in heart rate, body temperature and blood pressure, tremors, rapid speech, suppression of appetite, and twitching (i.e., involuntary movement of the muscles). The intense euphoria is short-lived (up to 30 minutes), and dependent on the route of administration and dose; the overall general stimulant effects may persist for up to 1 to 2 hours after administration (Couper and Logan, 2014; Verstraete and Legrand, 2014). These effects may be followed by a 'crash' or dysphoric phase which is characterized by agitation, irritability, anxiety, depression, craving, and paranoia. In order to delay the crash phase and maintain the more desirable stimulant effects of cocaine, many users will repeatedly administer the drug over a period of time ranging from hours to days (i.e., binge use). Even during a binge, the euphoric effects are gradually replaced by dysphoria, and will eventually end with a crash phase which is characterized by intense fatigue and sedation. Chronic high dose cocaine users may experience symptoms of toxic psychosis (i.e., cocaine induced excited delirium), which is characterized by paranoia, delirium, hallucinations, hyperthermia, extreme agitation, aggression, respiratory arrest, and even sudden death (Wetli and Fishbain, 1985).

Cocaine hydrochloride is an anaesthetic agent. It is used in very limited circumstances as an anaesthetic for specific types of surgeries (e.g., eye, nose, and throat procedures). It is available in solution for topical use. Systemic absorption would be expected to be minimal, and the clearance and degradation of cocaine is rapid, which limits the possibility that this drug would persist in a blood sample. Nevertheless, out of an abundance of caution, patients who have been administered cocaine should be advised not to operate a motor vehicle for a period of 24 hours after their procedure.

Cocaine impairs the ability to operate a motor vehicle. Cocaine impairment can occur in both the stimulant and crash phases. The stimulant effect leads to an overestimation of abilities and underestimation of risk associated with a particular driving action. This increased risk-taking behaviour when driving has been documented to include speeding, erratic driving, and loss of control (Siegel, 1987; Isenschmid, 2002; Jones *et al*., 2008). Since a predominant symptom after binge use is exhaustion with an increased need to sleep, impairment is also a concern after repeated administration of a stimulant. Users in the crash stage may have decreased alertness, attention, and vigilance. It has been suggested that low dose stimulants may improve performance; however, the dose and pattern of use are not typical of recreational cocaine use, and do not apply to drug abuse situations. In 20 cases of driving under the influence of drugs where no other psychoactive drugs were detected, cocaine blood

concentrations were detected at 80 to 500 ng/mL (Jones *et al*., 2008). Observations of these drivers included agitation, enlarged pupils, incoherent speech, and unsteady gait.

Cocaine stability is of particular concern. Cocaine is susceptible to degradation in the test tube during storage. Cocaine is also rapidly metabolized and has a short duration in the body. Therefore, considerations for decreasing the likelihood of cocaine breakdown include timely sample collection, storage at refrigerated temperatures with preservative added to the test tube, and expedited analysis. Benzoylecgonine is an inactive breakdown product of cocaine. It forms in the test tube and in the human body. Benzoylecgonine is indicative of cocaine use.

Of note, some countries have set a *per se* limit for cocaine and benzoylecgonine. *Per se* limits for cocaine of 10 ng/mL and 24 ng/mL have been implemented in the United Kingdom[iii] (10 µg/L) and Norway (Vindenes *et al*., 2012), respectively. The UK also set a *per se* limit for benzoylecgonine of 50 ng/mL (50 µg/L).

The Drugs and Driving Committee recommends a *per se* limit for cocaine of 30 ng/mL in blood (Table 2). The Committee recommends that there be no *per se* limit for benzoylecgonine. The following factors were considered when selecting a *per se* limit: analytical considerations, pharmacological properties, and established *per se* levels elsewhere. Furthermore, the time delay to sample collection and lack of an acceptable back extrapolation formula for drugs other than alcohol were important considerations when recommending a concentration.

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Gammahydroxybutyrate (GHB)

The origin of GHB can be exogenous (i.e., a drug) or endogenous (i.e., a compound found naturally in the body). As a drug, GHB is a central nervous system (CNS) depressant. It is most commonly encountered as a recreational drug, but has limited therapeutic potential for some medical conditions (Couper and Marinetti, 2002). The interpretation of GHB levels is complex and efforts have been made to explain the factors that have been considered in the ultimate recommendation.

GHB is a compound that can be produced endogenously in healthy humans, in elevated concentrations due to a rare genetic disorder, and as a postmortem artifact. GHB is a metabolite and a precursor of gamma-amino butyric acid (GABA), an important inhibitory neurotransmitter (Couper and Marinetti, 2002). Endogenous concentrations of GHB in blood are significantly lower than levels found after exogenous use. Typical concentrations detected in antemortem blood samples from humans are well below 5 mg/L. For example, in 240 blood samples GHB concentrations associated with endogenous production ranged from 0.17 to 1.51 mg/L (Elian, 2002); in an examination of 6 blood samples, GHB originating from normal physiological processes was detected at concentrations of 0.5 to 2.3 mg/L (Paul *et al*., 2006). In contrast, one individual arrested seven times for driving under the influence of a drug had GHB concentrations of 44 to 184 mg/L in blood samples collected 1.5 to 2.5 hours after contact with police (Couper and Logan, 2004). Furthermore, in 13 subjects arrested for impaired driving, blood GHB concentrations ranged from 26 to 155 mg/L (Couper and Logan, 2001). There are a few publications of note where elevated GHB has been associated with a rare genetic disorder, namely 4-Hydroxybutyric Aciduria or Succinic Semialdehyde Dehydrogenase Deficiency (Divry *et al*., 1983; Rahbeenu *et al*., 1994). Individuals with this disorder tend to demonstrate mental and motor impairments early in life, have seizure disorders, and may have family members with the same disorder (Divry *et al*., 1983; Rahbeenu *et al*., 1994). These individuals are unlikely to be operating a motor vehicle. Elevated GHB concentrations can also occur in postmortem samples. Postmortem production in blood is a well-established concept in Forensic Toxicology, and as such, interpretation of postmortem blood levels is distinct from antemortem samples.

Medical use of GHB in Canada is limited to specific conditions. Xyrem®[iv] is a drug available in liquid formulations for the treatment of narcolepsy. In other countries GHB may have wider uses as an anaesthetic or hypnotic agent, or to assist with treatment of alcohol dependence or opiate withdrawal (Couper and Logan, 2014). GHB can also arise from metabolism of 5-fluorouracil which is the active compound for some cancer treatments (Couper and Marinetti, 2002).

GHB can originate through administration of GHB, or through metabolism of gammabutyrolactone (GBL) or 1, 4-butanediol (1, 4-BD) (Couper and Marinetti, 2002). GBL is also a precursor in the clandestine manufacturing of GHB. GHB may occur in powder form but is typically available as a clear, viscous liquid with a salty and/or chemical taste. GHB is administered orally. Effects of GHB consumption will begin

shortly after absorption (10 to 20 minutes) and will generally last for 2 to 5 hours (Couper and Logan, 2014). GHB is rapidly metabolized and eliminated. Due to the ephemeral nature of GHB effects and the rapid clearance from the blood, timely collection is of importance. GHB is unlikely to be detected in a blood sample beyond 6 to 8 hours (Couper and Logan, 2014).

GHB is a powerful CNS depressant and its effects are dose dependent. As the administered dose increases and the peak concentration of GHB correspondingly rises, the CNS depressant effects would be expected to increase. GHB use may produce a large spectrum of side effects such as slow, slurred and incoherent speech, nausea, vomiting, sweating, incontinence, and hypothermia. At higher doses, GHB induces profound sedation, a state of unconsciousness, and respiratory depression which may result in death.

GHB impairs the ability to operate a motor vehicle. Observations of GHB-intoxicated drivers include erratic driving such as weaving, swerving, and ignoring road signs; physical indicia include lack of balance, decreased consciousness, and loss of coordination (Couper and Logan, 2001; Couper and Logan, 2004).

Selecting a *per se* level for GHB must incorporate a level above endogenous and thereby indicative of drug use, but also a level low enough to be of use considering the rapid metabolism of GHB in the blood resulting in a quickly decreasing blood concentration between the incident and sample collection. Therefore, timely sample collection is imperative if GHB is the drug of interest. There has been some suggestion that a citrate additive to the test tube may result in an elevation of the GHB concentration (LeBeau *et al*., 2000). With proper storage conditions and preservative (not citrate), GHB concentrations in antemortem samples are not expected to increase during storage (Beránková *et al*., 2006; Jones *et al*., 2015).

Of note, Norway has attempted to equate drug levels to BACs that are of relevance for their drinking and driving laws. A *per se* limit has been implemented for GHB of 10,300 ng/mL with 2 levels of graded sanctions at 30,900 ng/mL and 123,600 ng/mL which they have equated to BACs of 0.2, 0.5 and 1.2 g/L, respectively (Vindenes *et al*., 2012). These GHB levels convert to 10.3, 30.9 and 123.6 mg/L and the BACs convert to 20, 50 and 120 mg/100 mL. The percentage of cases that were over the GHB limits in the first year after implementation was low at 2.2%, 1.7% and 0.3%, respectively (Vindenes *et al*., 2014); this may be due to the inherent difficulty of GHB loss, or the low prevalence of GHB use.

The Drugs and Driving Committee recommends a *per se* limit for GHB of 10 mg/L in blood (Table 2). The following factors were considered when selecting a *per se* limit: analytical considerations, pharmacological properties, and established *per se* levels elsewhere. Furthermore, the time delay to sample collection and lack of an acceptable back extrapolation formula for drugs other than alcohol were important considerations when recommending a concentration.

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Heroin/ 6-monoacetylmorphine (6-MAM)

Heroin (diacetylmorphine) is an opioid analgesic which has central nervous system (CNS) depressant properties. Opioid analgesics are united by their common effect of pain control. Heroin was originally synthesized in 1874 and used therapeutically as an analgesic, an anti-tussive (treatment for persistent coughs), and an antidiarrheal agent (Stout and Farrell, 2003). It is no longer used for those purposes in Canada, and other than the recent inclusion of heroin for the purposes of risk reduction in drug addiction[v], heroin is an illicit substance. Administration is mainly by injection (typically intravenous), but it can also be smoked, or insufflated (snorted). The effects most frequently reported are euphoria, a feeling of well-being, sedation, and a feeling of warmth and heaviness. The onset of effects after smoked or injected heroin is within minutes, and can last up to approximately 4 hours (Jenkins *et al*., 1994). The onset of effects after insufflation of heroin is within several minutes, and has been documented to last for up to approximately 8 hours (Cone *et al*., 1993); this duration is due to the active metabolites formed that contribute to the overall drug effect.

Heroin itself is not typically analyzed in blood because the half-life is extremely short; heroin is almost immediately broken down to 6-MAM. 6-MAM also has a short half-life and can be present in the blood for up to approximately 2 hours after administration (Jenkins *et al*., 1994). However, the window of detection may be so brief that impaired drivers may be negative in the blood but positive for 6-MAM in the urine at the time of sample collection (Jones *et al*., 2012). As a result, the detection of 6-MAM in the blood is indicative of recent heroin use. 6-MAM is further metabolized to morphine, and the co-occurrence of 6-MAM and morphine is expected after heroin administration. The window for 6-MAM detection is short and collection of a blood sample in a timely manner is essential for an investigation into heroin use. Furthermore, 6-MAM may be subject to degradation in the sample and during the extraction process with factors such as storage temperature, time until analysis, and freeze/thaw cycles relating to stability of the compound (Rop *et al*., 1994) and, therefore, storage conditions and timely analysis are also of importance.

Heroin impairs the ability to operate a motor vehicle. Individuals under the influence of heroin can experience CNS depression ranging from moderate to severe after drug administration; the result is sedation and psychomotor impairment. A common observation after heroin use is the individual will be 'on-the-nod' implying an altered state of consciousness.

Due to the deleterious impact use of heroin would have on the faculties required for the operation of a motor vehicle, the active metabolite, 6-MAM, is recommended for zero tolerance in a blood sample (Table 2). Since this metabolite is recommended for zero tolerance, the Drugs and Driving Committee also recommends that all forensic laboratories within the government systems attempt to consolidate a cut-off concentration for their methodologies. This committee does not make a recommendation for the detection of heroin since this finding is an unlikely event.

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Ketamine

Ketamine is a drug that is classified as a dissociative anaesthetic. Ketamine was developed as a surgical alternative to phencyclidine (PCP) which had potential as an anaesthetic agent but resulted in emergence effects upon regaining consciousness that included violent and confused behaviour. Ketamine is not devoid of these effects but they are typically less severe in nature. Ketamine can be used as a pharmaceutical agent in human and veterinary medicine. When used in surgical procedures to induce anaesthesia, ketamine rapidly produces a hypnotic state that is characterized by profound analgesia, unresponsiveness to commands, and amnesia; however, the patient can breathe spontaneously and may have their eyes open during this hypnotic state. Patients administered ketamine in hospital should be advised to refrain from driving for a period of 24 hours. Due to ketamine's rapid clearance from the body, this time frame should be sufficient to remove the drug from the blood.

Ketamine is also used recreationally and is primarily administered by insufflation (snorted as a dried powder) or injection, and less commonly, by oral administration (sometimes in combination with other psychoactive substances). The onset of effects depends on the route of administration. In general, intramuscular injection, insufflation, and oral ingestion produce effects within 2 minutes, 5 to 10 minutes, and 15 to 20 minutes, respectively, after administration (Mozayani, 2002). Ketamine is fast acting, quickly eliminated, and generally of short duration; however, the effects of ketamine use may persist for a couple of hours (Couper and Logan, 2014). The effects of ketamine are dose related and at large doses the user experiences an intense detachment from reality (Morgan and Curran, 2011). The rapid onset, intensity of the experience, and short duration of action may lend itself to binge use of this drug (Morgan and Curran, 2011).

Ketamine impairs the ability to operate a motor vehicle. Individuals under the influence of ketamine may experience motor incoordination, out-of-body experiences, agitation, hallucinations, and be in a trance-like state. Both the physical and psychedelic experiences of ketamine use are inconsistent with the mental acuity and motor functioning essential for road safety.

Due to the deleterious impact use of ketamine would have on the faculties required for the operation of a motor vehicle this drug is recommended for zero tolerance in a blood sample (Table 2). Since this drug is recommended for zero tolerance, the Drugs and Driving Committee also recommends that all forensic laboratories within the government systems attempt to consolidate a cut-off concentration for their methodologies.

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Lysergic Acid Diethylamide (LSD)

LSD is a potent hallucinogen, with small doses causing vivid hallucinations. LSD was first synthesized in 1938 as an investigational drug. LSD is used recreationally and not available for medical use in Canada. LSD has low acute toxicity which means fatal intoxication due to LSD administration is very rare and unlikely. Deaths associated with LSD use are usually due to injuries received while under the influence of the drug. The hallucinogenic effects of LSD are commonly referred to as 'trips' and the effects are unpredictable varying with the amount ingested and the user's personality, mood, expectations, and surroundings.

The effects of LSD use can be classified into immediate and prolonged drug effects. LSD is typically administered orally via liquids, tablets, or blotter paper squares. The immediate effects are generally experienced within 20 to 30 minutes, peak at 2 to 4 hours, and return to baseline by 6 to 8 hours after administration (Couper and Logan, 2014). In 5 patients admitted to hospital for LSD intoxication, common observations included hallucinations, agitation, and combative behaviours; symptomology resolved within 4 to 6 hours after admission other than one patient who was kept for evaluation of acute psychosis (Blaho *et al*., 1997). The primary effect of LSD is perceptual distortion resulting in temporary psychosis. The perceptual disturbances include sensory distortion (visual and auditory) and hallucinations. Mood changes may also be experience by the user including euphoria, dysphoria, paranoia, anxiety, and panic. Further effects of LSD use are dizziness, confusion, agitation, hyperactivity, and hysterical behavior. Subsequent unpredictable hallucinations, referred to as flashbacks, may occur for weeks or months after drug use. These may be triggered by other factors such as stress, fatigue, drug use or anxiety, and can exacerbate pre-existing or underlying psychosis.

LSD impairs the ability to operate a motor vehicle. Evaluating LSD in a clinical setting is difficult in that the subject may become "too impaired" and unable to cooperate with the study due to the intense perceptual and physical changes (Passie *et al*., 2008). Individuals under the intoxicating effects of LSD are an extremely poor judge of their own abilities due to the mind-altering effects. Severe psychomotor, cognitive, and residual effects are associated with LSD use.

Some analytical considerations of note are metabolism and stability of the compound, and storage conditions. LSD is susceptible to degradation in samples exposed to increased temperatures, fluorescent or ultraviolet light (Li *et al*., 1998). Furthermore, LSD is taken in small doses and is rapidly metabolized which results in low blood concentrations and a short time frame to detect the drug. Due to these issues, ideal storage conditions are limited light exposure and refrigerated temperatures. Timely sample collection and expedited analysis are also important considerations.

Due to the deleterious impact use of LSD would have on the faculties required for the operation of a motor vehicle this drug is recommended for zero tolerance in a blood sample (Table 2). Since this drug is

recommended for zero tolerance, the Drugs and Driving Committee also recommends that all forensic laboratories within the government systems attempt to consolidate a cut-off concentration for their methodologies.

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Methamphetamine

Methamphetamine is a central nervous system (CNS) stimulant drug commonly used for its ability to increase alertness, relieve fatigue, and for its euphoric and stimulant effects. Methamphetamine can be orally ingested, injected, insufflated (snorted), or smoked. When methamphetamine is injected, smoked, or snorted, the onset of effects is rapid (i.e., within 10 minutes). Whereas oral administration of methamphetamine results in a comparatively delayed onset with a less intense drug experience. Overall the desired effects typically last 4 to 8 hours after use but may persist up to 12 hours (Couper and Logan, 2014). Repeated administration of methamphetamine, to prolong the drug effects and minimize the withdrawal effects, is a common pattern of use often referred to as binge use. Methamphetamine is metabolized to amphetamine which is an active metabolite and contributes to some of the drug effects. It is common to detect the presence of both compounds in a blood sample as a result of methamphetamine use. Since ephedrine and/or pseudoephedrine are used in the illicit manufacture of methamphetamine, it is also common to detect these compounds in combination with methamphetamine.

The effects of methamphetamine are dependent on the dose, pattern of administration, and time elapsed since last use. As the dose increases, the effects would correspondingly increase in intensity. During the acute intoxication phase, physical effects of methamphetamine include rapid movements and speech, talkativeness, dilated pupils, twitching (i.e., involuntary movement of muscles), and increased heart rate, respiration rate, body temperature and blood pressure. Furthermore, the individual may experience insomnia, lack of appetite, and a heightened sense of well-being. Single dose use produces CNS excitation characterized by increased energy, euphoria, and an elevated sense of confidence; sedation may follow the intense stimulant experience. Binge use may occur over hours or days and is initially characterized by the aforementioned effects, but is frequently followed by a crash phase which is accompanied by anxiety, weakness, fatigue, nervousness, and dysphoria. Frequent repeated administration in a binge pattern increases the possibility of psychotic symptoms such as paranoia and hallucinations. In two studies of methamphetamine-positive drivers concentrations ranged from <50 ng/mL to 9460 ng/mL, and common observations included rapid and confused speech, rapid pulse, agitation, paranoia, and violent/aggressive behaviours; erratic driving, speeding, and weaving were some of the reported driving observations (Logan, 1996; Lemos, 2009). It has been suggested that low dose stimulants may improve performance; however, the dose and pattern of use are not typical of recreational methamphetamine use, and do not apply to drug abuse situations.

There are properties of methamphetamine that may be used for therapeutic benefit. These properties include appetite suppression, nasal decongestion, and for treatment of narcolepsy and attention deficit hyperactivity disorder. Currently, there is no approved medical use for methamphetamine in Canada; it is not available over-the-counter or as a prescription drug. However, methamphetamine is available in other countries for medical purposes (e.g., Desoxyn®[vi]). Additionally, methamphetamine may also be

present due to metabolism of selegiline[vii], a drug available by prescription in Canada used for treatment of Parkinson's disease. There are other drugs not available in Canada which may result in the presence of methamphetamine due to the metabolism of the parent drug (Logan, 2002).

Methamphetamine impairs the ability to operate a motor vehicle. Impairment by methamphetamine results in lapses in attention and elevated risk-taking which leads to the increased potential for erratic and dangerous driving. Blood concentrations of methamphetamine would depend on the time elapsed since last administration as well as the pattern of use. The binge pattern of use for methamphetamine will result in elevated concentrations of this drug, and clearance of the drug from the blood could take hours to days. The impact would be that the user would be in a state of withdrawal rather than acute drug administration, but continue to have detectable methamphetamine blood concentrations. The symptomology associated with methamphetamine withdrawal, such as hyper-somnolence, lack of energy and overall weakness, is also of concern to road safety.

Of note, some countries have set a *per se* limit for methamphetamine. A *per se* limit for methamphetamine has been established in the United Kingdom[iii] and Norway (Vindenes *et al*., 2012) at 10 ng/mL (10 μg/L) and 45 ng/mL, respectively.

The Drugs and Driving Committee recommends a *per se* limit for methamphetamine of 50 ng/mL in blood (Table 2). The following factors were considered when selecting a *per se* limit: analytical considerations, pharmacological properties, and established *per se* levels elsewhere. Furthermore, the time delay to sample collection and lack of an acceptable back extrapolation formula for drugs other than alcohol were important considerations when recommending a concentration.

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Phencyclidine (PCP)

PCP, commonly referred to as 'angel dust', is a recreational drug that is categorized as a dissociative anaesthetic. PCP was first introduced as a potential surgical anaesthetic agent during the 1950s. PCP was found to induce a trance-like state in which an individual could be exposed to pain without experiencing the actual sensation of pain. However, PCP was quickly removed from the market as it was deemed to have unacceptable adverse effects, including emergence delirium in which patients coming out of anaesthesia would exhibit agitation, disorientation, vivid dreams, hallucinations, and emotional distress. PCP was also used as a veterinary anaesthetic, but this practice has also been discontinued. PCP is not available for medical use in Canada and, therefore, PCP is currently an illicit drug.

The routes of administration for PCP include inhalation (smoking), insufflation (snorting), ingestion and injection. PCP may be available in liquid or powder forms. The onset of effects after smoked or injected PCP occurs within seconds to minutes, can be within several minutes after snorting, and can take 20 to 40 minutes after oral ingestion (Mozayani, 2003). The effects of PCP generally last 4 to 8 hours but some symptoms may extend for up to 24 hours or more (Mozayani, 2003).

The effects of PCP can include features of a central nervous system (CNS) depressant, a CNS stimulant, and a hallucinogenic agent. Recreational effects commonly reported after using PCP are euphoria, and the feeling of strength and invulnerability. Other effects associated with PCP use include disorientation, out-of-body experiences, ataxia, drowsiness, agitation, hallucinations, and bizarre and/or violent behaviour. The effects and duration of action of PCP on an individual depend on the route of administration, dose, presence of other psychoactive substances, underlying psychiatric disturbances, experience with PCP, and the setting of the drug administration.

PCP impairs the ability to operate a motor vehicle. In 50 intoxicated drivers positive for PCP, observations included staggering, unsteady gait, blood-shot eyes, altered speech patterns (thick, slowed, slurred), nystagmus, and blank stares (Clardy *et al*., 1979). PCP can cause severe mental and physical impairment.

Due to the deleterious impact use of PCP would have on the faculties required for the operation of a motor vehicle this drug is recommended for zero tolerance in a blood sample (Table 2). Since this drug is recommended for zero tolerance, the Drugs and Driving Committee also recommends that all forensic laboratories within the government systems attempt to consolidate a cut-off concentration for their methodologies.

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Psilocybin/Psilocin

Psilocybin, commonly known as 'magic mushrooms', is a naturally occurring hallucinogenic compound. Psilocybin may effectively act as a pro-drug as it is rapidly and extensively metabolized into psilocin, the primary psychoactive compound in the body (Hasler *et al*., 1997). Typically, psilocybin mushrooms are ingested orally, either fresh, or dried. The effects are dose dependent; however, the potency of the drug is variable and related to growing conditions, species or variant, origin, and age of the mushroom (van Amsterdam *et al*., 2011). The onset of psychedelic effects occurs within 20 to 40 minutes of ingestion, with maximal effects occurring within 60 to 90 minutes, and the duration of action may persist for up to 6 hours post-ingestion (Hasler *et al*., 2004; van Amsterdam *et al*., 2011).

Although there have been academic attempts to use psilocybin for research, it is not available for medical use in Canada, and is a drug used for recreational purposes. Users consume psilocybin for the desired effects of relaxation, giddiness, increased energy, euphoria, and the psychedelic/mystical experience. Other effects include perceptual changes, synaesthesia, and alteration of thought and time sense. Sensory distortions may include one or more of the following: visual enhancements (e.g., colours become brighter); visual disturbances (e.g., surfaces appear to move or produce waves); altered perception of real events, images and faces; or hallucinations. Effects such as these have been associated with anxiety and paranoia in psilocybin users. Although fatal toxicity is unlikely, psilocybin use has been implicated in accidental deaths such as falls or exposure to the elements (van Amsterdam *et al*., 2011).

Psilocybin use impairs the ability to operate a motor vehicle. Individuals under the influence of this drug experience mind-altering effects removing them from the reality of the situation. The psychedelic experiences which follow psilocybin use are inconsistent with the mental functioning required for road safety.

Some analytical considerations of note are metabolism and stability of the compounds. Psilocin, the extensively and rapidly produced psychoactive component, may be light and temperature sensitive, and may not be stable in aqueous solutions (Bjornstad *et al*., 2009; Hasler *et al*., 1997). Therefore, storage conditions to reduce the potential degradation of the compound and timely analysis are of importance.

Due to the deleterious impact use of psilocybin would have on the faculties required for the operation of a motor vehicle, both the parent, psilocybin, and its active metabolite, psilocin, are recommended for zero tolerance in a blood sample. Detection of psilocybin, psilocin or both would make out the offence. Since this drug is recommended for zero tolerance (Table 2), the Drugs and Driving Committee also recommends that all forensic laboratories within the government systems attempt to consolidate a cut-off concentration for their methodologies.

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Table 2. Recommendations for detection or *per se* limits for selected drugs.

Drug	Detection in a Blood/Serum/Plasma Sample	*Per se* Limit in a Blood Sample
Cocaine		30 ng/mL
Gammahydroxybutyrate (GHB)		10 mg/L
Heroin (6-monoacetylmorphine*)	✓	
Ketamine	✓	
Lysergic Acid Diethylamide (LSD)	✓	
Methamphetamine		50 ng/mL
Phencyclidine (PCP)	✓	
Psilocybin/Psilocin	✓	

*6-monoacetylmorphine (6-MAM) detection; no recommendation for heroin

Endnotes

[i] The terms plasma and serum are used interchangeably for the purposes of THC and alcohol; although technically different sample types, they are considered an equivalent matrix for the purposes of conversion to blood values.

[ii] Conversion to blood concentrations using the median blood:plasma ratio of 0.68 (Desrosier *et al*., 2014). Many papers examine plasma/serum concentrations. The primary sample type for future *per se* legislation will be blood; therefore, the concentrations were converted for ease of comparison.

[iii] https://www.gov.uk/government/collections/drug-driving#table-of-drugs-and-limits
Accessed March 2017

[iv] Xyrem® Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association, CPhA monograph. Last revision: October 2016.

[v] http://www.gazette.gc.ca/rp-pr/p2/2016/2016-09-07/html/sor-dors239-eng.php

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[vii] Selegiline. Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association, CPhA monograph. Last revision: November 2011.