Canadian Society of Forensic Science
La Société canadienne des sciences judiciaires

Report on MDMA *Per Se* Limits and Approved Drug Screening Equipment Considerations

Canadian Society of Forensic Sciences
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April 2024

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Executive Summary

- MDMA (methylenedioxymethamphetamine) is a central nervous system stimulant and hallucinogen commonly produced in tablet or capsule form for oral ingestion.
- MDMA is controlled under Schedule I of the *Controlled Drugs and Substances Act*. The sale, possession, or production of MDMA is illegal unless authorized for medical, scientific, or industrial purposes.
- MDMA metabolism produces MDA (methylenedioxyamphetamine), which has similar effects to MDMA itself.
- There are limited studies of MDMA-positive drivers, but the research that is available suggests that MDMA use can impair a person's ability to operate a motor vehicle.
- Detrimental effects of MDMA on drivers may include increased impulsivity and risk-taking, hallucinations/delusions and a sense of detachment or distance from the real world.
- Binge* MDMA use at all-night dance parties can result in sleep deprivation and/or dehydration; while these may magnify the impairing effects of MDMA, their individual contributions to the resulting impairment are almost impossible to isolate and assess.
- Although low dose stimulant use has been suggested to improve driving performance, these low doses are not applicable to recreational MDMA use.
- MDMA is detectable in the blood up to several days after last use; detectability extends beyond the acute impairing effects and can correspond with residual effects which typically occur 1-2 days since last use.
- Residual MDMA effects include difficulty concentrating, loss of balance and fatigue; there is a lack of scientific studies examining whether these residual effects have any measurable impacts upon driving ability.
- Although scientific studies suggest that MDMA can impair driving ability, there is a paucity of scientific studies examining the direct relationship between MDMA blood concentrations and driving impairment. As such, determination of a specific *per se* blood concentration which directly correlates with MDMA-induced driving impairment is not currently feasible.
- MDMA and MDA's detection profiles in oral fluid makes them potential candidate compounds for approved drug screening equipment (ADSE).
- Immunoassay-based analyses for methamphetamine have a high potential for cross-reactivity with MDMA. As such, a positive immunoassay screening result for methamphetamine in ADSE could be caused by the presence of MDMA and/or methamphetamine. Subsequent laboratory analyses would then be required to identify which of these compound(s) contributed to the positive ADSE result.

* Binge use refers to using repeated MDMA administration over a period of time over hours to days.

Introduction

There are several points to consider in determining whether methylenedioxymethamphetamine (MDMA) should be added to Canadian blood drug concentration regulations. These include epidemiological, pharmacological, and practical considerations. This document is intended to serve as an overview of the topic and as a starting point for informed discussion and deliberation.

MDMA, commonly referred to as "ecstasy", "E" or "molly", is a recreational drug that is categorized as a central nervous system (CNS) stimulant, a hallucinogen and an empathogen. Currently, there are extremely limited legal therapeutic applications of MDMA in Canada. MDMA is typically accessed illicitly and is commonly produced in tablet form for oral ingestion.

The most common effects of recreational MDMA use include mild intoxication, euphoria, an enhanced sense of well-being, increased self-confidence and energy, sociability, extroversion, empathy, perceptual distortions of colours and sound, and blurred vision (de la Torre et al., 2004). When consumed at higher doses toxicity can occur, characterized by hallucinations, confusion, agitation, panic attacks, coma and even death. Physiological effects of MDMA include elevated blood pressure, heart rate, and body temperature, as well as sweating, pupil dilation, increased muscle rigidity, and involuntary jaw clenching or teeth grinding. These effects begin approximately 30 minutes after ingestion, peak after 1 to 2 hrs, and last for approximately 4 to 6 hours. Hartman et al., 2014 cite reports of residual symptoms such as insomnia, fatigue, sore jaw muscles, loss of balance and headache which may persist into the next day, with some users reporting confusion, depression, and anxiety several weeks after a single dose of MDMA.

The data used to determine whether a specific drug impairs driving ability are commonly obtained from several sources: laboratory studies of drug effects on driving-related tasks or abilities, closed course/driving simulator/other controlled studies of driving ability (e.g., roadway driving) using drug-positive drivers, and epidemiological studies of the relationship between drug presence/concentration and crash risk. This document outlines the evidence for MDMA-driving impairment, and the pharmacological and practical considerations pertinent to selection of blood drug levels for impaired driving legislation.

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 surveys have been conducted for many years to collect information on alcohol use by drivers, recent surveys have

also been able to gather information on drug use through the collection of oral fluid samples from drivers at the roadside.

The 2007 National Roadside Survey of Alcohol and Drug Use by Drivers in the United States reported that oral fluid samples from 11.1% of daytime and 14.6% of randomly stopped nighttime drivers were drug positive. Stimulants accounted for 1.6% and 3.2% of the positive specimens collected, respectively (National Highway Traffic Safety Administration, 2009).

Research indicates that MDMA is a drug that is used by Canadian drivers. In a recently published study of drug findings in suspected impaired drivers in Quebec, MDMA detection in biological samples rose from negligible levels in 2014 to above 5% of cases in 2018 (Vaillancourt et al., 2021).

The use of MDMA by the Canadian population supports further examination of the scientific, road safety, and practical merits of MDMA inclusion in new regulations.

Drug Use by Drivers Involved in Road Crashes

Studies examining the presence and/or concentration of drugs in drivers involved in motor vehicle collisions provide information on the frequency in which drug-positive drivers are involved in collisions relative to drug-negative drivers. Some studies are also able to determine whether the drug presence or concentration increased the likelihood of the driver being responsible for the collision.

The incidence of MDMA-positive drivers, as determined both by roadside surveys and by studies testing the drug-positivity rate of drivers involved in road crashes, is relatively low. As such, this type of study offers correspondingly little data to either directly support or refute a relationship between MDMA blood concentrations and driving impairment.

Risks Associated with Drug Use by Drivers

The limited studies performed on MDMA-positive drivers provide scientific evidence that MDMA use can impair a person's ability to operate a motor vehicle. Detrimental effects of MDMA on driving have been reported as reckless driving behaviour, including speeding, risk-taking (e.g., running red lights, passing when unsafe, loss of control), increased impulsivity (i.e., lack of judgement and decision making), hallucinations/delusions and a sense of detachment or distance from the real world (i.e., attention dysfunction) (Logan and Couper, 2000).

It has been suggested that low dose stimulants including MDMA may improve driving performance as the predominant effect is to increase energy and counter the effects of exhaustion; however, the dose and pattern of use in these studies are not applicable to recreational MDMA use. Indeed, it has been suggested that any aspects of driving performance

that are improved by MDMA are more than negated by the other aspects of driving performance that are impaired following typical MDMA use (Ramaekers, 2006).

Pharmacological Considerations

Pharmacokinetics

MDMA is commonly consumed orally, with typical doses ranging from 50 to 150 milligrams (mg). Doses ranging from 50 to 125 mg have been observed to produce peak blood concentrations ranging from 106 to 236 ng/mL (Kalant, 2001). However, a common pattern of use is binge consumption at all night rave or dance parties. MDMA users report consuming multiple doses (average 120 mg per dose) in a single session with up to 700 mg consumed in total (Couper and Logan, 2014). MDMA's pharmacokinetic profile indicates that both single and binge-dose use produce elevated blood concentrations that should be readily detectable in blood samples both shortly after use and for extended periods of time thereafter.

Following ingestion, MDMA is readily absorbed from the digestive tract into the body where it starts to be broken down into 4-hydroxy-3-methoxymethamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), and 3,4-methylenedioxyamphetmaine (MDA). Kolbrich et al., 2008 detected MDMA in the plasma of all study participants 30 minutes after ingestion, while MDA was detected by 1.25 hrs post-ingestion. Generally, peak concentrations of MDMA were reached 2.4 hrs post-ingestion, while those for MDA were reached after approximately 7.5 hrs.

MDMA remains in the bloodstream for extended periods following ingestion; one research article determined that more than 50% of study participants still had detectable plasma concentrations of MDMA 47 hrs after low dose ingestion. MDMA concentrations were all below limits of quantitation by 119 hrs post-ingestion for those participants who remained in the study (Kolbrich et al., 2008). Interestingly, MDA which is produced in the body when MDMA breaks down, is detectable in the body for shorter periods of time than MDMA itself. In this same study, only 24% of study participants had detectable MDA concentrations 47 hrs after ingestion of a low dose of MDMA, while only one participant still had detectable MDA plasma concentrations at 71 hrs. This apparent inconsistency may be explained by the fact the MDA is not the primary breakdown product of MDMA and when residual levels of MDMA remain in the plasma, concentrations of MDA have decreased to those below typical analytical levels of detection.

While MDA is most commonly produced in the body following MDMA ingestion, it can also be produced and consumed as a drug itself. Similar to MDMA, MDA is a scheduled substance in Canada where it does not currently have any legal therapeutic or recreational uses. A recent study reports that self-reported effects of MDA last longer than those of MDMA, with MDA effects remaining elevated at 8 hrs after administration while MDMA effects resolved by 6 hrs after use (Baggott et al., 2019). MDMA and MDA are similar in both their chemistry and their biological effects (Kalant, 2001) and thus studies of the effects of MDMA are considered largely

applicable to MDA. Like MDMA, MDA is reported to have both empathic and psychedelic effects on users (Baggott et al., 2019). Also similar to MDMA, there is a paucity of scientific literature on the impairing effects of MDA on driving.

Based on the pharmacological similarity of MDMA and MDA, similar consideration should be given to MDA's addition to the blood drug concentration regulations.

Pharmacodynamics

MDMA is typically used to produce a variety of desired recreational effects which include a marked increase in wakefulness, perceived increases in energy and endurance, sexual arousal, euphoria, increased self-confidence, greater sociability and extraversion, and heightened feelings of closeness to others (as reviewed by Kalant, 2001). MDMA use typically also produces several adverse physical effects, including involuntary jaw clenching or teeth grinding, restless leg movement, back and limb stiffness and pain, loss of balance, sweating, headache, nausea, blurred vision, increased heart rate and blood pressure, and dry mouth (*ibid*). Adverse psychological effects may also occur, including mild hallucinations, an inability to focus one's thoughts, insomnia, anxiety, decreased food intake, agitation which may lead to delirium, brief psychotic episodes, or bizarre and reckless behaviours (as reviewed by Kirkpatrick et al., 2012 and Kalant, 2001).

MDMA effects typically begin within 30 minutes of ingestion (Cooper and Logan, 2014) with the subjective effects peaking 1-2 hrs post-administration (Hartman, 2014). Subjective effects typically last for 4-6 hrs although during "binge" usage subjects may take additional doses when the subjective effects start to diminish (Kuypers, 2017). Residual effects may persist into the next 1-2 days after MDMA use. These typically include difficulty concentrating, depression, loss of balance, anxiety and/or fatigue (Logan and Cooper, 2001; as reviewed by Kalant, 2001).

As noted previously, there is a paucity of scientific literature which directly examines the impairing effects of MDMA and/or its metabolite MDA on driving. Those studies that do examine these effects focus on their acute effects (i.e., within the first hours after ingestion) as opposed to their residual effects. Thus, while residual MDMA effects such as difficulty concentrating, loss of balance and fatigue are inherently not conducive to safe driving, a lack of scientific studies prevents determination of whether the magnitude of these reported residual effects of MDMA are sufficient to have measurable impacts on driving ability. An additional layer of complexity is associated with the common patterns of MDMA use. Binge MDMA use at all-night dance parties can result in sleep deprivation and/or dehydration; while these may magnify the impairing effects of MDMA, their individual contributions to the resulting impairment are almost impossible to isolate and assess. Finally, the extended time frame for MDMA detection in blood extends over the period of acute effects as well as residual effects. Blood concentrations taken at a single point in time cannot specify time since last use; any consideration of blood *per se* limits for MDMA needs to take into account the difficulty in distinguishing between blood concentrations

associated with recent administration (i.e., within the first minutes to hours after consumption), with residual levels (i.e., greater than 1 day after last use), and with single versus binge use.

Chronic Use

Unlike some other drugs, the repeated administration of MDMA over time (chronic use) does not produce marked differences in the magnitude, characteristics, or time frame of its impairing effects on individuals. Similarly, chronic use has not been reported to alter blood MDMA concentrations within an individual. Currently there is a conflicting body of literature over whether chronic MDMA use can produce cognitive deficits. Although chronic use of MDMA has been associated with deficits in short-term memory, delayed information recall, attention, vigilance, and executive functions such as planning and self-control, there are inconsistencies and difficulties in interpretating findings (as noted by Wunderli et al., 2017).

Passive Inhalation/Exposure

As noted above, MDMA is primarily consumed by oral ingestion, thus minimizing the possibility of passive inhalation possible with some smoked drugs. Similarly, passive exposure by other means is an unlikely source of MDMA in an individual. To date, the scientific literature has not identified passive exposure as a significant source of MDMA in the body.

Time Delay in Sample Collection

For some drugs, the time delay between initial identification of a suspected drug-impaired driver and collection of a blood sample for toxicological analysis is of primary concern, however this is not the case for MDMA. MDMA and its metabolite MDA are both detectable in the body for an extended period of up to days following last use. Thus, in most situations, the potential is low for impairing concentrations of MDMA and/or MDA to decrease below limits of detection during the time interval between identification of suspected impaired drivers and subsequent blood sample collection.

MDMA and Alcohol

Although there are limited studies on the combined use of alcohol and MDMA, a study by Kuypers et al., 2006 showed that alcohol-induced impairment was not mitigated by coadministration of MDMA. While some studies show that stimulant drugs can counteract some of the impairing effects of alcohol, performance compensation after combined MDMA-alcohol administration was limited to a single driving parameter and was never sufficient to fully overcome alcohol impairment in all driver tasks.

Practical Considerations for ADSE Use

The DDC Report on Drug Screening Equipment – Oral Fluid (2018) provides general information about oral fluid drug screening, including information specific to target compounds. The following section provides details about oral fluid screening specific to MDMA.

MDMA Detectability in Oral Fluid

MDMA is readily detectable in oral fluid samples. Studies of recreational MDMA users found elevated oral fluid concentrations which peaked 2-3 hrs post-ingestion, but which varied 100-fold between subjects (Barnes et al., 2012; Samyn et al., 2002). MDMA is commonly detectable in oral fluid shortly after ingestion. Barnes et al., 2012 found MDMA was initially detected as early as 0.25 hr (the first collection time point) after dosing although the initial positive specimen more often occurred at 0.5 or 0.75 hr, and in all participants by 1.25 hr post-dose. Residual drug presence in the oral cavity following MDMA ingestion does not appear to be significant, as post-ingestion MDMA is typically first detected in plasma, and then later in oral fluid.

MDMA Metabolites in Oral Fluid

MDA is also detectable in oral fluid following MDMA ingestion, but at lower concentrations and for somewhat shorter time periods. Similar to MDMA, MDA also demonstrates considerable intra- and inter-subject variability in oral fluid concentrations (Barnes et al., 2012; Saymen et al., 2002). Barnes et al., 2012 analysed multiple oral fluid samples after both high and low MDMA doses and found that maximal MDA concentrations were only a small fraction of those for MDMA. MDA was not always detected following MDMA use, but when it was detected, it was in combination with MDMA (*ibid*). HMMA and HMA, despite also being products of MDMA metabolism, were not detected in any of the oral fluid specimen (*ibid*).

Potential for MDMA "False Negatives" in Oral Fluid

"False negatives" in which a negative oral fluid result on drug screening equipment is obtained despite that drug's presence in the individual's blood at or above a *per se* limit or level of detection, can occur dependent upon the drug in question, the specifics of its use, and its cut-off concentration in oral fluid. MDMA's extended period of detectability in blood after last use increases the potential for this type of false negative to occur, however it is most likely to occur after the acute impairing effects of MDMA have subsided.

Potential for MDMA "False Positives" in Oral Fluid

"False positives" in which a positive result on oral fluid drug screening equipment is not confirmed in a subsequent blood sample can arise by several means including drug contamination of oral fluid or oral fluid collection systems in the absence of drug consumption. Unlike some other drugs, MDMA is not commonly smoked, thus effectively negating concerns about passive exposure to this drug producing a false positive result.

"False positives" on oral fluid drug screening equipment can also be produced when the detectability of a drug in the oral fluid extends beyond the period for which it is present in the blood of that individual. Although MDMA is typically detectable in oral fluid for several hours following ingestion, this is far less than the time frame that MDMA can be detected in blood (Barnes et al., 2012; Kolbrich et al., 2008). Thus, MDMA is unlikely to produce this type of false positive in oral fluid screening.

"False positives" can also occur when blood drug concentrations decrease below *per se* limits or below limits of detection during the period between oral fluid testing and blood collection from the individual. The likelihood of this situation increases with increasing delay between oral fluid testing and blood collection, for drugs which are rapidly eliminated from blood, and for drugs which were present in blood at concentrations at or near their *per se* limits or analytical limits of detection at the time of oral fluid testing. The potential for these scenarios to occur is minimized by MDMA's prolonged detectability in blood.

"False positives" can also arise from drug degradation or loss from the blood sample between the time of collection and the time of analysis. With use of standard forensic laboratory practices, MDMA is not susceptible to this form of false positive situation.

Finally, "false positives" on oral fluid drug screening equipment can arise from residual drug deposits in the oral cavity prior to significant drug absorption into the body and blood. Although theoretically this situation could occur following oral MDMA ingestion, in scientific practice this phenomenon has not been noted. Indeed, MDMA has typically been detected in plasma prior to oral fluid (Barnes et al., 2012). MDMA is typically ingested in tablet form thereby minimizing oral cavity exposure and the formation of deposits.

Summary of ADSE Considerations

The ability to detect MDMA in oral fluid samples shortly after consumption suggests its amenability for identification by ADSE roadside screening. The presence of MDMA in oral fluid also correlates with its presence in blood during the time period when acute driving impairment is most likely to occur. However, immunoassays are commonly employed for roadside oral fluid drug screening, and these are known to have high-cross-reactivity between MDMA and methamphetamine. This suggests that specific identification of MDMA using ADSE may not be feasible. Instead, a positive result may arise from the presence of MDMA, or methamphetamine or both. In such situations, subsequent analyses would be required to identify the specific drug(s) present.

Proposed Legal Limits

While fundamentally, the adverse effects of MDMA such as loss of balance, blurred vision, mild hallucinations, delirium, and brief psychotic episodes may negatively affect driving performance, there is a relative paucity of scientific literature which directly examines the relationship between MDMA blood concentrations and impairment of driving-related functions. It has also been argued that the increased wakefulness produced as a dominant effect at relatively low doses of MDMA (75 and 125 mg) may positively impact skills related to driving in some circumstances (Cami et al., 2000). Additionally, studies examining the duration of MDMA-induced driving impairment are lacking, particularly with respect to driving while under the residual effects of MDMA which occur 1-2 days since last use. This makes recommending an appropriate *per se* level over which everyone would be impaired in their ability to operate a motor vehicle very challenging.

In previous reports, drug *per se* levels were recommended based on several factors such as analytical considerations, pharmacological properties, and established *per se* levels elsewhere. For MDMA, the analytical considerations and pharmacological properties are similar to methamphetamine, although there is more scientific literature available for methamphetamine. The DDC has previously recommended a *per se* limit of 50 ng/mL for methamphetamine (DDC, 2017). Reported MDMA *per se* limits for other countries range from 10-100 ng/mL, with most limits set between 10-25 ng/mL and the remainders between 50-100 ng/mL (Gjerde et al., 2023). Given the above, consideration could be given to a limit of below 50 ng/mL or at or above 50 ng/mL.

A limit below 50 ng/mL may be beneficial for public safety as it would be more in line with a ‘zero tolerance’ approach. It would extend the window of detection and more likely identify individuals who are experiencing residual effects. However, extended detection in blood could also identify individuals who had used MDMA but are no longer experiencing any effects

including impairment. Finally, a limit below 25 ng/mL may be below the current quantitative reporting level of some Canadian forensic laboratories.

A limit of 50 ng/mL or above would lower the risk of identifying individuals who are no longer experiencing effects from their MDMA use. Conversely, a higher *per se* level may result in not detecting individuals who are experiencing significant effects.

A final practical factor that may be relevant to setting a *per se* limit for MDMA is the impact on the approval and use of ADSE. Due to the cross reactivity of MDMA to methamphetamine assays, a positive ADSE result for methamphetamine may be caused by methamphetamine alone, MDMA alone or a combination of the two. If there is a positive ADSE result caused by methamphetamine alone, it is likely that the individual has a detectable methamphetamine blood concentration. In MDMA alone cases, a positive ADSE also likely means that the individual has a detectable level of MDMA in their blood. The higher the *per se* level the lower the confidence that a positive ADSE test result from MDMA alone will be followed by a blood test with MDMA at or above the *per se* level.

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