EXPERT REPORT ON TECHNICAL ISSUES ASSOCIATED WITH DRUG TESTING

1. **Introduction and Instructions**

   1.1. This expert report is provided by Professor Olaf H. Drummer jointly for Paliare Roland Rosenberg Rothstein LLP of Toronto, Canada representing the Power Workers Union of Canada and for Sonia Pylyshyn of the Society of Energy Professionals.

   1.2. This expert report provides a background to drug testing of employees to determine their fitness for duty and the technical aspects associated with blood and urine testing, and addresses a series of specific questions raised by the clients.

2. **Professional Background of the Expert**

   2.1. Professor Drummer is a forensic pharmacologist and toxicologist from the State of Victoria, Australia. Currently, he is employed as Deputy Director (Academic Programs) at the Victorian Institute of Forensic Medicine and as Professor and Head of the Department of Forensic Medicine, Monash University, of 65 Kavanagh street, Southbank in Melbourne, Australia.

   2.2. Professor Drummer completed his PhD from Melbourne University in 1980, and has been involved in the analysis of drugs and poisons, and the interpretation of their biological effects, for over 40 years. He has published extensively in the fields of forensic pharmacology and analytical toxicology, including in over 250 peer reviewed scientific papers in journals and in three professional books. He has acted as an expert forensic toxicologist in hundreds of cases in Australia and in other parts of the world including issues around the detection of drugs in biological fluids.

   2.3. He is a past President of the International Association of Forensic Toxicologists (TIAFT) and is the inaugural and continuing President of the Forensic and Clinical Toxicology Association of Australia (FACTA inc.). He is also a member of a number of other national and international associations. He sits on the current Standards Australia committee revising a standard for the testing of drugs in oral fluid and has served on a range of other committees tasked with reviewing and writing standards around drug detection.

   2.4. A current curriculum vitae is attached as a separate document.

3. **Documents Provided**

   3.1. Draft regulation document on Human Performance Management – Fitness for Duty – issued by Canada's Nuclear Regulator (REGDOC-2.2.4).

   3.2. Approved Breath Analysis Instruments Order as published by the Minister of

Justice and last amended May 27, 2013.

4. Drugs of Abuse

4.1. There are many drugs that can be used and abused, including the numerous legally-available drugs and the illegal drugs [1].

4.2. In the context of this report the focus is on drugs that can adversely affect human behaviour and function that can lead to an inability to safely and properly carry out functions required in a workplace. These drugs will be termed drugs of abuse for the purpose of this report.

4.3. Traditionally the most common drugs of abuse are the amphetamines, cocaine, cannabis, benzodiazepines and opioids.

4.4. Amphetamines include meth(yl)amphetamine, amphetamine, MDMA (3,4-methylendedioxy-methamphetamine, also known colloquially as Ecstasy), but can also include a host of other amphetamines or amphetamine-type stimulants (ATS) including the newer synthetic forms, sometimes referred to as "Bath Salts" that are analogs of amphetamines with similar adverse behavioural effects to methamphetamine.

4.5. Opioids include heroin and morphine but also oxycodone, hydrocodone, hydromorphone, methadone, meperidine, fentanyl, tramadol etc. Most of these are legally available drugs but are been known to be abused causing adverse behaviours.

4.6. Cannabis refers any one of the various forms of cannabis plant that contains Δ^9-tetrahydrocannabinol (THC) as the active form. THC is usually delivered by inhalation of smoke from a cigarette, blunt or joint but also can be consumed orally (cookies etc). Over the last several years synthetic forms of THC have become available, known as synthetic cannabinoids[1]. These drugs have similar adverse effects to THC but are chemically very different to THC [2, 3].

4.7. Benzodiazepines are a class of drugs available only as prescription drugs that can be abused, often in conjunction with other drugs, such as alcohol, cannabis, opioids and amphetamines. Examples include alprazolam, diazepam, lorazepam, oxazepam temazepam etc.

4.8. There are many other drugs that are abused that do not neatly fit into the 5 classes listed above. These may include hallucinogens, muscle relaxants and some other drugs that depress the functioning of the central nervous system (CNS), such as gamma-hydroxybutyrate (GHB) [1].

5. Detection Times for Drugs of Abuse in Blood and Urine

5.1. The most common biological fluids to detect drugs are blood and urine [4], although oral fluid (saliva) is now also often being used in roadside testing of drivers and in workplaces [5, 6].

5.2. The ability to detect drugs in any one of these fluids is determined by:

5.2.1. Dose, or doses, used by the person,

5.2.2. The time these drugs were last used,

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[1] sometimes known as "legal highs" or "spice" etc

5.2.3. The pharmacokinetic property of the drug, that is, the mode and rate of removal of the drug from the body, and

5.2.4. The detection method used by the laboratory with respect to sensitivity and specificity.

5.3. For example, cocaine, when administered by any one of the known methods (smoking, snorting etc) is rapidly absorbed into the body providing a quick onset of action, but is also relatively rapidly removed by the body. The time to remove half the drug in blood, known as the half-life, is about 1 hour. This means that within half a day there is little if any cocaine left to detect in the blood. However, the drug is also metabolized (converted into breakdown products) that can be targeted in urine and can be detected for a longer period, often at least one day. The main targeted metabolite of cocaine is benzoylecgonine (BE).

5.4. Similar principles apply for the other drugs, however they all have different half-lives, tissue concentrations and times to detect in blood and urine. The table below summarises these general properties as a guide since these times will also depend on the person and dose(s) used.

Table 1. Likely duration of action and detection times in blood and urine for selected drugs

Drug/Drug Metabolite	Duration of Action	Detection Times	
		Blood	Urine
Heroin	<6 hours	0-1 hours	Rarely detectable
6-Acetylmorphine (heroin metabolite)		1-3 hours	6 hours
Benzodiazepines	6-24 hours	12-24 hours	1-7 days
THC	<6 hours	1-12 hours	
Cannabis metabolite		1-3 days	3-28 days
Cocaine	<4 hours	1-12 hours	
Cocaine metabolite (BE)			1-3 days
Oxycodone	12-24 hours	1-2 days	1-3 days
Methadone	1-2 days	1-3 days	3-7 days
Methamphetamine	12-24 hours	1-3 days	2-4 days
Amphetamine	12-24 hours	1-3 days	2-4 days
MDMA	12 hours	1-3 days	2-4 days

The duration of action refers to any substantial behavioural response but will depend on dose, frequency of use and sensitivity to drug; for benzodiazepines it will also depend on the drug; hence times are only indicative of more typical use.

Detection times will depend on dose, pharmacokinetic differences, and which metabolite is targeted, as well as on other factors, and are therefore only indicative. For cannabis, significantly longer detection times are seen with persons using the drug repeatedly. Some screening kits based on immunoassay will detect more metabolites than others.

BE = benzoylecgonine, THC = Δ^9-tetrahydrocannabinol, MDMA = 3,4-methylendedioxy-methamphetamine, Ecstasy.

5.5. Persons using any one of these drugs on a regular basis (chronic use) or using any one of these drugs in a binge session (many doses in a short period of

time) will often give longer detection times since the cumulative dose is often quite high.

5.6. Persons using any one of these drugs on a regular basis is also likely to develop a tolerance to the drug, that is their sensitivity and response to the drug has diminished with repeated use usually leading to the use of higher doses. This also leads to longer detection times.

5.7. Regular use also tends to lead to a drug dependency situation where the user finds it becomes increasingly difficult to cease use of the drug without suffering a withdrawal syndrome.

6. **Drug Detection Techniques**

6.1. This section is not intended to provide a thorough review of drug detection techniques but rather illustrate the technical approach to drug detection, the analytical techniques often employed and their strengths and limitations.

6.2. The analytical process of measurement can be split into two; the initial screening test, and the confirmation step. The screening step provides a relatively quick process to establish if a drug, or drug class, is likely to present in a given specimen, whilst the second (confirmation) step ensures that the drug is present and may also provide an estimate of the amount present. The confirmatory test is required when drugs are detected presumptively in the initial test.

6.3. Consequently, analytical methods can be broadly classified into screening procedures, and confirmation procedures, however there are also specific methods available for a particular drug or for a narrow range of drugs.

Screening Procedure

6.4. The screening procedure is the most important part of the drug testing process since it defines the extent to which drugs or drug metabolites can be detected, and is sometimes called the "initial test". Methods are required to have sufficient sensitivity and coverage of substances in order to provide a reasonable basis for their detection, should they be present. While there is no one ideal methodology it is more often than not that more than one method is required to allow a sufficient coverage of substances that are required to be targeted.

6.5. Immunoassay screens for common drugs-of-abuse are commonplace and are often used as the first test. These assays are based on the interaction of the target drug or drug metabolite and a labelled form of the same drug or of the antibody that can be detected in some way (usually by colour) with a corresponding antibody that recognizes (binds) the target drug or drug metabolite. These are usually available in the form of commercial kits and are "run" using automated analysers in a similar way to standard biochemical tests.

6.6. A negative immunoassay result means that the sample does not contain a measureable amount of that drug or drug class. Immunoassays require little or no sample preparation and a laboratory can often screen hundreds of samples daily. However, positive results must always be confirmed by a more specific technique (e.g. chromatography-mass spectrometry [GC-MS] or liquid chromatography-mass spectrometry [LC-MS]) since they only give

an indication of a drug or drug group being present.

6.7. Examples of immunoassay screening test kits are CEDIA (cloned enzyme donor immunoassay), EIA (enzyme immunoassay including enzyme multiplied immunoassay or EMIT), ELISA (enzyme linked immunosorbent assay) and FPIA (fluorescence polarization immunoassay) and kinetic interaction of microparticles in solution (KIMS). EMIT and CEDIA are commonly used for urine, while ELISA is used for blood (and also oral fluid and hair).

6.8. These immunoassay kits provide useful methods when specimens are screened for various classes of drug. Most commonly these have been opiates and benzodiazepines. Unfortunately, no immunoassay-based kit is able to detect all members of the same class of drugs equally. In the case of opiates, immunoassays generally only detect morphine, codeine and possibly the heroin metabolite 6-acetylmorphine. They generally do not detect other opiates, let alone members of the wider opioid family that includes hydrocodone, hydromorphone, meperidine, oxycodone, methadone and fentanyl, unless kits are obtained for each specific opioid [7].

6.9. Even for benzodiazepines, while the kits are able to detect the prevalence of higher dose forms such as diazepam, oxazepam and temazepam they are less likely to detect use of the more potent members such as clonazepam, flunitrazepam, bromazepam, lorazepam and triazolam [8].

6.10. It is not common for laboratories conducting drugs of abuse screening (such as in urine) to use another form of screening technique besides immunoassay screens, however some of the more specialised laboratories employ chromatographic screens [9, 10]. These can either include GC or HPLC techniques, or better, one of more forms of mass spectrometry (MS) [10, 11].

6.11. More recently, high resolution MS (HRMS) has been used successfully as a screening tool to identify drugs and drug metabolites in urine using their accurate molecular mass [12, 13]. However, HRMS is not used routinely in pathology laboratories, rather, forensic facilities and sports doping laboratories.

6.12. The advantage of chromatographic screening methods and in particular those that combine chromatographic separation with one form of MS is that the methods can detect a far larger selection of drugs with higher sensitivity and specificity. An additional advantage over higher sensitivity is that it leads to longer detection times.

6.13. The five classes of drugs listed earlier, i.e. amphetamines, benzodiazepines, cannabis, cocaine and some opioids can be detected by commercial screening kits but most immunoassay-based kits used for screening will not cover all members of these classes equally, and sometimes one or more members may not be detected at all.

6.14. Consequently, it is essential that the client (and the employees) fully understand what drugs can be detected following use.

Confirmation Tests

6.15. Confirmation tests are used to confirm the presence of a drug when the screening test has indicated a positive response to a drug or a member of a

drug class, particularly when an immunoassay has been used as the initial test.

6.16. Confirmation tests must use one or more forms of mass spectrometry (MS). Various types of MS are used, but most commonly for confirmation GC-MS and tandem LC-MS is used.

6.17. MS provides structural information of a drug by providing what is effectively a fingerprint profile based on the fragmentation of the substance into fragment ions and providing a spectrum of the apparent molecular weight (actual weight of ion over its charge) against relative intensity. A computer provides the degree of match to library entries and only those matches with a high degree of certainty allow identification to be made. The laboratory will also apply other identification techniques, most typically comparison of the retention time with an authentic standard (calibrator).

6.18. If done properly and the drug has a sufficiently unique spectrum the risk of a false positive (see below) is very low.

6.19. Some drugs, particularly many of the amphetamines and some opioids have poor spectra for GC-MS and require more specialised analytical work-up, such as using chemical derivatives or what is known as tandem-MS where further fragmentation of one part of the molecule can be performed.

6.20. For example in the figure below spectra obtained in a GC-MS for methamphetamine and cocaine are illustrated showing the relative simple (few ions of any significance) but quite different profile for methamphetamine when compared to cocaine. Both spectra were downloaded from the National Institute of Standards and Technology (USA) and were obtained using electron impact (EI) ionisation of underivatised molecules.
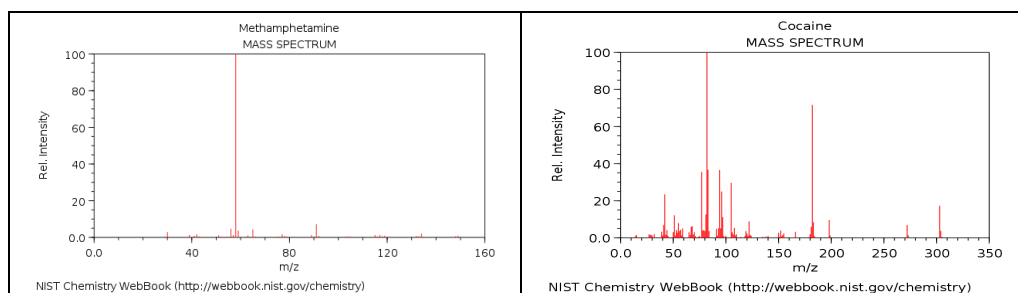

Figure showing EI mass spectra for methamphetamine and cocaine

Cut-offs

6.21. In "workplace" drug testing it is usual to apply a "cut-off" when applying both screening and confirmatory techniques. A cut-off is a concentration in the biological fluid which is used to determine a reportable concentration of drug. In the case of morphine the draft cut-offs in appendix D of REGDOC-2.2.4 for screening and confirmation is 2000 ng/mL. This means the laboratory cannot report a urine concentration of morphine below 2000 ng/mL no matter how certain the laboratory is for the presence of morphine in urine.

6.22. The laboratory will always have some error associated with a measurement.

This is normal. A measure of this error is uncertainty of measurement and is represented as a number that indicates the magnitude of this error based on statistical analysis of the laboratory measurements. Typically this may be 10-20%. It is normal practice to add this uncertainty (at least 95% of the error) to the cut-off. Hence for a cut-off of 2000 ng/mL and an uncertainty of 200 ng/mL (10% measurement error representing 95% of the error of measurement) a positive is only reported when the measured urine concentration is above 2200 ng/mL.

6.23. These cut-offs vary for each drug or drug metabolite. If blood were chosen as a fluid for detection cut-offs would also apply, but will be different to those used in urine.

6.24. Whatever technique is used there may be a possibility of either a false positive or a false negative.

False Negatives and False Positives

6.25. False negatives arise when the drug is not detected when it is actually present in a sample. This is much more common when immunoassay kits are used to screen for the presence of member of a drug class but does not have the sensitivity for some members of the class.

6.26. Much more importantly is when a false positive is reported. This means that a drug is reported when it is not present in the sample. This must not occur and is one of the reasons why a laboratory must confirm the presence of a drug using one or more mass spectral technique, such as GC-MS or LC-MS.

Adulteration and Substitution

6.27. Depending on the collection technique it is possible for patients (workers) to add a substance to adulterate a urine sample by adding a chemical to hinder the detection of a drug. These can be oxidants or other chemicals such as bleach, glutaraldehyde, pyridinium chlorochromate and nitrites.

6.28. Adulteration test strips are available commercially and are often used (indeed recommended) at the point of urine collection. When adulteration is suspected another urine should be collected.

6.29. The use of chemicals to adulterate urine is less of an issue when urine voiding is witnessed, but this is much less common and of course raises significant issues of privacy.

6.30. Substitution can also occur when the urine specimen is switched with another one (usually done in cubicle from an internally concealed sample).

6.31. Most commonly water loading is used to dilute the urine by forcing the kidneys to excrete large amounts of water effectively diluting the drug in the urine to the point that the concentration falls below the reporting cut-offs. Volumes of water of at least 1 litre consumed shortly before a test are required for this to occur.

6.32. Standard collection procedures have been published. These include those published by the Substance Abuse and Mental Health Services Administration (SAMSHA) for federal workers in the USA [4] and Standards Australia (AS4308:2008) [14]. These require strict collection protocols including specifications around urine colour, urine temperature on

collection, urine pH, urine specific gravity and urine creatinine.

6.33. Creatinine is a waste product from human metabolism. When water loading occurs the creatinine concentration (and colour of urine) reduces. Threshold concentration needs to be above 50 mg/100mL to avoid the suspicion of water loading [15]. This can be checked at point of collection using a test strip and/or in the laboratory using more accurate techniques.

6.34. The risk of adulteration and substitution when urine voiding is not witnessed can be reduced when the toilet cubicle is controlled such as to avoid the ability to add water to the collection vessel. Such control measures are defined in published protocols such as AS4308 [14].

6.35. In many workplace drug testing situations (e.g. Australia and New Zealand) a collected urine can be subject to a rapid on-site test (point-of-care testing) using either a collection cup with built-in test strips for the common drugs of abuse or use of a separate test kit from an aliquot of the urine. This initial test can be used to presumptively indicate if a drug is present. While this result requires formal confirmation in a laboratory the employer may use this result to temporarily stand-down an employee until the confirmation test result is received. This is seen to remove any potential risk that the result is real and the employee is a risk in a safety-critical area.

6.36. If blood is collected then issues of adulteration or substitution do not apply since a phlebotomist, nurse or medical practitioner collects the blood for the patient (worker) directly. Water loading is unlikely to affect blood concentrations.

7. Technical Issues Associated with Drug Testing

Cut-offs in urine

7.1. Thresholds for reporting drugs in biological fluids (i.e. cut-offs) are determined by evaluating negative and positive urines analysed using commonly employed analytical methods (immunoassay for screening and MS for confirmation) and establishing a cut-off from these data statistically to minimise false negatives and false positives in the screening stage.

7.2. Another consideration is setting cut-offs in urine that minimise the likelihood of other factors that may impact on the interpretation of a positive result. Examples include:

7.2.1. Presence of poppy seeds in foods with morphine causing low positives in urine;

7.2.2. False conclusion of heroin use when only morphine is present when this could have derived from legitimate use of codeine.

7.2.3. Absorption of small amounts of THC from side-stream smoke from persons using cannabis (marijuana);

7.2.4. An assessment of the pharmacokinetics of the drug (and relevant metabolite) and what concentrations are likely to be detected following its use over a period of time; and

7.2.5. Analytical sensitivity of test methods.

7.3. In Appendix D a series of drugs are listed together with their recommended

immunoassay screening and confirmation cut-offs.

7.4. A summary of these and those published in the Australian Standard (AS4308), the USA SAMSHA guidelines (including those newly proposed) and the European drugs as listed by the European Workplace Drug Testing Society (EWDTS).

Table 2. Screening cut-offs

	Canada Nuclear	Australia (AS4308)	USA (SAMSHA)	Europe (EWDTS)
Amphetamines	500	300	500	500
Cannabinoids	50	50	50	50
Cocaine metab.	150	300	150	50
6-Acetylmorphine	10		10	
Opiates[1]	2000	300	2000	300
Methadone metab.	100			300
Oxycodone	300		100	
Benzodiazepines	100	200		200
Hydromorphone	300		300	
Hydrocodone	300		300	
PCP			25	25

Table 3. Confirmatory Cut-offs

Drug/Country	Canada Nuclear	Australia (AS4308)	USA (SAMSHA)	Europe (EWDTS)
Amphetamines				
Amphetamine	250	150	250	200
Methamphetamine	250	150	250	200
MDMA	250	150	250	200
MDA	250	150	250	200
MDEA	250		250	200
Opiates and opioids				
Morphine	2000	300	2000	300
Codeine	2000	300	2000	300
6-Acetylmorphine	10	10	10	10
Hydromorphone	300		100	
Hydrocodone	300		100	
Methadone metab.	100			250
Oxycodone	300		50	
Benzodiazepines				
Alprazolam metab.	50	100		
Diazepam/nordiazepam	50	200		100
Oxazepam	50	200		100
Temazepam	50	200		100
Lorazepam	50			
Clonazepam	50	100[2]		
Triazolam	50			

Other drugs				
11-nor-THC-acid	15	15	15	15
Cocaine metab.	100	150	100	150
Phencyclidine (PCP)			25	25

Alprazolam metab = 1-hydroxy-alprazolam, Cocaine metab = benzoylecgonine (BE); methadone metab. -= EDDP; PCP = Phencyclidine, MDMA = 3,4-methylendedioxy-methamphetamine, or Ecstasy; MDA = 3,4-methylendedioxy-amphetamine, MDEA = 3,4-methylendedioxy-ethylamphetamine; [1] morphine and codeine, [2] clonazepam metab. = 7-aminoclonazepam. Coloured cells illustrate absence of a cut-off.

7.5. On review of these listed drugs and their respective cut-offs illustrate that there is no consensus in key parts of the world. The most obvious differences are the cut-offs for opiates (morphine and codeine); proposed as 2000 ng/mL, in line with the USA, whereas it is 300 ng/mL in Europe and Australia.

7.6. The reason for this difference is to exclude legitimate codeine users (who will also excrete small amounts of morphine) from those using heroin. Whereas the detection of 6-acetylmorhine in urine proves exposure to heroin the presence of morphine does not of itself prove use of heroin. The use of this higher cut-off for opiates and for morphine and codeine in confirmatory testing will mean a number of heroin users might be missed (false negative); however the great majority of opiate positive cases will be from legitimate codeine use; a drug that is also legal in Canada and unless abuse has occurred poses no significant safety risk.

7.7. There are other differences, such as the absence of benzodiazepines in the USA guidelines. Benzodiazepines are included in the Australian and European documents since they are a well-known group of abused drugs. However, they are also legally available by prescription and so their presence in a sample does not of itself indicate misuse or abuse. It is not possible to determine from a urine result whether misuse or abuse has occurred due to the great variability in urine concentrations due to individual metabolic variability, hydration and kidney function.

7.8. Targeting other legal drugs, such as the opioids – hydrocodone, hydromorphone, methadone and oxycodone – has similar issues. If a worker has a legitimate prescription for the drug detected it is not possible to opine whether the urine concentration reflects misuse of his/her prescribed dose; notwithstanding clinical issues that may or may not affect their ability to work safely.

7.9. There is less variation between the guidelines for the detection of cocaine, amphetamine and cannabis use. Generally speaking the proposed cut-offs in the draft document for these 3 drug classes is consistent with international practice.

Analysis of Blood

7.10. Cut-offs for drugs in blood are not established since this specimen is rarely analysed in a workplace drug-testing situation. Moreover, much lower concentrations of drugs are present in blood compared to urine requiring more specialist analytical techniques to detect reasonable use of drugs in blood.

7.11. Blood is the most common specimen in forensic toxicology when drug use may be relevant in an impaired driver or following an assault of some type, however cut-offs are not usually employed in this modality of testing, rather limits of detection associated with the analytical test method; usually mass spectrometry.

7.12. Blood usually gives a shorter window of detection than urine, reducing the ability to detect past use of a drug-of-abuse.

7.13. However, blood concentration can give some indication of the likely effect of drug, whereas it is not possible to do this from a urine result.

7.14. Analysis for a range of drugs in blood will also generally be more expensive than urine testing.

8. Likely Drug Effects and Impairment

8.1. The following provides a summary of each major drug class the likely adverse effects associated with their use in a workplace setting, i.e effects these drugs may have on safety and ability to maintain a secure workplace.

8.2. Adverse drug effects can best be simply categorised into effects on cognitive and psychomotor functions. Cognitive functions involve decision making, making rational and informed decisions, while psychomotor functions relate to the ability to make coordinated and appropriately speedy hand or leg movements [1, 16, 17].

8.3. Table 4 below summarises the general features of the target drugs.

Table 4. Likely Adverse Effects of Selected Drugs

Drug Class	Cognitive Effects	Psychomotor Effects
Alcohol	General depressants; will cause drowsiness and will adversely affect brain functions; disinhibition, unsteady gait, slurred speech	Increased reaction times and reduced accuracy of tasks
Amphetamines	Increases slightly short term; decreases long term; tunnel vision and impaired divided attention tasks; increased aggression	Increases slightly short term; decreases long term; tremor
Benzodiazepines	Very similar to alcohol if abused; tolerance sets in with repeated use; disinhibition when abused.	Very similar to alcohol if abused
Cannabis	Dulls brain function impairs ability to make rapid and informed decisions; impairs divided attention tasks	Increases reaction times; reduces accuracy of tasks
Cocaine	Similar to amphetamines	Similar to amphetamines
Opiates/opioids	General depressants; will cause drowsiness and may adversely affect brain functions; tolerance develops rapidly	Can increase reaction times and reduce accuracy of tasks but not as significant as cannabis and alcohol

Alcohol

8.4. Alcohol, or chemically ethanol, has complex pharmacology affecting almost all parts of the body but particularly the central nervous system (CNS), the cardiovascular system, and in many organs.

8.5. Alcohol acts as a general depressant of cellular and nervous functions but also is known to affect a number of excitatory and inhibitory amino acid transmitters required for normal functions. Alcohol enhances the effects seen with benzodiazepines and adversely affects learning and memory. Alcohol reduces inhibitions and increases aggression [18].

Amphetamines

8.6. While there differences between members of this class of drug there are characterised as strong stimulants (particularly methamphetamine); that is drugs that simulate the central nervous system. Generally, they can increase wakefulness and reduce manifestations of fatigue in the short term, but longer term use can even induce hypersomnolence – a situation where a person cannot stay awake or where their ability to function normally is grossly affected.

8.7. Persons abusing this class of drug, particularly the stronger forms such as methamphetamine can develop personality changes, develop uncharacteristic aggression and exhibit violent episodes and even become paranoid psychotics [19, 20]. Criminal activity is commonly associated with strong stimulants.

Cocaine

8.8. For the most part the effects are similar to the amphetamines [21]. As for methamphetamine tolerance develops rapidly with repeated use, which is then associated with drug dependency and the drug-seeking behaviours associated with this trait.

Cannabis

8.9. This is the most common abused drug in the world and possibly also Canada. When taken in low doses cannabis (largely through THC) causes a sense of euphoria and relaxation [22]. During its active intoxication phase that only last a few hours persons will have significant decrements in their cognitive and psychomotor functions, however the drug can be detected in urine (and blood using sensitive methods) for much longer, even up to days in urine.

8.10. Higher doses and binge use can lead to substantial intoxication even to the point of developing hallucinations and psychotic symptoms. These usually resolve quickly, often within a day or two.

8.11. Synthetic cannabinoids are prevalent. Many have similar effects to THC, others tend to be more toxic with greater behavioural adverse effects. None of these are detectable in methods designed for THC and its metabolites.

Benzodiazepines

8.12. These drugs are largely used to treat sleeplessness and to reduce the manifestations of anxiety. They can have adverse effects if used unprescribed or abused. These include impaired cognitive and psychomotor

functions.

8.13. In many ways these have similar effects to alcohol, and when used together adverse effects are more likely.

Opiates and opioids

8.14. This diverse group includes heroin, morphine and codeine, known as opiates due to their similarity chemically to morphine. Synthetic analogs that mimic the effects of morphine, i.e. narcotic analgesics, and have very similar effects to morphine itself. Many of these synthetic opioids have very high potency requiring low doses and may be difficult to detect. The opioids are not detected by the 'opiate' test and require targeted detection techniques. These drugs include methadone, oxycodone, hydrocodone etc.

8.15. Opioids also induce drowsiness and sleep, clearly an adverse symptom if wakefulness and vigilance is required in a job.

8.16. Like all other drugs listed here concomitant use of any combination of the above listed drugs and other CNS-active drugs will compound any impairment observed.

9. Drug Concentrations and Prediction of Impairment

9.1. Impairment for the purpose of this report is a diminution of one or more faculties that are required for the subject to work as effectively as when drug-free, and safely. The impairment must be measurable, by an assessment of clinical observations, fine motor skills and/or cognitive function. In traffic medicine an assessment of impairment can occur using a series of sobriety tests. Examples of these are those administered by many police forces in Canada and the USA through the Drug Expert Recognition System [23].

9.2. As already mentioned it is not possible to relate a urine concentration to any assessment of impairment.

9.3. The following table summarises the relative strengths and weaknesses of the specimens when testing for the presence of drug of abuse.

Table 4. Relative Strengths and Advantages of Testing in Blood and Urine

Blood (Serum/plasma)	Urine
1. In workplace testing blood is rarely employed; urine is most common followed by oral fluid (saliva)	1. Collection does not require a medical practitioner, nurse or phlebotomist, although a trained technician is still required to ensure procedures are followed
2. Collection of blood more difficult and requires a medical practitioner, nurse or phlebotomist	2. Analytically easier to analyse for drugs since concentration higher than in blood
3. Analytically more difficult to analyse due to matrix and lower concentration of drugs in this specimen compared to urine	3. Provides past evidence of exposure within a day or more but will not allow an opinion to be made if the person is still drug affected.
4. Provides better evidence of recent ingestion when drug may still be having a measureable effect	4. Concentration of drug or metabolite plays little value in determining likely dose or time of ingestion
5. More possible to infer a likely impairment or particular behavioural deficit	5. Urine contains mainly metabolites of drugs rather than parent drug, and in some cases

6. Concentration in fluid should be measured to allow an opinion to be made how much drug may have been used	hydrolytic processes are required to detect some metabolites, e.g. some opiates, benzodiazepines
7. Provides a shorter window of drug detection than urine	6. Adulteration or substitution of urine can occur if voiding is not witnessed directly unless steps taken to minimise this risk

Serum or plasma can be obtained from blood using special collection kits or following centrifugation. Some laboratories are able to analyse blood directly.

9.4. All that can be said from a positive urine result is that the person had used the drug in previous day or three (depending on the dose and type of drug). It is possible that the subject will not fail an impairment assessment even though the urine is positive for an impairing substance. In this situation is likely that the drug is (almost) not detectable in blood and is nearing the end of its excretion cycle.

9.5. Urine testing is used predominately to assess if a person is a user of drugs of abuse, and if so if s/he may pose a risk to the workplace at some stage in their employment; not necessarily whether they are impaired at that point in time.

9.6. Of course, in some situations workers may be targeted because of suspected drug impairment, or following an incident, and indeed may well be impaired. However, urine testing without evidence of behaviour deficits cannot be used to conclude a person is likely to be impaired.

9.7. Blood measurement is a much more useful technique to assess if impairment is likely, however this specimen cannot be analysed on-site when the person is being tested as part of a routine screening operation.

9.8. Despite the ability to make better predictions of impairment from a blood result there is nevertheless a poor correlation between blood concentration and impairment for all drugs. When drugs of abuse are given in controlled situations adverse behavioural effects are usually seen, particularly when doses likely to be used in an abuse setting are used. However, tolerance develops to all of the listed drugs. This means that an effect seen with the first dose at a particular concentration is diminished with repeated use even if the same blood concentration could be obtained.

9.9. Furthermore, there is substantial variability between individuals in their response to a given dose.

9.10. The exception is alcohol where is much better correlation, however this drug is atypical in that it partitions into tissues much more readily than other drugs.

10. Alcohol and Testing for Alcohol Presence

10.1. Alcohol is rapidly absorbed following ingestion and is mostly complete within 60 minutes from cessation of drinking in a fasting state [24]. When food is consumed just before or with alcohol the amount of alcohol that appears in the body is reduced [25].

10.2. For example, maximum blood concentrations following 0.80 gram/kg body weight were almost halved when volunteers consumed alcohol after a standard breakfast [25]. Also, food tends to reduce the amount of alcohol available, often by as much as 40 % as well as slightly increasing the rate of

elimination [25, 26].

10.3. The removal of alcohol from the body (elimination) ranges from approximately 10 to 30 milligram/100mL per hour (mg% per hour) with an average elimination rate of about 15 mg%/h.

10.4. Regular consumption can lead to higher elimination rates, up to 35 mg%/h and can even be higher in some circumstances [27].

10.5. Women tend to have a slightly higher blood alcohol concentration (BAC) than men drinking the same amount of alcohol. This is largely to do with their lower body weight.

10.6. The amount of alcohol eliminated through the breath is typically less than 1% of the ingested dose, however breath analysis of alcohol plays an important medico-legal tool in living persons due to its ability to be quickly measured [28]. The average exhaled air to blood ratio of alcohol is about 2400 although this depends on ventilation rate and body temperature. The reported range (95% confidence interval) is about 2000-2800 with only small differences between males and females [29, 30].

10.7. Most breath analysis instruments use a ratio of 2100. This gives some leeway for persons who have a lower partition. Comparison of breath readings with blood alcohol measurements when the BAC is corrected for elimination gives generally good agreement [29, 31].

10.8. The effects of alcohol in a social drinker[2] are usually apparent, or becoming apparent, when the BAC is about 20 mg/100mL. At this BAC a person should be sober, although it is possible to measure lower concentrations [16, 32]. The exception will be the heavy user (alcoholic) who has developed a significant tolerance to the effects of alcohol.

10.9. Very low BAC can also be caused by reasons other than drinking alcoholic beverages, e.g. endogenous production or even consuming some foods containing trace amounts of alcohol. This is invariably well below 20 mg/100mL and mostly even less than 1 mg/100 mL [33].

10.10. Consequently this source will not cause positive readings when a limit is set at either 10 or 20 mg/100mL. In most jurisdictions laboratory measurements have reporting limits at one of these concentrations. The accuracy of breath analysis instruments may also be somewhat lower at the 10 mg/100 mL blood concentration. Therefore, it is not unreasonable to set a threshold limit at 20 mg/100mL.

10.11. Epidemiological data of any relation between a BAC (or Breath alcohol concentrations) and impairment or risk of impairment has almost exclusively been studied in drinking drivers. Research shows that at around 50 mg/100mL the risk of having a crash whilst driving starts to increase [34]. This is in accord of what we know about alcohol and its effect on humans to reduce coordination and impair a range of cognitive functions and to cause disinhibition and impair the ability to make rationale and thoughtful decisions [32].

10.12. In an analysis of New Zealand motor vehicle collisions involving injury or

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2 A person who drinks less than 2-4 alcoholic drinks daily; in women this is about 1-2 drinks per day.

death has shown that the risk of injury escalates after about 50 mg/100mL. The odds of an alcohol-related crash increased about 23 fold over alcohol-free drivers [35].

10.13. In a meta-analysis[3] of published cases involving a fatality following a motor vehicle collision shows a relative risk of 3.6 against an alcohol-free driver, increasing to an estimated 6 at 50 mg/100mL and 13 at 80 mg/100 mL [36]. This study does show that low doses of alcohol (one drink can give a BAC of 20 mg/100mL) can impair and elevate crash risk.

10.14. A meta-analysis of a large number of psychometric[4] testing studies also confirm observable deficits are seen in most parameters when the BAC is between 30 and 60 mg/100mL [37].

10.15. In practice it is very difficult to prove impairment from clinical observations at this low BAC. Hence, most persons will pass a clinical assessment using standard sobriety tests at BAC of 50 mg/100ml or less. It is only when large number of collisions are analysed or a large number of laboratory studies are conducted on volunteers with known BAC that an adverse effect is seen at around 50 mg/100mL.

11. **Responses to Some Additional Questions**

Operation of Breath Analysis Instruments

11.1. As with all instruments they require regular servicing and in the case of breath analysis equipment regular calibration. The drift that may occur and how frequent evidentiary breath analysis instruments require calibration will vary from manufacturer to manufacturer.

11.2. The variables that affect breath alcohol include:

11.2.1.1. Whether person is in absorptive or distributive phase of alcohol pharmacokinetics;

11.2.1.2. Alveolar air and blood partition ratio. In practice most manufacturers and governments use a factor of 2100, although this ratio varies from person to person and whether they in the absorptive or distributive phase of alcohol pharmacokinetics;

11.2.1.3. Accuracy of instrument and whether the uncertainty of measurement has been subtracted. This uncertainty can be as much as 20%, although the better instruments are lower; but often is a proprietary secret;

11.3. The Breath Analysis Instruments Order provided only lists those instruments approved for use by the Canadian Government. They do not provide guidance over how they should be used or how they should be maintained.

11.4. Presumably this guidance is supplied by the manufacturers of the approved instruments. There is also some guidance provided by the Alcohol Test Committee of the Canadian Society of Forensic Science (May 4, 2014). A

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[3] Meta-analysis uses a statistical approach to combine the results from multiple published studies in an effort to obtain the best evidence for any association.

[4] Laboratory-based studies assessing performance of a whole range of responses including cognition.

number of standards have been produced by various countries throughout the world.

12. Summary

12.1. Urine testing for drugs of abuse is commonly employed around the world with a number of publications and published guidelines to control the collection, transport, continuity and analysis for common drugs.

12.2. Urine screening can be conducted at the point-of-collection (on-site) or in the laboratory. On-site testing offers an advantage in time particularly post-incident or where a potential drug-impairment is suspected.

12.3. Any positive screening test for a drug, or drug class must be confirmed by a mass spectral method in a laboratory before any lasting sanctions can apply to the employee.

12.4. The less common drugs of abuse require more specialist laboratory testing in order to cover any significant range. These include a number of opioid drugs, synthetic cannabinoids, designer stimulants and hallucinogens.

12.5. While blood is preferred over urine from the perspective of assessing likely adverse behavioural effects associated with drug use, the complexity of collection and analysis is likely to hinder any widespread workplace drug testing program.

12.6. The range of drugs included in the draft regulation document (REGDOC-2.2.4) covers most of the common drugs of abuse, however with urine testing no inference can be made as to whether the person was unfit or unsafe to work. This can only be done by a formal assessment for sobriety.

12.7. Urine testing only provides evidence of use within a few days for most drugs depending on the substance, frequency of use and other factors. Persons using cannabis on a regular basis (use at least a several times per week) can have cannabis metabolites detected in urine for at least a few weeks.

12.8. Urine concentrations of drugs that have a legal use, particularly the benzodiazepines and some opiates/opioids cannot be inferred as representing abuse rather than prescribed use, except in some exceptional circumstances.

12.9. The cut-offs recommended for the listed drugs in Appendix D are consistent with one or more of the key Countries that have adopted such limits, although there is variation from guideline to guideline.

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March 7, 2016

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Instructions and Questions Raised by the Clients

Drugs

1) Technical information on blood and urine testing:
    a) Please describe the technical process of establish the presence of drugs in urine (ie the detection of metabolites) and in blood, in layperson terms (ie immunoassay screening, gas chromatography-mass spectrometry, etc). What limitations, if any, arise from these processes (for example, metabolites vs parent drugs, false negatives or false positives, etc)?
    b) Are there generally accepted international standards thresholds for positive results for drug or drug metabolites in blood and urine?
    c) If so, are the threshold set out in Appendix D of the Guidelines consistent with those thresholds?
    d) If so, how are the thresholds for positive results for blood and urine developed?
    e) What are the retrospective detection window in which drugs may be detected in urine and blood (at all)? Please refer to the list of drugs to be tested in the Guidelines and address each of these drugs, and include any factors that may affect the presence or absence of drugs in blood or urine.

2) Evidence of Impairment for Individuals who test positive for drugs or drug metabolites:

    a) Please briefly describe the acute effects of drugs on a person, in particular cognitive skills, motor skills, etc.
    b) What does the presence or absence of drug or drug metabolites in urine or blood demonstrate, if anything, about the subject's drug-related impairment at the time the test was taken? Put differently, what are the limitations on using urine or blood to establish that the subject was impaired at the time the sample was taken? Please refer to the list of drugs to be tested in the Guidelines and address each of these drugs, and include any factors that may affect the impairment of the subject.
    c) What, if anything, does the quantity of a presence of a drug or drug metabolites in urine or blood demonstrate in terms of the subject's impairment, if anything?

Alcohol

3) On breath testing for alcohol use, are the guidelines to use qualified technicians and approved breath analysis instruments (as set out in the attached order) in accordance with generally established specimen collection procedures?

4) On breath testing, are the thresholds used appropriate to determine impairment at the time that the test is taken?

5) In particular, is the threshold of a finding of "negative" for a BAC below 20 mg/100mL in accordance with generally established specimen collection procedures?

6) What does a BAC from 20 to 39 mg/100mL demonstrate in terms of a subject's impairment at the time the test is taken?