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# THE ISSUE OF DRIVING WHILE A RELEVANT DRUG, $\Delta^9$ - TETRAHYDROCANNABINOL, WAS PRESENT IN SALIVA: EVIDENCE ABOUT THE EVIDENCE

LAURENCE E MATHER\*

*With the lawful use of medicinal cannabis becoming a closer reality across most of Australia, the matter of roadside testing and driving impairment will be of immediate concern to patients undergoing cannabinoid pharmacotherapy. Under current roadside testing laws, the same issues will pertain to the medical patient, who wishes or needs to drive, as to the 'recreational' cannabis user. While there is abundant public domain, scientific and medical literature, as well as published expert opinion, exploring the epidemiological, chemical and pharmacological research evidence of cannabis ingestion and driving, this paper analyses the evidence from roadside testing that is being used to support the notion that a driver may be 'impaired' or 'driving under the influence' of cannabis. By and large, the evidence undeniably shows that cannabis ingestion can impair driving. This paper however, comes to the pharmacological opinion that the current roadside testing of saliva/oral fluid for  $\Delta^9$ -tetrahydrocannabinol (THC), without other evidence, provides a poor predictor of impairment. This paper thus intends to stimulate re-evaluation of the present pharmacological criteria under which users of cannabis might be judged legally.*

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## I INTRODUCTION

In January 2016, an eminent Australian barrister discussed the issues raised when a person driving a motor vehicle is roadside tested and found positive for ingestion of cannabis (marijuana, marihuana).<sup>1</sup> The opinion also alluded to the extension of this legislation to future Australian medical patients who, having reasonably and lawfully ingested cannabis as part of their pharmacotherapy,<sup>2</sup> will inevitably face the same legal standards as those who have ingested cannabis ‘recreationally’. Furthermore, the opinion goes on to claim that the underlying drug driving laws are grossly unfair and are not based on data or scientific knowledge.<sup>3</sup> This opinion, thereby, calls into question not only the fairness of the laws, but also the very evidence supporting the roadside drug testing procedures, based on the testing of saliva/oral fluid, that underpin the present laws.<sup>4</sup>

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<sup>1</sup> Greg Barns, ‘Australia’s Drug Driving Laws are Grossly Unfair’, ABC News (online), 29 January 2016 <<http://www.abc.net.au/news/2016-01-29/greg-barns-drug-driving-laws-are-unfair/7116994>>.

<sup>2</sup> See generally Laurence E Mather et al, ‘(Re)introducing Medicinal Cannabis’ (2013) 199(11) *Medical Journal of Australia* 789; Laurence E Mather et al, ‘The Issue of Medicinal Cannabis in Contemporary Australia’ (2015) 3(2) *Griffith Journal of Law and Human Dignity* 287.

<sup>3</sup> Barns, above n 1.

<sup>4</sup> The terms ‘oral fluid’ and ‘saliva’ are often used interchangeably for the fluid of the mouth. The composition of mixed saliva when sampled from the oral cavity is complex. This fluid contains the watery secretions from the salivary glands along with many solutes such as cellular and food debris, microorganisms, etc, and additionally, responds in secreted volume to stimulation through chewing,

The views presented in this paper are of a research pharmacologist, not a forensic pharmacologist. The purpose of this paper is to stimulate discussion about the quality of such evidence as used in roadside testing of cannabis ingestion. The cited evidence draws upon published expert opinion, as well as epidemiological, chemical and pharmacological research reported in the scientific and medical literature. Because of the voluminous literature on this topic, the cited references are not exhaustive. Additionally, in various places, some pertinent scientific principles are presented, hopefully in an intelligible manner.

## II PHARMACOLOGICAL PRINCIPLES AND CANNABIS TESTING

Fundamental pharmacological principles (for almost any drug) propose that, within individuals, drug effect will be related in a 'graded response' manner to the drug dose, normally up to a maximum effect. After administration, the drug dose eventually equilibrates (not equalises) throughout the body fluids and tissues, and its degree of dilution in the body is reflected in the drug blood concentrations. The pharmacological effects are reflected in the relevant drug (or a relevant metabolite) concentrations in the receptor-containing 'biophase'.<sup>5</sup> After equilibration, sampled biofluid concentrations (almost always blood, plasma or serum)<sup>6</sup> of the drug can act as a proxy for those in the biophase, and thereby allow greater insight into drug responses than can be gained from the drug dose alone. This is relevant because an element of this paper discusses whether saliva/oral fluid provides a reliable proxy for the biophase of cannabis. The corresponding biological variability between individuals to doses of drug will be related in a 'quantal response' manner over a range of drug doses, this time describing the fraction of the particular population responding with some predefined effect.

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various chemicals, etc. Thus, as mentioned in the ensuing discussion, 'oral fluid' is the standard term in the present context.

<sup>5</sup> That is, the site of action or the milieu containing the parts of normal or deranged physiological or biochemical elements with which the drug interacts to produce the pharmacological effects attributed to that drug.

<sup>6</sup> Plasma and serum are the cell-free portions of blood. However, the measured drug concentrations within a defined blood specimen may differ quite markedly depending upon the extent of the drug's distribution into the blood cells and its affinity for the various proteins dissolved in the cell-free phase. In the case of THC, the blood concentration is nearly one half of the corresponding plasma or serum concentration due to the minimal uptake of THC into the blood cells. Serum is similar to blood but with clotting-factor proteins removed. This may seem like pharmacological minutia, but it affects many quantitative aspects of pharmacology. The various measures are used in particular contexts, including the evidence cited in this paper. Unless required for such context, the general term 'blood, etc' is used in this paper.

While variability within and between individuals derives from many temporal, constitutional, anatomical, physiological and biochemical sources, recent research incorporating genetic factors is allowing greater insight into the predictability. However, the intrinsic variability in how the body handles the drug becomes magnified by unpredictability in the rate and extent of systemic drug absorption associated with the mode of administration. This is typically referred to as pharmacokinetic variability.<sup>7</sup> The essential point is that the relationship between drug dose and the resultant time course of biofluid (particularly blood, etc) drug concentrations can be complex, and such drug concentrations are the primary determinants of drug effects. Moreover, the same drug doses or biofluid drug concentrations of drugs do not necessarily produce the same levels of pharmacological effects. This is referred to as pharmacodynamic variability,<sup>8</sup> and is typically reflected by the drug concentrations associated with the same effects differing between individuals, and even within individuals.

Cannabis is typically a variable mixture of chemical constituents, some of which are pharmacologically active.<sup>9</sup> Cannabis grown and prepared for medicinal purposes and/or research purposes normally has appropriate regulatory controls and analysis.<sup>10</sup> Many laboratory research studies of cannabis determine biofluid concentrations of THC, the principal psychoactive constituent, after ingestion of some form of cannabis, often after smoking a cannabis cigarette with a known THC content. These typically show marked

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<sup>7</sup> That is, what the body does to the drug in a quantitative sense.

<sup>8</sup> That is, what the drug does to the body in a quantitative sense.

<sup>9</sup> Cannabis, being a natural plant product, consists of many hundreds of phytochemical substances of which some hundred have chemical structures recognisably similar to THC, collectively referred to as cannabinoids. Both the actual and relative amounts of these substances vary with many influences, including the strain of the cannabis plant, the plant parts harvested, and methods of processing after harvesting. THC is the most studied substance, being recognised as having a variety of salutary pharmacological effects, and being the principal psychotropic substance. The potential therapeutic activity of cannabidiol (CBD) is also well recognised and it is the second main substance of pharmacotherapeutic interest. There is evidence that CBD can antagonise psychotropic effects of THC, but it is not presently known whether such effects pertain with cannabis used for pharmacotherapeutic purposes. Many other phytocannabinoids, such as the acid precursors of THC and CBD, cannabivarin, cannabigerol, etc are currently under investigation for possible pharmacotherapeutic uses and many will presumably enter clinical use at some time in the future, either alone or in some selectively enriched form of cannabis. Cannabis typically also contains several hundred non-cannabinoid substances, of which many, as judged by laboratory experiments, may contribute to the therapeutic and other pharmacological effects attributable to 'cannabis'. For further discussion, see Ethan B Russo, 'Taming THC: Potential Cannabis Synergy and Phytocannabinoid-Terpenoid Entourage Effects' (2011) 163(7) *British Journal of Pharmacology* 1344.

<sup>10</sup> See, eg, Justin Thomas Fishedick et al, 'Metabolic Fingerprinting of Cannabis Sativa L., Cannabinoids and Terpenoids for Chemotaxonomic and Drug Standardization Purposes' (2010) 71(17) *Phytochemistry* 2058; S M Crowther, L A Reynolds and E M Tansey (eds), *The Medicalization of Cannabis* (The Trustee of the Wellcome Trust, vol 40, 2010).

variability of the biofluid (blood, etc) THC concentration-time profiles despite apparently the same experimental conditions. A large body of research is focused on THC and its relationships to driving impairment as if THC is the sole active ingredient of cannabis, which it is not. Nonetheless, there is substantial research evidence underpinning both the epidemiological and the chemical-pharmacological basis of 'driving under the influence of cannabis' legislation. This evidence, mainly based on THC and various tests used to represent driving skills, supports the proposition that cannabis/THC ingestion can cause acute driver impairment, and that this is associated with an increased risk of a motor vehicle crash.<sup>11</sup>

Various controlled laboratory research studies performed in healthy volunteer subjects who use cannabis for 'recreational' purposes have found a reasonably consistent dose-blood, etc-THC concentration-impairment relationship.<sup>12</sup> However, the same conclusions have not been well supported from opportunistic studies performed by the comparison of fatal and non-fatal road traffic crashes where, for example, Andrews et al notes that:

Equating impairment to blood cannabinoid concentrations is not straightforward: a clear dose-response relationship has not been established, unlike for alcohol. The pharmacology of cannabis makes it difficult to interpret cannabinoid concentrations, both in life and in postmortem blood samples.<sup>13</sup>

Additionally, this paper is concerned with roadside testing for cannabis ingestion, and it is argued that the principle of using oral fluid for cannabis/THC testing is problematic. Oral fluid is an artefactual medium, rather than a body fluid pool such as blood, etc that contains drug concentrations in equilibrium with those in the biophase. It is argued that whereas blood, etc provides a reasonable proxy for the pharmacological effects of cannabis/THC, oral fluid THC concentrations may be associative with, but are not causative of, the pharmacological effects attributed to THC.

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<sup>11</sup> Mark Asbridge, Jill A Hayden and Jennifer L Cartwright, 'Acute Cannabis Consumption and Motor Vehicle Collision Risk: Systematic Review of Observational Studies and Meta-Analysis' (2012) 344(536) *The BMJ* 1.

<sup>12</sup> See, eg, David M Schwoppe et al, 'Psychomotor Performance, Subjective and Physiological Effects and Whole Blood  $\Delta^9$ -Tetrahydrocannabinol Concentrations in Heavy, Chronic Cannabis Smokers Following Acute Smoked Cannabis' (2012) 36(6) *Journal of Analytical Toxicology* 405.

<sup>13</sup> Rebecca Andrews et al, 'Cannabinoid Concentrations Detected in Fatal Road Traffic Collision Victims Compared With a Population of Other Postmortem Cases' (2015) 61(10) *Clinical Chemistry* 1256, 1260-1261 (citations omitted).



## III LABORATORY AND ROADSIDE TESTING METHODOLOGY

The main biofluids used in testing for drugs include blood, plasma or serum, oral fluid, expired air/breath, and occasionally urine and hair. Each sample offers various advantages and disadvantages in the context of research and of roadside testing. Blood, plasma, or serum samples are the most informative and are used extensively in laboratory and clinical pharmacological research. However, their sampling requires specialist techniques and the process is relatively invasive. Urine and hair samples can be informative but have limited applicability to roadside testing. Expired air/breath is a special case and is useful only where analytes, such as alcohol, have significant vapour pressure. Oral fluid, being the biofluid matrix of the present instance, is discussed in greater depth.

Standard testing methodology involves rigid definitions as to the qualitative (for what substance) and quantitative (how much of that substance) performances. Detection can be non-specific (responding to whatever substance is presented), selective (responding to substances with particular properties), or specific (for a unique substance). Most biological research and forensic laboratory methods include techniques to extract the analyte(s) from the biofluid matrix and/or concentrate them to improve detectability. This is usually followed by a gas-liquid chromatography (GLC) or high performance liquid chromatography (HPLC) procedure to separate the analyte(s) from other extracted components, preceding their detection  $\pm$  quantitation, normally by mass spectrometry (MS). Methods based on GLC-MS and HPLC-MS, that offer both specificity and the highest sensitivity, are widely used in forensic and research studies involving cannabis, as well as in confirmatory testing of roadside samples.

Immunoassay screening methods are commonly used for roadside screening for various “drugs of abuse”, including THC, and are specified by different criteria: numbers of analyte true positives, false positives, true negatives and false negatives after confirmatory GLC-MS or HPLC-MS testing. However, the performance specifications of commercially available devices used for THC screening may differ markedly.<sup>14</sup> Immunochromatographic (component separating) devices operate by diffusion of the oral fluid sample mixed with labelled antibodies that target and bind to specific drugs if

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<sup>14</sup> Anna Molnar, *Detecting and Quantifying Cannabinoids in Oral Fluid* (PhD Thesis, University of Technology, Sydney, 2015) 24.

present in the fluid sample,<sup>15</sup> and sometimes several drugs are tested for concurrently. The sensitivity (Limit of Detection, LOD) or cut-off for negativity, varies according to the kit, as does the specificity. An abundance of such validated methods is also found in the scientific literature, including many methods for THC testing that are used by various research and forensic laboratories.<sup>16</sup> Research evidence obtained in 'recreational' cannabis-using volunteer subjects demonstrates that cannabis/THC ingestion can diminish performance accuracy in a variety of psychomotor dominant tasks, including those simulating various aspects of motor vehicle control, and in the Standard Field Sobriety Test (SFST).<sup>17</sup> Roadside testing for cannabis/THC thus ought to be capable of providing a useful predictor of any such diminished performance, rather than just providing evidence of ingestion.

Although blood, etc concentrations of a drug can be useful proxies for the relevant 'biophase' concentrations, with modes of rapid systemic delivery, particularly intravenous and transpulmonary (inhaled into the lungs), there is often a marked and highly variable mismatch (hysteresis) between the times-courses of drug effects and the blood, etc concentrations until equilibration occurs. Hysteresis depends on many factors, including how and when the blood sampling is performed, as well as the properties of the drug. This has equally been observed with inhaled THC.<sup>18</sup> Hysteresis complicates the interpretation of effects from measured drug biofluid concentrations alone, mainly in the first several hours after drug ingestion. Thereafter, the time course

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<sup>15</sup> Antibodies, being any of a large variety of proteins normally present in the body, or produced in response to an antigen, act to neutralise their target, thus producing an immune response.

<sup>16</sup> See, eg, Olaf H Drummer, 'Drug Testing in Oral Fluid' (2006) 27(3) *Clinical Biochemistry Review* 147; Oscar Quintela et al, 'A Validated Method for the Detection of  $\Delta^9$ -Tetrahydrocannabinol and 11-nor-9-Carboxy- $\Delta^9$ -Tetrahydrocannabinol in Oral Fluid Samples by Liquid Chromatography Coupled with Quadrupole-Time-of-Flight Mass Spectrometry' (2007) 31 *Journal of Analytical Technology* 157; Robert F X Klein, 'Analysis of Marijuana by Liquid Chromatographic Techniques: A Literature Survey, 1990–2015' (2015) 12(1–4) *Microgram Journal* 1.

<sup>17</sup> See, eg, Wendy M Bosker et al, 'Medicinal  $\Delta^9$ -Tetrahydrocannabinol (Dronabinol) Impairs On-the-Road Driving Performance of Occasional and Heavy Cannabis Users But is Not Detected in Standard Field Sobriety Tests' (2010) 107(10) *Addiction* 1837; Wendy Miranda Bosker, *Where the Drug Meets the Road: Actual Driving, Psychomotor Performance and Roadside Drug Screening Methods in Cannabis and Ecstasy Users* (PhD Thesis, The University of Maastricht, 2011); Rebecca Lynn Hartman, *Drug Policy Implications of Inhaled Cannabis: Driving Skills and Psychoactive Effects, Vaporized Pharmacokinetic Disposition, and Interactions with Alcohol* (PhD Thesis, University of Maryland, 2015).

<sup>18</sup> See, eg, Edward J Cone and Marilyn A Huestis, 'Relating Blood Concentrations of Tetrahydrocannabinol and Metabolites to Pharmacologic Effects and Time of Marijuana Usage' (1993) 15(6) *Therapeutic Drug Monitoring* 527; A Weinstein et al, 'A Study Investigating the Acute Dose-Response Effects of 13 mg and 17 mg  $\Delta^9$ -Tetrahydrocannabinol on Cognitive-Motor Skills, Subjective and Autonomic Measures in Regular Users of Marijuana' (2008) 22(4) *Journal of Psychopharmacology* 441; N A Desrosiers et al, 'Smoked Cannabis' Psychomotor and Neurocognitive Effects in Occasional and Frequent Smokers' (2015) 39(4) *Journal of Analytical Toxicology* 251; David M Schwoppe et al, above n 12.

of drug, blood and effect occur essentially in parallel (pseudoequilibrium). The maximum measured biofluid drug concentration ( $C_{\max}$ ) is the most obviously affected metric, often occurring at a time well different to the maximum drug effect ( $E_{\max}$ ). Various pharmacokinetic-pharmacodynamic models have been proposed to account for this observation, and some have been proposed for THC,<sup>19</sup> but it seems that none have yet been developed specifically for THC and driving impairment.

#### IV ORAL FLUID TESTING OF “DRUGS OF ABUSE”

All Australian states and territories have now instituted roadside (and certain workplace) oral fluid testing for methamphetamine, methylenedioxymethamphetamine (MDMA) and THC based upon Australian Standard 4760. Oral fluid has the advantage that it can be simply and non-invasively collected for preliminary roadside testing, and then be referred to the forensic laboratory for further definitive testing. As elaborated below, oral fluid is useful for supposing the past ingestion of a drug, but has reliability limitations in predicting the acute pharmacological effects of a drug.

Studies from the 1970s suggested that salivary concentrations might present a non-invasive sampling proxy for ‘unbound’ (or ‘free’ or ‘dialysable’) blood concentrations of drugs in the context of research and pharmacotherapy on the premise that these are deemed to more closely resemble biophase concentrations. Accordingly, guidelines for understanding the relationship between blood, etc and saliva drug concentrations were formulated based on the known physicochemical characteristics of the drug and the anatomical, physiological and biochemical characteristics of saliva.<sup>20</sup> However, its usefulness was found to be more limited than anticipated, mainly because of unpredictable inter- and intra-individual variability. For example, a research study of that period (on erythromycin) concluded that ‘[t]he correlation between pharmacokinetic parameters estimated from serum and saliva was poor...indicating that estimates obtained from saliva are not useful predictors of the corresponding serum

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<sup>19</sup> See, eg, Zheng Guan et al, *IV-25 Zheng Guan Population PK/PD Modeling to Compare Cannabinoid Receptor Antagonists in the THC Challenge Test* (2012) Population Approach Group in Europe <<http://www.page-meeting.org/?abstract=2330>>; Jules A A C Heuberger et al, ‘Population Pharmacokinetic Model of THC Integrates Oral, Intravenous, and Pulmonary Dosing and Characterizes Short- and Long-Term Pharmacokinetics’ (2015) 54(2) *Clinical Pharmacokinetics* 209.

<sup>20</sup> M Danhof and D D Breimer, ‘Therapeutic Drug Monitoring in Saliva’ (1978) 3(1) *Clinical Pharmacokinetics* 39.

pharmacokinetic constants.<sup>21</sup> Saliva sampling was largely abandoned in pharmacotherapy research only to become progressively re-introduced over the past decade by the forensic quest for a convenient, non-invasive sampling matrix to test for “drugs of abuse”.

With some notable exceptions, such as anticoagulants, drugs rarely act by being in the blood. As discussed above, the blood ‘pool’ acts as a conduit for drug delivery to, and removal from, the tissues, including the biophase. The important point is that drugs typically distribute between blood, serum or plasma, blood cells, and tissues, in a rational manner so that sample-able blood drug concentration measurements may be used as a reasonable proxy for biophase concentrations and thus pharmacological effects. Drugs may diffuse from blood into saliva/oral fluid, but their overall concentrations are phenomenology, responding to extrinsic and intrinsic stimulation. Oral fluid is not a body ‘pool’ with an anatomically defined distribution, and the oral fluid concentrations of drugs need bear no rational relationship to the amount of that substance present in the body; moreover, unlike drug blood concentrations, they do not have an intrinsic role in driving the attributed pharmacological effect.

#### V THC TESTING AND THE LAWS

At the outset, it is unequivocally acknowledged that drug-impaired driving presents a serious threat to public safety, and that many drivers involved in motor vehicle crashes do test positive for particular drugs. As in many countries, Australian states and territories administer laws intended to deter non-medical use of illicit drugs, principally methamphetamine, MDMA, cocaine, diamorphine (heroin) and cannabis. The Australian states and territories also administer laws, with some differences in the wording but with the same specific intent, to deter driving under the influence of these drugs (DUID laws). It has been reported that the proportion of fatalities from fatal crashes involving a driver/rider with illicit drugs, including cannabis, present in their system in New South Wales was 16 per cent in 2013.<sup>22</sup> Thus, the intent of such laws, to prevent fatalities, is

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<sup>21</sup> K L Austin et al, ‘Intersubject and Dose Related Variability After Intravenous Administration of Erythromycin’ (1980) 10(3) *British Journal of Clinical Pharmacology* 273, 278.

<sup>22</sup> Evan Walker et al, ‘Drug Driving in NSW: Evidence-Gathering, Enforcement and Education’ (Paper presented at the Australasian Road Safety Conference, Gold Coast, Australia 14–16 October 2015) 2.

obvious. The present analysis is focussed entirely on cannabis, and whether or how other drugs are subject to the same issues, has not been assessed.

It is not argued that THC detected in oral fluid is not reasonable evidence of cannabis/THC ingestion, although second-hand contamination by THC is recognised and needs to be ruled out. Nor is it argued that ingested cannabis/THC cannot impair driving, as there is abundant evidence that it can, although the intensity and duration of any such impairment after acute cannabis consumption is not well defined. It is, however, argued that present Australian drug driving laws involving cannabis, and purportedly used as road safety measures, are based on an 'all-or-none' roadside test for the presence of THC in oral fluid, and that the result of this test, in isolation, is an unsound indicator of meaningful acute 'impairment' or of being 'under the influence'.

It is also argued that the result of such an oral fluid test is essentially artefactual, and the result may or may not be a reasonable predictor of any directly related acute pharmacological effect, notably impairment of driving ability. A more familiar analogy might be that of measured cholesterol levels in blood as part of 'heart attack' prevention strategies. A finding of a high cholesterol does not mean that the person will have a heart attack, and a finding of low cholesterol does not mean that the person will not have a heart attack; the blood cholesterol level is but one factor that needs to be considered in an overall risk assessment strategy. However, the present THC–oral fluid testing issue is more complex than this simple analogy because the pharmacological effect (impairment) is not caused by, or even directly related to, the presence of the THC concentration in oral fluid, whereas the cholesterol in the blood is causally related to the risk.

In February 2016, with the Australian Federal Parliament passing the Narcotic Drugs Amendment Bill 2016 (Cth), a first step for the lawful use of medicinal cannabis occurred,<sup>23</sup> and other laws concerning the regulation of its cultivation, manufacturing and supply have begun to follow.<sup>24</sup> However, it remains up to the individual states to decide on the details of if/how the drug will be allowed, prescribed, and dispensed, and

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<sup>23</sup> Ian Freckelton, 'Medicinal Cannabis Law Reform in Australia' (2016) 23(3) *Journal of Law and Medicine* 497.

<sup>24</sup> See, eg, *Access to Medicinal Cannabis Act 2016* (Vic); Penny Timms, 'Medicinal Marijuana to Become Legal to Grow in Australia — But How Will it Work?', ABC News (online), 29 October 2016 <<http://www.abc.net.au/news/2016-10-29/medicinal-marijuana-to-become-legal-explainer/7975194>>.

for whom. As of November 2016, medicinal cannabis can be prescribed under strict conditions in New South Wales and Western Australia, with Victoria, Queensland, Tasmania, and probably South Australia and the Australian Capital Territory, to follow in 2017. With the lawful medicinal use of cannabis, the inevitability of patients violating DUID laws will occur, and this could have potentially far-reaching impacts on their amenity and welfare. This would be of particular concern for those patients receiving cannabis pharmacotherapy using vaporised or oral transmucosal dosage forms because such patients will, due to locally deposited dosage, almost certainly return positive screens for cannabis if their medication contains more than trace quantities of THC. Indeed, one locally conducted pilot study has already confirmed the detectability of THC in the oral fluid of healthy volunteer subjects simulating cannabis pharmacotherapy.<sup>25</sup>

Over the past decade or so, considerable research effort has been applied to determining the effects of cannabis/THC on the impairment of driving, mainly in the context of 'recreational' cannabis. If societal attitudes about the legal use of 'recreational' cannabis change, as is occurring, for example, in various parts of the United States of America, then it is relevant to consider whether existent laws should be re-examined, as they form the basis of the legal framework also applied to users of medicinal cannabis. Whereas most expert reviewers indicate general agreement about the roadside and laboratory research findings, the interpretation and application of such findings in the context of road crash risk remains problematical. Two expert opinions, formulated from different perspectives after consideration of the evidence, are relevant and are quoted here.

In their review of the first large-scale study in America designed to estimate the risk associated with alcohol and drug positive driving, Compton and Berning commented:

There is evidence that marijuana use impairs psychomotor skills, divided attention, lane tracking, and cognitive functions. However, its role in contributing to the occurrence of crashes remains less clear. Many studies, using a variety of methods have attempted to estimate the risk of driving after use of marijuana. The methods have included experimental studies, observational studies, and epidemiological studies. While useful in identifying how marijuana affects the performance of driving tasks, experimental and

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<sup>25</sup> See Anna Molnar et al, 'The Detection of THC, CBD and CBN in the Oral Fluid of Sativex® Patients Using Two On-Site Screening Tests and LC-MS/MS' (2014) 238 *Forensic Science International* 113.

observational studies do not lend themselves to predicting real world crash risk...Caution should be exercised in assuming that drug presence implies driver impairment. Drug tests do not necessarily indicate current impairment.<sup>26</sup>

In a comprehensive review of the present American DUID laws, Larkin Jr, acknowledging the legalisation of nonmedical or 'recreational' cannabis in some states, wrote that:

punishing someone for a positive THC result merely penalizes him for having used marijuana within the last month, not for driving while under its influence. Even if there were indisputable proof that a person drove within four hours of having inhaled marijuana, the mere presence of THC in the blood cannot by itself justify the inference that a person was impaired. The effect of inhaled marijuana on a user's driving skills varies from person to person based on a host of individual factors: the absorption, distribution, metabolism, and excretion rate of THC; the quantity of past marijuana usage; THC tolerance; the time when a person last inhaled or ingested marijuana; the time since a person last ate, as well as the fat content of his meal; and individual smoking techniques...The bottom line is this: We cannot presently undertake roadside marijuana testing in the same way that we perform alcohol testing...Any particular level could be overinclusive or underinclusive...Society needs to be able to identify far better than it now can which drivers may be impaired by marijuana so that the medical marijuana and recreational initiatives do not increase the mortality that alcohol-impaired driving already imposes.<sup>27</sup>

#### VI EVIDENCE IN MEDICAL PATIENTS

As noted above, most of the prospective chemical-pharmacological research on cannabis and driving is performed in essentially healthy young adult volunteers who use cannabis for 'recreational' purposes, generally seeking conclusions based on (nominal) dose and frequency of use. Most retrospective epidemiologic studies of motor vehicle crashes measure THC in drivers' biofluid samples, including some taken post-mortem (and these have additional problems of post-mortem drug biofluid re-equilibration and losses). These, too, tend towards young, predominantly male, adults, who are known to be prone to risk-taking behaviours. Compared to typical research volunteers or forensically tested

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<sup>26</sup> Richard P Compton and Amy Berning, 'Drug and Alcohol Crash Risk' (Research Note, National Highway Traffic Safety Administration, 2015) 1, 4 (citations omitted).

<sup>27</sup> Paul J Larkin Jr, 'Medical or Recreational Marijuana and Drugged Driving' (2015) 52(453) *American Criminal Law Review* 453, 494-515 (citations omitted).

subjects, medical patients are likely to be relatively older and have co-morbidities.<sup>28</sup> Many will be driving vehicles legally, despite any limitations caused by their pathophysiological conditions and concomitant medications, along with other legal medications not subject to driving roadside testing, and any tolerance that may modify the respective dose-effect relationships.

Whereas ‘recreational’ cannabis users may consume the substance with the intention of experiencing psychotropic effects, medical patients reportedly eschew such effects.<sup>29</sup> Typically using incremental dosage to titrate dose to desire effect, the medical patient experience is analogous with the ‘patient-controlled analgesia’ paradigm used for managing pain after surgery.<sup>30</sup> Newhart discussed this difference in her thesis,<sup>31</sup> pointing out that drug experiences are created from a combination of ‘drug, set, and setting’<sup>32</sup> not just the drug itself, and that this is true of the effects of all drugs, whether they are used for ‘recreational’ or medical purposes.<sup>33</sup> In the latter, this also encompasses any ‘placebo effect’<sup>34</sup> with the essential purpose to ‘live a normal life and meet their social obligations’,<sup>35</sup> not to get high, but ‘to find an optimal dose in which the high was diminished but the medical effects were still experienced.’<sup>36</sup>

#### VII ORAL FLUID SAMPLE TESTING FOR “CANNABIS”

In Australia, roadside testing for THC (and/or methamphetamine and/or MDMA) normally consists of three stages: a first screen is performed with a commercial immunochromatographic assay kit; if positive, a second screen is performed with another commercial immunochromatographic kit; a third stage normally involves

<sup>28</sup> M A Ware, H Adams and G W Guy, ‘The Medicinal Use of Cannabis in the UK: Results of a Nationwide Survey’ (2005) 59(3) *International Journal of Clinical Practice* 291, 292.

<sup>29</sup> Ethan B Russo, ‘Current Therapeutic Cannabis Controversies and Clinical Trial Design Issues’ (2016) 7(309) *Frontiers in Pharmacology* 1, 2.

<sup>30</sup> See, eg, L E Mather and H Owen, ‘The Scientific Basis of Patient Controlled Analgesia’ (1988) 16 *Anaesthesia and Intensive Care* 427; H Owen, L E Mather and K Rowley, ‘The Development and Clinical Use of Patient Controlled Analgesia’ (1988) 16 *Anaesthesia and Intensive Care* 437; A Woodhouse and L E Mather, ‘Patient-Controlled Analgesia (PCA) for Postoperative Pain Relief: What Have We Learnt and Where Do We Go From Here?’ (1997) 3 *Analgesia* 1.

<sup>31</sup> Michelle Renee Newhart, *From “Getting High” to “Getting Well”: Medical Cannabis Use Among Midlife Patients in Colorado* (PhD Thesis, University of Colorado, 2013).

<sup>32</sup> *Ibid* 133–173.

<sup>33</sup> *Ibid* 134.

<sup>34</sup> *Ibid* 135.

<sup>35</sup> Nicky Britten, *Medicine and Society: Patients, Professionals and the Dominance of Pharmaceuticals* (Palgrave Macmillan, 2008) 57.

<sup>36</sup> Newhart, above n 31, 157.



subsequent definitive laboratory analysis of the samples using GLC-MS or HPLC-MS for the greatest precision, sensitivity and specificity.<sup>37</sup> Numerous academic research papers describe the performance of the various laboratory assays and immunochromatographic kits for detection and/or measurement of cannabinoids/THC and their metabolites in biofluids, as well as the performance of various oral fluid sampling devices. The presence of THC in oral fluid is taken as an indication of recent cannabis use, and its detectability diminishes over a period of many hours, depending on the amount of THC ingested and the frequency of use. Typically, THC will remain detectable for around 12 hours in infrequent, 'recreational' users, and around 30 hours in frequent users. As noted elsewhere, oral fluid THC concentrations may correlate with blood, etc concentrations, however, they are rarely individually predictable per se.<sup>38</sup>

Individuals who have smoked, vaporised or used an oral spray of cannabis invariably have their oral mucosa contaminated with residues from the dosage, producing oral fluid THC concentrations totally unrepresentative of concurrent blood concentrations. In various research studies of volunteering cannabis smokers, one study with nabiximols (Sativex®), an orally sprayed medicinal cannabis preparation, found that maximum oral fluid THC concentrations ranged from 1323–18 216 ng/ml, being up to 67 per cent the strength of the applied dose.<sup>39</sup> Similarly high oral fluid THC concentrations have been found after smoking a single cannabis cigarette.<sup>40</sup> Such concentrations, which are hardly pharmacologically meaningful, would, of course, 'wash away' over time, but at highly variable times, typically hours. Similar conclusions have also been found in some studies for CBD after ingestion of Sativex®.<sup>41</sup> CBD is mentioned specifically because there is

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<sup>37</sup> This summary provides a generalised overview of the roadside testing process; it is not always easy to obtain the actual procedures and performance specifications used by local authorities.

<sup>38</sup> See, eg, Sarah M R Wille et al, 'Evaluation of  $\Delta^9$ -Tetrahydrocannabinol Detection Using DrugWipe5S® Screening and Oral Fluid Quantification After Quantisal™ Collection for Roadside Drug Detection Via a Controlled Study With Chronic Cannabis Users' (2015) 7(3) *Drug Testing and Analysis* 178; Trudy Van der Linden, Peter Silverans and Alain G Verstraete, 'Comparison Between Self- Report of Cannabis Use and Toxicological Detection of THC/THCCOOH in Blood and THC in Oral Fluid in Drivers in a Roadside Survey' (2014) 6 *Drug Testing and Analysis* 137.

<sup>39</sup> Dayong Lee et al, 'Can Oral Fluid Cannabinoid Testing Monitor Medication Compliance and/or Cannabis Smoking During Oral THC and Oromucosal Sativex Administration?' (2013) 130(1–2) *Drug and Alcohol Dependence* 68, 72.

<sup>40</sup> See, eg, Marilyn A Huestis and Edward J Cone, 'Relationship of  $\Delta^9$ -Tetrahydrocannabinol Concentrations in Oral Fluid and Plasma After Controlled Administration of Smoked Cannabis' (2004) 28(6) *Journal of Analytical Toxicology* 394.

<sup>41</sup> See, eg, Anna Molnar et al, above n 25.

respectable evidence that it can oppose various effects of THC,<sup>42</sup> whilst having no significant psychomotor impairing effects of its own.<sup>43</sup> These studies do not, of course, invalidate oral fluid as a medium for detecting cannabis ingestion, but they do not give confidence in predicting resultant pharmacological effects from the THC concentrations. Other studies have reported on the duration of detectability of THC after smoking a cannabis cigarette. Primarily, its detectability is a function of the performance specifications of the testing system; clearly a lower cuff-off level determines a greater proportion of positives than the higher cut-off.<sup>44</sup> Other research indicates the variability of the THC oral fluid to blood, etc ratio between individuals.<sup>45</sup>

Much of the reported research testing of cannabis makes comparisons between volunteer users typically classified as 'regular', 'chronic' or 'heavy' in contrast to 'occasional' users. The data obtained from 'regular' users of 'recreational' cannabis indicate detectability (by GLC- or HPLC- based techniques) that can track the presence of the pharmacologically inactive end metabolite of THC (THC-COOH) for some 30 days after ingestion,<sup>46</sup> presumably being produced from THC that is slowly washed out from fatty stores.<sup>47</sup> In another influential study, for example, the coefficient of variation ( $R^2$ ) of blood THC concentration from oral fluid was found to be 0.122, indicating a very low predictability, and thus a very low predictability of psychomotor performance, as opposed to high predictability of detection of cannabis ingestion.<sup>48</sup>

Thus, the principal issues focus on whether the oral fluid concentration of THC alone is sufficient evidence to justify a conclusion of significant psychomotor impairment and/or impaired driving ability, given the probability of sample contamination from dosage residues, of individual misrepresentation by oral fluid of the THC blood

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<sup>42</sup> Sagnik Bhattacharyya et al, 'Opposite Effects of  $\Delta$ -9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology' (2010) 35(2) *Neuropsychopharmacology* 764, 769.

<sup>43</sup> John M McPartland et al, 'Are Cannabidiol and  $\Delta$ 9- Tetrahydrocannabivarin Negative Modulators of the Endocannabinoid System? A Systematic Review' (2015) 172(3) *British Journal of Pharmacology* 737, 746.

<sup>44</sup> Matthew N Newmeyer et al, 'Cannabinoid Disposition in Oral Fluid After Controlled Cannabis Smoking in Frequent and Occasional Smokers' (2014) 6(10) *Drug Testing and Analysis* 1002, 1009-1010.

<sup>45</sup> See, eg, Wendy M Bosker and Marilyn A Huestis, 'Oral Fluid Testing for Drugs of Abuse' (2009) 55(11) *Clinical Chemistry* 1910.

<sup>46</sup> Mateus M Bergamaschi et al, 'Impact of Prolonged Cannabinoid Excretion in Chronic Daily Cannabis Smokers' Blood on Per Se Drugged Driving Laws' (2013) 59 *Clinical Chemistry* 519, 519.

<sup>47</sup> Alexander Wong et al, 'Fasting and Exercise Increase Plasma Cannabinoid Levels in THC Pre-Treated Rats: An Examination of Behavioural Consequences' (2014) 231(20) *Psychopharmacology* 3987, 3987.

<sup>48</sup> V Vindenes et al, 'Detection of Drugs of Abuse in Simultaneously Collected Oral Fluid, Urine and Blood From Norwegian Drug Drivers' (2012) 219(1) *Forensic Science International* 165, 168.

concentrations,<sup>49</sup> and of antagonism to psychotropic effects of THC by concurrently ingested CBD.<sup>50</sup> One recent Australian study is noteworthy.<sup>51</sup> Here, 21 heavy cannabis users admitted to a Melbourne detoxication unit had their blood and oral fluid THC (and the end metabolite THC-COOH) concentrations measured by HPLC-MS daily, over seven days of abstinence.<sup>52</sup> Any impairment, if present, was not mentioned, but the subjects were abstemious during the tested period.<sup>53</sup> The concentration results showed marked inter-individual variability and unexpected intra-individual variability. For example, in the nearest (first or second) samples, the THC blood concentrations varied in these abstemious subjects from 1–13 ng/ml whilst the corresponding oral fluid concentrations varied from not detectable (in 6 of the 21 subjects) to 16 ng/ml, and the respective relative maximum blood and oral fluid concentrations ranged from 13–1 ng/ml after 31 hours in one subject to 6–16 ng/ml also at 31 hours in another subject.<sup>54</sup> Thus, variability is great, and predictability is poor. The authors concluded that:

The implications for forensic practitioners who have to interpret THC toxicology from the witness box are challenging. THC kinetics in heavy users appears to be highly variable and there is no easy interpretation which will allow a useful estimation of time of use from a single measurement.<sup>55</sup>

Forensically tested subjects include those selected randomly, those suspected of actual driving violations and those tested post-mortem after a fatal crash. In such cases, dosing and sampling variables are normally far from controlled, and documentation normally far from complete. This typically leads to wide-ranging and non-specific statements:

Epidemiologic data show that the risk of involvement in a motor vehicle accident (MVA) increases approximately 2-fold after cannabis smoking...Nearly two thirds of US trauma center admissions are due to motor vehicle accidents (MVAs), with almost 60% of such

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<sup>49</sup> See, eg, J G Ramaekers et al, 'Cognition and Motor Control as a Function of  $\Delta^9$ -THC Concentration in Serum and Oral Fluid: Limits of Impairment' (2006) 85(2) *Drug and Alcohol Dependence* 114.

<sup>50</sup> See, eg, A W Zuardi et al, 'A Critical Review of the Antipsychotic Effects of Cannabidiol: 30 Years of a Translational Investigation' (2012) 18(32) *Current Pharmaceutical Design* 5131; Tibor M Brunt et al, 'Therapeutic Satisfaction and Subjective Effects of Different Strains of Pharmaceutical-Grade Cannabis' (2014) 34(3) *Journal of Clinical Psychopharmacology* 344; Francesca Indorato et al, 'The Therapeutic Use of Cannabinoids: Forensic Aspects' (2016) 265 *Forensic Science International* 200; John M McPartland et al, above n 43.

<sup>51</sup> Morris S Odell et al, 'Residual Cannabis Levels in Blood, Urine and Oral Fluid Following Heavy Cannabis Use' (2015) 249 *Forensic Science International* 173.

<sup>52</sup> Ibid 174–175.

<sup>53</sup> Ibid 173.

<sup>54</sup> Ibid 176–177.

<sup>55</sup> Ibid 179.

patients testing positive for drugs or alcohol...Alcohol and cannabis are the drugs most frequently detected.<sup>56</sup>

In a widely cited research study performed in healthy volunteers with smoked cannabis cigarettes containing known amounts of THC,<sup>57</sup> the proportion of observations showing impairment of performance test skills related to driving progressively increased as a function of serum THC concentration, with a threshold of impairment occurring with serum concentrations between 2–5 ng/ml, and with significant impairment at serum concentrations between 5–10 ng/ml.<sup>58</sup> However, serum concentrations are assessed at the roadside only by oral fluid estimates. These authors also found that the THC concentrations in oral fluid were much higher than those in serum, and that the THC oral fluid to serum ratio decreased to eventually become essentially constant;<sup>59</sup> indeed, they found that there was a strong linear relation ( $r = 0.84$ ) between log-transformed THC concentrations in serum and oral fluid.<sup>60</sup> However, their data show that variability in the ratio was 10–30-fold.<sup>61</sup> Furthermore, they reported that:

Regression analysis indicated linear relations between changes in performance impairment and log-transformed THC levels in both serum and oral fluid. However, the associated correlations were always rather low, in the range of 0.15–0.40. The lack of a strong association seems to indicate that serum THC cannot be taken as an accurate predictor of the magnitude of performance impairment.<sup>62</sup>

Without question, this study showed that THC in oral fluid was a valid marker of recent ingestion of cannabis. However, if used forensically with oral fluid providing such a variable estimate of the serum THC concentration, and with the serum THC concentration providing such a variable estimate of the performance impairment, is it not unreasonable to conclude that the oral fluid THC provides a variable estimate of the performance impairment?

Increasing numbers of research studies are being performed using acute impairment measures in various psychometrics, including skills in driving vehicle simulators. This

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<sup>56</sup> Rebecca L Hartman and Marilyn A Huestis, 'Cannabis Effects on Driving Skills' (2013) 59(3) *Clinical Chemistry* 478, 478–79 (citations omitted).

<sup>57</sup> J G Ramaekers et al, above n 49.

<sup>58</sup> *Ibid* 114.

<sup>59</sup> *Ibid* 119.

<sup>60</sup> *Ibid* 118.

<sup>61</sup> *Ibid* 120.

<sup>62</sup> *Ibid* 119.

literature also broadly indicates increasing impairment with increasing THC concentrations in biofluids, but it is, so far, difficult to interpret as to where there is a reasonable cut-off corresponding to 'probably not impaired'. In comparison, useful information about alterations to the driving ability of medical patients having cannabis pharmacotherapy comes from observational reports, and these clinical studies are more pertinent because of the longer duration of routine treatments.<sup>63</sup> For example, in one recent report of adverse events in 77 patients with multiple sclerosis having 6 months of Sativex® for pharmacotherapy of spasticity, improved ability occurred in 5, no changes in 71, and only 1 had loss of ability; after 12 months, data from 57 patients indicated improvement in 2 and no change in 55.<sup>64</sup>

In the same context, Dr William Notcutt of James Paget University Hospital in the UK, one of the most experienced clinicians with medicinal cannabis in Europe, concluded his co-authored chapter in a major textbook about medicinal cannabis with a Questions and Answers section.<sup>65</sup> One of the questions, 'Can you drive when using medicinal cannabinoids?'<sup>66</sup> yielded the following answer:

Different countries will have different attitudes and laws concerning driving and the use of cannabis (whether used recreationally or medicinally). Most will have yet to produce appropriate advice to patients. In the UK it is for patients to determine their own fitness to drive and it may be the disease itself or the therapy or other medication that hinders this. Most patients manage this decision satisfactorily...However, it also seems likely that any impairment is probably well within the range of (or lower than) what is currently produced by other pharmaceutical agents which are commonly used for similar

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<sup>63</sup> See, eg, Donald E Greydanus et al, 'Cannabis: Effective and Safe Analgesic?' (2014) 7(3) *Journal of Pain Management* 209; T Rekand, 'THC: CBD Spray and MS Spasticity Symptoms: Data From Latest Studies' (2014) 71(1) *European Neurology* 4; M Freidel et al, 'Drug- Resistant MS Spasticity Treatment With Sativex® Add- On and Driving Ability' (2015) 131(1) *Acta Neurologica Scandinavica* 9; William G Notcutt, 'Clinical Use of Cannabinoids for Symptom Control in Multiple Sclerosis' (2015) 12(4) *Neurotherapeutics* 769;

Ó Fernández, 'THC: CBD in Daily Practice: Available Data from UK, Germany and Spain' (2016) 75(1) *European Neurology* 1.

<sup>64</sup> Celia Oreja-Guevara et al, 'Observational Safety Study of THC: CBD Oromucosal Spray (Sativex) in Multiple Sclerosis Patients with Spasticity' (2015) 5(184) *Clinical and Experimental Pharmacology* 2161, 2163.

<sup>65</sup> William Notcutt and Emily L Clarke, 'Cannabinoids in Clinical Practice: A UK Perspective' in Roger Pertwee *Handbook of Cannabis* (Oxford University Press, 2014) 415, 421–424.

<sup>66</sup> *Ibid* 423.

conditions (including opiates, benzodiazepines, tricyclic antidepressants, baclofen, etc).<sup>67</sup>

In other studies of motor traffic crashes, THC was the most frequently found drug in the first large-scale, case controlled, study of motor vehicle crashes in America to include drugs other than alcohol.<sup>68</sup> Compared to other drugs, the estimated relative risk rates reported from a crash risk study, it appears that THC is associated with a significantly elevated risk of crashing (by about 1.25 times).<sup>69</sup> Similarly, the use of any illegal drugs is associated with a significant increase in the risk of crashing (by 1.21 times).<sup>70</sup> However, the authors pointed out that:

These unadjusted odds ratios must be interpreted with caution as they do not account for other factors that may contribute to increased crash risk. Other factors, such as demographic variables, have been shown to have a significant effect on crash risk. For example, male drivers have a higher crash rate than female drivers. Likewise, young drivers have a higher crash rate than older drivers. To the extent that these demographic variables are correlated with specific types of drug use, they may account for some of the increased crash risk associated with drug use.<sup>71</sup>

The authors concluded that:

This study of crash risk found a statistically significant increase in unadjusted crash risk for drivers who tested positive for use of illegal drugs (1.21 times), and THC specifically (1.25 times). However, analyses incorporating adjustments for age, gender, ethnicity, and alcohol concentration level did not show a significant increase in levels of crash risk associated with the presence of drugs. This finding indicates that these other variables (age, gender, ethnicity and alcohol use) were highly correlated with drug use and account for much of the increased risk associated with the use of illegal drugs and with THC.<sup>72</sup>

Recently published statistical research (that reanalysed previously reported data) concluded that various previous estimates of odds ratios of cannabis driving risks had

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<sup>67</sup> Ibid 423–424 (citations omitted).

<sup>68</sup> Compton and Berning, above n 26, 1.

<sup>69</sup> Ibid 4.

<sup>70</sup> Ibid 8.

<sup>71</sup> Ibid 4.

<sup>72</sup> Ibid 8.

been over-estimated.<sup>73</sup> Another laboratory research study in chronic cannabis smokers found prolonged neurocognitive impairment to various laboratory tasks, only partially recovered over three weeks of continuously monitored abstinence after smoking cannabis.<sup>74</sup> Several possible explanations include that such impairments arose from withdrawal from daily cannabis use, or from residual THC concentrations in blood;<sup>75</sup> alternatively, that prolonged impairment may have resulted from cumulative lifetime intake and reflect persistent changes in psychomotor functions in chronic cannabis smokers.<sup>76</sup>

From studies on cannabis detection in 'recreational' users, it has been reported that their oral fluid concentrations progressively decreased and median concentrations fell from 218 (range 28.4–2354) ng/ml 1 hour after smoking, to 71.1 (7.5–350) ng/ml after 2 hours in chronic, frequent smokers, as compared to 93.6 (48.4–561) ng/ml to 78.3 (23.4–1080) ng/ml within the same interval in occasional smokers;<sup>77</sup> and that 13.5 hours after smoking, 100 per cent of 24 specimens were still THC positive with median concentrations of 2.8 (0.8–18.4) for frequent and 1.8 (0.8–34.5) ng/ml for occasional cannabis smokers.<sup>78</sup> Median THC last detection times for frequent and occasional smokers were >30 (13.5–>30) and 27 (21–>30) hours respectively, documenting no significant differences ( $p = 0.067$ ) up to 30 hours.<sup>79</sup> In all of these metrics, the variability is large, and the predictability is poor. Such variability includes that due to contamination from the ingested cannabis, as well as that inherent in all other parts of its physiological distribution, the specimen collection and measurement.<sup>80</sup>

Given that any impairment will be more related to THC in plasma and not oral fluid, how can one assess impairment from THC measured in oral fluid alone? Surely any

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<sup>73</sup> Ole Rogeberg and Rune Elvik, 'The Effects of Cannabis Intoxication on Motor Vehicle Collision Revisited and Revised' (2016) 111(8) *Addiction* 1348. For subsequent discussion on this research see Hallvard Gjerde and Jørge Mørland, 'Risk for Involvement in Road Traffic Crash During Acute Cannabis Intoxication' (2016) 111(7) *Addiction* 1492; Ole Rogeberg and Rune Elvik, 'Response: Cannabis Intoxication, Recent Use and Road Traffic Crash Risks' (2016) 111(8) *Addiction* 1495.

<sup>74</sup> Wendy M Bosker et al, 'Psychomotor Function in Chronic Daily Cannabis Smokers During Sustained Abstinence' (2013) 8(1) *Public Library of Science* 1, 5.

<sup>75</sup> *Ibid* 5–6.

<sup>76</sup> *Ibid* 6.

<sup>77</sup> Sebastien Anizan et al, 'Oral Fluid Cannabinoid Concentrations Following Controlled Smoked Cannabis in Chronic Frequent and Occasional Smokers' (2013) 405(26) *Analytical and Bioanalytical Chemistry* 8451, 8454.

<sup>78</sup> *Ibid*.

<sup>79</sup> *Ibid*.

<sup>80</sup> *Ibid* 8452.

correlation between oral fluid THC after cannabis smoking and pharmacological effects would be temporal due to comparable detection windows, rather than a causal relationship. The relevant question is: does the minimum detectable level of THC by the current standard roadside screen accurately (or even reasonably) define a driver, who has ingested cannabis, at risk of causing a road traffic crash beyond that of a driver without a minimum detectable THC level? Additionally, what cut-off level is reasonable to impose under more informative conditions? A fairer means to define a threshold level of meaningful impairment would need to be drawn from the probability of impairment as a function of THC blood-related concentration. This proposition reflects the suggestions made by prominent Australian cannabis policy researchers who concluded:

Given the limited scientific evidence for a per se level of THC the Australian drug testing regimes lack evidential support. The illegality of cannabis has prompted a 'zero tolerance' approach in Australia with any detectable amount of the drug tested constituting an offence. On this policy, the definition of a per se level is irrelevant because road safety benefits are secondary to enforcement of drug laws.<sup>81</sup>

#### VIII DRUG-DRIVING LAWS AND THE UNEASY ANALOGY OF CANNABIS WITH ALCOHOL

Although current drug-driving laws in Australia, as elsewhere, have been informed by alcohol-driving research, there are some marked dissimilarities between alcohol and cannabis/THC that merit further consideration with respect to driving impairment. Roadside testing procedures for alcohol have evolved to deter the driving of motor vehicles whilst under impairment (or risk of impairment) after the consumption of alcohol. These procedures have been accepted by society for several decades and are supported by extensive epidemiological and pharmacological evidence demonstrating that the risks of driving impairment and road crash are related to the dose of alcohol, and that the resultant body burden of alcohol that can be assessed from its readily measured concentrations in expired air/breath (and/or biofluids).

Alcohol is the same unique chemical substance (ethyl alcohol, ethanol) regardless of ingested form, and is typically consumed in knowable doses of 10s of grams. Roadside testing is satisfactorily performed on breath samples because alcohol is a volatile

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<sup>81</sup> Wayne Hall and Ross Homel, 'Reducing Cannabis- Impaired Driving: Is There Sufficient Evidence for Drug Testing of Drivers?' (2007) 102(12) *Addiction* 1918, 1918 (citations omitted).



substance and the combination of its high vapour pressure and large doses permit readily measurable quantities in breath. A dose-biofluid/breath alcohol concentration-impairment relationship (a graded response) has been agreed from vast research evidence. In Australia, an offence is caused by driving a motor vehicle whilst exceeding a lower threshold breath (and/or biofluid) alcohol concentration that has been deemed, after research, to be associated with impairment. Whereas in some countries, a similar threshold THC concentration-impairment (graded response) approach has been adopted for cannabis, in Australia, driving a motor vehicle and returning a positive test result for THC (all-or-none response) causes an offence, and no demonstration of influence or driving impairment is required.

Other research, also framed in this context of 'recreational' cannabis use, indicates that cannabis (THC) and alcohol may be additive in their influence on psychomotor performance and driving impairment.<sup>82</sup> For example, Hartman et al found on one test considered to be a sensitive vehicular control indicator that, allowing for inter-subject variability, blood THC concentrations of 3.2, 8.2 and 13.1 ng/ml produced similar impairments to 0.02, 0.05 and 0.08 g/210L breath alcohol concentrations respectively.<sup>83</sup> Regarding DUID laws, the authors of this study propose that '[c]hosen driving-related THC cut-offs should be considered carefully to best reflect performance impairment windows'<sup>84</sup> and suggest that their 'results will help facilitate forensic interpretation and inform the debate on drugged driving legislation.'<sup>85</sup>

While cannabis also may be ingested in a variety forms, the composition and doses of its various pharmacologically active components, including THC, are normally unknowable and depend on many factors, including the chosen mode of administration (whether smoked, or inhaled, or swallowed by mouth), with the resultant doses typically in the range of sub-milligrams to 10s of milligrams. The marked differences between alcohol and THC in chemical and physicochemical properties give rise to marked differences in pharmacokinetic properties. Whereas alcohol is totally water soluble and rapidly distributes throughout the body, THC and the principal cannabinoids are virtually water

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<sup>82</sup> See, eg, Rebecca L Hartman et al, 'Cannabis Effects on Driving Lateral Control With and Without Alcohol' (2015) 154 *Drug and Alcohol Dependence* 25.

<sup>83</sup> *Ibid* 28.

<sup>84</sup> Rebecca L Hartman et al, 'Controlled Cannabis Vaporizer Administration: Blood and Plasma Cannabinoids With and Without Alcohol' (2015) 61(6) *Clinical Chemistry* 850, 850. Note the use of the term 'cut-offs' in this literature.

<sup>85</sup> *Ibid*.

insoluble but are highly fat soluble, and this affects their body distribution by favouring their rapid and extensive uptake into fatty tissues, with slow release back into the blood, typically over periods measured in days to weeks.

The overall elimination of alcohol can be described by a capacity-limited model, with a high maximum rate of metabolism, and a biological half-life of a few to several hours.<sup>86</sup> In contrast, THC pharmacokinetics and pharmacodynamics are determined by the mode of administration, but with an overall biological half-life in the order of days to weeks due to the very slow rate of washout from body fat pools.<sup>87</sup> This is reflected by findings of traces of THC in blood for up to a month after ingestion of cannabis.<sup>88</sup> Clearly, with modern techniques allowing greater sensitivity, longer and longer durations of detection are possible, until long after the pharmacological effects have dissipated. With any drug, including THC, detector sensitivity is normally the limiting factor in any analysis; the lowest LOD will be reached despite an abundance of molecules of the substance being present in biofluids.

#### IX SOME CONCLUSIONS

The question fundamental to this paper, and to the issue of DUID laws, ultimately asks whether, after cannabis ingestion and positive roadside oral fluid testing, is the individual ‘cannabis-impaired, or, just cannabinoid positive?’<sup>89</sup> Cannabis is presently being treated as an illegal drug substance, not a medicine to be used by medical patients. As written, for example, in NSW legislation, the offence is to drive a car with ‘prescribed *illicit* drug present in oral fluid, blood or urine.’<sup>90</sup> Should cannabis be made a legal drug, a plain English reading of the Act suggests that ‘illicit’ would no longer pertain. Additionally, it is noted in sub-s (5) of the Act, that protection appears to be afforded to

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<sup>86</sup> See, eg, N H Holford, ‘Clinical Pharmacokinetics of Ethanol’ (1987) 13(5) *Clinical Pharmacokinetics* 273; Åke Norberg et al, ‘Role of Variability in Explaining Ethanol Pharmacokinetics’ (2003) 42(1) *Clinical Pharmacokinetics* 1.

<sup>87</sup> See, eg, Stig Agurell et al, ‘Pharmacokinetics and Metabolism of  $\Delta^1$ -Tetrahydrocannabinol and Other Cannabinoids With Emphasis on Man’ (1986) 38(1) *Pharmacological Reviews* 21; Franjo Grotenhermen, ‘Pharmacokinetics and Pharmacodynamics of Cannabinoids’ (2003) 42(4) *Clinical Pharmacokinetics* 327; Alexander Wong et al, above n 47.

<sup>88</sup> Mateus M Bergamaschi et al, above n 46, 519.

<sup>89</sup> John P Bederka Jr, ‘Marijuana-Impaired, or, Just Cannabinoid Positive?’ in James T O’Donnell II and James J O’Donnell III (eds), *O’Donnell’s Drug Injury* (Lawyers & Judges Publishing Company, 4<sup>th</sup> ed, 2016).

<sup>90</sup> *Road Transport Act 2013* (NSW) s 111(1) (‘the Act’) (emphasis added). In NSW at least, ‘prescribed illicit drug’ means ‘(a) delta-9-tetrahydrocannabinol (also known as THC), (b) methylamphetamine (also known as speed), (c) 3,4-methylenedioxyamphetamine (also known as ecstasy)’; at s 4.

the offence deemed by the presence of morphine in a person's blood or urine, in that it is a defence to a prosecution for an offence against sub-s (3):

It is a defence to a prosecution for an offence against subsection (3) if the defendant proves...the presence in the defendant's blood or urine of morphine was caused by the consumption of a substance for medicinal purposes...or if from a codeine-based medicine purchased from a pharmacy that has been taken in accordance with the manufacturer's instructions.<sup>91</sup>

This suggests some room for adaption towards cannabis. Until more becomes known, it is suggested that the lawful use of cannabis by patients should be preceded by medical practitioner counselling about the relevant effects of cannabis, along with a 'fitness to drive' medical assessment, as described under Austroads Medical Standards For Licensing.<sup>92</sup>

As related above, an oral fluid drug concentration measure is not causative of any pharmacological effect; it may correlate with some pharmacological effect, but then again it may not. A blood, plasma or serum measure would present a more reasonable case, if calibrated to exclude the lower portions of the dose-response relationship where uncertainty is greatest. In this regard, the analogy of alcohol is pertinent. Moreover, various reports indicate that even amongst seasoned 'recreational' users, most have insight as to their degree of mental impairment and would judge their ability to drive accordingly. Medical patients reportedly achieve the desired effects to live a normal life and to meet their social obligations.

This paper, prepared by a pharmacologist not trained in the law, is intended to stimulate re-evaluation of the criteria under which users of cannabis might be judged legally. It presents the opinion that, based on the available evidence, the issue of driving while a relevant drug, THC, was present in saliva, is not well-addressed by the current roadside testing of saliva/oral fluid for THC. It forms the opinion that, on pharmacological grounds, it is not possible to infer impairment from the roadside testing of THC in oral fluid alone.

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<sup>91</sup> Ibid sub-ss (5)-(6).

<sup>92</sup> Austroads and National Transport Commission, 'Assessing Fitness to Drive for Commercial and Private Vehicle Drivers: Medical Standards for Licensing and Clinical Management Guidelines' (Health Professional Resource, 5<sup>th</sup> ed, October 2016) 117.

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