LEGISLATIVE COUNCIL
Question Without Notice

Thursday, 5 August 2021

C459. Hon Brian Walker to the Minister representing the Minister for Police

I thank the minister for his response to my Question without Notice No. 350, asked and answered on 23 June 2021, on the devices in use in Western Australia for roadside drug testing. Seeking further clarification from the Minister, I now ask:

1) Which agency or firm determined an accuracy rate for the SecureTec Drug Wipe II Twin Combo for testing cannabis at 98%;

2) Is the minister aware of a 2019 study conducted by the Lambert Initiative for Cannabinoid Therapeutics at the University of Sydney and published in the journal *Drug Testing and Analysis*, which found the SecureTec Drug Wipe to have an accuracy rate for cannabis testing which included a 5% false-positive return, alongside a 10% false-negative return, well below the figure which the Minister provided in his previous answer;

3) How does the Minister explain this difference in findings; and,

4) If he has not yet had an opportunity to consider the Lambert Initiative report in detail, might I seek leave to table a copy, for the consideration of the government, alongside all members of this house?

Answer

I thank the Honourable Member for some notice of this question. The following information has been provided to me by the Minister for Police.

(1) The Western Australian Police Force advised the accuracy rate based on the current testing regime and the data available at 23 June 2021. Further, if a test on the Twin Combo displays positive, a sample is forwarded to the Chemistry Centre of Western Australia for analysis. These returns are for any drugs detected.

(2) No

(3) Not applicable

(4) Not applicable

Received: 9 June 2019 | Revised: 22 July 2019 | Accepted: 19 August 2019

DOI: 10.1002/dta.2687

RESEARCH ARTICLE

WILEY

Detection of Δ^9 THC in oral fluid following vaporized cannabis with varied cannabidiol (CBD) content: An evaluation of two point-of-collection testing devices

Thomas R. Arkell[1,2,3] | Richard C. Kevin[1,2,4] | Jordyn Stuart[1,2,4] | Nicholas Lintzeris[3,5] | Paul S. Haber[3,6] | Johannes G. Ramaekers[7] | Iain S. McGregor[1,2,4]

[1] Lambert Initiative for Cannabinoid Therapeutics, The University of Sydney, Sydney, New South Wales, Australia

[2] Brain and Mind Centre, The University of Sydney, Sydney, New South Wales, Australia

[3] Faculty of Medicine, Central Clinical School, The University of Sydney, Sydney, New South Wales, Australia

[4] Faculty of Science, School of Psychology, Brain and Mind Centre, The University of Sydney, Sydney, New South Wales, Australia

[5] The Langton Centre, Drug and Alcohol Services, South East Sydney Local Health District, NSW Health, New South Wales, Australia

[6] Drug Health Services, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

[7] Faculty of Psychology and Neuroscience, Maastricht University, The Netherlands

Correspondence
Iain S McGregor, Rm 605, Brain and Mind Centre M02F, Camperdown, NSW 2050 Australia.
Email: iain.mcgregor@sydney.edu.au.

Funding information
Lambert Initiative for Cannabinoid Therapeutics

Abstract

Point-of-collection testing (POCT) for Δ^9-tetrahydrocannabinol (THC) in oral fluid is increasingly used to detect driving under the influence of cannabis (DUIC). However, previous studies have questioned the reliability and accuracy of two commonly used POCT devices, the Securetec DrugWipe® 5 s (DW5s) and Dräger DrugTest® 5000 (DT5000). In the current placebo controlled, double-blind, crossover study we used liquid chromatography-tandem mass spectrometry (LC–MS/MS) to accurately quantify cannabinoid concentrations in the oral fluid of 14 participants at various timepoints (10, 60, 120, and 180 minutes) following vaporization of 125 mg of THC-dominant (11% THC; <1% CBD), THC/CBD equivalent (11% THC; 11% CBD) and placebo (<1% THC; <1% CBD) cannabis. At each timepoint, oral fluid was also screened using the DW5s (10 ng/mL THC cut-off) and DT5000 (10 ng/mL THC cut-off). LC–MS/MS analysis showed peak oral fluid THC concentrations at the 10 minute timepoint with a rapid decline thereafter. This trajectory did not differ with THC dominant and THC/CBD equivalent cannabis. With a 10 ng/mL confirmatory cut-off, 5% of DW5s test results were false positives and 16% false negatives. For the DT5000, 10% of test results were false positives and 9% false negatives. Neither the DW5s nor the DT5000 demonstrated the recommended >80% sensitivity, specificity and accuracy. Accuracy was lowest at 60 minutes, when THC concentrations were often close to the screening cut-off (10 ng/mL). POCT devices can be useful tools in detecting recent cannabis use; however, limitations should be noted, and confirmatory LC–MS/MS quantification of results is strongly advisable.

KEYWORDS

cannabis, CBD, oral fluid, point-of-collection testing, THC

(RPAH Zone) Human Research Ethics Committee. The trial was listed on the Australia New Zealand Clinical Trials Registry (No. 12616000414415).

2.2 | Study design and procedures

This randomized, placebocontrolled, within-subjects, double-blind, crossover study included three experimental sessions that were scheduled at least seven days apart to avoid carryover effects. Participants were instructed to abstain from illicit drugs for the duration of the study (i.e., from the time of study enrolment until the final session) and from alcohol on the night before research sessions, to maintain any use of regular medications, and to consume no more than their regular caffeine intake on the morning of research sessions. Participants arrived at the clinical research unit at 9 am on the morning of research sessions. Zero breath alcohol concentration (BrAC) was confirmed via breathalyzer (Alcotest 5510, Draeger, Lübeck, Germany) and participants were initially screened using the DrugWipe® 5 s to rule out acute drug intoxication and/or recent drug use. Participants testing positive for any drug (cannabis, amphetamine, methamphetamine, cocaine, or opiates) were sent home and the session was rescheduled.

Participants inhaled 125 mg THC-dominant ('THC'; 11% THC; <1% CBD), THC/CBD equivalent ('THC/CBD'; 11% THC, 11% CBD) or placebo (<1% THC; <1% CBD) cannabis (Tilray, BC, Canada) via vaporization at 200°C (Mighty Medic, Storz & Bickel, Tuttlingen, Germany), resulting in projected doses of approximately 13.75 mg THC and CBD. Cannabinoid concentrations were determined by Tilray using high-performance liquid chromatography (HPLC). Vaporization occurred over 5 minutes according to a standardized procedure (inhale 3 seconds, hold 3 seconds, exhale and rest 30 seconds). If vapor was still visible in exhaled breath at 5 minutes, then this procedure was continued until vapor was no longer visible to ensure complete vaporization of plant material. Across three sessions, separated by at least seven days, participants received the three study drugs (one per session) in a randomized and counterbalanced order. The randomization schedule was created by an independent researcher, and only the study pharmacist had access to the randomization code.

2.3 | Oral fluid collection and POCT procedures

Oral fluid samples were collected using Quantisal™ collection devices (Immunalysis, Pomona, CA, USA) at baseline and at 10, 60, 120, and 180 minutes post-vaporization. Devices were placed under the tongue until indicators turned blue (collecting 1.0 ± 0.1 mL of oral fluid), or for a maximum of 10 minutes, and placed into the stabilizing buffer. Samples were kept at 4°C until analysis which occurred within a month of collection. Food and drink consumption were disallowed for 10 minutes prior to collection.

Oral fluid tests were also performed at 10, 60, 120, and 180 minutes after vaporization using the Securetec DrugWipe® 5 s (Securetec, Neubiberg, Germany) and Dräger DrugTest® 5000 (Dräger, Lübeck, Germany) devices. Tests were performed in this order immediately following oral fluid sample collection. Both devices had a manufacturer-specified detection limit of 10 ng/mL THC.

The DW5s test device has two sampling pads which collect oral fluid from the tongue (about 10–20 µL). Participants are instructed to run their tongue around the inside of their mouth in a circular motion three times before slowly scraping the sampling pads down their tongue. Sufficient volume of collected oral fluid is indicated by a change in color of the sampling pads. The researcher then fastens the collection pads to the test strip and breaks an ampoule containing buffer. The test is held vertically for 10 seconds before being laid horizontally and results are visible within 10 minutes. A positive test is indicated by the appearance of a red line. Test results where the DW5s red 'positive' line was considered too ambiguous were excluded.

The DT5000 test consists of a test cassette, a buffer cartridge, and an analytical instrument. The test cassette comprises a collection pad which collects oral fluid from the cheeks and tongue. Participants are instructed to wipe this pad around the inside of their cheeks and across their gums until sufficient oral fluid has been collected which is indicated by the appearance of a blue line. The test cassette and the buffer cartridge are then inserted into the analyzing instrument. Results are available after 8 minutes (negative, non-negative, or invalid) and can be printed using an attached printer. Test results where the indicator line did not turn blue were excluded. Test results for both devices were read and filed by an independent observer and only made available to the researchers upon completion of the study.

2.4 | Oral fluid analysis via LC–MS/MS

Oral fluid samples were analyzed using LC–MS/MS. Duplicate 1 mL aliquots were fortified with an internal standard mixture containing d_3-THC and d_3-CBD. Duplicate calibrator samples were prepared using cannabinoid-free saliva (obtained from healthy volunteers using Quantisal™ collection devices, and checked for cannabinoid content via LC–MS/MS), spiked with THC, CBD, and internal standards to generate a standard curve for each analyte and quality control samples. THC and CBD were isolated using supported liquid extraction (SLE), where each sample aliquot was absorbed onto a 1 mL capacity ISOLUTE® SLE+ column (Biotage, Sydney, Australia), and analytes were eluted with 1.6 mL DCM, 3.5 mL methyl *tert*-butyl ether (MTBE), and 1.6 mL 1:5 ethyl acetate and MTBE. The eluate was evaporated without heating under a gentle stream of nitrogen, and analytes were reconstituted in 200 µL of 1:1 acetonitrile and 0.1% formic acid in water, transferred to 2 mL autosampler vials fitted with 200 µL capacity glass inserts, and placed in the LC–MS/MS autosampler held at 4°C.

Chromatographic separation was achieved using an Eclipse XDB-C18 column (50 mm x 2.1 mm i.d., particle size 3.5 µm; Agilent Technologies, Singapore) using gradient elution with mobile phases 0.1% formic acid in water and acetonitrile, at a flow rate of 0.3 mL/min. This was coupled to a Shimadzu LCMS-8030 mass spectrometer for analyte identification and quantification.

The LC–MS/MS analysis was validated for selectivity, linearity, accuracy, precision, bench-top and autosampler stability, dilution integrity, limit of detection (LOD), and limit of quantification (LOQ)

three test sessions. Oral fluid samples (N = 210) were collected prior to and up to 3 hours after vaporization. A total of 165/168 DW5s and 163/168 DT5000 tests were considered valid and subsequently evaluated against LC–MS/MS quantified confirmatory THC concentrations.

3.2 | LC–MS/MS method

The LC–MS/MS method was accurate, precise, and had LODs of 1 ng/mL for both THC and CBD, and LLOQs of 2 and 6 ng/mL for THC and CBD, respectively. Although some matrix effect was apparent, this was accounted for with the use of deuterated internal standards for both analytes. We also verified that other common phytocannabinoids that could also be present in saliva (THCA, THCV, CBN, CBDA, CBG, CBGA, and CBC) were chromatographically separated and did not interfere with CBD or THC quantification (data not shown).

3.3 | Oral fluid cannabinoid concentrations

Table 3 presents THC and CBD pharmacokinetic data for each individual, while Figure 1 shows median THC and CBD concentrations over time. All baseline THC concentrations were < LOQ with the exception of one sample with a concentration of 11.4 ng/mL THC. Because the corresponding DW5s drug screen was negative for THC and the participant reported nil cannabis use since the previous session, this test session continued as normal. All baseline CBD concentrations were also <LOQ with the exception of one sample which contained 5.5 ng/mL CBD.

Concentrations of oral fluid THC and CBD (Figure 1) were maximal (C_{max}) at the 10-minute post-vaporization timepoint for all individuals and declined rapidly thereafter. The mean (range) for THC C_{max} was 287.1 (19.9–1318) ng/mL in the THC condition, 285.5 (6.3–1740.6) ng/mL in the THC/CBD condition, and 7.26 (0–36.5) ng/mL in the placebo condition. At 3 hours, the mean (range) THC concentrations were 4.3 (0–21.6) and 3.8 (0–23.7) ng/mL in the THC and THC/CBD conditions, respectively, and 1.7 (0–12.3) ng/mL in the placebo condition.

The mean (range) for CBD C_{max} was 21.21 (0–84.9) ng/mL in the THC condition, 506.3 (15.3–2934.9) ng/mL in the THC/CBD condition, and 36.7 (3–209) ng/mL in the placebo condition. At 3 hours, the mean (range) CBD concentrations were 1.4 (0–3.0) and 9.4 (0–47.7) ng/mL in the THC and THC/CBD conditions, respectively, and 3.6 (0–20.1) ng/mL in the placebo condition.

Oral fluid THC concentrations differed significantly between the three conditions at 10 minutes (χ^2 (2) = 21.14, p < .001) and 60 minutes (χ^2 (2) = 21.57, p < .001) but not at baseline or at the 120-minute or 180-minute timepoints. At 10 minutes, oral fluid THC concentrations were significantly higher in both the THC (p < .001) and THC/CBD (p < .001) conditions than in the placebo condition. At 60 minutes, THC concentrations were also significantly higher than placebo in both the THC (p = .001) and THC/CBD (p < .001) conditions. There

TABLE 2 Validation parameters for oral fluid analysis of THC and CBD by LC–MS/MS

Parameter	THC	CBD
Retention time (min)	8.2	6.7
Quantifier transition (qualifier transition)	315.1 → 193.1 (315.1 → 259.1)	315.1 → 193.1 (315.1 → 259.1)
Internal standard (IS)	d_3-THC	d_3-CBD
IS quantifier transition (qualifier transition)	318.1 → 196.1 (318.1 → 123.1)	318.1 → 196.1 (318.1 → 123.1)
Specificity	No interferences found	No interferences found
Matrix effect % (n = 6)	79	87
LOD	1	1
LLOQ	2	6
Linearity		
R^2	>.996	>.997
Linear range	2–400	6–400
Accuracy %, intra-assay (n = 6)		
Low	96.8	97.2
Medium	108.6	109.2
High	101.1	101.7
Accuracy %, inter-assay (n = 9)		
Low	105.1	105.6
Medium	101.5	101.9
High	98.7	99.3
Precision %RSD, intra-assay (n = 6)		
Low	10.4	10.1
Medium	10.5	10.8
High	5.4	4.7
Precision %RSD, inter-assay (n = 9)		
Low	10.8	11.0
Medium	10.0	10.3
High	8.0	7.2
Autosampler stability (% 0 h timepoint)		
4 h	101.1	98.0
8 h	97.1	98.1
Dilution integrity (10x dilution; n = 6)		
Medium QC accuracy (%)	102.2	103.3
Medium QC precision (%RSD)	9.2	7.5

LOD = limit of detection. LLOQ = lower limit of quantification. N.B. For accuracy and precision, low = 10 ng/mL, medium = 100 ng/mL, and high = 400 ng/mL.

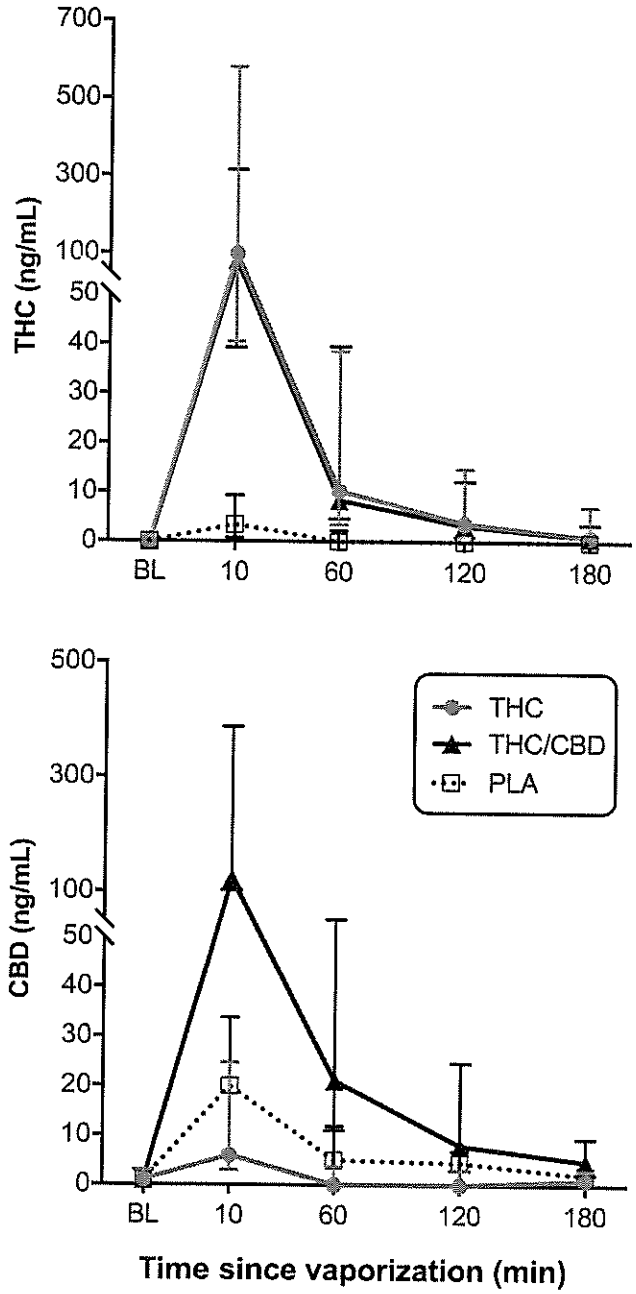

FIGURE 1 Median (Interquartile range) oral fluid THC and CBD concentrations over time as determined by confirmatory LC–MS/MS analysis following vaporization of THC-dominant (THC), THC/CBD-equivalent (THC/CBD), and placebo (PLA) cannabis [Colour figure can be viewed at wileyonlinelibrary.com]

3.4 | POCT device performance

Table 4 presents the test results (TP, TN, FP, FN) for the DW5s and DT5000 and overall device performance (sensitivity, specificity, and accuracy) at a 10 ng/mL confirmatory cut-off, while Table 5 describes these parameters when a 2 ng/mL and 1 ng/mL confirmatory cut-offs are applied. Figure 2 shows the LC–MS/MS quantified THC concentration corresponding to each test result.

3.5 | DrugWipe 5 s

A total of 165 DW5s test results involving four different time points were evaluated against LC–MS/MS verified oral fluid THC concentrations. With a 10 ng/mL confirmatory cut-off applied (Table 4), overall sensitivity, specificity, and accuracy were calculated as 45%, 92%, and 79%. Of the 30 test results that were positive, 9 false positives were detected with corresponding oral fluid THC concentrations ranging from 1.0 to 6.3 ng/mL. Of the 135 test results that were negative, 26 false negatives were detected, with corresponding oral fluid THC concentrations ranging from 10.1 to 1740 ng/mL. The occurrence of both false positives and false negatives was greatest at the 60-minute timepoint. As Table 5 shows, fewer false positives and more false negatives were observed with confirmatory cut-offs of 2 ng/mL and 1 ng/mL. Overall accuracy was greatest with a 10 ng/mL confirmatory cut-off applied.

3.6 | DrugTest 5000

A total of 163 DT5000 test results involving four different time points were evaluated relative to LC–MS/MS verified oral fluid THC concentrations. At a 10 ng/mL confirmatory cut-off (Table 4), overall sensitivity, specificity, and accuracy were calculated as 67%, 86%, and 80%. Of the 47 test results that were positive, 17 false positives were detected with corresponding oral fluid THC concentrations ranging from 0 to 6.4 ng/mL. Of the 116 test results that were negative, 15 false negatives were detected, with corresponding oral fluid THC concentrations ranging from 10.1 to 203 ng/mL. As with the DW5s, the incidence of false positives and false negatives were greatest at the 60-minute timepoint. Applying a confirmatory cut-off of 2 ng/mL or 1 ng/mL decreased the number of false positives but substantially increased the number of false negatives (Table 5). Overall accuracy was highest with a 10 ng/mL confirmatory cut-off.

4 | DISCUSSION

The present study was designed to provide insights into the accuracy and reliability of two commonly used POCT devices. We assessed the performance of the DW5s and DT5000 devices by comparing observed test results against confirmatory LC–MS/MS quantified oral fluid THC and CBD concentrations at various timepoints following controlled laboratory vaporization of three different cannabis types (placebo, THC-dominant, and THC/CBD-equivalent) using a within-subjects, crossover design.

Overall, our data confirm that oral fluid THC is a good indicator of very recent cannabis use.[20,24,34-36] As with previous studies,[24,25,34,36,37] oral fluid cannabinoid concentrations were maximal at the time point closest to vaporization (10 minutes) and declined rapidly thereafter. The high inter- and intra-individual variability in peak THC concentrations that we observed here is consistent with previous studies involving smoked or vaporized cannabis. For example, Toennes et al[38] reported peak oral fluid THC concentrations of 387–71,147 ng/mL in

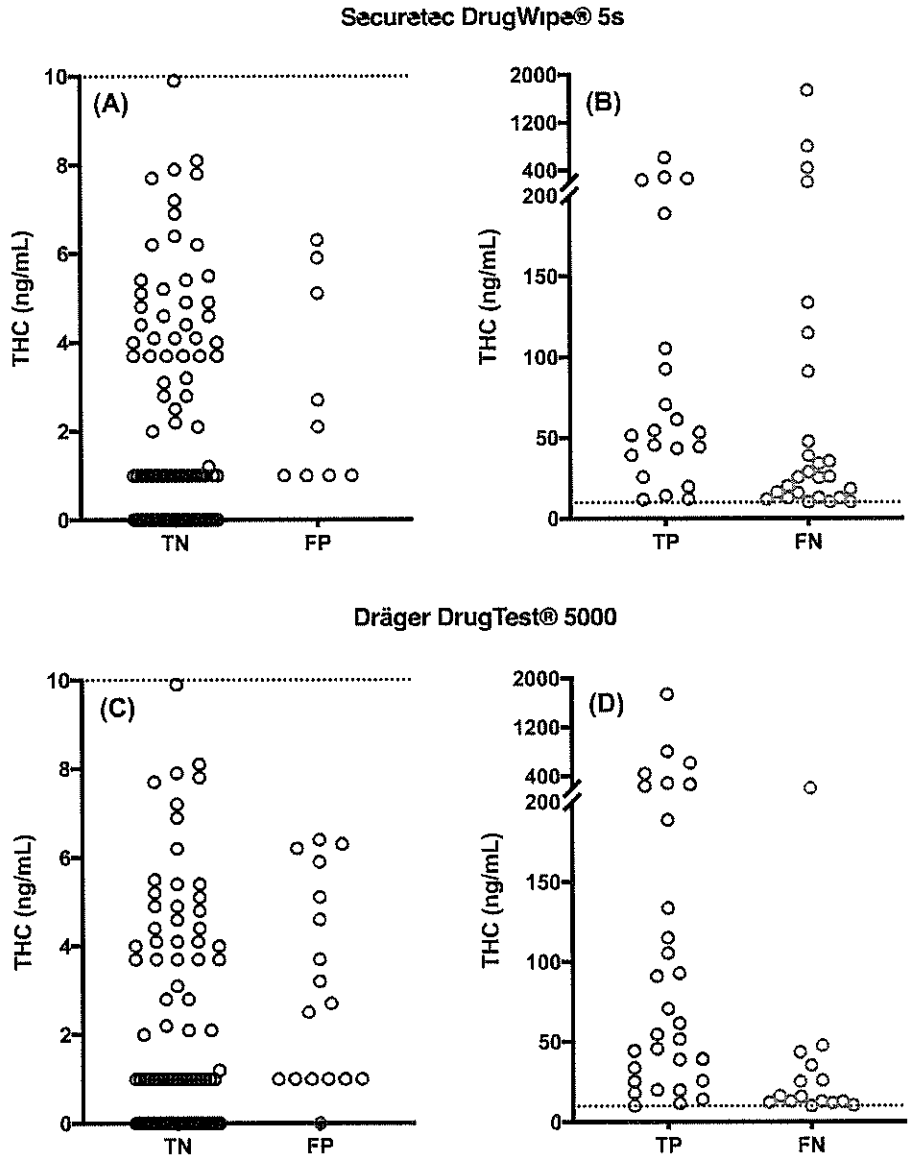

FIGURE 2 LC–MS/MS confirmed oral fluid THC concentrations corresponding to A, DrugWipe 5s true negative (TN) and false positive (FP) test results; B, DrugWipe 5s true positive (TP) and false negative (FN) test results; C, DrugTest 5000 TN and FP test results; and D, DrugTest 5000 TP and FN test results. The dotted line marks the screening cutoff (10 ng/mL) [Colour figure can be viewed at wileyonlinelibrary.com]

equivalent CBD and THC concentrations were examined here. In reality, cannabis chemovars and extracts may contain far higher ratios of CBD to THC. For example, the so-called 'light cannabis' varieties that are legally available through much of the EU must contain less than 0.2% THC but may contain up to 40% CBD.[29]

In a recent study, oral fluid THC concentrations reached 21.5 ng/mL at 30 minutes after participants smoked 1 g of 'light cannabis' containing 5.8% CBD (~ 58 mg) and 0.16% THC (~ 1.6 mg).[29] This matches and exceeds the observed THC C_{max} for several individuals in the present study and is well above the DW5s and DT5000 detection limit of 10 ng/mL. Consistent with this, it is notable that two participants in the present study had oral fluid THC concentrations >10 ng/mL after vaporizing placebo cannabis containing only minor amounts (< 1%) of THC. Taken together, these data suggest that consumption of high CBD cannabis with very low THC content may still result in a positive DW5s or DT5000 test result, even in the absence of any driving impairment.[32] This raises important questions around the validity of the MDT program and other DUIC programs involving POCT for oral fluid THC.

Both the DW5s and DT5000 showed high specificity, which is the proportion of confirmed negatives in cases where the POCT test result was negative. Sensitivity, however, was generally very poor. This reflects the high incidence of false negatives, where oral fluid samples corresponding to negative test results were found to have THC concentrations above the device screening cut-off (ie, > 10 ng/mL). The false positive rate was also concerning: 9 false positives were detected by the DW5s, and 17 by the DT5000. Only the DT5000 met DRUID criterion[9] for accuracy, which is the ability of a

REFERENCES

1. Ramaekers JG. Driving under the influence of cannabis: an increasing public health concern. *JAMA*. 2018;319(14):1433-1434.
2. Windle SB, Wade K, Filion KB, Kimmelman J, Thombs BD, Eisenberg MJ. Potential harms from legalization of recreational cannabis use in Canada. *Can J Public Health*. 2019;110(2):222-226.
3. Wong K, Brady JE, Li G. Establishing legal limits for driving under the influence of marijuana. *Inj Epidemiol*. 2014;1(1):26.
4. Watson TM, Mann RE. International approaches to driving under the influence of cannabis: a review of evidence on impact. *Drug Alcohol Depend*. 2016;169:148-155.
5. Gjerde H, Clausen GB, Andreassen E, Furuhaugen H. Evaluation of Dräger DrugTest 5000 in a naturalistic setting. *J Anal Toxicol*. 2018;42(4):248-254.
6. Musshoff F, Hokamp EG, Bott U, Madea B. Performance evaluation of on-site oral fluid drug screening devices in normal police procedure in Germany. *Forensic Sci Int*. 2014;238:120-124.
7. Van der Linden T, Wille SM, Ramirez-Fernandez M, Verstraete AG, Samyn N. Roadside drug testing: comparison of two legal approaches in Belgium. *Forensic Sci Int*. 2015;249:148-155.
8. Boorman M, Owens K. The Victorian legislative framework for the random testing drivers at the roadside for the presence of illicit drugs: an evaluation of the characteristics of drivers detected from 2004 to 2006. *Traffic Inj Prev*. 2009;10(1):16-22.
9. Blencowe T, Pehrsson A, Lillsunde P, et al. An analytical evaluation of eight on-site oral fluid drug screening devices using laboratory confirmation results from oral fluid. *Forensic Sci Int*. 2011;208(1–3):173-179.
10. Tang MH, Ching C, Poon S, et al. Evaluation of three rapid oral fluid test devices on the screening of multiple drugs of abuse including ketamine. *Forensic Sci Int*. 2018;286:113-120.
11. Gentili S, Solimini R, Tittarelli R, Mannocchi G, Busardò FP. A study on the reliability of an on-site oral fluid drug test in a recreational context. *J Anal Methods Chem*. 2016;2016:1-10.
12. Pehrsson A, Blencowe T, Vimpari K, Langel K, Engblom C, Lillsunde P. An evaluation of on-site oral fluid drug screening devices DrugWipe® 5+ and rapid STAT® using oral fluid for confirmation analysis. *J Anal Toxicol*. 2011;35(4):211-218.
13. Toennes SW, Schneider K, Wunder C, et al. Influence of ethanol on the pharmacokinetic properties of Δ9-tetrahydrocannabinol in oral fluid. *J Anal Toxicol*. 2013;37(3):152-158.
14. Wille SM, Samyn N, del Mar Ramírez-Fernández M, De Boeck G. Evaluation of on-site oral fluid screening using Drugwipe-5+®, RapidSTAT® and drug test 5000® for the detection of drugs of abuse in drivers. *Forensic Sci Int*. 2010;198(1–3):2-6.
15. Wille SM, Di Fazio V, Toennes SW, van Wel JH, Ramaekers JG, Samyn N. Evaluation of Δ9-tetrahydrocannabinol detection using DrugWipe5S® screening and oral fluid quantification after Quantisal™ collection for roadside drug detection via a controlled study with chronic cannabis users. *Drug Test Anal*. 2015;7(3):178-186.
16. Laloup M, Fernandez MD, Wood M, De Boeck G, Maes V, Samyn N. Correlation of Δ9-tetrahydrocannabinol concentrations determined by LC–MS–MS in oral fluid and plasma from impaired drivers and evaluation of the on-site Dräger DrugTest®. *Forensic Sci Int*. 2006;161(2–3):175-179.
17. Bosker WM, Theunissen EL, Conen S, et al. A placebo-controlled study to assess standardized field sobriety tests performance during alcohol and cannabis intoxication in heavy cannabis users and accuracy of point of collection testing devices for detecting THC in oral fluid. *Psychopharmacology (Berl)*. 2012;223(4):439-446.
18. Desrosiers NA, Milman G, Mendu DR, et al. Cannabinoids in oral fluid by on-site immunoassay and by GC-MS using two different oral fluid collection devices. *Anal Bioanal Chem*. 2014;406(17):4117-4128.
19. Desrosiers NA, Lee D, Schwope DM, et al. On-site test for cannabinoids in oral fluid. *Clin Chem*. 2012;58(10):1418-1425.
20. Swortwood MJ, Newmeyer MN, Abulseoud OA, et al. On-site oral fluid Δ 9-tetrahydrocannabinol (THC) screening after controlled smoked, vaporized, and oral cannabis administration. *Forensic Toxicol*. 2017;35(1):133-145.
21. Lintzeris N, Driels J, Elias N, Arnold JC, McGregor IS, Allsop DJ. Medicinal cannabis in Australia, 2016: the cannabis as medicine survey (CAMS-16). *Med J Aust*. 2018;209(5):211-216.
22. Russell C, Rueda S, Room R, Tyndall M, Fischer B. Routes of administration for cannabis use–basic prevalence and related health outcomes: a scoping review and synthesis. *Int J Drug Policy*. 2018;52:87-96.
23. Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. *J Psychoactive Drugs*. 2013;45(3):199-210.
24. Swortwood MJ, Newmeyer MN, Andersson M, Abulseoud OA, Scheidweiler KB, Huestis MA. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. *Drug Test Anal*. 2017;9(6):905-915.
25. Hartman RL, Anizan S, Jang M, et al. Cannabinoid disposition in oral fluid after controlled vaporizer administration with and without alcohol. *Forensic Toxicol*. 2015;33(2):260-278.
26. Zuardi A, de Souza Crippa J, Hallak J, Campos A, Guimarães F. The anxiolytic effects of Cannabidiol (CBD). In: *Handbook of Cannabis and Related Pathologies*. London, United Kingdom: Elsevier; 2017: e131-e139.
27. Zhornitsky S, Potvin S. Cannabidiol in humans—the quest for therapeutic targets. *Pharmaceuticals*. 2012;5(5):529-552.
28. Mannucci C, Navarra M, Calapai F, et al. Neurological aspects of medical use of Cannabidiol. *CNS Neurol Disord Drug Targets*. 2017;16(5):541-553.
29. Pacifici R, Pichini S, Pellegrini M, et al. Determination of cannabinoids in oral fluid and urine of "light cannabis" consumers: a pilot study. *Clin Chem Lab Med*. 2018;57(2):238-243.
30. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of Cannabidiol extracts sold online. *JAMA*. 2017;318(17):1708-1709.
31. Suraev A, Lintzeris N, Stuart J, et al. Composition and use of cannabis extracts for childhood epilepsy in the Australian community. *Sci Rep*. 2018;8(1):10154.
32. Arkell TR, Lintzeris N, Kevin RC, et al. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. *Psychopharmacology (Berl)*. 2019;236(9):2713-2724.
33. U.S. Department of Health and Human Services, F. a. D. A., Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), Bioanalytical Method Validation, Guidance for Industry. 2001; pp 1–22.
34. Lee D, Vandrey R, Mendu DR, Murray JA, Barnes AJ, Huestis MA. Oral fluid cannabinoids in chronic frequent cannabis smokers during ad libitum cannabis smoking. *Drug Test Anal*. 2015;7(6):494-501.
35. Andås HT, Krabseth H-M, Enger A, et al. Detection time for THC in oral fluid after frequent cannabis smoking. *Ther Drug Monit*. 2014;36(6):808-814.