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ORIGINAL ARTICLE

On-site oral fluid Δ^9-tetrahydrocannabinol (THC) screening after controlled smoked, vaporized, and oral cannabis administration

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Abstract Increasing driving under the influence of cannabis cases is an important short-term consequence of cannabis legalization. On-site oral fluid (OF) testing devices provide advantages for roadside drug screening, because OF Δ^9-tetrahydrocannabinol (THC) indicates more recent cannabis intake than urine, and it can be collected non-invasively by law enforcement personnel. THC presence in OF primarily results from oromucosal contamination during cannabis inhalation. To date, on-site OF devices were not investigated following edible cannabis. We evaluated sensitivity, specificity, and efficiency of the Dräger DrugTest® 5000 [DT5000] and Alere™ DDS®2 [DDS2] at various OF THC confirmatory cutoffs following controlled smoked, vaporized, and edible cannabis in frequent and occasional smokers. Times of last positive (t_{last}) were evaluated for each device, cutoff, and smoking group. At a 5 μg/L OF THC confirmation cutoff, overall performance criteria exceeded the recommended 80% for both devices. At lower THC confirmation cutoffs (1–2 μg/L), true positive results were maximized but sensitivity was <80%. When confirmation cutoffs were below manufacturers' screening cutoffs (5 μg/L DT5000, 25 μg/L DDS2), false negative results increased. No differences in t_{last} were observed for DT5000 between the three administration routes, but later t_{last} times were observed after smoking compared to vaporization with DDS2. Frequent smokers had significantly later median t_{last} (5 h) compared to occasional smokers (1.5–3.5 h) for all conditions. There were no true positive results at 44 and 50 h with the DT5000 and DDS2, respectively. OF screening followed by confirmatory OF analysis is an important strategy for investigations of driving under the influence of drugs, with these data improving interpretation of cannabinoid OF results.

Keywords Cannabinoids · Oral fluid · On-site testing · Dräger DrugTest® 5000 · Alere™ DDS®2 · Driving under the influence of drugs (DUID)

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Introduction

With increasing medicinal and legalized cannabis legislation in the US, driving under the influence of cannabis is a prominent public health and safety concern, as cannabis is associated with increased crash risk [1–4]. A recent 2013–2014 US survey revealed 12.6% of nighttime drivers' blood and/or oral fluid (OF) specimens were positive for Δ^9-tetrahydrocannabinol (THC) compared to 8.6% in 2007 [5], a 48% increase in prevalence in 6 years.

OF, once considered an alternative matrix, is increasingly popular for workplace, drug treatment, clinical, and forensic drug testing. In addition to advantages in specimen

collection over urine and blood, OF drug detection may indicate recent intake and, therefore, is a desirable biological matrix for driving under the influence of drugs (DUID) testing. Cannabinoid OF pharmacokinetics were thoroughly studied after controlled smoked [6–14] and vaporized administration [15]. Observed high (≤8503 μg/L) OF THC concentrations are primarily due to oromucosal contamination, with peak concentrations occurring during or immediately after inhalation [16]. The Substance Abuse and Mental Health Services Administration (SAMHSA) implemented a THC ≥2 μg/L confirmatory cutoff for detecting cannabis intake in workplace drug testing programs [17], while the European Union's Driving Under the Influences of Drugs, Alcohol, and Medicines (DRUID) project used a THC ≥1 μg/L OF confirmatory cutoff for DUID testing [18].

One of the strongest advantages of OF testing for DUID is the ability to screen specimens rapidly and sensitively at the roadside with on-site devices. DRUID suggested minimum performance of 80% for sensitivity, specificity, and efficiency for on-site devices [19]. The Dräger DrugTest® 5000 (DT5000, 5 μg/L THC cutoff; Lübeck, Germany) demonstrated 53.0–80.8 and 95.5–99.0% sensitivity, specificity, and accuracy with chromatographic OF THC 1 or 10 μg/L cutoffs, respectively, in OF collected from patients at drug addiction centers [20, 21]. Performance criteria of this device were 84.0–92.0% with a confirmatory OF THC 2 μg/L cutoff for drivers arrested for DUID [22]. A cohort of drivers stopped during roadside patrols showed improved parameters of 92.3–96.7% with a confirmatory OF THC 1 μg/L cutoff and confirmatory analysis performed with residual OF from the screening device swab [23]. Performance of the DT5000 also was evaluated in controlled research settings following smoked [24–26] and vaporized [15] cannabis; at least one performance criterion was <80% in these studies. Another available on-site screening device is the Alere™ DDS®2 (DDS2; Abingdon, UK), but fewer published performance data are available. A study of 38 OF samples from randomly stopped drivers demonstrated 100% agreement between its 25 μg/L THC cutoff screening results and a 2 μg/L THC confirmatory cutoff, but THC prevalence was low (only five drivers) [27].

Alternate cannabis administration routes, including inhalation via vaporization and consumption of edibles, are increasingly popular [28]. THC OF pharmacokinetic data following vaporized [15] or edible cannabis consumption [6, 29] are limited. Neither the DT5000 nor DDS2 were evaluated following oral cannabis administration. Previously, we described OF pharmacokinetics of THC, its metabolites, and minor cannabinoids following smoked, vaporized, and oral administration in frequent and occasional smokers [16]. Here, we characterize DT5000 and DDS2 performance in the same participant cohort.

Materials and methods

Participants

Healthy cannabis users (18–50 years) provided written informed consent to participate in this previously described National Institute on Drug Abuse (NIDA) Intramural Research Program Institutional Review Board-, FDA-, and DEA-approved study [16, 30]. All participants underwent extensive medical and psychological evaluations. Inclusion criteria were based on self-reported cannabis intake (≥2×/month, but <3×/week for occasional smokers or ≥5×/week for frequent smokers). Pregnant and nursing women were excluded and pregnancy tests were administered at screening and admission for each session to women with reproductive potential.

Study design

The study was randomized, double blind, and placebo-controlled with a crossover and double-dummy design. Participants entered the secure research unit ~19 h before dosing to preclude acute intoxication. Cannabis cigarettes were obtained through the NIDA Drug Supply Program. Active cigarettes (0.734 ± 0.05 g) contained 6.9 ± 0.95% (~50.6 mg) THC. Placebo cigarettes (0.713 ± 0.05 g) contained 0.001 ± 0.000% THC. Throughout four dosing sessions, participants were administered one active or placebo brownie followed by one active or placebo cigarette or one active or placebo vaporized ground cannabis dose (210 °C, Volcano® Medic, Storz & Bickel, Tuttlingen, Germany). No more than one active dose was administered per session. Brownies were prepared with Duncan Hines® Double Fudge brownie mix according to the manufacturer's instructions with addition of ground cannabis to wet batter [16, 30]. Oral and inhaled doses were each consumed ad libitum within 10 min. Frequent smokers remained on the unit 72 h post-dose and were discharged for ≥72 h between dosing sessions to reduce the incidence of cannabis withdrawal. Occasional smokers remained on the unit 54 h post-dose but had the option of remaining on the unit for multiple sessions depending on self-reported smoking frequency.

OF was collected with Quantisal™ collection device (Immunalysis, Pomona, CA, USA) followed by the DT5000 or DDS2 on-site OF screening devices (randomly assigned per participant). Paired OF samples were collected on admission (−19 h), before initiation of smoking/vaporization (baseline, −1.5 h), and at 0.17, 1.5, 3.5, 5, 8, 10, 12, 14, 20, 26, 32, 38, 44, and 50 h after smoking or vaporization initiation for all participants; at 54 h for occasional smokers only; and 56, 62, 68, and 72 h for frequent smokers only.

The Quantisal device has a volume adequacy indicator for collection of 1.0 ± 0.1 mL OF. The pad was stored upright in the elution/stabilizing buffer at 4 °C for >12 h prior to pad removal; the buffer/OF mixture was transferred to polypropylene cryotubes and stored at 4 °C until analysis. The DT5000 cassette was swiped throughout the mouth to collect 270 ± 40 µL OF; the DDS2 device collected ~600 µL OF. Both devices have volume adequacy indicators, with OF collected until the indicators turned blue or 5 min elapsed, whichever occurred first. Nothing was placed in the mouth for 10 min prior to any OF collection.

Oral fluid analysis

DT5000 and DDS2 OF specimens were analyzed immediately after collection on their respective analyzers with qualitative positive or negative results based on the manufacturer's assigned 5 or 25 µg/L THC screening cutoff, respectively. Quantisal OF specimens were quantified within 1 month (based on previous OF cannabinoid stability studies [31, 32]) for THC by a previously published liquid chromatography–tandem mass spectrometry (LC–MS/MS) method with 0.2 µg/L limit of quantification (LOQ) [33]. Inter-assay accuracy and precision were 88.1–106 and 5.8–8.2% coefficient of variation (CV), respectively ($n = 92$).

Data analysis

Qualitative DT5000 and DDS2 results were compared to concurrently collected quantitative Quantisal OF results. A true positive (TP) sample screened positive and confirmed positive for THC; a true negative (TN) sample screened and confirmed negative for THC. A false positive (FP) sample screened positive but THC was not detected above the designated cutoff in the confirmation test, and a false negative (FN) screened negative, but THC was confirmed above the specified cutoff in the confirmation test. Performance parameters (%) were calculated by the following formulae: sensitivity = [TP/(TP + FN)] × 100; specificity = [TN/(TN + FP)] × 100; and efficiency = [(TP + TN)/total] × 100. These parameters were determined at THC LOQ (0.2 µg/L), 1, 2, and 5 µg/L (both devices), and 25 µg/L (DDS2 only). Suggested optimal device performance criteria are ≥80% sensitivity, specificity, and efficiency [19]. Results were analyzed overall (all participants, all routes) and stratified by smoking group (all routes together) and by route (all participants together). Times of last detection (t_{last}) were compared between devices and between smoking groups at various cutoffs; results were stratified by route and analyzed via Mann–Whitney U tests. Finally, t_{last} between administration routes (within a single device) were evaluated via Friedman one-way ANOVA with Dunn's multiple comparison adjustment; $p < 0.05$ was considered significant.

Results

Participants

Demographics for 11 frequent and nine occasional cannabis smokers are summarized in Supplemental Table 1. Participants were 19–46 years old, 75% male, and 75% African Americans. Participant K was originally admitted as an occasional smoker, but later reclassified as a frequent smoker based on baseline and post-dose blood cannabinoid pharmacokinetics [16, 30]. Participant H smoking frequency at admission to session 1 was inconsistent with self-reported frequency at screening, but frequencies reported on admission to subsequent sessions were consistent with self-reported frequency at screening; his demographic data were not included in summary statistics. Frequent smokers were all African Americans, began smoking at a significantly younger age, smoked significantly more frequently over the previous 14 days, and smoked significantly more per smoking occasion.

Five frequent and five occasional smokers produced 551 paired DT5000-Quantisal results, and six frequent and four occasional smokers produced 545 paired DDS2-Quantisal results.

On-site device performance

A summary of device performance (sensitivity, specificity, efficiency) evaluated at different confirmatory cutoffs for DT5000 and DDS2 are described in Table 1.

Overall device performance

At the THC method's LOQ (0.2 µg/L), DT5000 and DDS2 demonstrated high specificity (each 99.3%), but low sensitivities (36.9 and 36.5%) and efficiencies (53.9 and 53.6%), respectively. Sensitivity and efficiency were <80% at a THC ≥1 µg/L cutoff; however, with a THC ≥2 µg/L cutoff, 37 and 50 previous FN results from the DT5000 and DDS2, respectively, became TN, improving efficiencies to >80%, but sensitivities remained low due to confirmation cutoffs below the screening cutoffs. When evaluated at a THC ≥5 µg/L cutoff, all performance criteria were ≥80%. Additionally, performance criteria for the DDS2 were >80% when evaluated with a THC ≥25 µg/L cutoff. Although optimal performances were observed with a THC ≥5 µg/L cutoff, more TP results were observed with THC ≥1 and 2 µg/L cutoffs.

Table 1 Performance characteristics for Dräger DrugTest 5000 (DT5000, 5 μg/L cutoff) and Alere DDS2 (DDS2, 25 μg/L cutoff) screening devices with different Δ^9-tetrahydrocannabinol (THC) oral fluid confirmation cutoffs overall (all participants and all routes), by smoking group (all routes), and by route (following controlled smoked, vaporized, or oral administration of 6.9% THC cannabis) up to 72 and 54 h post-dose for 11 frequent and nine occasional smokers, respectively

Quantitative THC confirmation cutoff (μg/L)	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	Efficiency (%)
Overall (all participants, all routes)							
DT5000 ($n = 551$)							
THC ≥5	116	373	33	29	80.0	91.9	88.7
THC ≥2 (SAMHSA)	138	332	11	70	66.3	96.8	85.3
THC ≥1 (DRUID)	145	295	4	107	57.5	98.7	79.9
THC ≥0.2 (LOQ)	148	149	1	253	36.9	99.3	53.9
DDS2 ($n = 545$)							
THC ≥25	70	398	76	1	98.5	84.0	85.9
THC ≥5	124	376	22	23	84.4	94.5	91.7
THC ≥2 (SAMHSA)	138	325	8	74	65.1	97.6	85.0
THC ≥1 (DRUID)	141	275	5	124	53.2	98.2	76.3
THC ≥0.2 (LOQ)	145	147	1	252	36.5	99.3	53.6
Frequent smokers (all routes)							
DT5000 ($n = 300$)							
THC ≥5	87	170	20	23	79.1	89.5	85.7
THC ≥2 (SAMHSA)	104	137	3	56	65.0	97.9	80.3
THC ≥1 (DRUID)	107	111	0	82	56.6	100	72.7
THC ≥0.2 (LOQ)	107	29	0	164	39.5	100	45.3
DDS2 ($n = 345$)							
THC ≥25	49	244	51	1	98.0	82.7	84.9
THC ≥5	83	231	17	14	85.6	93.1	91.0
THC ≥2 (SAMHSA)	96	191	4	54	64.0	97.9	83.2
THC ≥1 (DRUID)	98	153	2	92	51.6	98.7	72.8
THC ≥0.2 (LOQ)	100	75	0	170	37.0	100	50.7
Occasional smokers (all routes)							
DT5000 ($n = 251$)							
THC ≥5	29	203	13	6	82.9	94.0	92.4
THC ≥2 (SAMHSA)	34	195	8	14	70.8	96.1	91.2
THC ≥1 (DRUID)	38	184	4	25	60.3	97.9	88.4
THC ≥0.2 (LOQ)	41	120	1	89	31.5	99.2	64.1
DDS2 ($n = 200$)							
THC ≥25	21	154	25	0	100	86.0	87.5
THC ≥5	41	145	5	9	82.0	96.7	93.0
THC ≥2 (SAMHSA)	42	134	4	20	67.7	97.1	88.0
THC ≥1 (DRUID)	43	122	3	32	57.3	97.6	82.5
THC ≥0.2 (LOQ)	45	72	1	82	35.4	98.6	58.5
Smoked (all participants)							
DT5000 ($n = 184$)							
THC ≥5	45	114	11	14	76.3	91.2	86.4
THC ≥2 (SAMHSA)	51	95	5	33	60.7	95.0	79.3
THC ≥1 (DRUID)	55	87	1	41	57.3	98.9	77.2
THC ≥0.2 (LOQ)	56	41	0	87	39.2	100	52.7
DDS2 ($n = 183$)							
THC ≥25	27	118	37	1	96.4	76.1	79.2
THC ≥5	56	112	8	7	88.9	93.3	91.8
THC ≥2 (SAMHSA)	62	96	2	23	72.9	98.0	86.3

Table 1 continued

Quantitative THC confirmation cutoff (μg/L)	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	Efficiency (%)
THC ≥1 (DRUID)	63	81	1	38	62.4	98.8	78.7
THC ≥0.2 (LOQ)	63	42	1	77	45.0	97.7	57.4
Vaporized (all participants)							
DT5000 ($n = 182$)							
THC ≥5	31	131	8	12	72.1	94.2	89.0
THC ≥2 (SAMHSA)	35	117	4	26	57.4	96.7	83.5
THC ≥1 (DRUID)	36	103	3	40	47.4	97.2	76.4
THC ≥0.2 (LOQ)	38	60	1	83	31.4	98.4	53.8
DDS2 ($n = 182$)							
THC ≥25	20	147	15	0	100	90.7	91.8
THC ≥5	34	138	1	9	79.1	99.3	94.5
THC ≥2 (SAMHSA)	35	118	0	29	54.7	100	84.1
THC ≥1 (DRUID)	35	101	0	46	43.2	100	74.7
THC ≥0.2 (LOQ)	35	55	0	92	27.6	100	49.5
Oral (all participants)							
DT5000 ($n = 185$)							
THC ≥5	40	128	14	3	93.0	90.1	90.8
THC ≥2 (SAMHSA)	52	120	2	11	82.5	98.4	93.0
THC ≥1 (DRUID)	54	105	0	26	67.5	100	85.9
THC ≥0.2 (LOQ)	54	48	0	83	39.4	100	55.1
DDS2 ($n = 180$)							
THC ≥25	23	133	24	0	100	84.7	86.7
THC ≥5	34	126	13	7	82.9	90.6	88.9
THC ≥2 (SAMHSA)	41	111	6	22	65.1	94.9	84.4
THC ≥1 (DRUID)	43	93	4	40	51.8	95.9	75.6
THC ≥0.2 (LOQ)	47	50	0	83	36.2	100	53.9

TP true positive, *TN* true negative, *FP* false positive, *FN* false negative, *THC* Δ^9-tetrahydrocannabinol, *SAMHSA* Substance Abuse and Mental Health Services Administration, *DRUID* Driving Under the Influence of Drugs, Alcohol, and Medicines, *LOQ* limit of quantification

Device performance by smoking group

Because of differences in the time courses for frequent (72 h post-dose) and occasional (54 h) smokers, data for the groups are described separately. For frequent smokers, specificity for both devices was >80% with all cutoffs while efficiencies were >80% only for THC ≥2–25 μg/L cutoffs. DT5000 sensitivity in frequent smokers approached but never exceeded 80% (79.1% with THC ≥5 μg/L cutoff); sensitivities for DDS2 at THC ≥5 and ≥25 μg/L cutoffs were 85.6 and 98.0%, respectively.

Specificities and efficiencies for both devices with occasional smokers were >80% at all cutoffs, except efficiencies at the analytical LOQ. Sensitivities exceeded 80% for DT5000 only with a THC ≥5 μg/L cutoff, and for DDS2 with THC ≥5 and ≥25 μg/L cutoffs. As above, greater TP results were observed with confirmation cutoffs below the screening cutoffs.

Device performance by administration route

Following smoking, DT5000 efficiency was ≥80% with only a THC ≥5 μg/L cutoff; for DDS2, efficiencies were acceptable only at THC ≥2 and 5 μg/L cutoffs, while acceptable sensitivities were observed with THC ≥5 and 25 μg/L cutoffs. DT5000 performance following vaporization was similar to that following smoking: efficiency was ≥80% at THC ≥2 and 5 μg/L cutoffs, and sensitivity approached but never exceeded 80%. DDS2 specificity and efficiency were ≥80% with more cutoffs than after smoking; however, sensitivities were generally <80%. Finally, following oral administration, all DT5000 performance criteria were acceptable with the THC ≥2 and ≥5 μg/L cutoffs. For DDS2, all performance criteria were >80% only with the THC ≥5 and ≥25 μg/L cutoffs.

Detection rates and times

A comparison of DT5000 and DDS2 screening t_{last} alone and with different OF THC confirmation cutoffs is presented in Table 2. One occasional smoker never screened positive by DT5000 after the vaporized dose. DT5000 and DDS2 t_{last} were not significantly different with any cutoff when analyzed overall or by route.

When comparing routes for each device separately (data table not shown), no statistical differences in median DT5000 t_{last} were observed between any routes at any cutoff, whereas significant differences were observed with cutoffs for DDS2. When screening with the DDS2 alone and in combination with a THC ≥0.2 or ≥1 μg/L confirmation cutoff, multiple comparisons revealed significant differences between smoked and vaporized ($p = 0.022$) cannabis only. Multiple comparisons for THC ≥2 μg/L were similar, with a significant difference in t_{last} between smoked and vaporized ($p = 0.022$) observed. Finally, smoked and vaporized t_{last} times at THC ≥5 μg/L were significantly different, and a significant difference between smoked and oral ($p = 0.008$) also was observed.

When examining differences between occasional and frequent cannabis smokers, t_{last} data were analyzed by group regardless of screening device, as no significant differences were observed between devices (Table 2), and because sample sizes for frequent and occasional smokers were too small if stratified by devices. Comparisons of frequent and occasional smokers' OF THC t_{last} overall and by route are summarized in Table 3. Overall, frequent smokers had significantly later median t_{last} (5 h for all cutoffs) compared to occasional smokers (1.5–3.5 h) for all

Table 2 Median (range) time of last detection for Dräger DrugTest 5000 (DT5000, 5 μg/L THC cutoff) and Alere DDS2 (DDS2, 25 μg/L THC cutoff) oral fluid screening devices alone and with different THC oral fluid confirmation cutoffs overall (all participants and all routes) and by route (following controlled smoked, vaporized, or oral administration of 6.9% THC cannabis) for 11 frequent and nine occasional smokers

Quantitative confirmation cutoff (μg/L)	Median (range) t_{last} (h)		p value (DT5000 vs. DDS2)[a]
	DT5000	DDS2	
Overall (all participants, all routes)			
n	29[b]	30	
Screen positive only	5.0 (0.25–26)	4.3 (0.25–20)	0.9787
THC ≥5	3.5 (0.25–20)	3.5 (0.25–20)	0.6893
THC ≥2 (SAMHSA)	3.5 (0.25–26)	3.5 (0.25–20)	0.9729
THC ≥1 (DRUID)	5.0 (0.25–26)	4.3 (0.25–20)	0.9666
THC ≥0.2 (LOQ)	5.0 (0.25–26)	4.3 (0.25–20)	0.9787
Smoked (all participants)			
n	10	10	
Screen positive only	6.5 (0.25–20)	9.0 (1.5–20)	0.3783
THC ≥5	5.0 (0.25–20)	7.5 (1.5–20)	0.2580
THC ≥2 (SAMHSA)	5.0 (0.25–20)	7.5 (1.5–20)	0.3390
THC ≥1 (DRUID)	6.5 (0.25–20)	9.0 (1.5–20)	0.3573
THC ≥0.2 (LOQ)	6.5 (0.25–20)	9.0 (1.5–20)	0.3783
Vaporized (all participants)			
n	9[b]	10	
Screen positive only	1.5 (1.5–26)	1.5 (0.25–10)	0.9200
THC ≥5	1.5 (0.25–12)	1.5 (0.25–10)	0.6999
THC ≥2 (SAMHSA)	1.5 (1.5–26)	1.5 (0.25–10)	0.9200
THC ≥1 (DRUID)	1.5 (1.5–26)	1.5 (0.25–10)	0.9200
THC ≥0.2 (LOQ)	1.5 (1.5–26)	1.5 (0.25–10)	0.9200
Oral (all participants)			
n	10	10	
Screen positive only	5.0 (1.5–20)	4.3 (1.5–5)	0.3188
THC ≥5	4.3 (1.5–14)	1.5 (1.5–5)	0.1721
THC ≥2 (SAMHSA)	5.0 (1.5–20)	3.5 (1.5–5)	0.1732
THC ≥1 (DRUID)	5.0 (1.5–20)	4.3 (1.5–5)	0.3188
THC ≥0.2 (LOQ)	5.0 (1.5–20)	4.3 (1.5–5)	0.3188

t_{last} time of last detection

[a] Mann–Whitney U test was used to compare DT5000 vs. DDS2 results for each condition

[b] One occasional smoker never had a positive DT5000 screening result after the vaporized dose

confirmatory cutoffs. After smoking, frequent smokers' median t_{last} (10 h) were significantly later than occasional smokers (3.5 h) only when confirming at THC ≥2 and 5 μg/L. No significant differences in THC OF t_{last} were observed between groups after vaporized or oral cannabis administration.

Detection rates of positive screening tests alone (DT5000, 5 μg/L THC cutoff and DDS2, 25 μg/L THC cutoff) and in combination with different confirmatory cutoffs (TP) are presented overall, by device, and by smoking group in Figs. 1, 2, and 3, respectively. Overall, positive results by screening only tests lasted until 44 and 50 h for DT5000 and DDS2, respectively. There were no TP results with THC ≥0.2, 1, and 2 μg/L cutoffs at 44, 44, and 32 h, respectively, for DT5000 and at 50, 26, and 26 h, respectively, for DDS2 (Fig. 1); all tests from both devices were negative at 26 h with a THC ≥5 μg/L cutoff. When comparing the two screening devices by administration route, no TP occurred for DT5000 after any route at 44 and 32 h with THC ≥1 and 2 μg/L cutoffs, respectively (Fig. 2). For DDS2, no TP were observed after smoking or oral dosing at 26 h, and after vaporization at 12 h with THC ≥1 and 2 μg/L cutoffs. Sporadic positive tests (0.5–4.1 μg/L THC) occurred with the DDS2 device for two participants 12–20 h following the oral dose. A THC ≥5 μg/L cutoff did not shorten detection windows after smoking or oral dosing

Table 3 Median (range) time of last detection for frequent and occasional smokers for screening results alone and with different THC oral fluid confirmation cutoffs overall (both screening devices and all routes) and by route (following controlled smoked, vaporized, or oral administration of 6.9% THC cannabis) for 11 frequent and nine occasional smokers

Quantitative confirmation cutoff (μg/L)	Median (range) t_{last} (h)		p value (frequent vs. occasional)[a]
	Frequent	Occasional	
Overall (both devices, all routes)			
n	33	26	
Screen positive only	5.0 (0.25–26)	3.5 (0.25–20)	**0.0311**[b]
THC ≥5	5.0 (0.25–20)	1.5 (0.25–20)	**0.0154**
THC ≥2 (SAMHSA)	5.0 (0.25–26)	3.5 (0.25–20)	**0.0116**
THC ≥1 (DRUID)	5.0 (0.25–26)	3.5 (0.25–20)	**0.0281**
THC ≥0.2 (LOQ)	5.0 (0.25–26)	3.5 (0.25–20)	**0.0311**
Smoked (both devices)			
n	11	9	
Screen positive only	10 (0.25–20)	5.0 (0.25–20)	0.1170
THC ≥5	10 (0.25–20)	3.5 (0.25–20)	**0.0295**[b]
THC ≥2 (SAMHSA)	10 (0.25–20)	3.5 (0.25–20)	**0.0318**
THC ≥1 (DRUID)	10 (0.25–20)	5.0 (0.25–20)	0.0928
THC ≥0.2 (LOQ)	10 (0.25–20)	5.0 (0.25–20)	0.1170
Vaporized (both devices)			
n	11	8[c]	
Screen positive only	1.5 (1.5–26)	1.5 (0.25–8)	0.1207
THC ≥5	1.5 (1.5–12)	1.5 (0.25–8)	0.0694
THC ≥2 (SAMHSA)	1.5 (1.5–26)	1.5 (0.25–8)	0.1207
THC ≥1 (DRUID)	1.5 (1.5–26)	1.5 (0.25–8)	0.1207
THC ≥0.2 (LOQ)	1.5 (1.5–26)	1.5 (0.25–8)	0.1207
Oral (both devices)			
n	11	9	
Screen positive only	5.0 (1.5–20)	3.5 (3.5–5)	0.2439
THC ≥5	3.5 (1.5–14)	3.5 (1.5–5)	0.9100
THC ≥2 (SAMHSA)	5.0 (1.5–20)	3.5 (1.5–5)	0.3158
THC ≥1 (DRUID)	5.0 (1.5–20)	3.5 (3.5–5)	0.2439
THC ≥0.2 (LOQ)	5.0 (1.5–20)	3.5 (3.5–5)	0.2439

[a] Mann–Whitney *U* test was used to compare frequent vs. occasional smokers' results for each condition

[b] The *p* values less than 0.05 are shown in boldface letters

[c] One occasional smoker never had a positive DT5000 screening result after the vaporized dose

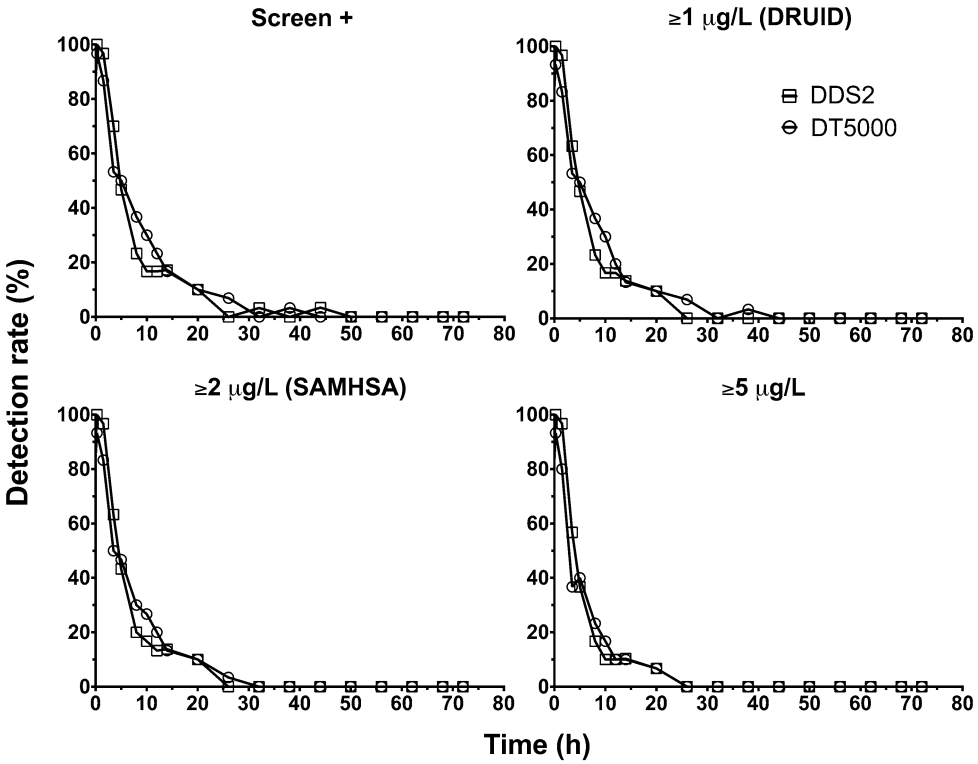

Fig. 1 Overall oral fluid (OF) detection rates after controlled smoked, vaporized, and oral cannabis [50.6 mg Δ^9-tetrahydrocannabinol (THC)] in 11 frequent and nine occasional smokers in samples collected with Dräger DrugTest 5000 (DT5000) or Alere DDS2 (DDS2) on-site screening test and Quantisal confirmation devices up to 72 h post-dose. Detection rates are shown for positive screening tests and true positive results at European Union's Driving Under the Influences of Drugs, Alcohol, and Medicines (DRUID, 1 μg/L), Substance Abuse and Mental Health Services Association (SAMHSA, 2 μg/L), and 5 μg/L confirmatory OF THC cutoffs

for DT5000, but no TP was observed at 14 h after vaporization; detection windows after smoking and vaporization with the DDS2 were similar with a THC ≥5 μg/L cutoff, but no TP after oral dosing was observed at 8 h. When examining detection windows by smoking group, no TP were observed for frequent smokers at 44 and 32 h after any administration with THC ≥1 and 2 μg/L cutoffs, respectively (Fig. 3); detection windows were shortened to 26 h when frequent smokers' OF samples were confirmed with THC ≥5 μg/L. For occasional smokers, no TP were observed 26 h after smoked cannabis administration when confirming with THC ≥1, 2, and 5 μg/L; detection windows were 10 and 8 h for vaporized and oral administration, respectively, regardless of confirmatory cutoffs.

Discussion

Few data are available for examining DT5000 on-site OF screening device performance following controlled vaporized or oral cannabis administration, while no data are available for the DDS2 screening device following any controlled cannabis administration. We previously published cannabinoid OF pharmacokinetics for this cohort [16]. Here, we describe paired on-site screening results with confirmatory Quantisal OF results in frequent and occasional smokers following controlled smoked, vaporized, and oral cannabis administration.

Overall, the OF on-site screening devices performed similarly in terms of sensitivity, specificity, and efficiency. Suggested performance criteria (≥80%) were generally met, regardless of smoking group, device or administration route, when confirming at OF THC ≥5 μg/L. However, sensitivity always decreased when confirming THC at the lower THC ≥1 and 2 μg/L cutoffs (Table 1). DT5000 sensitivity with a THC ≥5 μg/L cutoff was <80% in several other roadside and controlled administration studies [15, 20, 22, 26]. Reports of high sensitivity were often only examining a few hours after drug intake [34, 35], while we report up to 54 and 72 h for occasional and frequent smokers, respectively. The longer performance studies are conducted post-dose, the greater the opportunity for obtaining FN results when confirming below the manufacturers' screening cutoffs; however, TP results were maximized at these lower cutoffs (Table 1). It is important to understand device performance over short and long time frames, as times after cannabis intake and doses are generally not known in DUID cases.

Despite differences in screening cutoffs (5 vs. 25 μg/L THC for DT5000 vs. DDS2), the two devices exhibited similar performance criteria. Additionally, no significant differences for t_{last} were observed between devices (Table 2). There were no significant differences in t_{last} between routes for the DT5000. However, shortened t_{last} were observed after vaporization compared to smoking with the DDS2 for all evaluated cutoffs; a significant difference

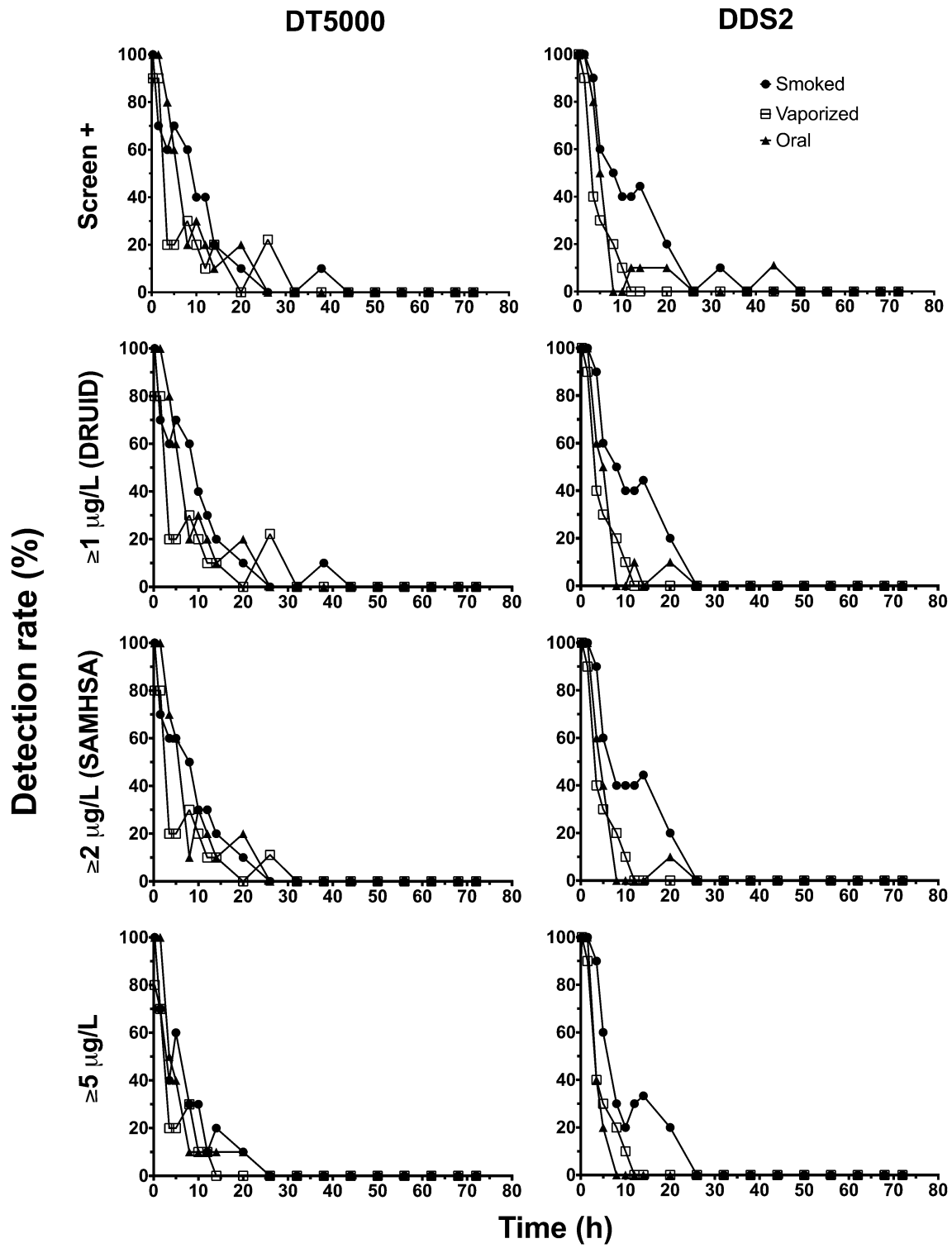

Fig. 2 OF detection rates by collection devices after controlled smoked, vaporized, and oral cannabis (50.6 mg THC) in 11 frequent and nine occasional smokers in samples collected with Dräger DrugTest 5000 (DT5000, *left*) or Alere DDS2 (DDS2, *right*) on-site screening test and Quantisal confirmation devices up to 72 h post-dose

was observed between smoked and oral doses when confirming at THC ≥5 μg/L (Fig. 2). It was noted previously that mean OF THC concentrations following vaporization trended lower (although not significantly) than those produced after smoking, but THC concentrations were significantly higher after inhaled (smoked and vaporized doses)

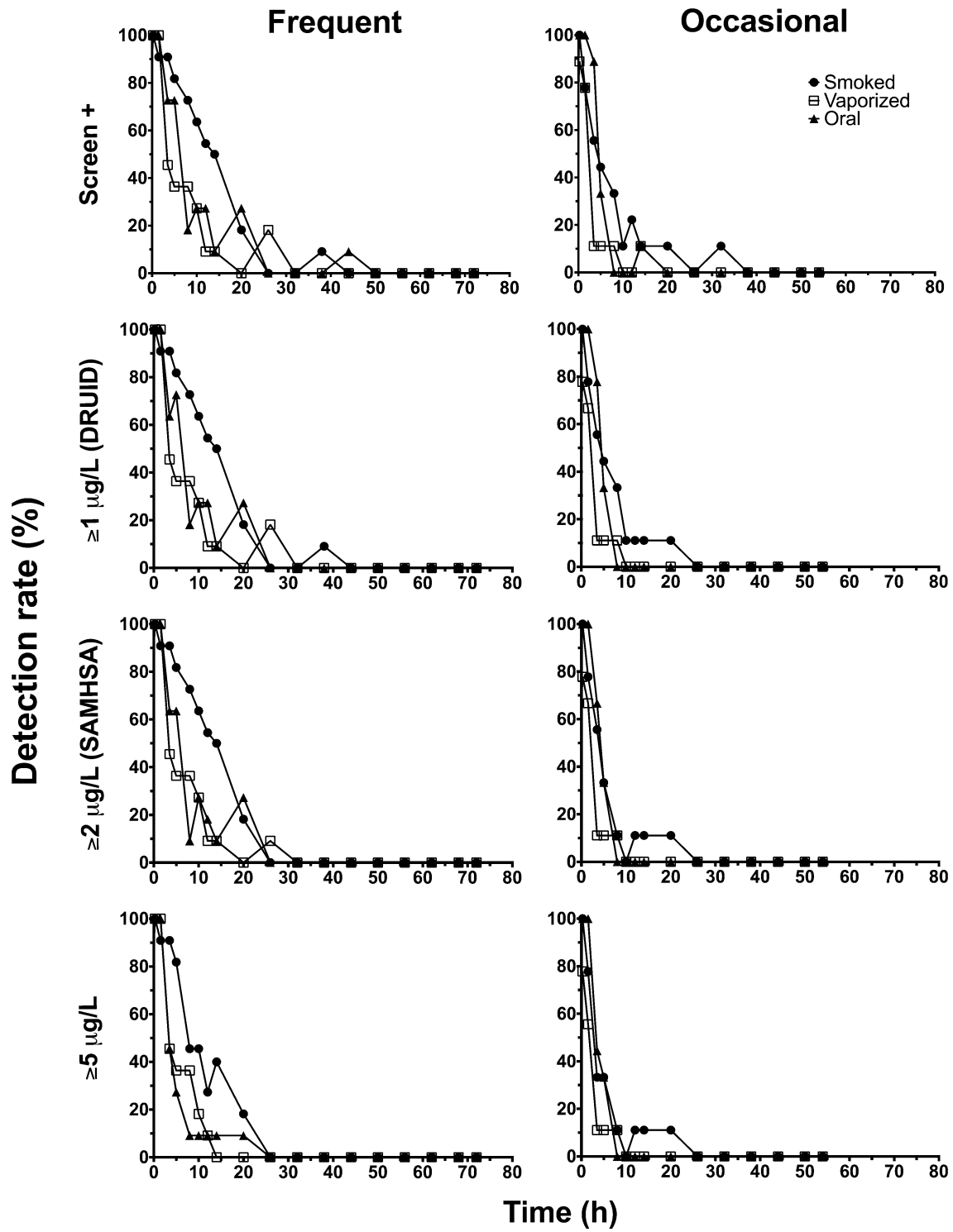

Fig. 3 OF detection rates by the frequent and occasional groups after controlled smoked, vaporized, and oral cannabis (50.6 mg THC) in 11 frequent (*left*) and nine occasional (*right*) smokers in samples collected with Dräger DrugTest 5000 or Alere DDS2 on-site screening test and Quantisal confirmation devices up to 72 h post-dose

compared to the oral dose [16]. These differences in t_{last} were observed with DDS2, but not with DT5000 (Fig. 2), likely due to the higher DDS2 screening cutoff.

Interpreting cannabinoid concentrations is difficult as different smoking histories produce different pharmacokinetic profiles. In this study, we examined differences

between frequent and occasional cannabis users. Because no differences between devices were observed (Table 2), we analyzed each group's samples from both on-site devices together. There was insufficient sample size to execute proper statistical evaluations between groups for each device separately. Overall t_{last} times were significantly later for frequent smokers for all evaluated conditions. After smoking, frequent smokers' t_{last} times were later compared to occasional smokers' when confirming at higher THC cutoffs (2 and 5 μg/L) (Table 3). Mean (range) OF THC C_{max} following smoking [2789 (141–8503) μg/L] and vaporization [1874 (68.6–7373) μg/L] were generally higher in frequent smokers (not significantly) compared to occasional smokers [837 (81.4–5914) and 845 (7.6–3279) μg/L, respectively] [16]. Higher observed THC concentrations in frequent smokers correspond to the observed higher detection rates and longer detection times (Fig. 3). According to our analytical assays with low LOQ, 6/11, 3/11, and 2/11 frequent and 0/9, 1/9, and 1/9 occasional smokers' Quantisal samples were still THC positive 72 and 54 h after smoked, vaporized, and oral cannabis, respectively, making it difficult to statistically assess differences in t_{last} between groups at lower THC cutoffs [16].

It is critically important to compare OF THC detection windows to windows of performance impairment. If these windows are nearly the same, then OF THC could be a good marker for DUID. If the OF THC detection windows are shorter than windows of performance impairment, OF THC will miss impairment cases; if they are longer than impairment windows, they may reliably identify past cannabis intake, but necessitate another method to identify cannabis impairment (e.g., standardized field sobriety tests performed by trained police officers).

The primary purpose of an on-site screening test is to identify as many TP cases as possible, and secondarily to avoid identification of FP tests (those that do not confirm). The performance of an OF THC on-site screening test to accomplish this goal is dependent on the quality of the on-site testing system, confirmation cutoff, time since cannabis intake, cannabis administration route, and use history. While TP were observed for the DT5000 device up to 44 h post-dose, detection rates fell below 20% within 20 h, regardless of route or confirmation cutoff (Fig. 1). The detection window for the DDS2 after smoking was similar to the DT5000, but shorter following vaporized and oral cannabis (Fig. 2). Positive results following previous consecutive negatives observed at 44 h post-dose (Figs. 2, 3) coincided with the first collection of the day (6 a.m.) and could be the result of previous THC deposits releasing into oral fluid as stimulated by the collection device. This phenomenon requires additional research to determine if this is a consistent result and elucidate why this might occur. A combination of higher DDS2 screening cutoff and lower THC concentrations produced by vaporized and oral cannabis can account for the shortened detection windows. When considering smoking group and route regardless of screening device, detection windows could be shortened to 14–20 h for frequent smokers when confirming with a THC ≥5 μg/L cutoff. Occasional smokers exhibited overall shorter detection windows as expected due to lower OF THC concentrations compared to frequent smokers (Fig. 3). However, when investigating DUID, smoking frequency, time since last use, and dosage will not be available, and investigators will be tasked with interpreting a single OF specimen. In order to use OF THC concentrations for DUID, higher confirmatory cutoffs (5 μg/L) appear preferable, but also must be considered alongside standardized field sobriety test results and observed poor driving behavior. For purposes of workplace testing, emergency room, drug treatment, and drug court testing, longer detection windows are desired and require lower OF THC confirmatory cutoffs (1–2 μg/L). As OF cannabinoid concentrations generally reflect recent (within 1 day) use, confirmatory cutoffs should be selected to best serve the purpose of the OF drug testing.

Conclusions

We have presented performance of two on-site devices for screening OF THC in frequent and occasional cannabis smokers following controlled smoked, vaporized, and oral cannabis administrations. These data fill a necessary knowledge gap in on-site (or roadside) OF screening performance and aid interpretation of OF THC data. Overall, devices did not differ in their performance; at a THC ≥5 μg/L confirmation cutoff, overall performance criteria were ≥80% for both devices. At lower THC ≥1–2 μg/L cutoffs, TP results were maximized, but sensitivity was <80% from increased FN results due to a confirmation cutoff lower than the screening cutoff. Therefore, the confirmatory cutoff relative to the screening cutoff must be considered when interpreting OF THC results. Additionally, differences in screening cutoffs between devices must be considered; for example, significantly later t_{last} times were observed after smoking compared to vaporization at all cutoffs for DDS2 due to its higher screening cutoff (25 μg/L) compared to DT5000 (5 μg/L). Given that OF cannabinoid concentrations result from oromucosal contamination, care must be taken in interpreting results because concentrations may not be directly correlated with blood concentrations or impairment. The confirmatory OF THC cutoff should be selected to best support the needs of the OF drug testing program, as our data demonstrated in this study.

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Compliance with ethical standards

Conflict of interest The authors have no personal or financial conflicts of interest to disclose.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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