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Article

Urinary Pharmacokinetic Profile of Cannabinoids Following Administration of Vaporized and Oral Cannabidiol and Vaporized CBD-Dominant Cannabis

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Abstract

Cannabis products in which cannabidiol (CBD) is the primary chemical constituent (CBD-dominant) are increasingly popular and widely available. The impact of CBD exposure on urine drug testing has not been well studied. This study characterized the urinary pharmacokinetic profile of 100-mg oral and vaporized CBD, vaporized CBD-dominant cannabis (100-mg CBD; 3.7-mg ∆9-THC) and placebo in healthy adults ($n = 6$) using a within-subjects crossover design. Urine specimens were collected before and for 5 days after drug administration. Immunoassay (IA) screening (cutoffs of 20, 50 and 100 ng/mL) and LC–MS-MS confirmatory tests (cutoff of 15 ng/mL) for 11-nor-9-carboxy-∆9-tetrahydrocannabinol (∆9-THCCOOH) were performed; urine was also analyzed for CBD and other cannabinoids. Urinary concentrations of CBD were higher after oral (mean C_{max}: 776 ng/mL) versus vaporized CBD (mean C_{max}: 261 ng/mL). CBD concentrations peaked 5 h after oral CBD ingestion and within 1 h after inhalation of vaporized CBD. After pure CBD administration, only 1 out of 218 urine specimens screened positive for ∆9-THCCOOH (20-ng/mL IA cutoff) and no specimens exceeded the 15-ng/mL confirmatory cutoff. After inhalation of CBD-dominant cannabis vapor, nine samples screened positive at the 20-ng/mL IA cutoff, and two of those samples screened positive at the 50-ng/mL IA cutoff. Four samples that screened positive (two at 20 ng/mL and two at 50 ng/mL) confirmed positive with concentrations of ∆9-THCCOOH exceeding 15 ng/mL. These data indicate that acute dosing of pure CBD will not result in a positive urine drug test using current federal workplace drug testing guidelines (50-ng/mL IA cutoff with 15-ng/mL confirmatory cutoff). However, CBD products that also contain ∆9-THC may produce positive urine results for ∆9-THCCOOH. Accurate labeling and regulation of ∆9-THC content in CBD/hemp products are needed to prevent unexpected positive drug tests and unintended drug effects.

Introduction

Recent national and international policy reforms have made cannabis legal in an unprecedented number of jurisdictions. Medicinal cannabis use is permitted in 34 US states, the District of Columbia and various international locations (e.g., Australia, much of the European Union), while non-medicinal, or "recreational," cannabis use is permitted in 11 US states, Canada and Uruguay. Moreover, the legalization of hemp (defined in the USA as cannabis plants with ≤0.3% Δ-9-tetrahydrocannabinol (1), Δ9-THC, the primary psychoactive constituent of cannabis) is also expanding. For instance, the Agriculture Improvement Act of 2018 (*aka* the "Farm Bill"), recently removed hemp and its derivative products from the list of controlled substances in the USA (https://www.congress.gov/115/bills/hr2/BILLS-115hr2enr.pdf). These and other policy reforms have led to the development of a litany of products that contain cannabis, or individual cannabinoids, which are widely available for retail purchase.

Cannabidiol (CBD) is a key chemical constituent of many cannabis and hemp products (2). CBD has garnered widespread attention for its purported therapeutic benefits, and a cannabis-derived CBD product (Epidiolex) has been approved by the US Food and Drug Administration (FDA) for treatment of pediatric seizure disorders. In addition, many individuals use non-FDA-approved CBD-dominant cannabis or hemp products as therapeutics for various health conditions, as well as for general wellness (3–8). Products that contain high concentrations of CBD are widely available in cannabis dispensaries, and, in the case of hemp-derived CBD products, a variety of other retail locations (including in jurisdictions where cannabis remains illegal) (2). Beyond CBD-dominant cannabis plant material, which can be inhaled using conventional methods (e.g., joints, bowls and vaporizers), there are many products that contain concentrated hemp or cannabis-derived CBD extracts, which are intended for oral (e.g., tinctures), pulmonary (e.g., vaporizers or vape pens), topical and other methods of administration (2, 8, 9).

Due to the proliferation of CBD-dominant products, there is an urgent need to understand the impact CBD use has on urine drug-testing programs commonly used in workplace, criminal justice, drug treatment and other settings. Urine remains the primary biological matrix for drug testing and the most commonly targeted analyte to evaluate cannabis exposure is 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (Δ9-THCCOOH), a metabolite of Δ9-THC (10, 11). Though CBD is not an analyte of interest in extant drug-testing procedures, there are several ways that the use of CBD products could theoretically produce a positive result for cannabis on a urine drug test. First, as a result of the unregulated nature of the cannabis industry, products advertised as containing only CBD often contain Δ9-THC in concentrations that range from trace levels to levels capable of producing intoxication/impairment (9, 12). Further, hemp-derived CBD products can legally contain up to 0.3% Δ9-THC (1). Even the FDA-approved CBD medication Epidiolex may contain trace levels (<0.1%) of Δ9-THC (13). Thus, individuals who use CBD products may inadvertently expose themselves to Δ9-THC and potentially increase their risk of testing positive for cannabis. Second, some evidence suggests that acidic gastric fluid can convert CBD to THC, though whether this conversion happens in the human gut remains a hotly debated topic (14–16). When CBD is introduced, *in vitro*, to acidic conditions analogous to the human gut, it can be converted to Δ8 and Δ9-THC (17, 18). The limited supportive *in vivo* evidence for the metabolic conversion of CBD to Δ9-THC includes a case study in which Δ8 and Δ9-THC were detected in the urine of woman taking daily oral doses of CBD (600 mg) (19) and another study that detected Δ9-THC in serum and brain tissue of rodents given oral and subcutaneous (but not vaporized) doses of pure CBD (10 or 60 mg/kg) (20). Detractors of these findings note that the *in vitro* conditions under which CBD was converted to Δ8 and Δ9-THC were too artificial (i.e., not reflective of the human gut), and that clinical studies that have administered extremely high oral doses of CBD have generally not observed THC-like subjective effects or impairment in study participants, which presumably would occur if CBD converted to Δ9-THC or its active metabolite 11-hydroxy-Δ-9THC (11-OH-Δ9-THC) (15, 16).

The present study was conducted to evaluate, under controlled conditions, the urine drug-testing outcomes of acute administration of CBD via both oral ingestion and vaporization, which represent two common routes of CBD product administration. In addition, we evaluated vaporized whole-plant cannabis that had a CBD-dominant chemotype, but that also contained a low concentration of Δ9-THC. This human laboratory study investigated the likelihood that an acute dose of CBD (orally ingested or and inhaled with a vaporizer), can, by itself, impact urine drug testing for cannabis. It also allowed for a comparative evaluation to an acute inhaled dose of a high CBD/low Δ9-THC concentration botanical cannabis product.

Method

Participants

Study volunteers were recruited using media advertisements and word-of-mouth. Individuals who appeared eligible after a brief telephone interview were invited for a screening visit at the Johns Hopkins Behavioral Pharmacology Research Unit (BPRU). At this screening visit, participants provided written informed consent, and completed procedures to ascertain study eligibility.

In order to be eligible, participants were required to: (i) be in good health (as determined using medical history, a 12-lead electrocardiogram or EKG, blood chemistry, hematology, and serology analysis and a physical examination); (ii) self-report no cannabis use for at least one month prior to screening; (iii) have prior experience inhaling cannabis; (iv) test negative for recent use of cannabis and other illicit drugs (via urinalysis) and alcohol (via breathalyzer) at screening and at the beginning of each study visit; (v) be between the ages of 18 and 45 and have a body mass index (BMI) between 19 and 36 kg/m^2 and (vi) for females, test negative for pregnancy (tested via serum at screening and via urine before each session). Additional factors that were exclusionary included: current use of prescription/OTC medications or other drug products (e.g., herbal supplements), which would interfere with the participants' safety (namely those metabolized via CYP2D6, CYP2C9 and CYP2B10 enzymes, or which induce/inhibit CYP3A4 enzymes; (21, 22); and use of dronabinol in the past 6 months or hemp seeds/hemp oil in the past 3 months.

A total of six participants provided informed consent and completed all study procedures (three men; three women). Table I details demographic and select substance use characteristics for each individual. Participants were predominantly Caucasian, all non-tobacco users, and on average, had not used cannabis for 127 days (range 32–365) at study entry. Mean BMI's were 25.9 kg/m^2 for men and 29.2 kg/m^2 for women.

The Institutional Review Board of Johns Hopkins University School of Medicine approved this study, which was conducted in accordance with ethical standards established in the Helsinki

Table I. Participant Characteristics

ID#	Gender	Age	Race	Ethnicity (hispanic: Y/N)	Height (ft' in)	Weight (lbs)	BMI (kg/m^2)	Last cannabis use (days)	Cigarette smoker (Y/N)	Session order
038	M	27	White	N	5'7$^{3/4}$	182	27.9	365	N	c,b,d,a
053	F	31	White	Y	5'1$^{1/2}$	194	36.1	32	N	c,b,d,a
054	F	29	Black	N	5'10$^{1/2}$	204	28.9	150	N	a,c,b,d
063	F	38	White	N	5'3$^{1/4}$	128	22.5	36	N	b,d,a,c
066	M	23	White	N	5'6	159	25.7	60	N	d,a,c,b
068	M	37	White	N	6'4$^{1/2}$	202	24.3	120	N	d,a,c,b

Note: a = placebo; b = 100-mg oral CBD; c = 100-mg vaporized CBD; d = vaporized cannabis (100-mg CBD: 3.7-mg Δ9-THC).

Declaration. Participants were compensated for their time following each study visit.

Study design and procedure

All participants completed four experimental conditions, each spanning five consecutive days. For each condition, participants were housed in a closed residential research unit on Days 1–3 (58 h total) and completed brief outpatient visits on Days 4 and 5. This study used a double-dummy dosing procedure to control for expectancy effects, meaning participants received both an oral and vaporized study dose in each study condition. The four study conditions were: (i) oral ingestion of placebo CBD followed by inhalation of 100-mg vaporized CBD; (ii) oral ingestion of 100-mg CBD followed by inhalation of vaporized placebo cannabis; (iii) oral ingestion of placebo CBD followed by inhalation of CBD-dominant cannabis (100-mg CBD; 3.7-mg Δ9-THC) and (iv) oral ingestion of placebo CBD followed by inhalation of placebo cannabis (placebo condition). Experimental sessions were completed in a randomized order and dose administration across sessions was separated by at least 1 week to facilitate drug washout between visits. Participants and research staff were both blinded to the study doses in each session.

Study drug

Two separate batches of cannabis (CBD-dominant and placebo) were obtained for this study from the National Institute on Drug Abuse (NIDA) Drug Supply Program. The CBD-dominant batch of cannabis contained (based on dry weight percent): 10.5% CBD, 0.39% Δ-9-THC, 0.02% Δ-8-THC and 0.05% Cannabinol (CBN). The placebo cannabis batch contained 0.001% Δ-9-THC, 0.003% CBD, 0.005% CBN and had no detectable Δ-8-THC. The same quantity of plant material (953 mg) was used for both active (total CBD dose = 100 mg) and placebo cannabis vapor administration sessions. Cannabis was vaporized using the Volcano Medic® (Storz and Bickel, Tuttelingen, Germany) desktop vaporizer with the temperature set at 204°C (400°F).

Pure CBD in crystalline powder form (purity by HPLC = 100%) was obtained from Albany Molecular Research Inc. for this study. Independent testing confirmed Δ9-THC was not present in this product. For oral dosing, the Johns Hopkins BPRU Pharmacy placed 100-mg CBD into a size 00 gelcap and filled the remaining space with microcrystalline cellulose. Placebo capsules were identical gelcaps, but filled only with cellulose. For vaporization, the Volcano Medic® was used to heat and aerosolize the CBD powder (placed on a stainless-steel dosing pad). All study drugs were prepared and dispensed by the Johns Hopkins BPRU Pharmacy.

With respect to dose selection, a 100-mg CBD dose was selected for two primary reasons. First, 1 mL (single unit dose) of the FDA-approved CBD medication Epidiolex contains 100-mg CBD. Second, 100 mg is approximately the amount of CBD a person would inhale from a 1g cannabis cigarette containing 10% CBD, which is a typical amount of cannabis consumed by frequent cannabis users; 10% CBD potency is also common for CBD-dominant cannabis flowers sold in cannabis dispensaries. We maintained the 100-mg CBD dose for the botanical cannabis product to enable comparison with the pure CBD dose conditions. The inclusion of 3.7-mg Δ9-THC equates to a 25:1 CBD:THC ratio, which is a common ratio for CBD-dominant cannabis products currently in the retail market. Moreover, the Δ9-THC concentration of 0.39% in the botanical product is a close proxy to what is currently defined as hemp in the USA.

Experimental session procedures

On Day 1 of each experimental dosing session, participants arrived at ~07:30 h. Upon arrival, participants completed a urine drug test, a urine pregnancy test (females only) and an alcohol breathalyzer; they were required to test negative on all tests to participate in each session. Participants also self-reported their use of cannabis, alcohol and tobacco since the last laboratory visit using the Timeline Follow-Back questionnaire (23) and were asked about concomitant medication. Baseline pharmacodynamic measures (i.e., cognitive performance, subjective effects and vital signs) and baseline biological specimens (i.e., urine, blood, oral fluid and hair) were also collected at this time. After completing baseline assessments and consuming a standard low-fat breakfast (toast and jam), participants swallowed an oral gelcap containing either placebo or 100-mg CBD, and exactly 1 h later, inhaled the vaporized study dose (either pure CBD, placebo or CBD-dominant cannabis) using the Volcano Medic®. Each vaporized study dose was heated at 204°C (400°F) and captured in a balloon; participants inhaled three full balloons *ad libitum* within 10 min to ensure complete dose delivery. New balloons were used for each session to avoid contamination from previous study doses. Each balloon was covered with an opaque bag to minimize aerosol visibility to participants and study staff. For ~8 h after drug administration, participants stayed at the BPRU, where they provided all urine voids and completed pharmacodynamic assessments. Participants were then taken to a nearby closed residential research unit, where they resided and were monitored for the next 2 days and continued to provide all urine voids (they were discharged 58 h after oral dosing). On the second day after discharge from the residential unit (Days 4 and 5 relative to dose administration), participants returned to the BPRU for brief outpatient visits (one on each day), where they provided single urine specimens. These outpatient visits were completed at the

participant's convenience, and thus the times for biological specimen collection on Days 4 and 5 varied across participants/conditions.

On Day 1 of each experimental dosing session, urine samples were collected at baseline and 1, 2, 3 and 4 h after oral drug administration. Following the 4 h collection time point, urine voids were pooled between 4–6, 6–8, 8–10, 10–12, 12–22, 22–26, 26–30, 30–34, 34–46, 46–50, 50–54 and 54–58 h post-oral drug administration. The exact timing of urine collection varied occasionally across participants/sessions (by ~±5 min) due to a variety of reasons (e.g., participants were unable to void immediately). Thus, these time points should be viewed as nominal values. At the end of each of these pooled time periods, participants were asked to void. Single urine specimens were also collected on Days 4 and 5 after dosing for each drug condition (specific post-dosing times for these specimens are provided in Table II). Following collection of each specimen, urine was aliquoted into two 30 mL polypropylene bottles. All specimens were then wrapped with parafilm and stored at –20°C until they were shipped overnight (on dry ice) to the Clinical Reference Laboratory (CRL; Lenexa, KS) for testing.

Immunoassay

Initial analyses of specimens by IAs were conducted according to manufacturer's procedure with the DRI Cannabinoid Assay (Thermo Fisher Scientific, Fremont, CA) on a Beckman AU5800 analyzer for cannabinoids in urine and calibrated with DRI 20-, 50- and 100-ng/mL calibrators. The manufacturer's package insert indicated the following cannabinoids produced a positive result [calibrated at 50 ng/mL with 11-nor-Δ9-tetrahydrocannabinol-9-carboxlic acid (Δ9-THCCOOH)] at the indicated concentrations: 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-Δ9-THC), 100 ng/mL; Δ8-THCCOOH, 100 ng/mL; 8-β-hydroxy-Δ9-THC (8-β-OH-Δ9-THC), 100 ng/mL; 8-β,11-dihydroxy-Δ9-THC (8,11-diOH-Δ9-THC), 50 ng/mL; Δ9-THC, 50 ng/mL; cannabinol (CBN), 100 ng/mL and CBD, 10,000 ng/mL. Creatinine was determined with Siemens modified Jaffe reagent. Specific gravity was determined with a Rudolph J57 refractometer. Determinations of pH were made with Axiom pH reagents (Axiom Diagnostics, Tampa, FL).

Hydrolysis methods for confirmation

It was anticipated that two types of conjugated metabolites would be present in urine specimens from this study (i.e., ether-linked CBD and acid-linked THCCOOH). Because ether-linked cannabinoid conjugates are less susceptible to base-hydrolysis, a separate enzyme hydrolysis method was developed for potential ether-linked conjugates. Base hydrolysis was conducted with 0.1 mL of 5N KOH solution added to 0.3 mL of urine specimens, calibrators and controls and 0.1 mL of internal standard solution. Samples were incubated at 50°C for 15 min. Following incubation, 0.1 mL of 5N formic acid and 0.4 mL of potassium phosphate buffer, pH 6.8 was added prior to extraction. Enzyme hydrolysis was conducted with 0.1 mL of BGTurbo® solution (Kura Biotec, Rancho Dominguez, CA) added to 0.3 mL of urine specimens, calibrators and controls and 0.1 mL of internal standard solution. Samples were incubated at 50°C for 30 min. Following incubation, 0.5 mL of potassium phosphate buffer, pH 6.8 was added prior to extraction.

Extraction

Base and enzyme hydrolyzed samples were extracted with Clean Screen XCEL II 3 mL/130-mg SPE cartridges (UCT, Bristol, PA). After sample passage through the cartridge, the extraction column was washed with 3 mL of hexane and eluted with 2 mL of solvent (49/49/2 hexane/ethyl acetate/acetic acid). Extracts were evaporated and reconstituted with 0.4M of equal parts of 0.1% formic acid in water and methanol and analyzed in separate runs (base hydrolyzed and enzyme hydrolyzed samples by LC–MS-MS).

LC–MS-MS analyses

Extracts from base hydrolyzed samples were analyzed by LC–MS-MS for the following cannabinoids: Δ9-THCCOOH, Δ8-THCCOOH, 11-nor-Δ9-tetrahydrocannabivarin-9-carboxlic acid (THCVA) and 8-β-OH-Δ9-THC. 8-β-OH-Δ9-THC was included in the base hydrolysis because in preliminary studies it was found to be stable in the base hydrolysis procedure but not in the enzyme hydrolysis procedure. Extracts from enzyme hydrolyzed samples were analyzed by LC/MS/MS for the following cannabinoids: Δ9-THC, Δ8-THC, 8,11-diOH-Δ9-THC, 11-OH-Δ9-THC, THCV, CBD and CBN (see Table III). Analyses were conducted with an API6500 QTrap by electrospray ionization (in positive or negative mode) with a source temperature of 450°C.

The linearity was determined by five replicate analyses of the analytes with a single point calibrator at 10 ng/mL for all analytes. The analytical range was verified with four levels below the calibrator and five levels above the calibrator. The limit of detection (LOD) for Δ9-THCCOOH, 8-OH-THC, THCVA and 8,11-diOH-THC was 1.0 ng/mL; the LOD for other analytes was 0.25 ng/mL. The upper limit of linearity and carry over limit for all analytes was 1,000 ng/mL. The criterion for acceptance of results was based on the ion ratio of ±20% for the analyte and internal standard, relative retention time of ±2%, internal standard response of 20–200%, asymmetry of peak from ≥0.5 to ≤3.0, and resolution of a co-eluting peak at ≥90%. The analytical range for the low control (40% of calibrator) and positive control (125% of calibrator) was ±20% of target. Analytes were reported as negative if the value was less than the LOD.

The recovery of the solid phase extraction was performed by the addition of internal standard to post-extraction and analyzed samples. The percent recovery for the analytes ranged from a low of 52% for Δ8-THC to 86% for 8-OH-THC. At 4 (low control for the batch, n = 5) and 12.5 ng/mL (positive control for the batch, n = 5), the within-run precision was 1.5–3.6% CV, respectively, and the between-run precision was 2.9–16.4% CV, respectively. The percent bias was for these analyses ranged from –5.5 to 3.8%.

An interference study was performed to test 127 compounds, including over-the-counter drugs, prescription drugs and drugs of abuse, for specific interference. About 12 interference standard solutions were prepared and diluted in negative and low-control samples; from these, 10 negative samples were randomly selected and used to perform a quantitative matrix effect study to evaluate for unidentified method interferences. An aliquot of each sample was fortified with analyte to the low-control concentration and analyzed with a corresponding aliquot of the negative sample. The interference study results were evaluated for acceptance using the criterion established for participant samples.

Data presentation and analysis

Participant demographics and LC–MS-MS urine results are presented for each individual participant and summarized using descriptive

Table II. Analyses of Urine Specimens Following Administration of Oral and Vaporized CBD and CBD-dominant Cannabis

Subject#	Time (h)	Dose (mg)	Volume (mL)	Creatinine (mg/dL)	20 IA Δ9-THC-COOH (ng/mL)	50 IA Δ9-THC-COOH (ng/mL)	100 IA Δ9-THC-COOH (ng/mL)	CBD (ng/mL)	Δ9-THC-COOH (ng/mL)	Δ8-THC-COOH (ng/mL)	THC-VA (ng/mL)
038_M	BL	100 CBD_O	100	88.4	–1	0	2	1.3	0.0	0.0	0.0
038	1.5	100 CBD_O	175	26.2	3	4	4	3.3	0.0	0.0	0.0
038	2	100 CBD_O	75	78.2	1	0	2	13.7	0.0	0.0	0.0
038	3	100 CBD_O	175	38.0	2	2	4	12.4	0.0	0.0	0.0
038	4	100 CBD_O	150	40.0	9	9	10	682.5	0.0	0.0	0.0
038	4–6	100 CBD_O	75	34.5	14	14	10	924.8	0.0	0.0	0.0
038	6–8	100 CBD_O	175	28.5	9	8	8	812.3	0.0	0.0	0.0
038	8–10	100 CBD_O	100	62.1	31	26	20	2,941.0	0.0	0.0	0.0
038	10–12	100 CBD_O	400	5.8	5	4	5	122.0	0.0	0.0	0.0
038	12–22	100 CBD_O	1,670	49.0	13	11	12	89.8	0.0	0.0	0.0
038	22–26	100 CBD_O	800	40.9	11	10	11	60.4	0.0	0.0	0.0
038	26–30	100 CBD_O	1,500	19.3	9	9	8	20.2	0.0	0.0	0.0
038	30–34	100 CBD_O	1,300	27.1	10	8	8	22.6	0.0	0.0	0.0
038	34–46	100 CBD_O	1,950	48.2	9	6	7	23.0	0.0	0.0	0.0
038	46–50	100 CBD_O	1,100	38.7	6	7	5	14.7	0.0	0.0	0.0
038	50–54	100 CBD_O	1,000	25.1	6	6	6	15.2	0.0	0.0	0.0
038	54–58	100 CBD_O	1,300	32.1	3	4	4	6.7	0.0	0.0	0.0
038	77	100 CBD_O	75	154.9	2	2	3	16.6	0.0	0.0	0.0
038	98	100 CBD_O	125	120.8	2	2	3	14.3	0.0	0.0	0.0
038	BL	100 CBD_V	125	81.0	–3	–5	–1	0	0.0	0.0	0.0
038	1.5	100 CBD_V	200	29.5	0	–1	1	631.1	0.0	0.0	0.0
038	2	100 CBD_V	75	31.8	2	–2	2	416.4	0.0	0.0	0.0
038	3	100 CBD_V	125	54.6	–3	–4	1	366.9	0.0	0.0	0.0
038	4	100 CBD_V	50	132.9	0	–1	0	546.6	1.2	0.0	0.0
038	4–6	100 CBD_V	150	51.4	–2	–2	1	159.1	0.0	0.0	0.0
038	6–8	100 CBD_V	175	31.1	–2	–4	2	47.9	0.0	0.0	0.0
038	8–10	100 CBD_V	400	47.0	–2	–3	2	38.6	0.0	0.0	0.0
038	10–12	100 CBD_V	1,000	14.2	–2	–4	1	5.2	0.0	0.0	0.0
038	12–22	100 CBD_V	855	99.8	–6	–4	–1	14.2	0.0	0.0	0.0
038	22–26	100 CBD_V	600	25.7	–2	–4	0	1.9	0.0	0.0	0.0
038	26–30	100 CBD_V	1,600	48.2	–4	–4	0	9.3	0.0	0.0	0.0
038	30–34	100 CBD_V	1,150	26.8	–3	–4	–2	2.4	0.0	0.0	0.0
038	34–46	100 CBD_V	1,650	61.3	–4	–3	0	2.2	0.0	0.0	0.0
038	46–50	100 CBD_V	1,950	21.7	–3	–3	0	1.1	0.0	0.0	0.0
038	50–54	100 CBD_V	1,250	22.4	–5	–3	1	0.7	0.0	0.0	0.0
038	54–58	100 CBD_V	1,475	92.4	–8	–8	–4	0.0	0.0	0.0	0.0
038	77	100 CBD_V	50	105.0	–2	–4	0	2.2	0.0	0.0	0.0
038	96	100 CBD_V	100	143.4	–4	–3	–2	4.2	0.0	0.0	0.0
038	BL	100 CBD/4 THC	100	89.5	–6	–8	–4	2.9	0.0	0.0	0.0
038	1.5	100 CBD/4 THC	151	18.1	2	0	3	506.0	0.0	0.0	0.0
038	2	100 CBD/4 THC	149	12.6	6	4	4	233.5	1.3	0.0	0.0
038	3	100 CBD/4 THC	110	55.9	50	36	24	539.1	11.2	0.4	1.2
038	4	100 CBD/4 THC	62	64.6	59	48	30	424.4	19.1	0.8	1.8
038	4–6	100 CBD/4 THC	125	134.2	73	59	37	363.6	29.9	1.2	2.9
038	6–8	100 CBD/4 THC	ms	ms	ms	ms	ms	ms	ms	ms	ms
038	8–10	100 CBD/4 THC	600	38.3	16	13	10	49.6	10.4	0.3	0.0
038	10–12	100 CBD/4 THC	300	52.2	7	6	5	26.4	5.4	0.0	0.0
038	12–22	100 CBD/4 THC	1,525	51.4	6	4	3	15.8	5.4	0.0	0.0
038	22–26	100 CBD/4 THC	500	52.4	7	6	5	22.9	5.7	0.0	0.0
038	26–30	100 CBD/4 THC	1,300	7.3	–2	–1	1	3.9	1.6	0.0	0.0
038	30–34	100 CBD/4 THC	700	34.7	0	–1	1	9.0	3.1	0.0	0.0
038	34–46	100 CBD/4 THC	1,700	57.8	0	1	1	6.2	2.6	0.0	0.0
038	46–50	100 CBD/4 THC	300	73.5	–1	0	0	10.5	2.5	0.0	0.0
038	50–54	100 CBD/4 THC	500	40.1	–1	–3	0	5.8	1.3	0.0	0.0
038	54–58	100 CBD/4 THC	900	48.6	–3	–3	–1	3.1	1.1	0.0	0.0

Continued

Table II. Continued

Subject#	Time (h)	Dose (mg)	Volume (mL)	Creatinine (mg/dL)	20 IA Δ9-THC-COOH (ng/mL)	50 IA Δ9-THC-COOH (ng/mL)	100 IA Δ9-THC-COOH (ng/mL)	CBD (ng/mL)	Δ9-THC-COOH (ng/mL)	Δ8-THC-COOH (ng/mL)	THC-VA (ng/mL)
038	77	100 CBD/4 THC	25	236.1	–5	–6	–4	8.8	2.3	0.0	0.0
038	95	100 CBD/4 THC	50	214.0	–7	–5	–4	16.1	2.6	0.0	0.0
053_F	BL	100 CBD_O	20	79.4	1	0	0	0.0	0.0	0.0	0.0
053	1.5	100 CBD_O	30	94.8	1	1	2	138.4	0.0	0.0	0.0
053	2	100 CBD_O	20	90.3	1	2	3	210.2	0.0	0.0	0.0
053	3	100 CBD_O	ms	ms	ms	ms	ms	ms	ms	ms	ms
053	4	100 CBD_O	100	83.7	2	1	4	121.1	0.0	0.0	0.0
053	4–6	100 CBD_O	75	37.7	3	0	1	26.0	0.0	0.0	0.0
053	6–8	100 CBD_O	80	83.6	–2	–2	–1	22.7	0.0	0.0	0.0
053	8–10	100 CBD_O	75	26.5	2	1	1	3.3	0.0	0.0	0.0
053	10–12	100 CBD_O	495	23.6	2	0	3	2.7	0.0	0.0	0.0
053	12–22	100 CBD_O	2,500	16.0	4	2	3	0.6	0.0	0.0	0.0
053	22–26	100 CBD_O	300	12.6	2	3	4	0.4	0.0	0.0	0.0
053	26–30	100 CBD_O	ms	ms	ms	ms	ms	ms	ms	ms	ms
053	30–34	100 CBD_O	550	23.8	1	1	3	0.2	0.0	0.0	0.0
053	34–46	100 CBD_O	1,960	31.5	2	3	4	0.1	0.0	0.0	0.0
053	46–50	100 CBD_O	500	74.7	0	–1	1	0.3	0.0	0.0	0.0
053	50–54	100 CBD_O	1,050	23.1	0	2	3	0.0	0.0	0.0	0.0
053	54–58	100 CBD_O	300	60.6	0	1	1	0.0	0.0	0.0	0.0
053	76	100 CBD_O	125	41.6	0	1	0	0.0	0.0	0.0	0.0
053	96	100 CBD_O	75	164.2	–4	–2	–2	0.0	0.0	0.0	0.0
053	BL	100 CBD_V	40	153.0	–9	–9	–4	0.0	0.0	0.0	0.0
053	1.5	100 CBD_V	ms	ms	ms	ms	ms	ms	ms	ms	ms
053	2	100 CBD_V	75	35.6	–4	–4	0	15.3	0.0	0.0	0.0
053	3	100 CBD_V	75	15.0	–3	–4	1	3.1	0.0	0.0	0.0
053	4	100 CBD_V	100	72.1	–6	–6	0	6.5	0.0	0.0	0.0
053	4–6	100 CBD_V	150	53.9	–7	–7	–3	6.0	0.0	0.0	0.0
053	6–8	100 CBD_V	75	23.5	–4	–5	–2	1.4	0.0	0.0	0.0
053	8–10	100 CBD_V	50	113.0	–10	–10	–3	3.1	0.0	0.0	0.0
053	10–12	100 CBD_V	1,100	11.3	–3	–4	2	0.0	0.0	0.0	0.0
053	12–22	100 CBD_V	1,100	47.3	–3	–4	0	0.3	0.0	0.0	0.0
053	22–26	100 CBD_V	550	51.8	–6	–4	0	0.3	0.0	0.0	0.0
053	26–30	100 CBD_V	2,000	12.4	–4	–4	1	0.0	0.0	0.0	0.0
053	30–34	100 CBD_V	1,080	23.2	–4	–5	0	0.0	0.0	0.0	0.0
053	34–46	100 CBD_V	1,500	42.9	–5	–5	0	0.0	0.0	0.0	0.0
053	46–50	100 CBD_V	600	52.2	–7	–6	–1	0.0	0.0	0.0	0.0
053	50–54	100 CBD_V	550	37.2	–7	–6	–2	0.0	0.0	0.0	0.0
053	54–58	100 CBD_V	1,100	22.2	–6	–3	1	0.0	0.0	0.0	0.0
053	71	100 CBD_V	175	64.9	–9	–8	–1	0.0	0.0	0.0	0.0
053	102	100 CBD_V	50	178.2	–11	–10	–6	0.0	0.0	0.0	0.0
053	BL	100 CBD/4 THC	30	113.9	–9	–7	–6	0.0	0.0	0.0	0.0
053	1.5	100 CBD/4 THC	ms	ms	ms	ms	ms	ms	ms	ms	ms
053	2	100 CBD/4 THC	55	31.1	0	–1	2	126.1	0.0	0.0	0.0
053	3	100 CBD/4 THC	100	23.0	0	–1	2	38.7	0.0	0.0	0.0
053	4	100 CBD/4 THC	ms	ms	ms	ms	ms	ms	ms	ms	ms
053	4–6	100 CBD/4 THC	125	ms	ms	ms	ms	ms	ms	ms	ms
053	6–8	100 CBD/4 THC	175	22.6	–4	–3	0	10.0	0.0	0.0	0.0
053	8–10	100 CBD/4 THC	180	36.8	–5	–4	–1	10.1	0.0	0.0	0.0
053	10–12	100 CBD/4 THC	450	18.4	–2	–4	1	2.3	0.0	0.0	0.0
053	12–22	100 CBD/4 THC	1,500	20.4	–3	–2	–1	0.8	0.0	0.0	0.0
053	22–26	100 CBD/4 THC	180	125.0	–5	–4	–2	3.6	1.2	0.0	0.0
053	26–30	100 CBD/4 THC	950	12.1	–4	–2	–1	0.3	0.0	0.0	0.0
053	30–34	100 CBD/4 THC	800	15.9	–4	–3	–2	0.2	0.0	0.0	0.0
053	34–46	100 CBD/4 THC	1,500	18.9	–2	–3	–1	0.0	0.0	0.0	0.0
053	46–50	100 CBD/4 THC	450	33.9	–6	–4	–2	0.4	0.0	0.0	0.0

Continued

Table II. Continued

Subject#	Time (h)	Dose (mg)	Volume (mL)	Creatinine (mg/dL)	20 IA Δ9-THC-COOH (ng/mL)	50 IA Δ9-THC-COOH (ng/mL)	100 IA Δ9-THC-COOH (ng/mL)	CBD (ng/mL)	Δ9-THC-COOH (ng/mL)	Δ8-THC-COOH (ng/mL)	THC-VA (ng/mL)
053	50–54	100 CBD/4 THC	380	36.1	–6	–5	–2	0.3	0.0	0.0	0.0
053	54–58	100 CBD/4 THC	1,000	26.4	–5	–4	–2	0.2	0.0	0.0	0.0
053	Day 4	100 CBD/4 THC	ms	ms	ms	ms	ms	ms	ms	0.0	0.0
053	98	100 CBD/4 THC	15	314.3	–21	–18	–13	1.1	0.0	0.0	0.0
054_F	BL	100 CBD_O	125	122.4	–1	2	3	0.3	2.3	0.0	0.0
054	1.5	100 CBD_O	175	107.7	1	1	1	40.1	2.9	0.0	0.0
054	2	100 CBD_O	100	48.9	3	4	4	127.2	1.2	0.0	0.0
054	3	100 CBD_O	175	21.5	4	3	4	61.7	0.0	0.0	0.0
054	4	100 CBD_O	100	71.4	5	5	5	496.1	1.5	0.0	0.0
054	4–6	100 CBD_O	200	124.9	6	6	5	383.5	2.2	0.0	0.0
054	6–8	100 CBD_O	275	90.2	7	7	6	123.2	2.0	0.0	0.0
054	8–10	100 CBD_O	30	125.3	8	6	7	75.2	2.0	0.0	0.0
054	10–12	100 CBD_O	490	38.3	4	5	5	11.7	0.0	0.0	0.0
054	12–22	100 CBD_O	800	87.7	6	6	5	12.4	1.8	0.0	0.0
054	22–26	100 CBD_O	1,120	41.3	4	4	4	6.1	1.0	0.0	0.0
054	26–30	100 CBD_O	760	49.3	2	2	1	6.3	1.0	0.0	0.0
054	30–34	100 CBD_O	430	68.1	3	3	2	8.8	1.3	0.0	0.0
054	34–46	100 CBD_O	1,300	68.0	4	2	5	4.0	1.0	0.0	0.0
054	46–50	100 CBD_O	750	43.7	3	4	2	2.5	0.0	0.0	0.0
054	50–54	100 CBD_O	500	57.3	0	–1	2	3.7	0.0	0.0	0.0
054	54–58	100 CBD_O	350	91.1	1	–1	2	3.7	0.0	0.0	0.0
054	79	100 CBD_O	70	184.1	–5	–5	–3	4.3	1.8	0.0	0.0
054	103	100 CBD_O	100	144.8	–2	–3	0	1.8	1.3	0.0	0.0
054	BL	100 CBD_V	125	88.2	–10	–11	–3	0.0	0.0	0.0	0.0
054	1.5	100 CBD_V	250	24.7	0	–1	0	60.1	0.0	0.0	0.0
054	2	100 CBD_V	175	29.0	–5	–6	–1	79.3	0.0	0.0	0.0
054	3	100 CBD_V	100	45.5	–6	–8	–2	63.9	0.0	0.0	0.0
054	4	100 CBD_V	130	ms	ms	ms	ms	ms	ms	ms	ms
054	4–6	100 CBD_V	645	24.7	–5	–5	–1	13.1	0.0	0.0	0.0
054	6–8	100 CBD_V	300	52.1	–7	–8	1	7.1	0.0	0.0	0.0
054	8–10	100 CBD_V	325	63.2	–6	–6	–2	4.6	0.0	0.0	0.0
054	10–12	100 CBD_V	350	47.6	–6	–6	–1	2.3	0.0	0.0	0.0
054	12–22	100 CBD_V	1,200	73.9	–7	–7	–1	2.0	0.0	0.0	0.0
054	22–26	100 CBD_V	1,250	40.9	–5	–7	1	1.0	0.0	0.0	0.0
054	26–30	100 CBD_V	240	80.5	–8	–9	–1	0.7	0.0	0.0	0.0
054	30–34	100 CBD_V	1,300	32.8	–5	–6	0	0.3	0.0	0.0	0.0
054	34–46	100 CBD_V	910	99.3	–9	–10	–3	0.9	0.0	0.0	0.0
054	46–50	100 CBD_V	400	115.7	–9	–8	–2	0.9	0.0	0.0	0.0
054	50–54	100 CBD_V	1,100	ms	ms	ms	ms	ms	ms	ms	ms
054	54–58	100 CBD_V	250	175.3	–11	–11	–3	1.2	0.0	0.0	0.0
054	76	100 CBD_V	100	103.9	–12	–10	–4	0.5	0.0	0.0	0.0
054	103	100 CBD_V	150	165.0	–15	–14	–6	0.7	0.0	0.0	0.0
054	BL	100 CBD/4 THC	175	79.0	–9	–7	–4	0.2	0.0	0.0	0.0
054	1.5	100 CBD/4 THC	200	21.4	–3	–4	–1	157.9	0.0	0.0	0.0
054	2	100 CBD/4 THC	200	26.2	–1	0	1	160.1	0.0	0.0	0.0
054	3	100 CBD/4 THC	75	116.7	22	18	13	232.8	4.5	0.2	1.7
054	4	100 CBD/4 THC	25	128.7	26	19	15	155.3	5.5	0.3	2.0
054	4–6	100 CBD/4 THC	200	70.5	10	8	7	56.9	4.7	0.3	1.1
054	6–8	100 CBD/4 THC	200	73.1	7	6	4	28.6	4.3	0.3	0.0
054	8–10	100 CBD/4 THC	250	158.9	10	8	5	44.6	7.3	0.5	1.6
054	10–12	100 CBD/4 THC	125	158.8	1	1	1	23.9	6.8	0.5	1.0
054	12–22	100 CBD/4 THC	700	122.6	1	2	0	11.3	4.1	0.3	0.0
054	22–26	100 CBD/4 THC	ms	61.3	–2	0	1	4.1	2.0	0.0	0.0
054	26–30	100 CBD/4 THC	ms	101.0	–1	1	–3	7.2	4.5	0.2	0.0
054	30–34	100 CBD/4 THC	200	136.0	–4	–2	–1	5.8	3.7	0.2	0.0

Continued

Table II. Continued

Subject#	Time (h)	Dose (mg)	Volume (mL)	Creatinine (mg/dL)	20 IA Δ9-THC-COOH (ng/mL)	50 IA Δ9-THC-COOH (ng/mL)	100 IA Δ9-THC-COOH (ng/mL)	CBD (ng/mL)	Δ9-THC-COOH (ng/mL)	Δ8-THC-COOH (ng/mL)	THC-VA (ng/mL)
054	34–46	100 CBD/4 THC	850	121.2	–4	–2	–2	3.4	2.5	0.0	0.0
054	46–50	100 CBD/4 THC	450	97.3	–5	–4	–2	2.7	1.8	0.0	0.0
054	50–54	100 CBD/4 THC	800	36.0	–4	–4	–1	1.2	0.0	0.0	0.0
054	54–58	100 CBD/4 THC	ms	67.8	–5	–6	–4	1.6	1.3	0.0	0.0
054	71	100 CBD/4 THC	150	137.2	–6	–5	–2	2.4	2.0	0.0	0.0
054	95	100 CBD/4 THC	100	245.3	–11	–9	–6	3.1	2.2	0.0	0.0
063_F	BL	100 CBD_O	75	59.8	–1	0	2	0.0	0.0	0.0	0.0
063	1.5	100 CBD_O	80	25.9	1	2	2	87.4	0.0	0.0	0.0
063	2	100 CBD_O	77	21.7	2	3	3	7.8	0.0	0.0	0.0
063	3	100 CBD_O	150	23.3	3	2	4	214.6	0.0	0.0	0.0
063	4	100 CBD_O	60	20.2	2	3	4	117.3	0.0	0.0	0.0
063	4–6	100 CBD_O	235	24.6	1	3	3	93.9	0.0	0.0	0.0
063	6–8	100 CBD_O	ms	ms	ms	ms	ms	ms	ms	ms	ms
063	8–10	100 CBD_O	620	22.7	1	2	2	41.9	0.0	0.0	0.0
063	10–12	100 CBD_O	500	15.0	4	4	4	6.2	0.0	0.0	0.0
063	12–22	100 CBD_O	700	60.5	3	2	4	17.0	0.0	0.0	0.0
063	22–26	100 CBD_O	250	44.0	2	1	4	18.2	0.0	0.0	0.0
063	26–30	100 CBD_O	1,100	23.4	3	2	3	8.1	0.0	0.0	0.0
063	30–34	100 CBD_O	1,200	14.8	4	1	3	6.3	0.0	0.0	0.0
063	34–46	100 CBD_O	1,700	33.7	1	2	2	10.2	0.0	0.0	0.0
063	46–50	100 CBD_O	600	25.5	1	2	4	6.9	0.0	0.0	0.0
063	50–54	100 CBD_O	1,250	14.3	3	1	4	3.3	0.0	0.0	0.0
063	54–58	100 CBD_O	1,200	22.3	2	3	4	3.6	0.0	0.0	0.0
063	74	100 CBD_O	125	63.9	–1	0	1	6.4	0.0	0.0	0.0
063	102	100 CBD_O	150	13.1	3	2	2	0.0	0.0	0.0	0.0
063	BL	100 CBD_V	30	51.0	–7	–7	–1	0.2	0.0	0.0	0.0
063	1.5	100 CBD_V	175	11.9	–4	–4	0	179.6	0.0	0.0	0.0
063	2	100 CBD_V	75	28.1	–5	–5	1	248.7	0.0	0.0	0.0
063	3	100 CBD_V	125	42.7	–5	–6	0	189.7	0.0	0.0	0.0
063	4	100 CBD_V	175	11.1	–6	–4	1	39.9	0.0	0.0	0.0
063	4–6	100 CBD_V	400	15.2	–4	–4	–1	18.5	0.0	0.0	0.0
063	6–8	100 CBD_V	200	17.4	–5	–4	1	8.7	0.0	0.0	0.0
063	8–10	100 CBD_V	600	22.5	–6	–6	–3	5.6	0.0	0.0	0.0
063	10–12	100 CBD_V	500	13.5	–4	–5	0	3.0	0.0	0.0	0.0
063	12–22	100 CBD_V	1,000	43.4	–6	–4	–1	5.9	0.0	0.0	0.0
063	22–26	100 CBD_V	500	59.7	–8	–11	–2	8.5	0.0	0.0	0.0
063	26–30	100 CBD_V	1,350	21.6	–4	–3	0	2.1	0.0	0.0	0.0
063	30–34	100 CBD_V	750	29.3	–4	–7	0	1.9	0.0	0.0	0.0
063	34–46	100 CBD_V	500	36.1	–6	–7	0	1.8	0.0	0.0	0.0
063	46–50	100 CBD_V	400	65.4	–7	–7	–2	3.6	0.0	0.0	0.0
063	50–54	100 CBD_V	1,300	16.3	–5	–5	0	0.7	0.0	0.0	0.0
063	54–58	100 CBD_V	ms	27.7	–6	–5	–1	1.0	0.0	0.0	0.0
063	78	100 CBD_V	200	ms	ms	ms	ms	ms	ms	ms	ms
063	98	100 CBD_V	125	27.3	–5	–5	–3	0.4	0.0	0.0	0.0
063	BL	100 CBD/4 THC	50	149.5	–10	–8	–6	0.0	0.0	0.0	0.0
063	1.5	100 CBD/4 THC	175	45.8	–2	–1	0	195.9	0.0	0.0	0.0
063	2	100 CBD/4 THC	75	27.8	6	6	5	181.2	1.0	0.0	0.0
063	3	100 CBD/4 THC	150	11.9	0	–1	0	39.2	0.0	0.0	0.0
063	4	100 CBD/4 THC	225	14.4	0	2	1	28.3	1.3	0.0	0.0
063	4–6	100 CBD/4 THC	200	13.2	–2	–1	0	13.0	1.1	0.0	0.0
063	6–8	100 CBD/4 THC	175	17.4	–1	–2	–1	6.7	1.0	0.0	0.0
063	8–10	100 CBD/4 THC	300	28.9	–1	–1	0	4.5	1.0	0.0	0.0
063	10–12	100 CBD/4 THC	200	26.8	–2	–3	0	2.4	0.0	0.0	0.0
063	12–22	100 CBD/4 THC	1,100	36.0	–2	–2	–1	3.4	1.0	0.0	0.0
063	22–26	100 CBD/4 THC	400	66.4	–3	–3	0	9.0	1.6	0.0	0.0

Continued

Table II. Continued

Subject#	Time (h)	Dose (mg)	Volume (mL)	Creatinine (mg/dL)	20 IA Δ9-THC-COOH (ng/mL)	50 IA Δ9-THC-COOH (ng/mL)	100 IA Δ9-THC-COOH (ng/mL)	CBD (ng/mL)	Δ9-THC-COOH (ng/mL)	Δ8-THC-COOH (ng/mL)	THC-VA (ng/mL)
063	26–30	100 CBD/4 THC	1,300	18.0	–3	–4	–2	2.7	0.0	0.0	0.0
063	30–34	100 CBD/4 THC	450	43.1	–2	–3	–1	5.3	0.0	0.0	0.0
063	34–46	100 CBD/4 THC	1,800	26.9	–3	–2	–2	2.4	0.0	0.0	0.0
063	46–50	100 CBD/4 THC	650	21.0	–4	–4	–1	1.3	0.0	0.0	0.0
063	50–54	100 CBD/4 THC	1,100	24.8	–4	–4	–2	0.9	0.0	0.0	0.0
063	54–58	100 CBD/4 THC	400	45.0	–4	–4	–2	1.0	0.0	0.0	0.0
063	74	100 CBD/4 THC	150	25.6	–4	–4	–3	0.5	0.0	0.0	0.0
063	96	100 CBD/4 THC	60	81.8	–5	–6	–4	6.1	0.0	0.0	0.0
066_M	BL	100 CBD_O	45	134.6	–2	–3	–1	0.0	0.0	0.0	0.0
066	1.5	100 CBD_O	50	173.9	–4	–4	–1	13.9	0.0	0.0	0.0
066	2	100 CBD_O	ms	ms	ms	ms	ms	ms	ms	ms	ms
066	3	100 CBD_O	110	94.7	–2	–2	0	110.7	0.0	0.0	0.0
066	4	100 CBD_O	225	28.6	3	1	3	156.5	0.0	0.0	0.0
066	4–6	100 CBD_O	150	106.2	–1	0	2	526.0	0.0	0.0	0.0
066	6–8	100 CBD_O	175	77.5	0	0	3	260.6	0.0	0.0	0.0
066	8–10	100 CBD_O	300	35.0	3	3	2	33.7	0.0	0.0	0.0
066	10–12	100 CBD_O	300	75.9	0	0	1	54.2	0.0	0.0	0.0
066	12–22	100 CBD_O	275	175.7	6	7	5	65.3	0.0	0.0	0.0
066	22–26	100 CBD_O	150	133.6	8	7	5	57.4	0.0	0.0	0.0
066	26–30	100 CBD_O	250	144.8	1	2	4	16.8	0.0	0.0	0.0
066	30–34	100 CBD_O	300	116.6	1	1	0	5.4	0.0	0.0	0.0
066	34–46	100 CBD_O	1,500	73.8	3	4	2	1.8	0.0	0.0	0.0
066	46–50	100 CBD_O	200	203.2	0	1	1	5.1	0.0	0.0	0.0
066	50–54	100 CBD_O	250	99.2	–1	–1	0	1.4	0.0	0.0	0.0
066	54–58	100 CBD_O	600	59.0	0	0	0	0.6	0.0	0.0	0.0
066	79	100 CBD_O	125	309.6	–7	–4	–4	1.7	0.0	0.0	0.0
066	96	100 CBD_O	100	343.0	–5	–5	–3	1.2	0.0	0.0	0.0
066	BL	100 CBD_V	75	353.9	–17	–15	–7	0.0	0.0	0.0	0.0
066	1.5	100 CBD_V	75	323.7	–13	–10	–6	394.2	0.0	0.0	0.0
066	2	100 CBD_V	ms	ms	ms	ms	ms	ms	ms	ms	ms
066	3	100 CBD_V	125	134.2	–8	–8	–4	201.3	0.0	0.0	0.0
066	4	100 CBD_V	125	97.0	–8	–7	–4	47.6	0.0	0.0	0.0
066	4–6	100 CBD_V	220	77.5	–6	–8	–2	27.2	0.0	0.0	0.0
066	6–8	100 CBD_V	100	129.6	–10	–13	–6	17.5	0.0	0.0	0.0
066	8–10	100 CBD_V	100	71.5	–8	–8	–2	3.4	0.0	0.0	0.0
066	10–12	100 CBD_V	220	61.8	–7	–8	–3	2.5	0.0	0.0	0.0
066	12–22	100 CBD_V	275	174.3	–8	–8	–4	2.0	0.0	0.0	0.0
066	22–26	100 CBD_V	230	134.5	–9	–12	–5	3.5	0.0	0.0	0.0
066	26–30	100 CBD_V	540	53.7	–6	–7	–2	0.7	0.0	0.0	0.0
066	30–34	100 CBD_V	400	51.9	–7	–6	–3	0.5	0.0	0.0	0.0
066	34–46	100 CBD_V	450	175.2	–9	–9	–2	0.6	0.0	0.0	0.0
066	46–50	100 CBD_V	155	ms	ms	ms	ms	ms	ms	ms	ms
066	50–54	100 CBD_V	300	86.8	–9	–8	–3	0.4	0.0	0.0	0.0
066	54–58	100 CBD_V	420	96.0	–3	–3	–2	0.4	0.0	0.0	0.0
066	73	100 CBD_V	50	284.4	–12	–14	–5	0.5	0.0	0.0	0.0
066	102	100 CBD_V	125	318.8	–14	–12	–7	0.0	0.0	0.0	0.0
066	BL	100 CBD/4 THC	60	292.8	–13	–10	–8	0.0	1.0	0.0	0.0
066	1.5	100 CBD/4 THC	75	249.3	–7	–6	–5	216.0	1.2	0.0	0.0
066	2	100 CBD/4 THC	50	227.2	4	4	2	351.0	3.0	0.0	1.3
066	3	100 CBD/4 THC	25	223.2	4	3	2	198.3	3.9	0.0	1.2
066	4	100 CBD/4 THC	50	217.0	–2	–2	–2	111.4	4.7	0.0	1.0
066	4–6	100 CBD/4 THC	125	180.9	–5	–5	–4	36.2	3.3	0.0	0.0
066	6–8	100 CBD/4 THC	100	192.0	–3	–4	–4	38.5	4.0	0.0	0.0
066	8–10	100 CBD/4 THC	80	216.7	–4	–4	–4	18.9	2.6	0.0	0.0
066	10–12	100 CBD/4 THC	ms	ms	ms	ms	ms	ms	ms	ms	ms

Continued

Table II. Continued

Subject#	Time (h)	Dose (mg)	Volume (mL)	Creatinine (mg/dL)	20 IA Δ9-THC-COOH (ng/mL)	50 IA Δ9-THC-COOH (ng/mL)	100 IA Δ9-THC-COOH (ng/mL)	CBD (ng/mL)	Δ9-THC-COOH (ng/mL)	Δ8-THC-COOH (ng/mL)	THC-VA (ng/mL)
066	12–22	100 CBD/4 THC	520	172.1	–5	–5	–2	6.7	2.2	0.0	0.0
066	22–26	100 CBD/4 THC	450	72.6	–5	–3	–3	2.6	0.0	0.0	0.0
066	26–30	100 CBD/4 THC	600	57.9	–6	–5	–3	1.2	0.0	0.0	0.0
066	30–34	100 CBD/4 THC	680	59.0	–4	–6	–4	0.6	0.0	0.0	0.0
066	34–46	100 CBD/4 THC	750	138.4	–8	–7	–5	0.9	0.0	0.0	0.0
066	46–50	100 CBD/4 THC	200	ms	ms	ms	ms	ms	ms	ms	ms
066	50–54	100 CBD/4 THC	390	63.3	–6	–5	–3	0.6	0.0	0.0	0.0
066	54–58	100 CBD/4 THC	ms	101.4	–7	–6	–5	0.6	0.0	0.0	0.0
066	72	100 CBD/4 THC	425	280.8	–10	–7	–6	0.6	0.0	0.0	0.0
066	96	100 CBD/4 THC	350	202.6	–11	–9	–7	0.6	0.0	0.0	0.0
068_M	BL	100 CBD_O	125	138.3	–2	–2	–1	1.3	1.3	0.0	0.0
068	1.5	100 CBD_O	425	54.5	1	1	1	6.4	0.0	0.0	0.0
068	2	100 CBD_O	60	50.9	1	1	1	32.1	0.0	0.0	0.0
068	3	100 CBD_O	275	28.2	2	1	2	28.4	0.0	0.0	0.0
068	4	100 CBD_O	125	67.6	3	2	1	200.5	0.0	0.0	0.0
068	4–6	100 CBD_O	225	91.8	1	0	–1	135.8	1.2	0.0	0.0
068	6–8	100 CBD_O	250	61.2	2	2	1	236.3	0.0	0.0	0.0
068	8–10	100 CBD_O	125	103.2	0	–1	–1	269.6	1.0	0.0	0.0
068	10–12	100 CBD_O	300	85.7	0	0	–1	85.4	1.0	0.0	0.0
068	12–22	100 CBD_O	1,500	43.0	1	1	2	28.7	0.0	0.0	0.0
068	22–26	100 CBD_O	1,050	17.8	3	4	1	4.1	0.0	0.0	0.0
068	26–30	100 CBD_O	450	72.0	0	0	–1	7.2	0.0	0.0	0.0
068	30–34	100 CBD_O	1,000	35.2	2	1	–1	1.5	0.0	0.0	0.0
068	34–46	100 CBD_O	1,600	44.8	1	–1	1	1.0	0.0	0.0	0.0
068	46–50	100 CBD_O	ms	75.3	0	–1	–1	1.1	0.0	0.0	0.0
068	50–54	100 CBD_O	ms	45.1	–2	–1	–1	0.7	0.0	0.0	0.0
068	54–58	100 CBD_O	600	35.5	1	0	0	0.4	0.0	0.0	0.0
068	72	100 CBD_O	550	101.9	–1	–3	0	1.0	0.0	0.0	0.0
068	96	100 CBD_O	350	42.6	1	1	2	0.3	0.0	0.0	0.0
068	BL	100 CBD_V	75	104.7	–5	–6	0	0.7	1.5	0.0	0.0
068	1.5	100 CBD_V	550	13.3	2	1	3	194.5	0.0	0.0	0.0
068	2	100 CBD_V	200	20.9	–3	–6	1	83.3	0.0	0.0	0.0
068	3	100 CBD_V	750	11.5	–3	–4	1	24.9	0.0	0.0	0.0
068	4	100 CBD_V	200	52.7	–3	–3	3	63.6	1.0	0.0	0.0
068	4–6	100 CBD_V	ms	45.6	–3	–4	2	40.1	0.0	0.0	0.0
068	6–8	100 CBD_V	550	34.6	–3	–4	0	10.8	0.0	0.0	0.0
068	8–10	100 CBD_V	200	71.8	–4	–5	–2	14.3	1.3	0.0	0.0
068	10–12	100 CBD_V	300	58.4	–4	–5	1	8.5	1.1	0.0	0.0
068	12–22	100 CBD_V	3,700	12.7	–5	–5	–1	1.3	0.0	0.0	0.0
068	22–26	100 CBD_V	1,600	23.6	–3	–5	0	1.3	0.0	0.0	0.0
068	26–30	100 CBD_V	3,000	13.0	–4	–7	0	0.7	0.0	0.0	0.0
068	30–34	100 CBD_V	2,200	18.4	–5	–6	0	0.6	0.0	0.0	0.0
068	34–46	100 CBD_V	4,900	15.3	–4	–4	–2	0.6	0.0	0.0	0.0
068	46–50	100 CBD_V	2,150	12.4	–5	–5	–1	0.6	0.0	0.0	0.0
068	50–54	100 CBD_V	2,600	13.7	–4	–5	–1	0.5	0.0	0.0	0.0
068	54–58	100 CBD_V	2,600	27.7	–5	–4	0	1.3	0.0	0.0	0.0
068	72	100 CBD_V	1,150	41.1	–4	–7	–1	0.8	0.0	0.0	0.0
068	96	100 CBD_V	100	161.0	–8	–9	–4	3.1	2.0	0.0	0.0
068	BL	100 CBD/4 THC	ms	36.3	–3	–4	–2	0.0	0.0	0.0	0.0
068	1.5	100 CBD/4 THC	250	22.4	3	3	4	399.0	1.1	0.0	0.0
068	2	100 CBD/4 THC	75	10.6	6	6	4	20.5	2.8	0.0	0.0
068	3	100 CBD/4 THC	250	11.8	5	4	5	40.2	2.1	0.0	0.0
068	4	100 CBD/4 THC	225	15.1	6	6	5	16.4	4.4	0.0	0.0
068	4–6	100 CBD/4 THC	350	80.8	72	61	38	61.6	23.2	0.5	2.5
068	6–8	100 CBD/4 THC	250	61.5	43	34	21	27.3	15.5	0.4	1.8

Continued

Table II. Continued

Subject#	Time (h)	Dose (mg)	Volume (mL)	Creatinine (mg/dL)	20 IA Δ9-THC-COOH (ng/mL)	50 IA Δ9-THC-COOH (ng/mL)	100 IA Δ9-THC-COOH (ng/mL)	CBD (ng/mL)	Δ9-THC-COOH (ng/mL)	Δ8-THC-COOH (ng/mL)	THC-VA (ng/mL)
068	8–10	100 CBD/4 THC	180	74.7	30	25	18	20.4	11.1	0.3	1.6
068	10–12	100 CBD/4 THC	600	29.5	11	10	7	5.8	6.0	0.0	0.0
068	12–22	100 CBD/4 THC	1,500	43.5	21	16	11	5.1	9.3	0.0	0.0
068	22–26	100 CBD/4 THC	1,550	18.2	4	3	2	1.2	2.0	0.0	0.0
068	26–30	100 CBD/4 THC	1,500	25.2	2	2	2	1.6	2.2	0.0	0.0
068	30–34	100 CBD/4 THC	1,100	33.3	2	2	1	7.1	3.4	0.0	0.0
068	34–46	100 CBD/4 THC	2,500	32.9	0	2	2	2.3	2.5	0.0	0.0
068	46–50	100 CBD/4 THC	800	36.5	–2	–2	0	1.0	1.2	0.0	0.0
068	50–54	100 CBD/4 THC	1,200	27.0	–4	–3	–1	0.6	0.0	0.0	0.0
068	54–58	100 CBD/4 THC	1,100	39.1	–3	–3	–1	0.6	0.0	0.0	0.0
068	72	100 CBD/4 THC	750	68.9	–2	–2	–1	1.2	1.4	0.0	0.0
068	96	100 CBD/4 THC	350	67.6	–1	0	–1	4.5	1.8	0.0	0.0

Note: ms = missing sample; O = oral dose; V = vaporized dose. Time = h relative to oral dosing (dose inhalation occurred 1 h after oral dosing). BL = baseline; M = male and F = female.

statistics. Sensitivity, specificity and agreement between immunoassay (IA) and LC–MS-MS results were calculated for Δ9-THCCOOH for all non-placebo conditions. There were three IA screening cutoffs used in these analyses: 20, 50 and 100 ng/mL. The confirmatory LC–MS-MS cutoff was 15 ng/mL for all analyses, which corresponds with the mandatory guidelines for federal workplace drug testing (24).

Urinary Δ9-THCCOOH test results were categorized into the following four categories: true positive (TP; IA response ≥ cutoff concentration and LC–MS-MS positive, i.e., ≥ 15 ng/mL), true negative (TN; IA response < cutoff concentration and LC–MS-MS negative, i.e., < 15 ng/mL), false positive (FP; IA response ≥ cutoff concentration and LC–MS-MS negative, i.e., < 15 ng/mL) or false negative (FN; IA response < cutoff concentration and LC–MS-MS positive, i.e., ≥ 15 ng/mL). Sensitivity, specificity and agreement were calculated using the following formulas: sensitivity (100 × [TP/(TP + FN)]), specificity (100 × [TN/(TN + FP)]) and agreement (100 × [(TP + TN)/(TP + TN + FP + FN)]).

Results

Table II displays full IA and LC–MS-MS urinary results for select cannabinoids for each participant and time point (note that 8,11-diOH-THC, THCV, Δ-9-THC and 8-OH-THC were not detected in urine during any session, and 11-OH-THC, CBN and Δ-8-THC were only detected at trace concentrations (<1 ng/mL) and are thus not listed in Table II). Figure 1 displays mean urinary CBD and Δ9-THCCOOH concentrations before and after drug administration, and Table IV displays C_{max} and T_{max} values and time to first and last detection for Δ9-THCCOOH and CBD for each individual participant. Figure 2 shows the urinary Δ9-THCCOOH concentrations across time in the CBD-dominant cannabis condition for each participant.

LC–MS-MS results

100-mg oral CBD

Following oral administration of 100-mg CBD, urinary C_{max} concentrations for CBD ranged from 214 to 2,941 ng/mL (mean C_{max}: 776.3 ng/mL), while T_{max} values for CBD ranged from 2 to 9 h after oral dosing (mean T_{max}: 5.3 h). On average, urinary CBD concentrations were higher for men (mean C_{max} for men: 1,245.5 ng/mL) compared to women (mean C_{max} for women: 307.0 ng/mL) following oral dosing. The overall percentage of the 100-mg oral CBD dose that was excreted as total drug (free and hydrolyzed) in urine ranged from 0.03 to 1.0 % (mean: 0.3 %). For three out of six participants, CBD was still detected in urine 5 days after acute oral CBD dosing (Day 5 collection times ranged from 96 to 103 h post-dosing). Notably, despite the 1-week washout between doses, three participants, each of whom had vaporized CBD the previous week, had detectable urinary CBD at the baseline timepoint for the oral-dosing session. Thus, urinary levels of CBD were elevated at baseline for these individuals due to residual CBD from the prior dose. For the three participants with no CBD present in urine at baseline, CBD was first detected in urine 1.5 h after oral ingestion and last detected between 48 and 96 h.

Trace amounts of Δ9-THCCOOH were detected during oral CBD dosing sessions for two study participants (#054 and #068). In both cases, Δ9-THCCOOH was detected at baseline (prior to drug administration) and only sporadically at subsequent time points, typically in specimens that also had higher creatinine concentrations compared with samples in which Δ9-THCCOOH was not detected. Participant #054 received the oral CBD dose during the third week of study participation, but was not exposed to the Δ9-THC-containing cannabis dose in the study prior to this dosing session. Participant #068 received the oral CBD dose during the fourth week of study participation and was administered the Δ9-THC-containing cannabis vapor dose during Week 1. Note, low concentrations of Δ9-THCCOOH were also measured at multiple time points for Participant #68 during the placebo (Week 2) and CBD vapor (Week 3) dosing sessions as well. Because Δ9-THCCOOH was present at baseline, was not consistently observed, and was detected only at very low concentrations (1.0–2.9 ng/mL), these results most likely reflect residual excretion of prior Δ9-THC exposure. Δ8-THC was detected for two participants, both at a concentration of 0.3 ng/mL (#038 at the 8–10 h time point and #066 at the 4–6 h time point). The remaining cannabinoids were not detected following oral CBD ingestion.

Table III. LC–MS-MS Method Development Metrics

Analyte	Internal standard	Ionization mode	Transitions (± 0.3 amu)	Retention time (± 0.3 min)
Enzyme hydrolysis assay				
8,11-diOH-Δ9-THC		Positive	347.3 > 311.4	2.3
			347.3 > 293.3	
	8,11-diOH-Δ9-THC-D6	Positive	353.3 > 317.4	2.3
			353.3 > 299.3	
11-OH-THC		Positive	331.2 > 193.1	4.6
			331.2 > 201.1	
	11-OH-THC-D3	Positive	334.2 > 196.1	4.6
			334.2 > 201.1	
THCV		Positive	287.3 > 165.1	5.5
			287.3 > 231.1	
	CBD-D3	Positive	318.2 > 196.2	7.3
			318.2 > 123.2	
CBD		Positive	315.2 > 193.2	5.8
			315.2 > 123.2	
	CBD-D3	Positive	318.2 > 196.2	5.8
			318.2 > 123.2	
CBN		Positive	311.1 > 223.1	7.3
			311.1 > 241.0	
	CBN-D3	Positive	314.1 > 223.1	7.3
			314.1 > 241.0	
Δ9-THC		Positive	315.1 > 193.2	8.0
			315.1 > 259.2	
	Δ9-THC-D3	Positive	318.1 > 196.2	8.0
			318.1 > 262.2	
Δ8-THC		Positive	315.1 > 193.2	8.2
			315.1 > 259.2	
	Δ8-THC-D9	Positive	324.1 > 202.2	8.2
			324.1 > 268.2	
Base hydrolysis assay				
8-β-OH-Δ9-THC		Positive	331.2 > 201.1	3.5
			331.2 > 271.1	
	11-OH-THC-D3	Positive	334.2 > 196.1	5.1
			334.2 > 201.1	
THCVA		Negative	315.2 > 217.1	3.05
			315.2 > 163.1	
	Δ8-THCCOOH-D6		349.1 > 251.1	5.25
			349.1 > 191.1	
Δ8-THCCOOH		Negative	343.1 > 245.1	5.25
			343.1 > 191.1	
	Δ8-THCCOOH-D6	Negative	349.1 > 251.1	5.25
			349.1 > 191.1	
Δ9-THCCOOH		Negative	343.1 > 245.1	5.45
			343.1 > 191.1	
	Δ9-THCCOOH-D9	Negative	352.1 > 254.1	5.45
			352.1 > 194.1	

100-mg vaporized CBD

For the 100-mg vaporized CBD condition, urinary C_{max} concentrations for CBD ranged from 15 to 631 ng/mL (mean C_{max}: 261 ng/mL) while T_{max} values for CBD ranged from 0.5 to 1 h after inhalation (mean T_{max}: 0.8 h). On average, urinary CBD concentrations were higher for men (mean C_{max} for men: 406.6 ng/mL) compared to women (mean C_{max} for women: 114.4 ng/mL) following CBD inhalation. The overall percentage of the 100-mg vaporized CBD dose that was excreted in urine ranged from 0.003 to 0.3% (mean: 0.10 %). For participants #063 and #068 in the 100-mg vaporized CBD condition, CBD was first detected in urine at baseline and last detected on Day 5 (95–97 h post-dose inhalation). For the remaining four participants (participants #038, #053, #054 and #066), CBD was detected 0.5–1 h after dose inhalation, and lasted detected between 23 and 102 h post-administration.

Trace amounts of Δ9-THCCOOH were detected for two participants in the 100-mg vaporized CBD condition (participants #038 and #068). For participant #038, Δ9-THCCOOH was detected at only one time point (3 h post-inhalation; concentration = 1.2 ng/mL). For participant #068, Δ9-THCCOOH concentration was

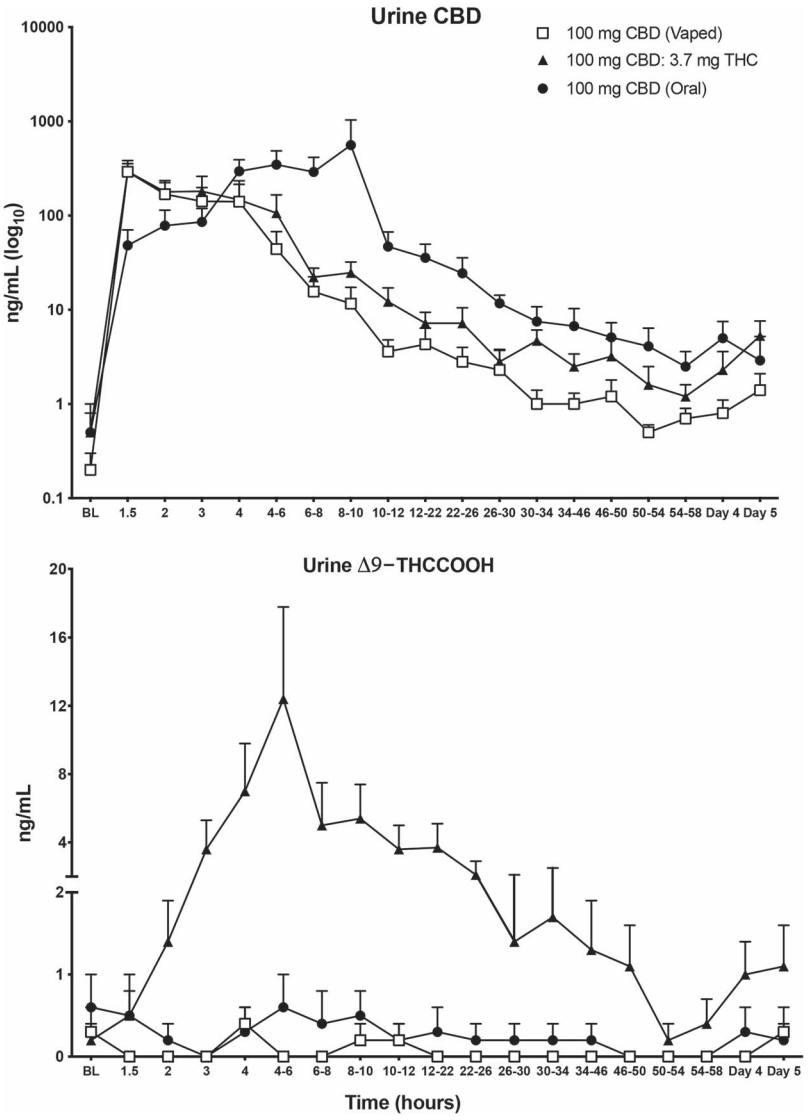

Figure 1. Quantitative urinary concentrations (mean ± SEM) of CBD and Δ9-THCCOOH. Δ9-THCCOOH is on $\log_{10}$ axis; CBD is on linear axis. BL = baseline.

1.5 ng/mL at baseline, fell below the limit of quantification for several hours, and then was detected again 3, 7–9 and 9–11 h after dose inhalation. Δ9-THCCOOH was subsequently detected again for this participant on Day 5 (95 h after dose inhalation) at 2 ng/mL. 11-OH-THC (not included in Table II) was detected for participant #054 (concentration = 0.5 ng/mL) at the 34–46 h time point and for participant #066 (concentration = 0.2 ng/mL) at the 30–34 h time point; remaining cannabinoids were not detected in the 100-mg vaporized CBD condition.

CBD-dominant cannabis

Following inhalation of CBD-dominant cannabis (containing ~100-mg CBD and 3.7-mg Δ9-THC; Figure 2), urinary C_{max} concentrations for CBD ranged from 126 to 539 ng/mL (mean C_{max}: 307 ng/mL) while T_{max} values for CBD ranged from 0.5 to 2 h after inhalation (mean T_{max}: 1.2 h; Table IV). On average, urinary CBD concentrations were higher for men (mean C_{max} for men: 429.7 ng/mL) compared to women (mean C_{max} for women: 184.9 ng/mL) following cannabis inhalation. The overall percentage of the 100-mg vaporized CBD dose that was excreted in urine ranged from 0.01 to 0.3% (mean: 0.12%). CBD was first detected at baseline for two participants (#38 and #54) and between 0.5 and 1 h after dose inhalation for the other four participants. CBD was detected in urine until Day 5 (94–97 h post-cannabis inhalation) for all study participants. Δ9-THCCOOH was also detected for all participants in the CBD-dominant cannabis condition; C_{max} values ranged from 1.2 to 29.9 ng/mL. T_{max} values for Δ9-THCCOOH ranged from 3 to 23 h post-cannabis inhalation. Men excreted higher concentrations of Δ9-THCCOOH (mean C_{max} for men: 19.3 ng/mL) compared to women (mean C_{max} for women: 3.4 ng/mL), on average. There was large inter-individual variability with respect to first and last detection for Δ9-THCCOOH (Table IV). For 3/6 participants (i.e., #038, #054 and #068), Δ9-THCCOOH concentrations were first detected shortly after cannabis inhalation (0.5–2 h) and last detected on Day 5 (94–95 h). For participant #053, Δ9-THCCOOH was only detected once, at the 22–26 h pooled urine collection time point, while for participant #063 the window for detection for

Table IV. Maximum Concentrations (C_{max}), Time to Maximum Concentrations (T_{max}) and Detection Windows for Cannabinoids in Urine Following Administration of Oral and Vaporized CBD and CBD-dominant Cannabis

Subject ID#	CBD C_{max} (ng/mL)	CBD T_{max} (h)	CBD dose excreted (%)	CBD first detected (h)	CBD last detected (h)	Δ9-THC-COOH C_{max} (ng/mL)	Δ9-THC-COOH T_{max} (h)	Δ9-THC-COOH first detected (h)	Δ9-THC-COOH last detected (h)
Placebo									
038	14.1	5	N/A	BL	103	2	5	BL	5
053	3.1	1.5	N/A	BL	97	ND	ND	ND	ND
054	0.4	2	N/A	1.5	3	ND	ND	ND	ND
063	2.3	48	N/A	BL	73	ND	ND	ND	ND
066	2	2	N/A	1.5	52	ND	ND	ND	ND
068	4.7	32	N/A	BL	96	2.2	BL	BL	BL
Mean (total)	4.4	15.1				0.7	2.5		
100-mg oral CBD									
038	2,941	9	1.0	BL	98	ND	ND	ND	ND
053	210.2	2	0.03	1.5	48	ND	ND	ND	ND
054	496.1	4	0.22	BL	103	2.9	1.5	BL	103
063	214.6	3	0.12	1.5	74	ND	ND	ND	ND
066	526	5	0.22	1.5	96	ND	ND	ND	ND
068	269.6	9	0.23	BL	96	1.3	BL	BL	11
Mean (total)	776.3	5.3	0.30			0.7	0.8		
100-mg vaporized CBD									
038	631.1	0.5	0.26	0.5	95	1.2	3	3	3
053	15.3	1	0.003	1	23	ND	ND	ND	ND
054	79.3	1	0.05	0.5	102	ND	ND	ND	ND
063	248.7	1	0.09	BL	97	ND	ND	ND	ND
066	394.2	0.5	0.05	0.5	72	ND	ND	ND	ND
068	194.5	0.5	0.17	BL	95	2	96	BL	95
Mean (total)	260.5	0.75	0.10			0.5	54		
Vaporized cannabis (100-mg CBD/3.7-mg THC)									
038	539.1	2	0.28	BL	94	29.9	4	1	94
053	126.1	1	0.01	1	97	1.2	23	23	23
054	232.8	2	0.11	BL	94	7.3	8	2	94
063	195.9	0.5	0.08	0.5	95	1.6	23	1	23
066	351	1	0.06	0.5	95	4.7	3	BL	16
068	399	0.5	0.17	0.5	95	23.2	4	0.5	95
Mean (total)	307.3	1.2	0.12			11.3	10.8		

Note: N/A = not applicable for that analyte; ND = analyte not detected for that participant/condition; BL = baseline. Midpoint time value used for pooled specimens. T_{max} and time to first and last detection are relative to oral dosing for 100-mg oral CBD and relative to dose inhalation for 100-mg vaporized CBD and CBD-dominant cannabis. Note: 038, 066 and 068 were males; 053, 054 and 063 were females.

Δ9-THCCOOH was 1–23 h post-cannabis inhalation. For participant #066, Δ9-THCCOOH was first detected at baseline and last detected 16 h post-cannabis inhalation. Inhalation of CBD-dominant cannabis resulted in detection of several other cannabinoids for participants #038, #054, #066 and #068. Specifically, THCVA was detected in all four of these individuals, CBN was detected in #038, #054 and #068; Δ8-THC was detected in #066 and #068 and Δ8-THCCOOH was detected in #038, #054 and #068 (see Table II).

Of note, following inhalation of CBD-dominant cannabis, two participants (#038 and #068; both males) excreted Δ9-THCCOOH concentrations above 15 ng/mL (the confirmatory cutoff concentration listed in the Mandatory Guidelines for federal workplace drug testing). Specifically, participant #038 provided two specimens (at the 4 and 4–6 h collection points) and Participant #068 provided two specimens (at the 4–6 and 6–8 h collection points) that exceeded 15 ng/mL (see Figure 2). Δ9-THCCOOH concentrations were well below 15 ng/mL in both oral and vaporized CBD conditions.

Sensitivity, specificity and agreement

Sensitivity, specificity and agreement results between IA and LC–MS-MS for urinary Δ9-THCCOOH concentrations are presented in Table V. Specifically, three different IA screening cutoffs (20, 50 and 100 ng/mL) were compared to the confirmatory LC–MS-MS results (confirmation of positive test was always: ≥15 ng/mL). For the 100-mg oral CBD condition, using the 20 ng/mL IA screening cutoff, one specimen was deemed a false positive while the remaining 109 specimens were deemed true negatives. The lone specimen that was a false positive at the 20 ng/mL IA cutoff occurred for participant #038 at the 8–10 h pooled urine collection time point (this specimen also contained trace amounts of Δ8-THC; Table II). When tested at the 50 and 100 ng/mL IA cutoffs, all specimens from the 100-mg oral CBD condition were considered true negatives. For the 100-mg vaporized CBD condition, all specimens (108/108) were characterized as true negatives at each of the three IA screening cutoffs. Specificity (ability to detect true negatives for Δ9-THCCOOH), was 99.1% at the 20 ng/mL IA cutoff and 100% at the 50 and 100 ng/mL IA cutoffs.

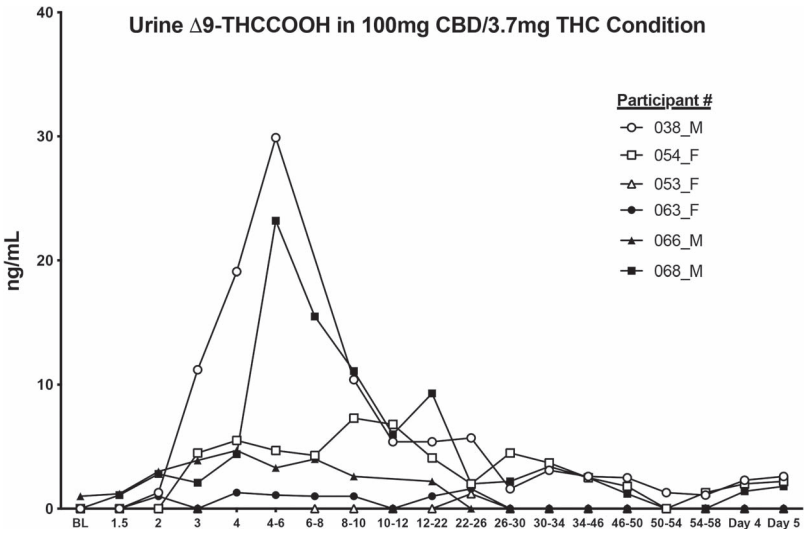

Figure 2. Quantitative urinary concentrations of Δ9-THCCOOH for all six participants following administration of CBD-dominant cannabis (100-mg CBD; 3.7-mg Δ9-THC). Numbers in legend refer to individual participants (see Tables I, II and IV). BL = baseline; M = male and F = female.

Sensitivity (ability to detect true positives for Δ9-THCCOOH) could not be measured in the oral or vaporized CBD conditions because Δ9-THC was not administered.

As noted above, there were four specimens (two from #038 and two from #068) with Δ9-THCCOOH concentrations that exceed 15 ng/mL in the CBD-dominant cannabis condition. At the 20-ng/mL IA screening cutoff, each of these four samples were confirmed as true positives. At the 50-ng/mL cutoff (screening cutoff suggested by the Mandatory Guidelines for federal workplace drug testing), two of the samples were considered true positives (one from #038 and one from #068) and the remaining two were categorized as false negatives. All four specimens over 15 ng/mL were categorized as false negatives at the 100-ng/mL IA screening cutoff. Sensitivity, specificity and agreement in the CBD-dominant cannabis condition were: 100, 95 and 95% at the 20-ng/mL IA cutoff, 50, 100 and 98% at the 50-ng/mL IA cutoff, and 0, 100 and 96% at the 100-ng/mL IA cutoff.

Adverse events

No adverse events occurred in this study.

Discussion

Oral and inhalable CBD products have become ubiquitous in both legal and illicit cannabis markets. Commercial CBD products often contain low levels of Δ9-THC (1, 9, 12, 13) and there is limited pre-clinical evidence suggesting that CBD may be converted to Δ8 and Δ9-THC in the human gut (17, 18). Given these issues, there is an urgent need to understand whether CBD products can influence results of urine drug tests, which remains the primary method to evaluate recent cannabis use in the workplace and many other settings.

In the present study, acute administration of neither 100-mg oral CBD nor 100-mg vaporized CBD produced a positive urine toxicology result based on current US drug testing guidelines (screening via IA at a cutoff of 50-ng/mL Δ9-THCCOOH and confirmation via LC/MS/MS at a cut-off of 15 ng/mL). Only 1 of 218 specimens screened positive (at 20-ng/mL Δ9-THCCOOH cutoff) after administration of pure CBD (oral dose of 100-mg encapsulated CBD), and no samples screened positive at 50 or 100ng/mL after pure CBD administration. The specimen that screened positive at 20 ng/mL occurred at the 8–10 h timepoint for participant #038, which also coincided with peak urine CBD concentration (2,941 ng/mL) for that participant. LC–MS-MS testing of that sample showed no Δ9-THC or Δ9-THCCOOH, suggesting that the positive screen may have been due to cross-reactivity with the IA assay at the very high CBD concentration or other CBD metabolites. Additional research is needed to identify factors that contribute to the observed increased IA activity in the presence of high urine CBD concentrations.

Another important finding of the present study was that there was no indication that orally administered CBD converted to Δ8-THC or Δ9-THC, as has been observed in pre-clinical studies (17, 18). Though trace amounts of Δ9-THC metabolites were observed in some specimens obtained during experimental sessions in which pure CBD was administered, the detection was sporadic with respect to time (i.e., very few consecutive samples had Δ9-THCCOOH above LOQ when pure CBD was administered), also occurred in baseline and placebo session samples, and was typically in samples with high creatinine concentration relative to surrounding time points with no detection. Together, this suggests the low concentration of Δ9-THCCOOH and other cannabinoids detected in these samples was likely due to prior exposure to Δ9-THC.

This study also demonstrated that inhaling vaporized CBD-dominant cannabis (approximate concentrations of CBD and Δ9-THC were 100 and 3.7 mg, respectively) can produce positive results for IA screening assays up to 50 ng/mL and LC–MS-MS confirmatory testing at a cutoff of 15-ng/mL Δ9-THCCOOH. Specifically, following inhalation of CBD-dominant cannabis, two participants (#038 and #068) each produced two urine specimens, between 4 and 8 h post-cannabis administration, with Δ9-THCCOOH concentrations above the widely used confirmatory cutoff of 15 ng/mL; all specimens tested positive at the 20-ng/mL IA cutoff and 50% of specimens tested positive at the 50-ng/mL IA cutoff. The implications of this outcome will vary, depending on diverse regulatory and national drug control regulations. For example, the CBD-dominant cannabis product used in this study contained 0.39%

Table V. Comparisons of IA Responses to Confirmation Analyses (LC–MS-MS) in Urine Specimens Following Administration of Oral and Vaporized CBD and CBD-dominant Cannabis

	Urine Δ9-THCCOOH IA (cutoff = 20 ng/mL) vs Δ9-THCCOOH LC–MS-MS (confirmation = 15 ng/mL)	Urine Δ9-THCCOOH IA (cutoff = 50 ng/mL) vs Δ9-THCCOOH LC–MS-MS (confirmation = 15 ng/mL)	Urine Δ9-THCCOOH IA (cutoff = 100 ng/mL) vs Δ9-THCCOOH LC–MS-MS (confirmation = 15 ng/mL)
100-mg oral CBD			
#True positive (%)	0 (0.0)	0 (0.0)	0 (0.0)
#True negative (%)	109 (99.1)	110 (100.0)	110 (100.0)
#False positive (%)	1 (0.9)	0 (0.0)	0 (0.0)
#False negative (%)	0 (0.0)	0 (0.0)	0 (0.0)
Sensitivity (%)	0	0	0
Specificity (%)	99.1	100.0	100.0
Agreement (%)	99.1	100.0	100.0
100-mg Vaporized CBD			
#True positive (%)	0 (0.0)	0 (0.0)	0 (0.0)
#True negative (%)	108 (100.0)	108 (100.0)	108 (100.0)
#False positive (%)	0 (0.0)	0 (0.0)	0 (0.0)
#False negative (%)	0 (0.0)	0 (0.0)	0 (0.0)
Sensitivity (%)	0	0	0
Specificity (%)	100.0	100.0	100.0
Agreement (%)	100.0	100.0	100.0
Vaporized cannabis (100-mg CBD/3.7-mg THC)			
#True positive (%)	4 (3.7)	2 (1.9)	0 (0.0)
#True negative (%)	99 (91.7)	104 (96.3)	104 (96.3)
#False positive (%)	5 (4.6)	0 (0.0)	0 (0.0)
#False negative (%)	0 (0.0)	2 (1.9)	4 (3.7)
Sensitivity (%)	100.0	50.0	0
Specificity (%)	95.2	100.0	100.0
Agreement (%)	95.4	98.1	96.3

Δ9-THC by dry weight, which exceeds the 0.3% THC concentration limit for "hemp" products that have been legalized in the USA under the 2018 "Farm Bill" (1), but this product would be legal in Canada. Thus, additional studies are needed to determine the impact of acute and chronic exposure to CBD-dominant products that conform to various legal definitions (e.g., <0.3% Δ9-THC for hemp in the USA). Nevertheless, the current data suggest that individuals subject to drug testing should be aware that even modest amounts of Δ9-THC in a CBD/hemp product may contribute to a positive urine drug test. Such consumer awareness is critical given that retail "CBD" products labeled as being free of Δ9-THC often contain Δ9-THC at concentrations comparable to, or above, that of the cannabis used in this study (9, 12).

To our knowledge, this study is the first to directly compare the urinary excretion profile of CBD and other cannabinoids across multiple routes of CBD administration (oral and vaporized). Overall, peak urinary concentrations of CBD were later relative to dose administration, but generally much higher, following oral administration of CBD compared with inhalation. CBD remained present in urine until the final collection point (i.e., 5 days after administration) for 4/6 oral administration sessions and 4/6 vaporized dosing sessions. In both oral and vaporized pure CBD sessions, most cannabinoids were not detected at all (CBN, 8,11-diOH-THC, THCV, THCVA, Δ9-THC, 8-OH-THC and Δ8-THCCOOH) and the remaining cannabinoids examined (Δ8-THC, Δ9-THCCOOH and 11-OH-Δ9-THC) were only detected at trace levels in a minority of samples collected. Importantly, this study also enabled a direct pharmacokinetic comparison between the same dose of vaporized CBD (100 mg), with and without a low dose of Δ9-THC. Interestingly, though peak urinary CBD concentrations were similar for vaporized CBD and vaporized CBD-dominant cannabis (with 3.7-mg Δ9-THC), CBD concentrations tended to be higher after administration of CBD-dominant cannabis at later urine collection time points (see Figure 1), suggesting that the simultaneous co-administration of CBD and Δ9-THC altered the elimination of CBD. The seemingly slower elimination rate of CBD in the presence Δ9-THC lends support to the notion that CBD and Δ9-THC can inhibit each other's metabolism because they are hydrolyzed by similar cytochrome P450 enzymes (20, 22, 25, 26). Last, inhalation of CBD-dominant cannabis resulted in detection of additional cannabinoids for some participants including Δ9-THCCOOH, THCVA, CBN, Δ8-THC and Δ8-THCCOOH.

Several limitations of this study warrant discussion. First, in some cases, the time between experimental sessions was seemingly not long enough for sufficient drug washout. For example, there were several occasions where CBD and/or Δ9-THCCOOH were detected at baseline (prior to drug administration), suggesting the study dose from the week prior had not been completely eliminated. Future controlled studies with multiple CBD/Δ9-THC dosing conditions may consider extending the window of observation after drug exposure to longer than 5 days, as this could help to characterize the full urinary excretion profile of CBD and other cannabinoids and also elucidate unequivocally, whether CBD is converted to Δ9-THC in the human gut. Second, this study was limited by the use of only one type of vaporizer, one batch of CBD-dominant cannabis, and one dose of CBD and Δ9-THC. Additional studies are needed to evaluate a

greater range of acute doses of CBD, and to evaluate chronic CBD dosing. Last, the small, homogeneous sample in this study limits the overall generality of these findings.

Conclusion

Acute oral ingestion or inhalation of a 100-mg dose of CBD did not result in positive urine drug test when using screening and confirmatory cutoffs in the Mandatory Guidelines for federal workplace drug testing. In contrast, inhalation of cannabis containing 100-mg CBD and 3.7-mg Δ9-THC resulted in positive test results for two out of six participants. Urinary concentrations of CBD were higher, and peaked later, when CBD was orally ingested compared with when it was inhaled. CBD appeared to be eliminated at a slower rate when Δ9-THC was simultaneously administered, compared with administration of CBD alone. Study results did not indicate that CBD converts to Δ-8 and/or Δ-9-THC in the human gut under the conditions tested, but future research should examine whether this occurs in conditions in which the gut is more acidic (e.g., during a fasted state). Several areas of need for additional research have been identified through this study, which is of ever-greater importance with the increased availability and legality of CBD/hemp products.

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