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Article

Cannabinoids Tetrahydrocannabinol, Cannabinol, Cannabidiol, Tetrahydrocannabivarin and 11-nor-9-carboxy-Δ^9-THC in Hair

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Abstract

The cannabinoids tetrahydrocannabinol (THC), tetrahydrocannabivarin (THCV), cannabidiol (CBD), cannabinol (CBN) and (-)-11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH) were determined in 4,773 hair samples. Confirmation of THC-COOH was by GC–MS-MS (gas chromatography–mass spectrometry-mass spectrometry). Confirmation of THC, THCV, CBN and CBD was by LC–MS-MS (liquid chromatoraphy–mass spectrometry-mass spectrometry) on an AB Sciex QTRAP 6500+ LC–MS-MS. The purpose of this work was not to utilize any analyte other than THC-COOH as indicative of ingestion, but to assess the absence or presence, and relative concentrations, of the other cannabinoid analytes in hair of marijuana users *vs.* primarily CBD users. In this regard, 10% of samples contained significantly higher concentrations of CBD relative to THC than the other 90%. A concentration of CBD that is five times greater than that of THC was proposed as good evidence of primarily CBD ingestion. THC concentrations in the samples ranged from below the limit of detection (5 pg/mg) to 47,808 pg/mg hair, varying widely in the relationship between parent THC and the metabolite THC-COOH. CBN was present in most samples, but concentrations relative to THC decreased with increasing THC concentrations. Only 26% of the samples contained THCV detectable by the method. When present, THCV concentrations averaged 1.77% of THC. A limitation of this study is the lack of subject histories to determine the types and amounts of products used and the mode of ingestion. Also, not all THC from external contamination may be removed. Nonetheless, the data provide a useful guide as to what cannabinoids may be found in hair, at what concentrations and under conditions of marijuana use *vs.* likely primarily CBD use.

Introduction

Public interest in cannabidiol (CBD) in the USA has dramatically increased over the last 3–4 years, as evidenced by a survey of internet queries, which numbered ~100,000/year in 2014 and 6.4 million in 2019 (1). Increased interest is accompanied by the increased use of CBD, particularly in states where cannabis products have been legalized, in some cases for medical use and in others unrestricted recreational use. The 2014 US Farm Bill (2) legalized the sale of 'non-viable hemp material' grown within states participating in the Hemp Pilot Program, which defined 'hemp' as cannabis containing <0.3% of THC. The 2018 US Farm Bill (3) led some states to interpret the bill as enabling private farmers to grow hemp for extraction and retail of CBD. However, federal agencies—including the FDA (Food and Drug Administration) and DEA (Drug Enforcement Agency)—retained regulatory authority over hemp-derived CBD as a Schedule I substance. As a workplace testing laboratory, it appeared that identifying the nature of the cannabis products being used by workplace subjects was becoming increasingly relevant, especially since CBD products may in practice contain significantly higher amounts of THC than the 0.3% level set by the legislation.

The upsurge in CBD availability as well as the changes in marijuana legality prompted the development of an additional assay to characterize the cannabinoid analytes tetrahydrocannabinol (THC), cannabinol (CBN), tetrahydrocannabivarin (THCV) and CBD as well as 11-nor-9-carboxy-Δ^9-THC (THC-COOH) in hair. From the results of these studies, along with those of others prior to 2014 when popularization of hemp/CBD products began, we aimed to be able to identify subjects who primarily use CBD products although these are known to contain variable amounts of THC.

Experimental

Samples

Samples were anonymized workplace testing samples, plus 335 high-school students and 145 drug rehabilitation subjects, collected in 2018–2019 and totaling 4,773 subjects. Within the figures throughout the report, the number of samples per category is provided.

The samples typically arrived in the laboratory within 1–2 days after collection; upon arrival, they were screened unwashed for cannabinoids by a microplate enzyme immunoassay at a cutoff of 1 pg of THC-COOH equivalents/mg hair (4); by the next day, the non-negative screening samples were washed and analyzed for THC-COOH by GC–MS-MS and then weighed again within 2–3 days for the cannabinoids THC, CBD, CBN and THCV by LC–MS-MS. Storage was at ambient temperature.

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Prior to confirmation, samples were washed by the following method. Two milliliters of dry isopropanol was added to a tube with hair (6–12 mg), and the tube was shaken in a water bath for 15 minutes at 37°C and 100–120 oscillations/minute. Isopropanol was removed; 2 mL of wash buffer (0.01 M phosphate buffer, pH 6.0, containing 0.1% BSA [bovine serum albumin]) were added to the tube, and the sample was shaken for 30 minutes at 37°C. The buffer was removed. This step was repeated two more times. In a previous study where negative hair was contaminated with extreme marijuana smoke exposure (5), effectiveness of the wash method was shown to be 100% effective at removing THC-COOH (5). Not only was there very little THC-COOH deposited from the smoke exposure, but the traces of THC-COOH from smoke were 100% removed by the washing. Also, after soaking the smoke-laden hair in water or saline, the result was the same (4).

In a smoke-exposure scenario similar to that in Hill's study (5), an average of ~60,000 pg THC/mg was deposited on two negative hair samples. With this extreme load of THC, the same wash method employed for THC-COOH removed 76% and 81% of THC.

Reagents

Methanol (CAS # [67-56-1]), 45% potassium hydroxide solution (CAS # [1310-58-3]), hexane (CAS # [110-54-3]) and ethyl acetate (CAS # [141-78-6]) were obtained from VWR (Van Waters and Rogers, Radnor, PA). 11-nor-9-Carboxy-Δ^9-THC (CAS #56354-06-4), (–)-Δ^9-THC (CAS 81586-39-2), CBD (CAS 13956-29-1), CBN (CAS 521-35-7) and THCV (CAS 31262-37-0) were obtained from Cerilliant (Round Rock, TX), as were the deuterated forms of THC-COOH, THC, CBD and CBN (no CAS numbers for the deuterated compounds available at this time). Derivatizing reagents, 2,2,3,3,4,4,4-heptafluoro-1-butanol (HFBO) (CAS # [375-01-9]), 2,2,3,3,3-pentafluoro-1-propanol (PFPO) (CAS # [422-05-9]) and heptafluorobutyric anhydride (HFBA) (CAS # [336-59-4]), were obtained from Millipore Sigma (St Louis, MO).

Apparatus

Analysis of C-THC was performed using an Ultra Trace 2000 GC equipped with a split/splitless injector using helium (carrier gas), ammonia (chemical ionization gas) and argon (collision gas) and a J&W DB-XLB capillary column, 30 m × 0.25 mm I.D. × 0.25 μm film thickness. Analysis of THC, CBD, CBN and THCV was performed on an AB Sciex QTRAP 6500+ LC–MS-MS with binary Shimadzu LC-30AD pumps and a Leap PALHTC-xt autosampler system with DLW (Dynamic Load and Wash, a feature of the CTC Analytics PAL injection platform).

Confirmation analysis

Confirmation of THC-COOH by GC–MS-MS, previously published (5) and in use for over 20 years, is as follows. Washed hair was digested in methanol/0.45% KOH (1:1) at 70°C for 1 hour, followed by addition to an SPE (solid phase extraction) cartridge that had been conditioned sequentially by ethyl acetate, methanol and HCl. The SPE column was washed sequentially with 2.25% KOH, 60:40 (v/v) 0.1 M HCl:methanol, 1% ammonium hydroxide, 85:15:1 (v:v:v) acetonitrile:water:ammonium hydroxide, 85:15:0.5 (v:v:v) methanol:acetonitrile:ammonium hydroxide, ethyl acetate and 100:0.5 (v:v) isooctane:glacial acetic acid before elution with 2 mL of 90:10:1 (v:v:v) isooctane:ethyl acetate:glacial acetic acid. The eluate was evaporated at 40°C with nitrogen and then derivatized for 1 hour with a mixture of 10 μL of 1:1 HFBO:PFBO added to 20 μL of HFBA and 25 μL of methylene chloride.

For THC-COOH chromatography, constant flow was at 1.0 mL/min. Splitless pressure surge was at 36 psi for

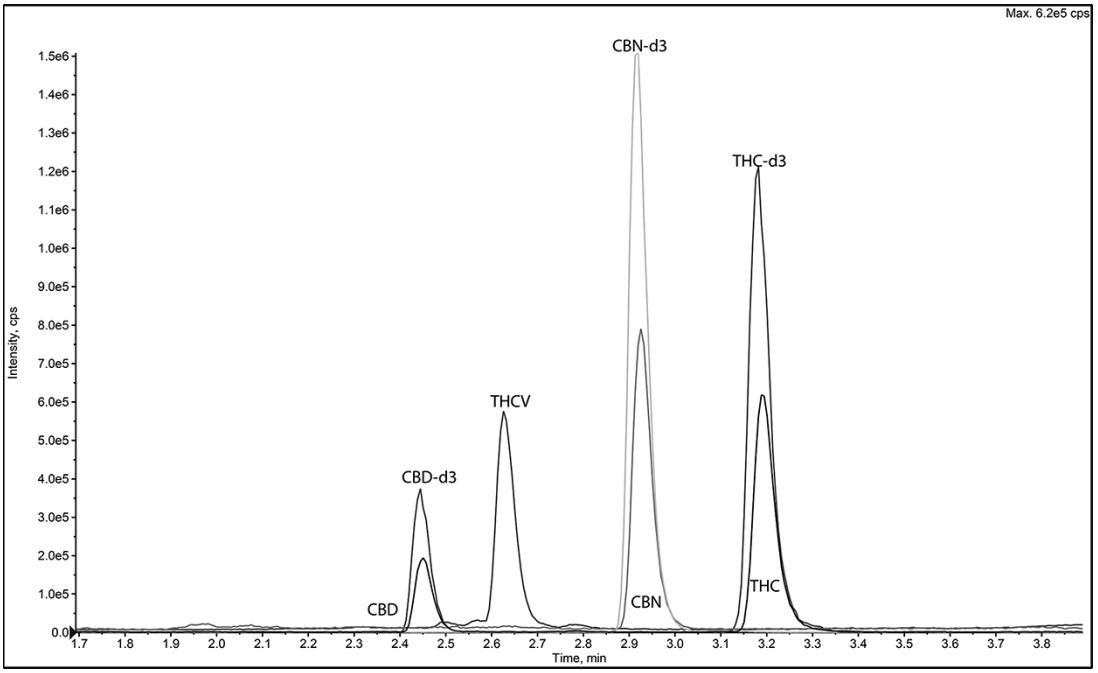

Figure 1. A typical chromatogram for THC, CBD, CBN and THC-V at 40 pg/mg hair.

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Table I. Cannabinoids LC–MS-MS Validation Parameters

	THC	CBD	CBN	THCV
Intra-assay precision				
10 pg/mg hair				
Average ($n = 5$)	8.78	8.45	8.24	7.80
SD	0.32	0.41	0.39	0.35
%CV	3.70	4.82	4.77	4.52
20 pg/mg hair				
Average ($n = 5$)	19.31	19.25	18.59	16.89
SD	0.37	0.46	0.49	0.48
%CV	1.92	2.37	2.66	2.86
50 pg/mg hair				
Average ($n = 5$)	46.30	50.03	46.06	47.66
SD	3.01	1.39	3.25	2.79
%CV	6.50	2.78	7.06	5.85
75 pg/mg hair				
Average ($n = 5$)	69.39	70.15	71.86	74.37
SD	0.69	1.27	0.76	5.17
%CV	1.00	1.81	1.06	6.96
100 pg/ mg hair				
Average ($n = 5$)	94.43	99.07	93.03	101.37
SD	2.50	2.77	2.36	3.04
%CV	2.65	2.80	2.53	3.00
125 pg/mg hair				
Average ($n = 5$)	111.28	117.31	112.89	125.50
SD	1.01	3.18	1.50	6.41
%CV	0.91	2.71	1.33	5.10
150 pg/1 mg hair				
Average ($n = 5$)	145.74	146.84	141.12	151.10
SD	1.19	2.44	2.28	3.94
%CV	0.82	1.66	1.61	2.61
Upper limit of linearity				
5,000 pg/ mg hair				
Average ($n = 5$)	4,367	4,601	4,606	4,518
SD	–72.05	–42.42	–59.60	–183.42
%CV	–1.65	–0.92	–1.29	–4.06
Inter-assay precision ($n = 25$, 5 assays over 5 days)				
50 pg/mg hair				
Average		46.25	49.35	45.62
SD		1.70	3.32	1.86
%CV		3.68	6.74	4.08
100 pg/ mg hair				
Average	94.15	97.29	93.04	96.47
SD	3.65	4.99	2.62	7.67
%CV	3.87	5.13	2.81	7.95
150 pg/1 mg hair				
Average	143.05	141.36	139.39	139.13
SD	5.56	9.99	3.08	11.30
%CV	3.89	7.07	2.21	8.12

%CV, % coefficient of variation; SD, standard deviation.

0.5 minutes, transfer line: 265°C. Oven parameters were as follows: initial temperature: 170°C; initial time: 0.5 minutes; ramp at 35°C/minute to 275°C, hold for 2.5 minutes; ramp at 35°C/minute to 300°C, hold for 2.0 minutes; septum purge: ON and splitless time: 0.50 minute. Ions of interest (using C-THC-d_9 for quantitation) were C-THC (HFBA + PFPO) *m/z* 474; C-THC (HFBA + HFBO) *m/z* 524; C-THC- d_9 (HFBA+ PFPO) *m/z* 483 and C-THC-d_9 (HFBA + HFBO) *m/z* 533.

Confirmation of THC, CBN, CBD and THCV by LC–MS-MS was developed specifically in order to assess the effects of increased CBD use on cannabinoids in hair. Twelve milligrams of hair was placed in a 13 × 75-mm screw-top borosilicate glass culture tube to which was added 100 µL of internal standard solution containing 2,000 pg each of THC-d_3, CBD-d_3 and CBN-d_3 in methanol. THC-d_3 was used as an internal standard for THCV. Then, 0.9 mL of a solution of methanol:H_2O:45% potassium hydroxide (5:4:1) was added, and the tubes were tightly capped and placed in a 70°C heating block for 60 minutes. Each batch included controls at 40, 125 and 2,000 pg/mg of each analyte. After 60 minutes of heating, 3.0 mL of a solution 9:1 hexane:ethyl acetate was added to the tubes, which were capped tightly, shaken for 2 minutes and centrifuged for 5 minutes at 3,200 rpm. The supernatant was transferred to a new 13 × 100-mm borosilicate glass culture tube and evaporated on a nitrogen evaporator set at 40°C. Once this supernatant was completely evaporated, 150 µL of methanol: deionized H_2O (85:15) solution was added. Tubes were vortexed, and the solution was transferred to an autosampler vial. Vials were sealed with PTFE-lined caps.

DLW wash 1 was 0.1% formic acid in H_2O. DLW wash 2 was CH_3CN:isopropanol:acetone (60:30:10). Chromatographic separation was accomplished using a Phenomenex® Kinetex® 1.7 mm C18 100 Å 150 mm × 2.1 mm column. The mobile phases were 0.1% formic acid in water and 0.1% formic acid in methanol. The method employed a gradient elution with a variable flow rate over 4.1 minutes. Analyst® (Sciex) software was used for all calculations, after calibration of the instrument with a single cutoff calibrator. The concentration of the calibrator was set at 100 pg/mg hair. Open controls included a negative, 40, 125 and 2,000 pg/mg.

Results

LC–MS-MS for THC, CBD, CBN and THCV

The retention times for the four analytes (at 40 pg/mg hair) were approximately 3.1, 2.5, 2.9 and 2.7 minutes for THC, CBD, CBN and THCV, respectively. A typical chromatogram is shown in Figure 1.

Validation of the method followed Clinical Laboratory Improvement Amendments 493.1253 and American National Standards Institute/Academy Standards Board Standards and the method performance validation requirements set by the College of American Pathology. The following parameters were included in the method validation: selectivity, calibration model (linearity), accuracy (bias) and precision, lower limit of quantification (LLOQ), upper limit of quantification (ULOQ and ULOL) and limit of detection (LOD). Precision data are shown in Table I. Carryover was negative at ULOL (5,000 pg/mg hair). The recovery was 110.9%, 97.6%, 106.2% and 80.4% for THC, CBD, CBN and THCV, respectively. Matrix effects (ion suppression) performed in 10 different hair samples at 10 pg were –25%, –30%, –25% and –21% for THC, CBD, CBN and THCV, respectively. For the deuterated standards, they were –29%, –41% and –38% for THC, CBD and CBN, respectively. Selectivity was studied with 10 different hair samples and with negative hairs spiked separately with 74 compounds, including opioids, amphetamines, benzodiazepines, OTC analgesics and barbiturates; no interference was observed. The LLOQ and LOD of cannabinoids were set at 10 and 5 pg/mg, respectively, for THC, CBN and CBD and at 10 and 7.5 pg/mg for THCV.

Cannabinoids in hair

The range of THC concentrations in the samples was from below LOD (5 pg/mg) to 47,808 pg/mg hair. This range

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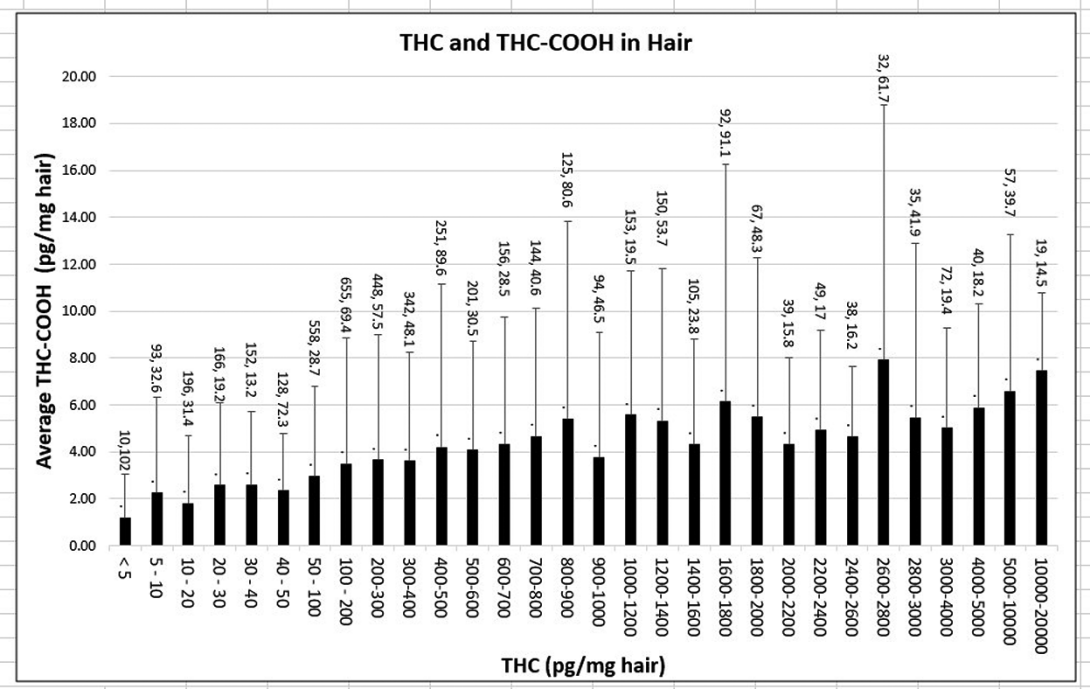

Figure 2. The population (>4,700 samples) is broken into segments of increasing THC concentrations. The bars show the THC-COOH concentrations of the samples in each THC range. Above each bar is shown the number of samples in the segment, followed by the highest CTHC concentration in the group (*n*, highest CTHC). Three samples are not shown as they appeared to be severe outliers (21,586, 28,925 and 47,808).

(up to 20,000 pg/mg) is displayed in Figure 2, which shows THC-COOH concentrations at increasing THC concentrations (three samples with 21,586, 28,925 and 47,808 pg THC/mg are not shown). Wide variability in the relationship between parent THC and the metabolite THC-COOH is apparent. Comparing two sets of samples illustrates the unpredictable nature of the relationship between THC and THC-COOH in hair: one set ($n = 28$) was completely negative (below LOD) for THC, CBD, CBN and THCV, the other set ($n = 10$) contained >10,000 pg THC/mg with the presence of CBD, CBN and THCV and both sets contained 1–10 pg THC-COOH/mg hair. In spite of the exceptions, however, an overall pattern of increased THC-COOH concentrations with increased THC concentrations is apparent.

CBN does not show a linear trend with increasing THC in hair. Rather, while CBN does increase with increasing THC concentrations (Figure 3A), the percent of CBN relative to THC decreases as THC concentrations increase (Figure 3B).

THCV was detected above LOD in only 26% of THC-containing samples; in these, the average concentration of THCV was 1.77% of THC (SD 1.62, median 1.38). The concentrations of THCV at increasing THC concentrations are shown in Figure 4A. The same samples are shown in Figure 4B as percent of THC.

Sixty-nine percent of the samples had CBD concentrations above LOD. Figure 5A shows the concentrations of CBD in hair relative to THC concentrations. Figure 5B shows the CBD levels as percent of THC. Very large standard deviations are evident in both graphs. Figure 6 shows that low CBD levels relative to THC concentrations are predominant in the population. Where 31% of samples contained <1% CBD, another 24% contained from 1% to 5% CBD, and a further 34% contained from 5% to 50% CBD. The remaining 11% of samples contained CBD concentrations from 50% to over 5,000% of THC, with 8.8% having equal or higher concentrations of CBD than THC. Not shown are the samples in THC categories above THC of 6,000 pg/mg; these contained no samples with high CBD levels.

Discussion

The large variations in ratios of parent:metabolite (THC:THC-COOH) concentrations challenge the common pattern in hair analysis of large and fairly predictable parent:metabolite ratios. Our results, however, are supported by other studies of sufficiently large sample sizes to serve as corroboration (6, 7). Huestis et al. (6) provide THC and THC-COOH hair values for 20 daily and 33 non-daily (1–5 times/week) self-reported and urine-tested marijuana users. Five of the 20 daily users had no THC (at LOD of 1 pg/mg) in the hair but did contain from 0.25 to 2.6 pg THC-COOH/mg hair. Among the 33 non-daily users, 9 had no THC in the hair but did contain from 0.1 to 0.75 pg THC-COOH/mg hair. These results agree with our data in that samples with THC, CBD, CBN or THCV all below LOD contained up to 10 pg/mg THC-COOH. Conversely, there are also samples with very high THC but little metabolite.

Minoli et al. (7) performed an analysis of THC and THC-COOH in 120 samples. Their data also showed a high variation in the parent:metabolite relationship but, like ours, showed an apparent overall increase of THC-COOH with increasing THC. This group analyzed only THC-COOH-positive samples for THC, and therefore, the data do not address the quandary of metabolite presence in the absence of parent compound.

While some THC may remain on hair from external sources, it is not likely that a person is exposed to very high

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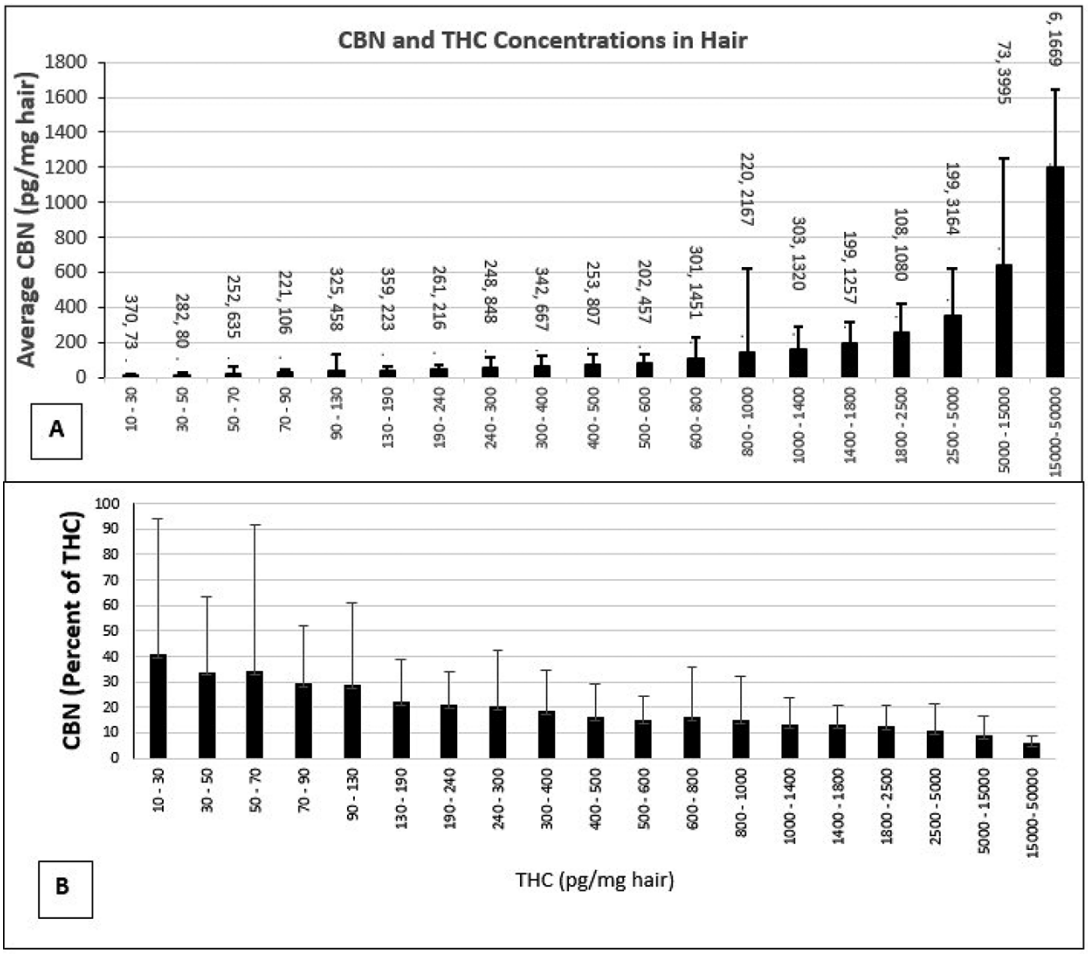

Figure 3. (A) The population (>4,500 samples) is broken into segments of increasing THC concentrations (280 samples, not included, did not contain ≥5 pg/mg CBN). The bars show the CBN concentrations in each THC range. Above each bar is shown the number of samples in the segment, followed by the highest CBN concentration in the group (*n*, highest CBN). (B) The same population as in (A), broken into the same segments of increasing THC concentrations. The bars in this figure show the CBN levels in each range as percent of the THC levels. CBN as percent of THC decreases with increasing THC concentrations.

levels of marijuana smoke without ingesting, either passively or actively.

The presence of THC in or on the hair shows at a minimum that the subject was exposed to THC, and, in the absence of CBD in the hair, the source of the THC-COOH in the hair was THC and not CBD.

Although high levels of THC on hair could reflect incomplete washing, the absence of THC with the presence of THC-COOH is harder to explain. The wash procedure used in this study was proven to remove traces of externally deposited THC-COOH from hair. Reports of THC-COOH in sections of hair with proven abstinence histories are not convincing unless the complete removal by the wash procedure applied in the study is demonstrated (8).

Minoli et al. (7) performed analysis of THC and THC-COOH in 120 samples. Their data also showed high variation in the parent:metabolite relationship but, like ours, showed an apparent overall increase of THC-COOH with increasing THC.

The variabilities in the relationships between parent and metabolite for THC and THC-COOH may be due to plant composition, preparation and storage (9, 10), mode of use (oral, smoking and vaping) (11, 12), and body weight, fat make-up and liver enzyme profile (11–14), as well as possible remaining externally derived THC after washing.

The decrease in CBN as percent of THC with increasing THC may reflect that higher potency marijuana products are processed to maximize tetrahydrocannabinolic acid and THC concentration and preservation, while minimizing degradation to CBN. High-potency hashish oil extracts with names including 'wax,' 'dabs,' 'crumble,' 'budder' or 'shatter' may contain as much as 80–90% THC (13, 14).

Only ~26% of the samples contained THCV above LOD, and in these, the concentrations averaged 1.77% of THC. While the concentrations generally increase with increasing THC (Figure 4A), THCV as percent of THC appears to decrease with higher THC (Figure 4B), although not nearly as dramatically as is the case for CBN. Although it is known that THCV is not present in Marinol® (15), information on its presence in high-potency THC oil extracts does not appear to be available.

Forty-one percent of the samples contained CBD < LOQ. Another 56.5% contained up to 200% of the THC concentrations. Publications on cannabinoids between 2002 and 2012 reported CBD concentrations generally <100% of THC, only

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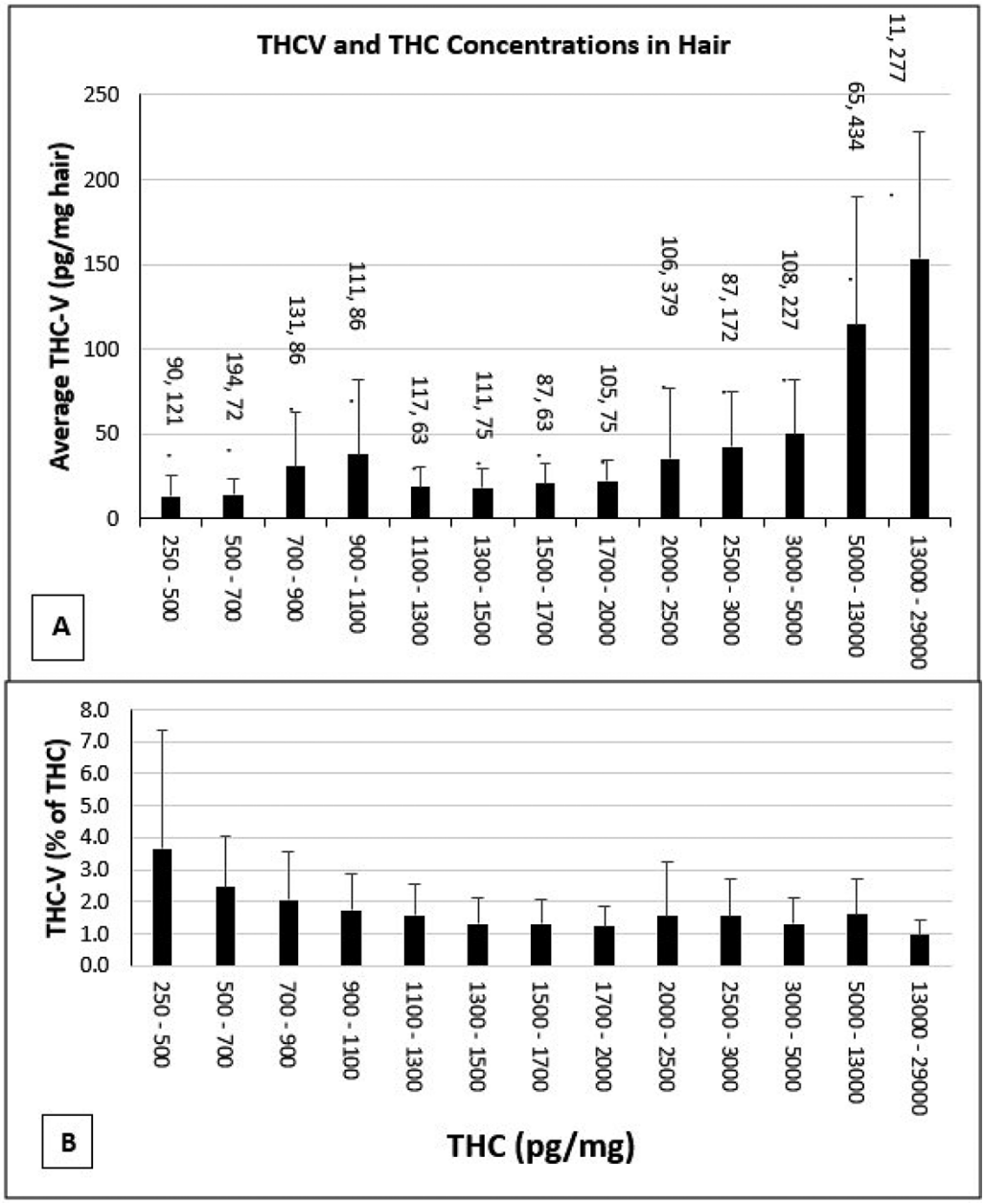

Figure 4. (A) Only 1,240 of >4,700 samples contained THCV ≥ LOD (7.5 pg/mg). These are shown in the chart in segments of increasing THC concentrations. The bars show the THCV concentrations in each THC range. Above each bar is shown the number of samples in the segment, followed by the highest THCV concentration in the group (*n*, highest THCV). (B) The same 1,240 samples shown in (a) are shown, with the same ranges of THC concentration segments. The bars show the THCV concentrations as percent of THC concentration in each THC range.

occasionally reaching 200% (16–19). A reasonable conclusion from the studies overall is that a concentration of CBD that is five times greater than that of THC is good evidence of primarily CBD use.

Conclusion

To our knowledge, the data presented provide the largest data set available characterizing THC, CBN, CBD, THCV and THC-COOH in hair. It appears in most cases that levels of CBD relative to THC in hair since the increased availability of hemp and CBD products have not changed dramatically from levels reported before this increased availability. Considering previous data and the present report, a finding of 5-fold concentrations of CBD compared to THC may argue for an exclusive use of CBD products that may also contain 0.3%, or sometimes more, THC.

A shortcoming of this study is that the results are not accompanied by known histories of dose and mode of use. Not only various modes of use such as vaping, eating, smoking or dermal application but also the increasingly creative product compositions such as 'wax,' 'dabs,' 'crumble,' 'budder,' 'shatter' or 'moonrocks' (13) may influence the relative amounts of THC, CBN, CBD, THCV and THC-COOH in the

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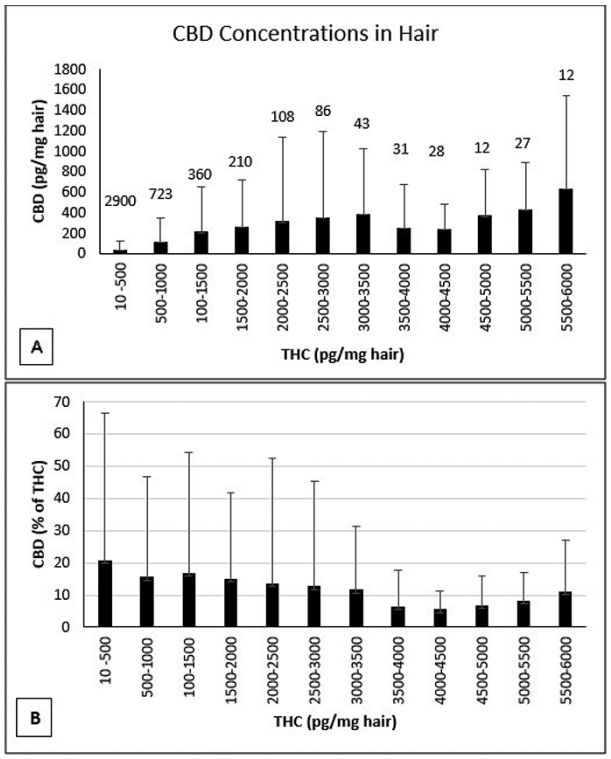

Figure 5. (A) The concentrations of CBD relative to those of THC are shown with increasing THC levels, with the number of samples per group above the standard deviation lines for each group. (B) CBD as percent of THC in the same sets of samples as in (A) is presented.

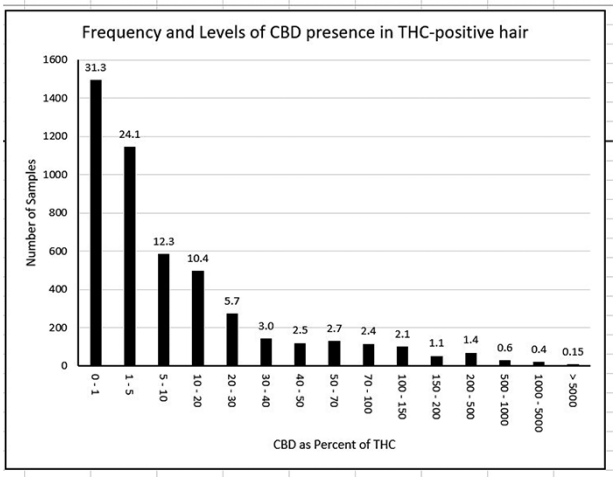

Figure 6. The chart shows the population of samples in categories defined by CBD as percent of THC. The bars show the number of samples in each category. In ~89% of samples, CBD was <50% of THC. These results may serve as a guide as to whether the subject has ingested primarily CBD, but containing THC due to the residual contamination of the CBD preparation with THC. When CBD is five times the THC content, it is an indication of primarily CBD ingestion.

hair. Further investigations to relate compositions and mode of use of both older and more recent marijuana products to the analytes found in hair would be welcome.

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