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Special Issue

Driving Under the Influence of Marijuana Versus Driving and Dying Under the Influence of Marijuana: A Comparison of Blood Concentrations of Δ^9-Tetrahydrocannabinol, 11-Hydroxy-Δ^9-Tetrahydrocannabinol, 11-Nor-9-Carboxy-Δ^9-Tetrahydrocannabinol and Other Cannabinoids in Arrested Drivers Versus Deceased Drivers

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Cannabis intoxication in living and deceased drivers is an important medico-legal topic, but only a limited number of studies examine cannabinoids in living and deceased humans. This study compares cannabinoid concentrations (in ng/mL) in driving under the influence of drug (DUID) drivers with blood cannabinoids to those in drivers who died while driving with cannabinoids in their postmortem (PM) peripheral blood. From 2010 to 2013, there were 318 cannabis-positive DUID cases (mean, median THC: 4.9, 3); 88 had cannabis-only in their bloods (mean, median THC: 5.8, 4). In 23 DUID cases, Huestis' Predictive Models with 95% confidence intervals were applied and evaluated, demonstrating that the actual case time points in all 23 cases fell within the predicted time ranges. Among deceased drivers, 19 had cannabis-positive toxicology (mean, median THC: 11.7, 4.5) and 8 had cannabis-only (mean, median THC: 20.3, 19.5). Motorcyclists and bicyclists comprised the majority of deceased vehicle operators, with bicyclists averaging the highest mean and median THC concentrations overall. The analysis of variance between living and deceased drivers' cannabinoid concentrations showed that THC-OH and THC-COOH concentrations are not statistically different between the two groups, but that THC concentrations are statistically different, making it difficult to directly correlate PM with antemortem THC concentrations between living and deceased drivers.

Introduction

The State of California is currently one of the 25 US states and territories (including the District of Columbia and Guam) to have existing or pending legislation permitting the use of cannabis for medicinal purposes (1, 2), the State having enacted this legislation since 1996. The National Traffic and Highway Safety Administration (NHTSA) has provided impairment, interpretation and other relevant information of the effects of cannabis on driving behavior in their most recent fact sheet pertaining to this drug (3). Additionally, a limited number of studies have been conducted concerning cannabis intoxication in drivers (4–6), as well as a handful of studies have been published in the scientific literature on postmortem (PM) cannabinoids (7–9), including the first such study published by this Office in October 2011 (10). Although one study sought to compare plasma with blood concentration ratios of cannabinoids in living and deceased individuals (7), to date, there is no literature comparing whole blood concentrations between living and deceased drivers. Consequently, a void currently exists on the topic of whole blood cannabinoid findings in deceased versus arrested drivers, providing a weak scientific foundation for forensic toxicologists, medical examiners, coroners, law enforcement agents, attorneys, judges and others in need of scientific literature on whole blood cannabinoid concentrations in arrested drivers suspected of driving under the influence of drugs (DUID), or deceased drivers with cannabinoids found in their PM blood specimens, often forcing them to rely on data obtained in clinical chemistry research settings involving carefully screened, pre-selected volunteers and analyses in plasma/serum rather than in whole blood.

The present study examines and compares cannabinoid concentrations measured in two groups of vehicle operators in San Francisco: (i) arrested operators of vehicles who allegedly operated their vehicles in San Francisco while impaired by cannabis and (ii) deceased operators of vehicles involved in fatal traffic accidents whose PM bloods were found to contain cannabinoids. Our goals were to determine blood cannabinoid concentrations and to better characterize any differences observed between these two groups of drivers, who theoretically have access and use similar cannabis preparations available in the City and County of San Francisco, thus removing any bias based on geolocation and cannabis product availability, and whose bloods were analyzed by the same ABFT-accredited laboratory, thus removing any bias based on analytical capability differences.

In addition, we apply and evaluate the Huestis' Predictive Models I and II for a subgroup of our living drivers suspected of driving under the influence of cannabis for whom we were able to identify the time interval between the driving incident (and, therefore, the last time they had the opportunity to be exposed to cannabis) and the time of blood draw. This portion of our study was designed to determine the consistency between the predicted times of cannabis exposure provided by the Huestis' models and the true Δt (time of alleged driving incident to time of blood draw) obtained from police reports and chain of custody records, in order to assess the usefulness of these research-derived, plasma-based predictive models in a forensic toxicology, whole blood setting after converting whole blood concentrations into plasma equivalent concentrations using various plasma to whole blood ratios and including the 95% confidence intervals (CIs) for each of these cases (11–14).

Methods

Subject selection

In our present study, we undertook a retrospective examination of the relevant electronic and printed records of the San Francisco Office of the Chief Medical Examiner (SF OCME) from January 2010 to December 2013, in order to identify all subjects of interest. We classified drivers into two groups based on the criteria detailed below.

Group 1 consisted of all vehicle operators (exclusively drivers) who were arrested by the San Francisco Police Department (SFPD) or the California Highway Patrol (CHP) from January 2010 to December 2013, for allegedly driving while impaired in the City and County of San Francisco, and who were subsequently discovered to have cannabinoids confirmed and quantified in their blood.

Group 2 consisted of vehicle operators (including automobile, motorcycle, bicycle and motorized scooter operators) who operated their vehicles on public roadways of the City and County of San Francisco, and who died while operating said vehicles from January 2010 to December 2013, and whose subsequent PM toxicology reports confirmed and quantified cannabinoids in their blood.

Group 1 subjects were subjected to human performance (HP) forensic toxicology investigations, whereas Group 2 subjects were subjected to PM forensic toxicology investigations by the SF OCME's Forensic Laboratory Division (FLD), which performs all forensic toxicologic analyses in the City and County of San Francisco. Police reports pertaining to Group 1 subjects were obtained from local law enforcement agencies, and case histories pertaining to Group 2 subjects were obtained from the Investigative Division of the SF OCME. Demographic and other data for both groups were tabulated and analyzed using Microsoft Excel (Version: 14.0.7145.5000) by Microsoft Corporation (Redmond, WA, USA).

Biologic specimen collection

Group 1 HP cases

BL-V (venous blood) was collected by venipuncture within 3 h of the alleged time of impaired driving by a state-certified phlebotomist as dictated by the Code of Regulations of the State of California into three sterile blood collection glass tubes (non-speckled gray 10 mL BD Vacutainer® by Becton Dickinson and Company, East Rutherford, NJ, USA), after the driver's forearm was disinfected using a fresh benzalkonium chloride (BZK) antiseptic and germicide towelette (PSS World Medical, Inc., Jacksonville, FL, USA). Each test tube contained 100 mg of sodium fluoride as a preservative and 20 mg of potassium oxalate as an anticoagulant, and was inverted several times after the blood collection for mixing purposes. The BL-V specimens were transported to the FLD of the SF OCME under chain of custody, and stored at 4°C from the time of accessioning through the time of analyses (a few hours for ethanol to several days to weeks for drugs), and until the time of disposal (more than a year later).

Group 2 PM cases

Autopsies normally took place several hours after time of death, but that interval could have been significantly greater based on scheduling requirements and/or the need for a more extensive case investigation. Blood specimens collected during the autopsy were labeled as peripheral blood, BL-P, and cardiac/central blood, BL-C, and were normally refrigerated overnight at 4°C in the morgue, and received by the FLD on the following business day. Blood specimens were submitted in multiple non-speckled gray 10 mL BD Vacutainer® test tubes, containing potassium oxalate and sodium fluoride. BL-P specimens were assumed to contain blood not derived from the inferior vena cava, or from the larger central area of the body, but the FLD has no means of independently verifying that a proper specimen collection including ligation of the vessel took place at autopsy. BL-C specimens were typically submitted in amber glass jars. After receipt and accessioning at the FLD, all PM blood specimens were stored at 4°C through the time of analyses and until the time of disposal (similar to the HP cases previously described).

Laboratory analyses

BL-V specimens of Group 1 and BL-P specimens of Group 2 were initially subjected to duplicate Forensic Alcohol Analyses under Title 17 of the Code of Regulations of the State of California soon after receipt (normally, within the same or next few business days). Subsequently, a fresh aliquot from the BL-V specimens of Group 1 and the BL-C specimens from Group 2 were subjected to the FLD's standard drug screening protocol employing commercially available screening techniques, including enzyme-linked immunosorbent assay (ELISA) by Venture Laboratories (Redwood City, CA, USA) and full-scan gas chromatography–mass spectrometry (GC–MS) by Agilent Technologies (Santa Clara, CA, USA) for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, phencyclidine and opiates/opioids, in addition to over 100 other drugs and their metabolites. Specifically for cannabinoids, the ELISA cutoff used in the screening of blood was 5 ng/mL. Following a positive ELISA result in the BL-V specimens of Group 1 or the BL-C specimens of Group 2, a fresh aliquot of BL-V specimens of Group 1 and the BL-P specimens of Group 2 were subjected to liquid–liquid extraction for the purposes of confirmation and/or quantitation of five common cannabinoids (i.e., THC: Δ^9-tetrahydrocannabinol; THC-COOH: 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH: 11-hydroxy-Δ^9-tetrahydrocannabinol; CBD: cannabidiol; CBN: cannabinol) by liquid chromatography–tandem mass spectrometry (LC–MS/MS) by Agilent Technologies, as previously described (8, 9). The lower limit of quantitation for all cannabinoids was 1 ng/mL, except for THC-COOH, which had a limit of quantitation of 5 ng/mL.

Application and evaluation of Huestis' Predictive Models I and II

Huestis' Predictive Models I and II were used to predict the time of last cannabis exposure in a subgroup of Group 1 drivers who had cannabinoids confirmed and quantified in their BL-V, and known time intervals between the alleged times of their DUID and the blood draws (Δt). The alleged times of DUID were obtained from available police reports provided by the SFPD or the CHP; the known time of blood draw was obtained from the biological Evidence Envelopes, which are part of the biological evidence collection kits issued by the FLD of the SF OCME to its client agencies.

We used adjusted terms for Huestis' Predictive Models I and II in our calculations, in order to account for the differences in concentration for THC and THC-COOH between whole blood and plasma as recently described in the literature (14). Compound-specific conversion factors were incorporated into the originally published Huestis' Predictive Models I and II. The original models are reproduced below, with T being the time (in h) since last exposure to cannabis, [THC] representing plasma concentration of THC in ng/mL, [THCCOOH] representing

plasma concentration of THC-COOH in ng/mL and CI representing the 95% confidence interval for the predictive models (CI_1 for Model I and CI_2 for Model II). The κ_1 value represents the converted whole blood into plasma THC concentrations in ng/mL using 0.68 : 1 as the conversion factor. The κ_2 value represents the converted whole blood into plasma THC-COOH concentrations in ng/mL using 0.59 : 1 as the conversion factor.

Model I (based on plasma concentrations):

$$\log\ T = -0.698 \log[\text{THC}] + 0.687$$

Model I (based on whole blood concentrations):

$$T = 10^{(-0.698 \log \kappa_1 + 0.687)}$$

Model II (based on plasma concentrations):

$$\log\ T = (0.576\ \log[\text{THCCOOH}]/[\text{THC}]) - 0.176$$

Model II (based on whole blood concentrations):

$$T = 10^{(0.576\ \log\ [\kappa_2/\kappa_1] - 0.176\ )}$$

CI_1 (for Model I; based on plasma concentrations):

$$\log\ \text{CI}_1 = \log T \pm 1.975\sqrt{\frac{0.030\{1.006 + (\log\ [\text{THC}] - 0.996)^2\}}{89.937}}$$

CI_1 (for Model I; based on whole blood concentrations):

$$\log\ \text{CI}_1 = \log T \pm 1.975\sqrt{\frac{0.030\{1.006 + (\log\ [\kappa_1] - 0.996)^2\}}{89.937}}$$

CI_2 (for Model II; based on plasma concentrations):

$$\log\ \text{CI}_2 = \log T \pm 1.975\sqrt{\frac{0.045\{1.006 + (\log\ [\text{THC}] - 0.283)^2\}}{123.420}}.$$

CI_2 (for Model II; based on whole blood concentrations):

$$\log\ \text{CI}_2 = \log T \pm 1.975\sqrt{\frac{0.045\{1.006 + (\log\ [\kappa_2/\kappa_1] - 0.283)^2\}}{123.420}}$$

Results

Group 1 DUID cases

In the four calendar years from 2010 to 2013, 3,565 DUID investigations involving blood evidence were submitted to the SF OCME's FLD. Of these, 318 (8.9%) involved drivers with cannabinoids confirmed and quantified in their BL-V. Cannabis was found in combination with other psychoactive substances in 230 (72.3%) of the 318 cases, and was the sole psychoactive compound in 88 of the 318 cases (27.7%). The mean age of the 318 drivers was 30.8 years, with a median of 28 years and range of 14–68 years. In addition, 86.1% ($n = 274$) were men; it should be noted that there was one driver whose sex was not specified. The racial distribution of the 88 cannabis-only drivers was 32.9% White ($n = 29$), 27.2% Black ($n = 24$), 25.0% Hispanic ($n = 22$), 6.8% Other ($n = 6$), 5.6% Asian ($n = 5$) and 2.2% Pacific Islander ($n = 2$). The mean age of the cannabis-only drivers was 28.7 years, with a median of 25 years and range of 14–58 years. Women comprised 15.9% of the 88 cannabis-only drivers of Group 1.

The three most common psychoactive substances found in combination with cannabis in the BL-V of the 230 drivers were ethanol ($n = 146$), cocaine/benzoylecgonine ($n = 39$) and methamphetamine/amphetamine ($n = 33$). Figure 1 presents the drugs most frequently encountered in combination with cannabis in DUID cases from 2010 to 2013 in this jurisdiction. The concentrations of cannabinoids found in the BL-V of all 318 drivers whose BL-V contained cannabinoids, in addition to other psychoactive substances, are statistically summarized in Table I.

Demographic and toxicologic data of the 88 DUID drivers whose BL-V specimens were found to only contain cannabinoids are presented in Table II and statistically summarized in Table III.

Group 2 PM cases

In the four calendar years from 2010 to 2013, 5,190 PM toxicology investigations were undertaken by the SF OCME's FLD. Of these, 194 (3.7%) were vehicular deaths, and 81 of the 194 (41.7%) involved drivers/vehicle operators. Men comprised 71 of the 81 deceased drivers (87.7%). The frequency of positive toxicology among the 81 deceased drivers was 82.7% (67 cases), and cannabis was confirmed and quantified in 23 of the 81 cases (28.4%). In 9 of the 23 cannabis-positive cases (39.1%), cannabis was determined to be the sole psychoactive substance in the bloods of the deceased vehicle operators. Table IV presents demographic and toxicologic data of the 23 cannabis-positive PM vehicle operators, and Table V presents statistical data for the 19 PM cases that involved cannabinoids confirmed and quantified in BL-P. Table VI presents demographic and toxicologic data for the nine cannabis-only PM vehicle operators, and Table VII presents demographic and toxicologic data for the eight PM cases with only cannabis confirmed and quantified in BL-P.

For the 23 PM cases involving drivers with cannabis (Tables IV and V), women comprised only 13.0% ($n = 3$) of the PM cannabis-positive population. The racial distribution of the 23 PM cannabis-positive drivers was 52.1% White ($n = 12$), 21.7% Black ($n = 5$), 13.0% Hispanic ($n = 3$), 4.3% Other ($n = 1$) and 8.6% Asian ($n = 2$). The mean age of the 23 PM cannabis-positive vehicle operator population was 31.6 years, with a median of median 30 years and range of 17–60 years. Drivers in these cases were more likely to have operated a motorcycle (56.5%, $n = 13$), followed by four-wheeled motor vehicles (26.0%, $n = 6$) and bicycles (13.0%, $n = 3$), while one case involved a motorized scooter (4.3%). The mean lapsed interval between time of death and autopsy in all PM cannabis-positive cases was 50.8 h, with a median of 47.3 h and range of 18.4–109.8 h.

Analysis of variance for data in Groups 1 and 2

Table VIII presents analysis of variance (ANOVA) results for THC, THC-COOH and THC-OH between all Group 1 and 2 subjects, showing a *P*-value for THC of 0.000009 as well as for THC-COOH and THC-OH of 0.5 and 0.1, respectively.

Table IX presents ANOVA results for THC, THC-COOH and THC-OH between Group 1 drivers with cannabis-only and

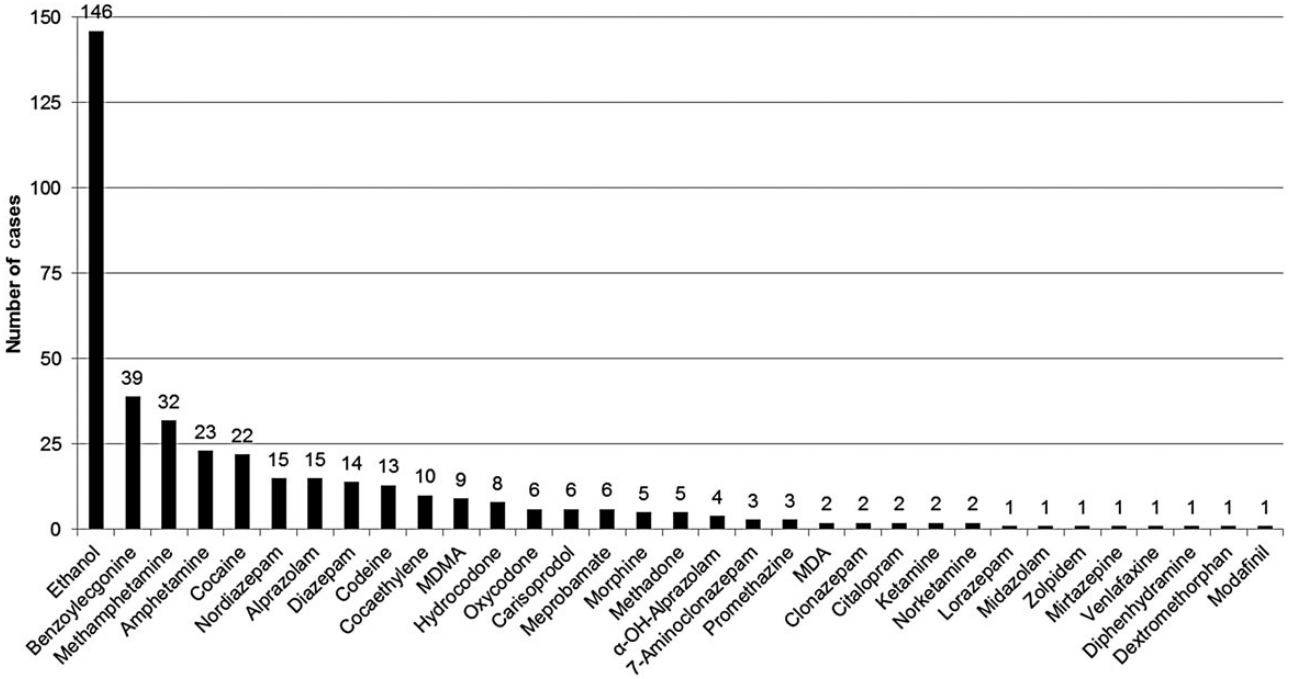

Figure 1. Drugs encountered with cannabis in DUID-arrested drivers of Group 1 in the City and County of San Francisco from 2010 to 2013.

Table I
Statistical Analysis of the Cannabinoid Concentrations (in ng/mL) Measured in 318 DUID-Arrested Drivers Comprising Group 1 Whose Bloods Contained Cannabinoids either Alone or in Addition to Other Psychoactive Substances

Group 1	THC	THC-COOH	THC-OH	CBN
Mean	4.9	64.0	4.7	1.3
Median	3	41	3	1
Standard deviation	4.9	79.7	4.1	0.5
Minimum	1	2	1	1
Maximum	33	720	22	2
Count	253	315	96	6

THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol; CBN, cannabinol.

Group 1 drivers who had cannabis along with other drugs. In this statistical evaluation, all *P*-values are >0.05.

Table X presents ANOVA results for THC, THC-COOH and THC-OH between Group 2 operators with only cannabis in their BL-P and Group 2 operators who had cannabis along with other drugs in their BL-P. In this statistical comparison, the *P*-value for THC is 0.02, but higher for THC-COOH and THC-OH ($P = 0.32$ and 0.40, respectively).

Table XI presents ANOVA results for THC, THC-COOH and THC-OH between Group 1 drivers with cannabis along with other drugs and Group 2 operators with cannabis along with other drugs in their BL-P. In this statistical evaluation, all *P*-values are >0.05 (specifically, >0.65).

Table XII presents ANOVA results for THC, THC-COOH and THC-OH between Group 1 drivers with only cannabis and Group 2 operators with only cannabis in their BL-P. In this statistical comparison, the *P*-value for THC is 1.1×10^{-6}, but higher for THC-COOH and THC-OH ($P = 0.38$ and 0.07, respectively).

Application and evaluation of Huestis' Predictive Models I and II on 23 Group 1 DUID drivers

For 23 of the Group 1 DUID cases in which drivers had cannabinoids as the only confirmed and quantified psychoactive substance in their BL-V, the FLD obtained police reports from the SFPD and CHP. For these 23 DUID cases, we were able to calculate the interval of time (Δt) between the driving incident (and, therefore, the last opportunity for cannabis exposure before apprehension by the police) and the time of blood draw. The FLD obtained the corresponding police reports in order to apply Huestis' Predictive Models I and II and related CIs, and evaluate their usefulness in these 23 DUID cases involving cannabinoid concentrations measured in whole blood.

Table XIII tabulates the THC and THC-COOH concentrations as measured in whole blood, the time in minutes between the latest opportunity of these drivers to be exposed to cannabis (approximated as the time of alleged driving, i.e., just prior to being in police custody) and the time of blood draw, the predicted time of cannabis exposure and associated 95% CI ranges for most recent exposure to cannabis based on Huestis' Predictive Models I and II after conversion of whole blood concentrations to plasma equivalents and a determination of whether or not the time ranges predicted by these whole-blood adjusted models were consistent with each case's actual time points as indicated by police and blood draw records.

As shown in Figure 2a, 16 of the 23 cases (69.9%) fell within the predicted time frames and had a Δt that fell within the 95% CI for Model I. It is noteworthy that while using Model I predictions, one reaches a predicted time of last marijuana exposure suggesting cannabis use after the driving incident (values lower than the true Δt) in 7 of the 23 cases (30.4%).

Figure 2b incorporates the predictions and 95% CIs of Huestis' Predictive Model II, and shows that 17 of the 23 cases (73.9%)

Table II

Demographic and Toxicologic Data for Group 1 DUID-Arrested Drivers with Only Cannabis in their Bloods, with Concentrations in ng/mL

Case number	Age (years)	Sex	Race	THC	THC-COOH	THC-OH	CBN	Height (m)	Weight (kg)	BMI
1	24	M	W	2	23			1.82	74.8	22.3
2	49	M	O		22			1.82	79.4	23.7
3	18	M	W	3	120			1.78	72.6	22.9
4	14	M	B	4	85			1.70	79.8	27.5
5	18	M	O	6	59			1.70	65.8	22.7
6	31	M	W	2	46			1.60	65.8	25.6
7	20	M	W	2	25			1.68	81.6	29.0
8	21	M	H	5	81	8		1.70	81.6	28.1
9	58	M	B	1	13			1.80	72.6	22.3
10	21	M	B	2	18			1.73	72.6	24.3
11	23	F	B	12	92			1.65	80.3	29.4
12	51	M	H	4	29			1.70	108.9	37.5
13	21	M	A		16			1.78	63.5	20.0
14	22	M	H	2	11			1.73	62.6	20.9
15	28	M	W	3	26			1.82	86.2	25.7
16	24	M	H	2	36			1.65	59.0	21.6
17	21	M	B	5	46			1.70	57.6	19.8
18	28	M	W	3	50			1.75	79.4	25.8
19	24	M	O	16	120			1.78	74.8	23.6
20	33	M	W	1	56					
21	19	M	B	5	29			1.80	70.3	21.6
22	27	M	W	8	96			1.82	79.4	23.7
23	19	M	H		16			1.82	102.0	30.5
24	20	M	W		6			1.68	63.5	22.5
25	30	F	B	10	40			1.73	63.5	21.2
26	35	F	W	13	66			1.65	58.5	21.4
27	25	M	O	5	100			1.82	104.3	31.1
28	25	M	B		16			1.88	83.1	23.7
29	21	M	W	6	20			1.82	77.1	23.0
30	27	M	B	13	130			1.75	74.8	24.3
31	58	M	H		12			1.70	77.1	26.6
32	19	F	W	26	320	14		1.70	86.2	29.7
33	35	M	H	4	32			1.65	68.0	24.9
34	21	M	H		21			1.85	77.1	22.4
35	21	M	A	2	20			1.68	68.0	24.2
36	41	M	H	6	74	5		1.75	81.6	26.5
37	28	M	H	16	66			1.70	65.8	22.7
38	20	F	H	4	17			1.65	59.0	21.6
39	27	M	W	5	86			1.82	81.6	24.4
40	19	M	O	9	40	5		1.78	61.2	19.3
41	22	M	W	2	35			1.73	77.1	25.8
42	33	M	B	10	100	5		1.85	95.3	27.7
43	56	F	W	10	85	9		1.68	61.2	21.7
44	25	F	B		8			1.60	117.9	46.0
45	21	F	B	7	73	6		1.68	65.8	23.4
46	21	F	A	3	57			1.73	54.4	18.2
47	30	M	A	11	95			1.70	65.8	22.7
48	22	M	W	5	55			1.73	65.8	22.0
49	26	M	B	4	24			1.82	63.5	18.9
50	21	M	W	3	40			1.73	63.5	21.2
51	17	M	W	3	26			1.80	86.2	26.5
52	21	M	W	4	24	2		1.93	81.6	21.9
53	20	M	A	1	13	1		1.73	63.5	21.2
54	54	M	H		5			1.73	83.9	28.1
55	27	M	B		15			1.85	102.1	29.6
56	29	F	H	1	15	1		1.73	49.9	16.7
57	52	M	W	6	51	3		1.80	90.7	27.8
58	22	M	B	13	222	9		1.80	117.9	36.2
59	22	M	P	3	65	1		1.78	104.3	33.0
60	41	M	H	5	153	2		1.70	72.6	25.0
61	24	M	W	18	424	13		1.70	63.5	21.9
62	22	F	W	3	121	4		1.73	81.6	27.3
63	21	M	H	3	55	1		1.70	59.9	20.6
64	38	M	B	1	38	1		1.80	74.8	23.0
65	39	M	H	1	34	1		1.73	90.7	30.4
66	20	M	H	4	275	2		1.60	68.0	26.5
67	35	M	H	22	720	22	2	1.50	54.4	24.2
68	41	M	W	4	94	4		1.88	86.2	24.3
69	19	M	P	2	25			1.82	81.6	24.4
70	36	M	B	7	158	4		1.75	72.6	23.6
71	34	M	O	1	41			1.73	84.3	28.2
72	22	M	B	7	94	5		1.80	88.4	27.1
73	21	M	H	5	76			1.75	88.4	28.7
74	30	M	W	2	26	1		1.91	113.4	31.2
75	22	F	B	10	116			1.73	74.8	25.0

(*continued*)

Table II Continued

Case number	Age (years)	Sex	Race	THC	THC-COOH	THC-OH	CBN	Height (m)	Weight (kg)	BMI
76	25	M	B	11	301	9		1.63	127.0	48.0
77	51	M	W		7			1.91	97.5	26.8
78	29	M	H	3	14	1		1.75	61.2	19.9
79	53	M	B	7	115	3		1.85	81.6	23.7
80	56	M	B	3	95			1.70	68.0	23.4
81	17	M	B	15	99			1.82	60.8	18.1
82	39	M	W	1	10			1.82	90.7	27.1
83	18	F	W	7	69	3	1	1.65	59.0	21.6
84	25	F	H	4	72	2		1.55	59.0	24.5
85	40	M	W	2	76			1.68	77.1	27.4
86	20	M	B	4	126	3		1.82	81.6	24.4
87	34	M	H	3	128	3		1.78	79.4	25.1
88	33	M	W	2	35	2		1.78	81.6	25.8

THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol; CBN, cannabinol; F, female; M, male; B, Black; H, Hispanic; A, Asian; W, White; O, Other; P, Pacific Islander.

Table III
Statistical Analysis of the Cannabinoid Concentrations (in ng/mL) Measured in 88 DUID-Arrested Drivers from Group Whose Bloods Only Contained Cannabinoids

Group 1 (cannabis-only)	THC	THC-COOH	THC-OH	CBN
Mean	5.8	77.1	4.6	1.5
Median	4	50.5	3	1.5
Standard deviation	5.0	100.3	4.6	0.7
Minimum	1	5	1	1
Maximum	26	720	22	2
Count	76	88	33	2

THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol; CBN, cannabinol.

had a Δt that fell within the 95% CIs for Model II. It is noteworthy that while using Model II predictions, one reaches a predicted time of last cannabis exposure suggesting cannabis use prior to the driving incident (values higher than the true Δt) in 6 of the 23 cases (26.0%).

Finally, Figure 2c shows that jointly considering the Models and 95% CIs for both of Huestis' Predictive Models I and II allows for the most realistic predictions as all 23 of our 23 cases (100.0%) had predictions that were in agreement with each case's actual time points.

Discussion

Group 1 HP cases

In the City and County of San Francisco, cannabis-positive drivers represented nearly 1 out of 9 DUID cases from 2010 to 2013, and demonstrated an increasing proportion of the overall DUID driver population during this time as well (Figure 3). The increase in proportion of cannabis-positive DUIDs is observed, despite a decrease in overall DUID submissions to the FLD in the same period. Cannabis-positive drivers had a mean and median age of 30.8 and 28 years, respectively. The mean and median THC concentrations in the whole blood of the 318 drivers of Group 1 (4.9 and 3 ng/mL, respectively) should be carefully considered if *per se* limits for intoxication and impairment due to cannabis are to be enacted in the State of California.

For those 230 drivers in Group 1 who were cannabis-positive and had other psychoactive drugs in their blood, ethanol was the most prevalent drug found in combination with cannabis, representing more than half of the Group 1 population. Stimulants, such as cocaine and methamphetamine, were also frequently encountered in combination with cannabis in Group 1 living drivers (Figure 1).

For the 88 drivers of Group 1 who only had cannabis in their blood, the mean THC concentration was higher than that in the overall Group 1 population (5.8 versus 4.9 ng/mL), and may be due to the lack of other drugs present in Group 1 drivers.

A comparison of the median THC concentration values of the various subgroups of Group 1 suggests that the median THC concentrations in San Francisco DUID-arrested drivers never reach 5 ng/mL, but instead ranges from 3 to 4.5 ng/mL (Tables III, V and VII). This is a significant finding as it could be used to assist in establishing an appropriate whole blood THC *per se* concentration in California if the establishment of one was deemed necessary.

Application and evaluation of Huestis' Predictive Models I and II on 23 Group 1 DUID drivers

In 23 DUID cases from Group 1 (with known Δt values) who had cannabinoids-only in their BL-V, Huestis' Predictive Models I and II and their associated 95% CIs predicted times of exposure to marijuana, consistent with each case's actual time points in 100.0% ($n = 23$) of cases with a known Δt (Figure 2c). This significant demonstration of predictive power of the Huestis' Models is even more impressive if one considers that the Models were applied and evaluated in a forensic setting instead of a research one, using converted whole blood concentrations into plasma concentrations for both THC and THC-COOH, with the amount and frequency of cannabis use for all subjects remaining unknown as factors. In addition, our findings seem to further support the discussion point made by Huestis *et al.* (13), who favor combining the 95% CIs of Models I and II to estimate the time of last cannabis ingestion, as the combined confidence intervals improve the accuracy of these predictions 'regardless of the number of doses or choice of total versus free cannabinoid concentrations', which highlight their usefulness in a forensic setting.

However, as described in the same study by Huestis *et al.*, there are limitations to applying the Predictive Models I and II in a forensic setting, and the observations made after their application and evaluation in our 23 Group 1 DUID population with a known Δt are similar to the findings of that study involving the estimation of time since last oral ingestion of cannabis. First, Model I was found to be less reliable than Model II in predicting a time

Table IV
Demographic and Toxicologic Data for Group 2 Deceased Drivers with Cannabis-Positive PM Toxicology Reports.

Case	Age (years)	Sex	Race	Drugs detected in peripheral blood	Vehicle operated	Height (m)	Weight (kg)	BMI	Manner of death	Δt (h) between time of death and time of autopsy
1	32	M	H	THC-OH—5 ng/mL Ethanol—0.22% w/v	Motorcycle	1.70	81.6	28.2	Accident	27.42
2	44	M	W	THC—1 ng/mL Ethanol—0.21% w/v Nordiazepam—250 ng/mL Bupropion—0.23 mg/L MDMA—0.24 mg/L	Motorcycle	1.75	95.3	31.0	Accident	19.88
3	22	M	W	THC—24 ng/mL THC-COOH—78 ng/mL THC-OH—5 ng/mL	Bicycle	1.73	88.0	29.5	Accident	18.42
4	25	M	W	THC—2 ng/mL THC-COOH—26 ng/mL	Motorcycle	1.73	77.1	25.8	Homicide	39.78
5	33	M	O	THC*—2 ng/mL THC-COOH*—30 ng/mL Ethanol*—0.10% w/v	Motorcycle	1.91	125.1	34.5	Accident	142.83
6	20	F	B	THC—2 ng/mL THC-COOH—7 ng/mL Ethanol—0.04% w/v	Automobile	1.75	83.9	27.3	Accident	119.13
7	26	M	H	THC—3 ng/mL THC-COOH—28 ng/mL THC-OH—3 ng/mL Ethanol—0.12% w/v Benzoylecgonine—0.21 mg/L Cocaethylene—0.05 mg/L Methamphetamine—0.05 mg/L	Motorcycle	1.73	78.9	26.5	Accident	84.83
8	25	M	W	THC*—1 ng/mL THC-COOH*—30 ng/mL Ethanol—0.05% w/v		1.73	64.0	21.4	Accident	73.57
9	20	M	W	THC—6 ng/mL THC-COOH—108 ng/mL THC-OH—6 ng/mL Ethanol—0.07% w/v	Automobile	1.88	75.7	21.4	Accident	41.33
10	17	M	B	THC—1 ng/mL THC-COOH—10 ng/mL THC-OH—1 ng/mL	Motorcycle	1.80	80.7	24.8	Homicide	109.82
11	37	M	A	THC—1 ng/mL	Motorcycle	1.68	97.1	34.5	Accident	38.50
12	42	M	B	THC—2 ng/mL THC-COOH—19 ng/mL THC-OH—2 ng/mL Cocaine—0.06 mg/L Benzoylecgonine—1.99 mg/L	Automobile	1.78	93.9	29.7	Accident	59.17
13	48	F	W	THC—46 ng/mL THC-COOH—44 ng/mL THC-OH—4 ng/mL	Bicycle	1.63	51.7	19.6	Accident	47.83
14	25	M	A	THC—15 ng/mL THC-COOH—7 ng/mL	Automobile	1.73	68.0	22.8	Accident	35.58
15	21	M	W	THC—24 ng/mL THC-COOH—86 ng/mL THC-OH—3 ng/mL	Bicycle	1.65	65.8	24.1	Accident	50.28
16	30	M	W	THC—1 ng/mL Ethanol—0.13% w/v Diazepam—94 ng/mL Nordiazepam—161 ng/mL Clonazepam—25 ng/mL 7-Aminoclonazepam—56 ng/mL Oxycodone—0.05 mg/L Methadone—0.46 mg/L	Motorcycle	1.75	96.6	31.5	Accident	60.72
17	39	M	B	THC—1 ng/mL THC-COOH—7 ng/mL Ethanol—0.13% w/v Amphetamine—0.05 mg/L Methamphetamine—0.78 mg/L	Automobile	1.78	105.7	33.4	Accident	36.63
18	60	F	B	THC*—13 ng/mL THC-COOH*—28 ng/mL THC-OH*—7 ng/mL	Automobile	1.70	101.1	34.9	Accident	47.38
19	30	M	W	THC—20 ng/mL THC-COOH—123 ng/mL THC-OH—5 ng/mL Ethanol—0.11% w/v	Motorcycle	1.85	89.4	26.0	Accident	55.00
20	22	M	H	THC—50 ng/mL THC-COOH—552 ng/mL THC-OH—43 ng/mL Cannabinol*—2 ng/mL	Motorcycle	1.70	69.4	24.0	Accident	70.35

(*continued*)

Table IV Continued

Case	Age (years)	Sex	Race	Drugs detected in peripheral blood	Vehicle operated	Height (m)	Weight (kg)	BMI	Manner of death	Δt (h) between time of death and time of autopsy
21	31	M	W	THC*—4 ng/mL THC-COOH*—37 ng/mL THC-OH*—3 ng/mL Ethanol—0.03% w/v	Motorized scooter	0.91	37.6	45.0	Accident	56.00
22	56	M	W	THC—7 ng/mL THC-COOH—41 ng/mL Ethanol—0.22% w/v Venlafaxine—0.10 mg/L	Motorcycle	1.80	151.0	46.4	Accident	53.53
23	24	M	W	THC—6 ng/mL THC-COOH—52 ng/mL Ethanol—0.10% w/v Nordiazepam—5 ng/mL Tramadol—67 ng/mL *O*-Desmethyltramadol—24 ng/mL	Motorcycle	1.80	86.6	26.6	Homicide	34.73

The four sets of concentrations marked with asterisks indicate measurements in central/cardiac blood.
THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol; CBN, cannabinol; F, female; M, male; B, Black; H, Hispanic; A, Asian; W, White; O, Other.

Table V
Statistical Analysis of the Cannabinoid Concentrations (in ng/mL) Measured in 19 Deceased Drivers from Group 2 who were Cannabis-Positive in their BL-P

Group 2	THC	THC-COOH	THC-OH
Mean	11.7	79.2	7.7
Median	4.5	41	4.5
Standard deviation	15.4	136.0	12.4
Minimum	1	7	1
Maximum	50	552	43
Count	18	15	10

THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol.

since last cannabis exposure, frequently suggesting an interval of time where the subject is unlikely to have an opportunity to smoke cannabis as seen in Figure 2a (i.e., while under police custody), but generally provided a smaller margin of error when factoring in the 95% CIs. Secondly, Model II was found to be more accurate in predicting a time of last cannabis exposure, frequently incorporating the true Δt value in a majority of cases, but provided a much larger margin of error as observed in Figure 2b, with the largest 95% CIs between 2 and 16 h (Case 62). Finally, the combination of ranges provided by the predicted values and 95% CIs of both Models I and II brackets the true Δt in 100.0% of our cases and, therefore, may be used in court to offer opinions regarding last exposure to the drug and possible impairment to safely operate a vehicle.

Ideally, additional studies will soon be performed that will allow for the development of models for exposure to cannabis (and inferences regarding impairment), which would predict a value greater than the Δt (indicating cannabis use prior to being in police custody) similar to the predictive values provided by Model II, but with smaller ranges thus narrowing the window of time of cannabis exposure (comparable to the 95% CIs of Model I). Unfortunately, the required research in this area is currently greatly hindered by Federal regulations, and other restrictions on cannabis research, and remains an area of much-needed investigation as the incidence of cannabis DUIDs appears to be on the rise.

In addition, forensic toxicologists typically deal in whole blood concentrations, and currently, a weakness of applying Huestis' Predictive Models I and II involves the conversion of whole blood concentrations into plasma concentrations, which introduces potential error and highlights a limitation of applying these algorithms in forensic casework. As recent research indicated the existence of different whole blood-to-plasma ratios in living individuals for both THC and THC-COOH (14), the Huestis' Predictive Model II may be susceptible to greater errors when accounting for these differences in whole blood-to-plasma ratios, since Model II utilizes a ratio of THC-COOH to THC in plasma (0.68 : 1 and 0.59 : 1 whole blood to plasma, respectively, for THC and THC-COOH).

As forensic toxicologists often handle biological evidence obtained from subjects who had no controlled cannabis administration in a non-clinical setting, these clinically derived models may not accurately predict the time of last cannabis exposure for subjects involved in forensic casework. On a related note, a limitation of this study is the unknown time of cannabis exposure by the DUID subjects, as the lack of a controlled clinical setting versus the real-world forensic setting frequently involves individuals whose time since last cannabis exposure is often not disclosed, as it may be considered incriminating. Even if this information is provided by the subject, the time provided may neither be true nor accurate, as subjects may misreport due to memory problems, or falsify the time of last exposure to cannabis in an effort to avoid an allegation of cannabis consumption and/or impairment at or near the time of driving.

Our study of 23 DUID cases with known time points suggests that the two Huestis' Predictive Models may be prone to erroneous predictions in as many as 30% of the cases when used in isolation, but they are able to accurately predict times of cannabis exposure consistent with each case's actual time points in 100.0% of the cases when considered in combination with each other, including both of their associated 95% CIs.

Group 2 PM cases

Over the period of 2010–2013, a 65% increase in the number of vehicular deaths in San Francisco has been observed, but the number of deaths with cannabis-positive toxicology findings has seen 175% increase in the same period (Figure 4).

For the PM vehicular deaths from 2010 to 2013 in the City and County of San Francisco, cannabis-positive PM vehicle operators

Table VI
Demographic and Toxicologic Data for Group 2 Deceased Drivers with Cannabis-Only PM Toxicology Reports, with Concentrations in ng/mL

Case	Age (years)	Sex	Race	Drugs in peripheral blood	Vehicle type	Height (m)	Weight (kg)	BMI	Manner of death	Δt (h) between time of death and time of autopsy
1	22	M	W	THC—24 ng/mL THC-COOH—78 ng/mL THC-OH—5 ng/mL	Bicycle	1.73	88.0	29.5	Accident	18.42
2	25	M	W	THC—2 ng/mL THC-COOH—26 ng/mL	Motorcycle	1.73	77.1	25.8	Homicide	39.78
3	17	M	B	THC—1 ng/mL THC-COOH—10 ng/mL THC-OH—1 ng/mL	Motorcycle	1.80	80.7	24.8	Homicide	109.82
4	37	M	A	THC—1 ng/mL	Motorcycle	1.68	97.1	34.5	Accident	38.50
5	48	F	W	THC—46 ng/mL THC-COOH—44 ng/mL THC-OH—4 ng/mL	Bicycle	1.63	51.7	19.6	Accident	47.83
6	25	M	A	THC—15 ng/mL THC-COOH—7 ng/mL	Automobile	1.73	68.0	22.8	Accident	35.58
7	21	M	W	THC—24 ng/mL THC-COOH—86 ng/mL THC-OH—3 ng/mL	Bicycle	1.65	65.8	24.1	Accident	50.28
8	60	F	B	THC*—13 ng/mL THC-COOH*—28 ng/mL THC-OH*—7 ng/mL	Automobile	1.70	101.1	34.9	Accident	47.38
9	22	M	H	THC—50 ng/mL THC-COOH—552 ng/mL THC-OH—43 ng/mL Cannabinol*—2 ng/mL	Motorcycle	1.70	69.4	24.0	Accident	70.35

The one concentration marked with an asterisk indicates a measurement in central/cardiac blood.
THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol; CBN, cannabinol; F, female; M, male; B, Black; H, Hispanic; A, Asian; W, White.

Table VII
Statistical Analysis of the Cannabinoid Concentrations (in ng/mL) Measured in Eight Deceased Drivers From Group 2 With Cannabis-Only in their BL-P

Group 2 (cannabis-only)	THC	THC-COOH	THC-OH
Mean	20.3	114.7	11.2
Median	19.5	44	4
Standard deviation	20	195	18
Minimum	1	7	1
Maximum	50	552	43
Count	8	7	5

THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol.

represented a large portion of the PM vehicle operator population (11.8%), and had a mean and median age of 31.6 and 30 years, respectively.

For the 11 drivers in Group 2 who were cannabis-positive and had other psychoactive drugs in their BL-P, the mean concentration of THC for this group is lower than the overall mean for the entire Group 2 population (4.9 versus 11.7 ng/mL, respectively), perhaps due to this population's moderation of cannabis use in the setting of cannabis use in combination with other drugs.

For the eight drivers in Group 2 who had cannabinoids-only in their BL-P, the mean THC concentration was higher than that in the overall Group 2 population (20.3 versus 11.7 ng/mL, respectively), and may be due to the use of higher amounts of cannabis when the drug is use exclusively (i.e., in the absence of other drugs) or a very recent exposure to the drug (even during the act of driving itself).

Motorcyclists and bicyclists make up the two largest portions of the deceased vehicle operator population (56.5 and 13.0%, respectively). This may be due to the added need for balance and spatial orientation that these two-wheeled vehicles demand for safe transport (abilities that cannabis is known to impair), but could also be due to inherent added risk factors associated with these types of vehicles, e.g., lack of protective steel cage

Table VIII
ANOVA Between Cannabinoid Concentrations in BL-V of 318 Group 1 Living DUID-Arrested Drivers Whose Bloods had Cannabis either alone or with Other Psychoactive Compounds and in 19 Group 2 Deceased Drivers Whose BL-P Bloods Had Cannabis either alone or with Other Psychoactive Compounds Showing A Statistically Significant Difference in THC Concentrations, but not in THC-COOH or THC-OH Concentrations Between These Two Populations

THC ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Group 1	254	4.9	24.9			
Group 2	18	11.7	237.8			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	778.5	1	778.5	20.3	0.000009	4
Within groups	10343.9	270	38			
Total	11122.4	271				

THC-COOH ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Group 1	316	64.0	6351.9			
Group 2	15	79.2	18519.7			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	3210.1	1	3210.1	0.5	0.5	3.9
Within groups	2260188.0	329	6869.7			
Total	2263328.1	330				

THC-OH ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Group 1	96	4.7	17.5			
Group 2	10	7.7	156.2			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	80.5	1	80.5	2.7	0.1	3.9
Within groups	3069.5	104	29.5			
Total	3150.0	105				

Table IX
ANOVA for THC, THC-COOH and THC-OH Mean Blood Concentrations Between 230 Group 1 Drivers with Cannabis and Other Psychoactive Compounds in Their BL-V Versus 88 Group 1 Drivers with Cannabis-Only in Their BL-V Showing No Statistical Difference in THC, THC-COOH and THC-OH Concentrations Between these Two Populations

THC ANOVA: single factor

Summary						
Group 1	Count	Average	Variance			
Cannabis and other drugs	177	4.5	24.2			
Cannabis-only	77	5.8	25.5			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	83.9	1	83.9	3.4	0.06	3.8
Within groups	6216.8	252	24.6			
Total	6300.8	253				

THC-COOH ANOVA: single factor

Summary						
Group 1	Count	Average	Variance			
Cannabis and other drugs	228	59.2	4902.7			
Cannabis-only	88	77.1	9973.1			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	20251.4	1	20251.4	3.2	0.07	3.8
Within groups	1980590.1	314	6307.6			
Total	2000841.5	315				

THC-OH ANOVA: single factor

Summary						
Group 1	Count	Average	Variance			
Cannabis and other drugs	63	4.7	15.7			
Cannabis-only	33	4.6	21.4			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	0.02	1	0.02	0.001	0.97	3.9
Within groups	1663.3	94	17.6			
Total	1663.4	95				

Table X
ANOVA for THC, THC-COOH and THC-OH Mean Blood Concentrations Between 11 Group 2 Operators with Cannabis and Other Psychoactive Compounds in Their BL-P Versus 8 Group 2 Operators Who Had Cannabis-Only in Their BL-P Showing a Statistically Significant Difference for THC Concentrations, but not for THC-COOH or THC-OH Concentrations Between These Two Populations

THC ANOVA: single factor

Summary						
Group 2	Count	Average	Variance			
Cannabis and other drugs	10	4.9	33.4			
Cannabis-only	8	20.3	382.5			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	1064.3	1	1064.3	5.7	0.02	4.4
Within groups	2978.7	16	186.1			
Total	4043.1	17				

THC-COOH ANOVA: single factor

Summary						
Group 2	Count	Average	Variance			
Cannabis and other drugs	8	48.1	1984.6			
Cannabis-only	8	115.7	32698.5			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	18292.5	1	18232.5	1.0	0.32	4.6
Within groups	242782.3	14	17341.5			
Total	261074.9	15				

THC-OH ANOVA: single factor

Summary						
Group 2	Count	Average	Variance			
Cannabis and other drugs	5	4.2	2.7			
Cannabis-only	5	11.2	318.2			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	122.5	1	122.5	0.7	0.40	5.3
Within groups	1283.6	8	160.4			
Total	1406.1	9				

Table XI
ANOVA for THC, THC-COOH and THC-OH Mean Blood Concentrations Between 230 Group 1 Drivers with Cannabis and Other Psychoactive Compounds in Their BL-V Versus 11 Group 2 Operators with Cannabis and Other Psychoactive Compounds in their BL-P, Showing No Statistical Difference in THC, THC-COOH and THC-OH Concentrations Between These Two Populations

THC ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Cannabis and other drugs (Group 1)	177	4.5	24.2			
Cannabis and other drugs (Group 2)	10	4.9	33.4			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	0.8	1	0.8	0.03	0.84	3.8
Within groups	4575.6	185	21.7			
Total	4576.5	186				

THC-COOH ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Cannabis and other drugs (Group 1)	228	59.2	4902.7			
Cannabis and other drugs (Group 2)	8	48.1	1984.6			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	957.3	1	957.3	0.1	0.65	3.8
Within groups	1126816.1	234	4815.4			
Total	1127773.4	235				

THC-OH ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Cannabis and other drugs (Group 1)	63	4.7	15.7			
Cannabis and other drugs (Group 2)	5	4.2	2.7			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	1.3	1	1.3	0.8	0.76	3.9
Within groups	989.2	66	14.9			
Total	990.5	67				

around the operator, lack of airbags to protect the operator in the event of an accident, etc.

In addition, our deceased population of bicyclists was found to have the highest mean and median blood concentrations of THC, the primary psychoactive cannabinoid (31 and 24 ng/mL, respectively), when compared with all other deceased vehicle operators in San Francisco. This may be due to many reasons. One may be that bicyclists operate their bicycles on public roadways soon after using the drug and while under the influence of relatively high amounts of THC. However, the higher concentrations of THC in the blood of deceased bicyclists may also be an indication that bicyclists die more often when involved in accidents, whereas operators of other types of vehicles (who could theoretically have equal or even higher levels of THC in their PM bloods) survive the accidents (due to airbags, protective steel cage, etc.) and therefore never get counted toward the numbers of deceased vehicle operators who come under the jurisdiction of the SF OCME.

Demographic discrepancies in Group 1 and 2 cases

The 2013 US Census data for the City and County of San Francisco present its racial distribution as follows: 41.6% White, 34.4% Asian, 15.3% Hispanic, 6.0% Black, 0.5% Pacific Islanders and 2.2% Other (mostly those self-identifying with more than one race) (15). The racial distribution among the 88

Table XII
ANOVA for THC, THC-COOH and THC-OH Mean Blood Concentrations Between 88 Group 1 Drivers with Cannabis-Only in Their BL-V Versus 8 Group 2 Operators Who Had Cannabis-Only in Their BL-P, Showing a Statistically Significant Difference for THC Concentrations, But Not for THC-COOH or THC-OH Concentrations Between These Two Populations

THC ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Cannabis-only (Group 1)	77	5.8	25.5			
Cannabis-only (Group 2)	8	20.3	382.5			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	1530.1	1	1530.1	27.4	1.1×10^{-6}	3.9
Within groups	4620.0	83	55.6			
Total	6150.1	84				

THC-COOH ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Cannabis-only (Group 1)	88	77.1	9973.1			
Cannabis-only (Group 2)	7	114.7	38138.2			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	9167.4	1	9167.4	0.7	0.38	3.9
Within groups	1096496.2	93	11790.2			
Total	1105663.7	94				

THC-OH ANOVA: single factor

Summary						
Groups (1 and 2)	Count	Average	Variance			
Cannabis-only (Group 1)	33	4.6	21.4			
Cannabis-only (Group 2)	5	11.2	318.2			
ANOVA						
Source of variation	SS	d.f.	MS	*F*	*P*-value	*F*-critical
Between groups	183.6	1	183.6	3.3	0.07	4.1
Within groups	1957.7	36	54.3			
Total	2141.3	37				

cannabis-only drivers in Group 1 examined in this study depicts a different racial distribution with 32.9% White ($n = 29$), 27.2% Black ($n = 24$), 25.0% Hispanic ($n = 22$), 6.8% Other ($n = 6$), 5.6% Asian ($n = 5$) and 2.2% Pacific Islander ($n = 2$). Although the White population is still the most prevalent, the Black and Hispanic populations are significantly overrepresented, whereas San Francisco's Asian population is significantly underrepresented. These observations are similar for the PM vehicle operators of Group 2, except that the White population is overrepresented in the PM population (52.1 versus 41.6%), and the Hispanic population is more comparable in both the census and the PM vehicle operators of Group 2.

In addition, the US Census reports that the median age of San Franciscans is 38.5 years, yet this study shows a median age of 28 years for the 318 arrested drivers with cannabis-positive toxicology and range of 14–68 years, and a median age of 30 years, with a range of 17–60 years, for the 23 PM drivers with cannabis-positive toxicology.

Another discrepancy between the US Census data and the present study's findings pertains to the proportion of the 318 living and 23 deceased drivers who are female since females only accounted for 13.5 and 13.0% of Groups 1 and 2, respectively, when the US Census indicated that females constitute 49.1% of San Franciscans.

An additional factor influencing the population discrepancies of our Groups 1 and 2 may be the possibility that drivers suspected of DUID were arrested and booked in the jurisdiction of the City and County of San Francisco or expired while operating a vehicle on San Francisco public roadways, but actually resided in and/or originated their commute from the neighboring cities and counties

Table XIII
Application and Evaluation of Huestis' Predictive Models I and II on 23 Cannabis-Only Cases of Group 1 DUID Drivers, with a Known Interval Between the Time of Driving and the Time of Blood Draw

Case number (from Table II)	THC ng/mL (BL-V)	THC-COOH ng/mL (BL-V)	Time of driving incident (T_1)	Time of blood draw (T_2) (n = next day)	Δt ($T_2 - T_1$) (min)	Model I prediction (min)	Range of Model I prediction using 95% CI		Model II prediction (min)	Range of Model II prediction using 95% CI		Δt relative to range
							−95% CI (min)	+95% CI (min)		−95% CI (min)	+95% CI (min)	
3	3	120	4 : 33	7 : 24	171	105	48	232	363	137	964	Within
8	5	81	15 : 55	17 : 11	76	74	33	163	216	82	570	Within
37	16	66	20 : 28	22 : 01	93	33	15	74	98	37	259	Within
43	10	85	23 : 10	0 : 54 n	104	46	21	101	149	56	393	Within
45	7	73	1 : 20	2 : 36	76	59	26	130	168	64	442	Within
46	3	57	3 : 40	5 : 11	91	105	48	232	237	90	626	Within
47	11	95	3 : 00	3 : 00	115	43	19	95	150	57	396	Within
50	3	40	0 : 39	1 : 27	48	105	48	232	193	73	510	Within
51	3	26	23 : 23	1 : 16	113	105	48	232	151	57	397	Within
52	4	24	1 : 14	2 : 49	95	86	39	190	122	46	321	Within
57	6	51	16 : 52	19 : 42	170	65	29	144	149	56	393	Within
58	13	222	23 : 34	0 : 22 n	48	38	17	85	223	84	588	Within
59	3	65	22 : 59	1 : 22 n	143	105	48	232	255	97	675	Within
61	18	424	3 : 10	4 : 36	86	31	14	68	268	101	709	Within
62	3	121	1 : 24	3 : 48	144	105	48	232	365	138	968	Within
63	3	55	2 : 29	3 : 33	64	105	48	232	232	88	613	Within
65	1	34	18 : 17	20 : 23	126	224	102	493	331	125	877	Within
67	22	720	1 : 05	3 : 39	124	27	12	59	324	122	858	Within
74	2	26	14 : 41	16 : 46	125	139	63	306	190	72	502	Within
75	10	116	2 : 15	3 : 38	83	46	21	101	178	68	470	Within
81	15	99	3 : 00	5 : 24	144	35	16	77	129	49	339	Within
83	7	69	15 : 13	17 : 02	109	59	26	130	162	61	428	Within
84	4	72	13 : 06	14 : 38	92	86	39	190	229	87	606	Within

'Range' is the time interval based on Model I and II predictions including the 95% CIs. The 'Δt Relative to Range' is marked as 'Within' if the actual time points fall within the predictions of Models I and II or within the 95% CIs. Times are indicated using the 24-h clock. Whole blood cannabinoid concentrations converted to plasma equivalents using a ratio (whole blood to plasma) of 0.68 : 1 for THC, and 0.59 : 1 for THC-COOH.

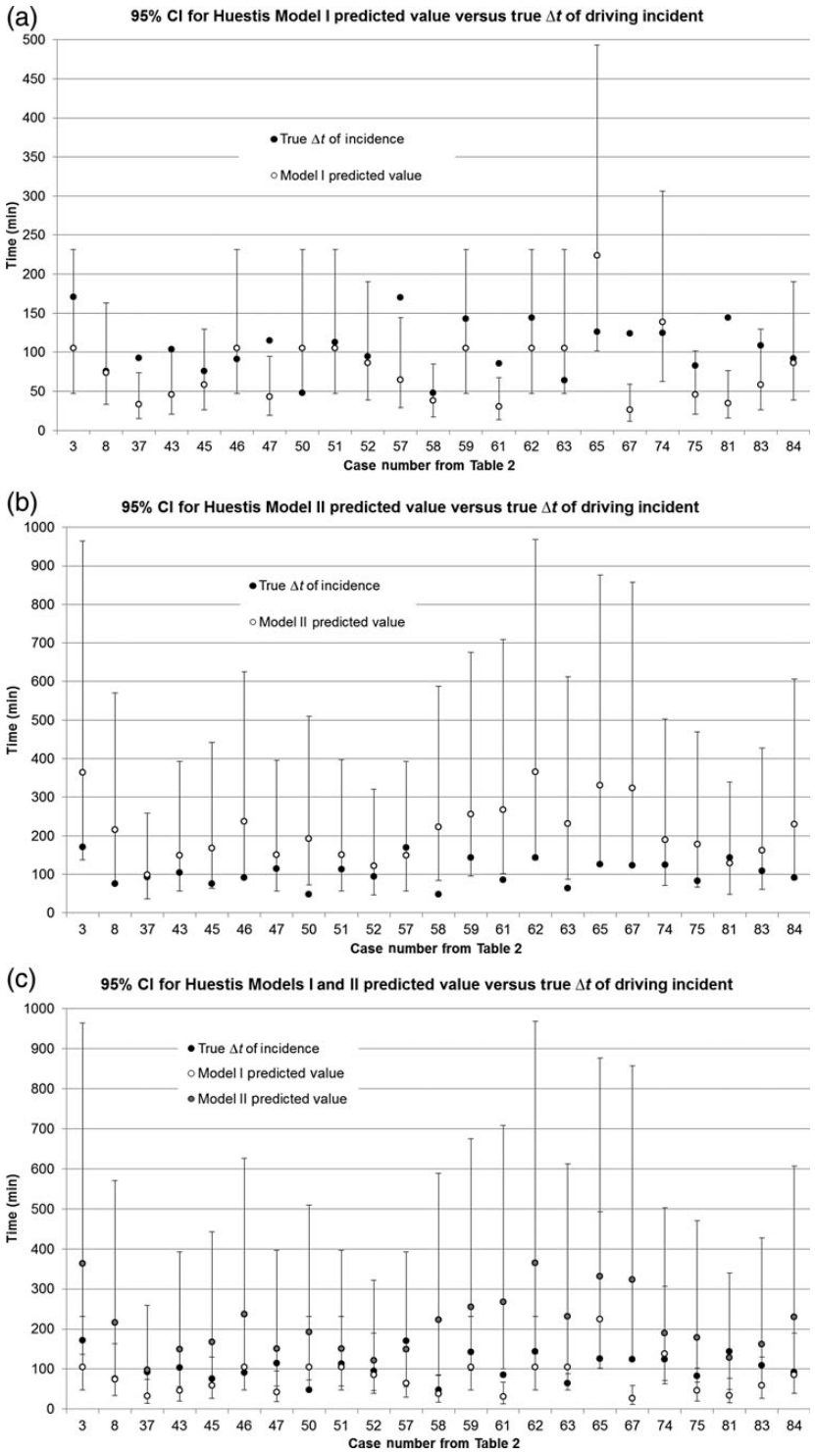

Figure 2. (a) Application and evaluation of Huestis' Predictive Model I on 23 DUID cannabis-only cases. The open point represents the predicted value provided by Model I, and the black point represents actual time difference (Δt) between time of driving (obtained from police reports) and time of blood draw (obtained from FLD Toxicology Reports). Lower and upper margins associated with each open point represent the $\pm$ 95% CI for each predicted value, using a whole blood-to-plasma ratio of 0.68 : 1 for THC. Case numbers correlate with those listed in Table II. (b) Application and evaluation of Huestis' Predictive Model II to 23 DUID cannabis-only cases. The open point represents the predicted value provided by Model I, and the black point represents actual time difference (Δt) between time of driving (obtained from police reports) and time of blood draw (obtained from FLD Toxicology Reports). Lower and upper margins associated with each open point represent the $\pm$ 95% CI for each predictive value, using a whole blood-to-plasma ratio of 0.68 : 1 for THC, and 0.59 : 1 for THC-COOH. Case numbers correlate with those listed in Table II. (c) Application and evaluation of Huestis' Predictive Models I and II on 23 DUID cannabis-only cases. This graph is an overlay of (a and b), with the black point representing the actual time difference (Δt) between time of driving (obtained from police reports) and time of blood draw (obtained from FLD Toxicology Reports), the open dot being the Model I predicted value and the gray dot being the Model II predicted value. Lower and upper margins associated with each open and gray point represent the $\pm$ 95% CI for each predicted value, using a whole blood-to-plasma ratio of 0.68 : 1 for THC, and 0.59 : 1 for THC-COOH. Case numbers correlate with those listed in Table II.

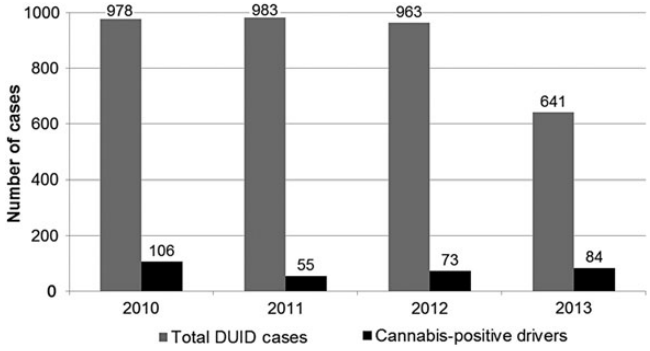

Figure 3. Annual DUID cases submitted to the SF OCME versus annual number of submitted DUID cases found to be cannabis-positive.

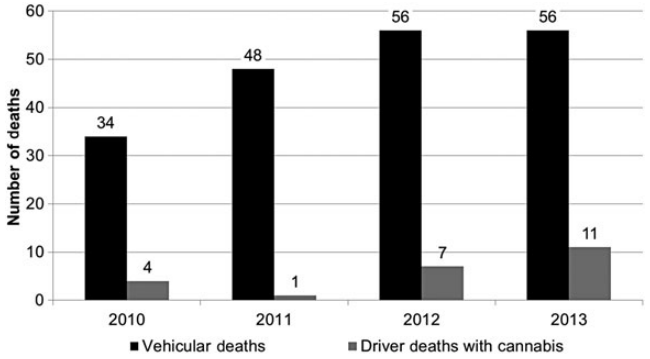

Figure 4. Total annual vehicular deaths versus annual driver deaths with cannabis-positive toxicology in the City and County of San Francisco from 2010 to 2013.

located in the Greater San Francisco Bay Area, or simply were visitors or tourists. As our DUID data does not incorporate a subject's actual place of residence, but only that they were arrested in San Francisco, we recognize that this represents a limitation of the present study that should be considered for further research.

ANOVA in Group 1 and 2 cases

Comparison of the concentrations of the three most common cannabinoids (i.e., THC, THC-COOH and THC-OH) in DUID-arrested drivers' BL-V with those measured in deceased drivers' BL-P suggests that caution should be exercised when attempting to interpret PM concentration based on comparisons with antemortem or clinical findings. The present study clearly demonstrates that the three common cannabinoids do not exhibit similar patterns of change between life and death. Specifically, whereas THC-OH and THC-COOH mean concentrations show no statistically significant differences between living and deceased drivers, mean THC concentrations between the two groups of drivers cannot be directly correlated as they exhibit statistically significant differences (Table VIII). This finding is consistent with previous published research into the behavior of cannabinoids in PM forensic toxicology, which indicated that THC is influenced differently by PM interval than THC-OH and THC-COOH (10).

Moreover, when we examine mean blood cannabinoid concentrations in HP drivers with cannabis-with-other-drugs and compare them with those of HP drivers with only cannabis in their blood, the concentrations of all three common cannabinoids show no statistically significant differences between the two types of cannabis-positive living drivers of Group 1 (Table IX). This may be partly due to the ongoing metabolism of cannabis by drivers in Group 1, even while under police custody. This process may enable drivers of both types within Group 1 (i.e., cannabis-only drivers versus cannabis-with-other-drugs drivers) to exhibit comparable levels of blood cannabinoid concentrations by the time of the eventual blood draw, which could have been different at the time of the alleged cannabis DUID. This inherent limitation of forensic toxicologists needing to determine blood cannabinoid concentrations near/at the time of driving constitutes an obvious challenge for our study as well.

When the mean BL-P cannabinoid concentrations between deceased vehicle operators with cannabis-with-other-drugs are compared with those of deceased vehicle operators with only cannabis in their blood, THC concentrations exhibit statistically significant differences and are not comparable between the two types of cannabis-positive deceased operators of Group 2 (Table X). The same cannot, however, be said for THC-OH and THC-COOH. One possible explanation could be that subjects engaging in polypharmacy often exhibit different concentrations of THC from those who only use cannabis. Poorly understood and described contributions by PM redistribution and PM interval could also affect the measured cannabinoid concentrations in deceased vehicle operators.

Our data further support the notion that drivers with polypharmacy (230 HP cases and 11 PM cases) and drivers with cannabis-only (88 HP cases and 8 PM cases) exhibit different concentrations of THC from each other, yet retain comparable concentrations of THC-COOH and THC-OH. When considering arrested and deceased San Francisco drivers with cannabis and other drugs in their blood, the two populations are fairly comparable as they exhibit statistically insignificant differences when ANOVA is performed. The arrested and deceased drivers with cannabis-only in their blood exhibit statistically significant differences when THC concentrations are concerned, but still retain THC-COOH and THC-OH concentrations that do not exhibit statistically significant differences.

Finally, the present study suggests that it is reasonable to expect that mean THC-OH and THC-COOH concentrations do not significantly change between living and deceased drivers, and that the PM concentrations of these two compounds may be more closely associated with their respective antemortem concentrations. The same does not appear to be true for THC, and this may be, partly, due to the observed differences in THC concentrations of drivers with cannabis in combination with other drugs in their bloods, when compared with those of drivers with cannabis-only in their bloods.

Interpretation of results

Forensic practitioners should exercise caution when attempting to correlate or compare PM with antemortem THC concentrations such as those found in DUID-arrested drivers or in *per se* legislative codes, as this present study suggests that concentrations of THC found in living and deceased subjects exhibit statistically significant differences. Forensic practitioners may correlate THC-OH and THC-COOH PM concentrations with clinical THC-OH and THC-COOH concentrations, as these two cannabinoid compounds do not appear to suffer any statistically significant concentration changes between HP and PM cases (Tables VIII–XII). Expert opinions about intoxication and impairment may be best

formed after careful consideration of the totality of circumstances including a driver's toxicology and symptomology. Such opinions may be achieved even in the absence of a *per se* blood THC limit as a toxicologic concentration can be best interpreted when put in the context of each case including one's driving behavior, ability to follow instructions and performance in field sobriety tests.

This study is the first of its kind in which blood concentrations of cannabinoids in living and deceased drivers or vehicle operators, who presumable had access to the same types of marijuana within the same jurisdiction, were directly compared with each other. The information provided is useful and much needed, especially as legislation may soon be proposed for enactment in the State of California and other jurisdictions regarding *per se* driving blood THC concentrations when driving under the influence of drugs, similar to those previously enacted elsewhere (16, 17). It is expected that legislators, law enforcement personnel, forensic toxicologists, medical examiners and other concerned parties will see increases in cannabis-involved DUID cases as well as in cannabis-positive PM driving cases, as more States legalize marijuana for recreational as well as medicinal use.

The present analysis of cannabinoid blood concentrations in HP and PM forensic toxicology cases acts as a reference to those concerned with the interpretation of these compounds in their cases and provides a strong framework for sound judicial and legislative codes concerning public safety on California roads. In addition, this study can serve as a foundational model for much-needed future studies examining cannabis incidence in other metropolitan areas.

Conclusion

In reviewing 4 years of forensic toxicology cases involving cannabis in the City and County of San Francisco, it was found that driving under the influence of cannabis and dying while driving under the influence of cannabis result in statistically different blood THC concentrations. Additionally, there are significant considerations pertaining to the drivers' polypharmacy exposure that appear to affect the measured cannabinoid concentrations in living and in deceased drivers. However, blood THC-OH and THC-COOH concentrations are statistically similar in the two groups of drivers regardless of circumstances. This finding suggests that antemortem and PM concentrations of these two cannabinoids are more comparable between living and deceased drivers. Representation of the San Franciscan population seems to be skewed when it comes to sex and race in both living and deceased cannabis-positive drivers, and bicyclists and motorcyclists represent the majority of deceased cannabis-positive vehicle operators. Furthermore, deceased bicyclists have, on average, the highest THC concentrations among all deceased vehicle operators, but this may be due to the inherent risks associated with operating a bicycle on public roadways. Finally, it was determined that the Huestis' Predictive Models and associated 95% CI remain useful and relevant as demonstrated by the time point analyses performed in a group of 23 THC-positive DUID-arrested drivers.

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