

Passive Cannabis Smoke Exposure and Oral Fluid Testing. II. Two Studies of Extreme Cannabis Smoke Exposure in a Motor Vehicle

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Abstract

Two studies were conducted to determine if extreme passive exposure to cannabis smoke in a motor vehicle would produce positive results for Δ^9 -tetrahydrocannabinol (THC) in oral fluid. Passive exposure to cannabis smoke in an unventilated room has been shown to produce a transient appearance of THC in oral fluid for up to 30 min. However, it is well known that such factors as room size and extent of smoke exposure can affect results. Questions have also been raised concerning the effects of tobacco when mixed with marijuana and THC content. We conducted two passive cannabis studies under severe passive smoke exposure conditions in an unventilated eight-passenger van. Four passive subjects sat alongside four active cannabis smokers who each smoked a single cannabis cigarette containing either 5.4%, 39.5 mg THC (Study 1) or 10.4%, 83.2 mg THC (Study 2). The cigarettes in Study 1 contained tobacco mixed with cannabis; cigarettes in Study 2 contained only cannabis. Oral fluid specimens were collected from passive and active subjects with the Intercept[®] Oral Specimen Collection Device for 1 h after smoking cessation while inside the van (Study 1) and up to 72 h (passive) or 8 h (active) outside the van. Additionally in Study 1, Intercept collectors were exposed to smoke in the van to assess environmental contamination during collection procedures. For Study 2, all oral fluid collections were outside the van following smoking cessation to minimize environmental contamination. Oral samples were analyzed with the Cannabinoids Intercept MICRO-PLATE EIA and quantitatively by gas chromatography–tandem mass spectrometry (GC–MS–MS). THC concentrations were adjusted for dilution ($\times 3$). The screening and confirmation cutoff concentrations for THC in neat oral fluid were 3 ng/mL and 1.5 ng/mL, respectively. The limits of detection (LOD) and quantitation (LOQ) for THC in the GC–MS–MS assay were 0.3 and 0.75 ng/mL, respectively. Urine specimens were collected, screened (EMIT, 50 ng/mL cutoff), and analyzed by GC–MS–MS for THCCOOH (LOD/LOQ = 1.0 ng/mL). Peak oral fluid THC concentrations in passive subjects recorded at the end of cannabis

smoke exposure were up to 7.5 ng/mL (Study 1) and 1.2 ng/mL (Study 2). Thereafter, THC concentrations quickly declined to negative levels within 30–45 min in Study 1. It was found that environmentally exposed Collectors contained 3–14 ng/mL in Study 1. When potential contamination during collection was eliminated in Study 2, all passive subjects were negative at screening/confirmation cutoff concentrations throughout the study. Oral fluid specimens from active smokers had peak concentrations of THC approximately 100-fold greater than passive subjects in both studies. Positive oral fluid results were observed for active smokers 0–8 h. Urine analysis confirmed oral fluid results. These studies clarify earlier findings on the effects of passive cannabis smoke on oral fluid results. Oral fluid specimens collected in the presence of cannabis smoke appear to have been contaminated, thereby falsely elevating THC concentrations in oral fluid. The risk of a positive test for THC was virtually eliminated when specimens were collected in the absence of THC smoke.

Introduction

The primary goal of the United States Federal Workplace Drug Testing Program is to identify illegal drug users in the workplace. This program routinely mandates urine testing for cannabis and other illegal drugs (1). Concerns regarding passive cannabis exposure have been dealt with in this program largely by the adoption of administrative cutoff concentrations that are difficult to achieve under realistic passive exposure conditions (2–4). The Department of Transportation, which oversees the largest drug testing program in the United States, indicates that Medical Review Officers should not recognize passive drug exposure to be a “legitimate medical explanation” for a positive test (5).

Similar concerns regarding passive drug exposure have been expressed about oral fluid testing, particularly cannabis (6). Active use of cannabis products is primarily through smoke inhalation. When cannabis products are smoked, Δ^9 -tetrahydro-

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cannabinol (THC) is present both in mainstream smoke and sidestream smoke. The amount of THC present in sidestream smoke has been estimated in smoking-machine studies to range from 40% to 50% of the original THC content in cannabis (7). THC released into air is most likely to exist incorporated as part of an aerosol particle whose concentration, following mixing, becomes highly dilute. The degree of passive exposure to airborne THC by individuals in the immediate vicinity of cannabis smokers depends upon many factors, including cannabis potency, pattern of smoking by the active user, duration of exposure, environmental conditions such as room size and ventilation, and individual characteristics of the passively exposed individual (2).

Oral fluid testing for cannabis is based on detection and measurement of THC. During active cannabis smoking, THC is deposited in the upper respiratory tract mucosa (7). Passive exposure to airborne THC would also allow deposition of small amounts in the mucosa. Earlier studies on the effects of passive cannabis smoke exposure have indicated that positive confirmation tests and/or screening tests can be obtained by oral fluid testing when conducted immediately after exposure for up to 30 min (8). The purpose of this study was to extend earlier findings to more extreme conditions. This study reports the results of screening and confirmation tests from two studies that included four passive subjects in each study seated in an unventilated motor vehicle alongside four active cannabis smokers who smoked high potency cannabis (Study 1, 5.4%, 39.5 mg THC, cannabis mixed with tobacco), (Study 2, 10.4%, 83.2 mg THC, pure cannabis) cigarettes. These cigarettes were higher in potency than used in previous studies. Oral fluid and urine specimens from both passively exposed individuals and active smokers were analyzed by immunoassay and gas chromatography–tandem mass spectrometry (GC–MS–MS). In addition, Intercept Oral Specimen Collection Devices were exposed to smoke inside the van in Study 1 in order to assess possible contamination of collection devices.

Experimental

Participants

Study 1. The subjects participating in the study were eight healthy, Caucasian, male volunteers. The ages of the cannabis smokers (Smokers #1–4) were from 18 to 24 years, and the ages of the passive subjects (Subjects #A–D) were from 34 to 50 years. The four cannabis smokers reported prior use of cannabis on an infrequent basis. The four passive subjects were cannabis-free at the time of the study based on self-reports, oral fluid, and urine tests for cannabis conducted prior to the start of the study.

Study 2. The subjects participating in the study were eight healthy, Caucasian, male volunteers. The ages of the cannabis smokers (Smokers #1–4) were from 18 to 24 years, and the ages of the passive subjects (Subjects #A–D) were from 25 to 50 years. The four cannabis smokers reported prior use of cannabis on an infrequent basis. The four passive subjects

were cannabis-free at the time of the study based on self-reports, oral fluid, and urine tests for cannabis conducted prior to the start of the study.

Marijuana doses

Commercial cannabis was purchased from a coffee house in the Netherlands. Analysis of THC content was performed by GC–MS (Pharmacy Academisch Ziekenhuis, Groningen, The Netherlands). The cigarettes in Study 1 contained an average of 5.4% THC per cigarette (approximately 39.5 mg of THC, cannabis mixed with tobacco); cigarettes in Study 2 contained 10.9% THC per cigarette (approximately 83.2 mg of THC, pure cannabis).

Study conditions, procedures, and specimen collections

Both Study 1 and Study 2 were conducted under severe passive smoke exposure conditions in an eight-passenger van. The van had an approximate interior volume of 15.3 m³. During each Study, four experienced, male cannabis users smoked a single cannabis cigarette while seated inside the closed van in the presence of four passive, drug-free, male non-smokers. There were four rows of seats in the van; one cannabis smoker sat on each row alongside one passive subject. The smokers lit the cannabis cigarettes and smoked them in their entirety within 20 min. All doors and windows were closed and the engine was turned off, providing no ventilation.

Oral fluid specimens were collected with the Intercept Oral Specimen Collection Device (OraSure Technologies, Bethlehem, PA) according to manufacturer's instructions. In Study 1, Oral fluid collections were made inside the van for the first 45 min. Participants were allowed outside the van after 60 min where specimen collection continued. Bilateral oral fluid collections (left and right side of the mouth) were made from all subjects at the following times: baseline (–30 min); 0 (immediately at the end of smoking); 15, 30, and 45 min inside the van and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, and 8 h outside of the van. Collection of oral fluid specimens for passive subjects continued at 10, 12, 24, 36, 48, 60, and 72 h.

In Study 2, all oral fluid collections were made in a cannabis smoke-free environment outside the van immediately following the cessation of smoking. Bilateral oral fluid collections (left and right side of the mouth) were made from all subjects at the following times: baseline (–30 min); 0 (immediately at the end of smoking outside the van); 15, 30, 45 min, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, and 8 h outside of the van. Collection of oral fluid specimens for passive subjects continued at 10, 12, 24, 36, 48, 60, and 72 h. Both bilateral collector samples were analyzed in Study 2 by immunoassay while only a single side was analyzed by GC–MS–MS.

Briefly, oral fluid specimens are collected with the Intercept collection device, which consists of a treated absorbent cotton fiber pad affixed to a nylon stick and a preservative solution (0.8 mL) in a plastic container. With this device, an average of 0.4 mL of oral fluid is collected. The collection device pads are placed between the lower gum and cheek (both sides of the mouth) for 3 min and then placed in the preservative solution (0.8 mL). The specimen container is sealed and express-shipped to the laboratory for testing.

Also during Study 1, Intercept collector pads were opened and passively exposed to the smoke inside the van for a period equivalent to oral fluid collection (about 3 min). These devices were sealed as if collected from subjects and analyzed in the same fashion as all other samples. One additional test for human IgG was performed to verify that these specimens were not exposed to human samples.

In Study 1, urine specimens were collected in standard collection vials from all subjects at baseline (–30 min), 1, 4, 6, and 8 h. Collection was continued at 10, 12, 24, 36, 48, 60, and 72 h for passive subjects. The specimens were sealed and express-shipped to the laboratory for testing.

In Study 2, urine specimens were collected in standard collection vials from all subjects at baseline (–30 min), 1, 2, 4, 6, and 8 h. The specimens were sealed and express-shipped to the laboratory for testing.

Immunoassay

Oral fluid specimens were analyzed with the Cannabinoids Intercept MICRO-PLATE Enzyme Immunoassay (EIA) by Ora-Sure Technologies (Bethlehem, PA) following manufacturer's procedures. Details of the EIA procedure have been published (9). THC concentrations were adjusted for dilution ($\times 3$) and are reported based on estimated oral fluid concentration. Consequently, the EIA cutoff concentration for a neat oral fluid specimen was 3 ng/mL.

Urine specimens were analyzed on an AU400 Analyzer (Olympus America, Inc., Melville, NY) following Dade Behring manufacturer's procedures with the Dade Behring Syva Emit II Plus Cannabinoid Assay Kit (Syva Company, Dade Behring, Cupertino, CA). The EIA cutoff concentration for urine was 50 ng/mL. Urine creatinine was measured on an Ortho Vitros 250 (Ortho-Clinical Diagnostics, Inc. Rochester, NY) using an enzymatic method.

Confirmation methods

Quantitative analysis of THC in oral fluid specimens was performed by GC–MS–MS on a Saturn 2000 ion trap quadrupole (Varian, Walnut Creek, CA) equipped with a 5% phenyl methyl silicone capillary column (15-m \times 0.25-mm i.d.). Details of the assay have been published (8). The limit of quantification (LOQ) for THC was 0.25 ng/mL for a 0.4-mL extracted diluted specimen. THC concentrations were adjusted

for dilution ($\times 3$) and are reported based on estimated oral fluid concentration. The limit of detection (LOD)/LOQ for THC in neat oral fluid was 0.3/0.75 ng/mL. The administrative cutoff concentration for THC was 1.5 ng/mL.

Quantitative analysis of THCCOOH in urine specimens was performed by GC–MS–MS on a Varian 1200 triple stage quadrupole (Varian) equipped with a 5% phenyl methyl silicone capillary column (15-m \times 0.25-mm i.d.). Details of the assay have been published (8). The assay LOQ/LOD for THCCOOH was 1.0 ng/mL for a 1-mL extracted specimen. The administrative cutoff for THCCOOH was 15 ng/mL.

Results

Testing of cannabis smoke-contaminated Intercept devices

The effect of THC smoke contamination of Intercept devices was determined by exposing Intercept collectors to environmental air inside the van during smoking for a period equivalent to collection of oral fluid specimens (about 3 min). Instead of placing the devices in the mouth, they were held in the air by a passive participant who was careful not to touch the collector pads. GC–MS–MS analysis of the contaminated devices showed that THC concentrations were as high as 14 ng/mL and ranged from 3 to 14 ng/mL during the 45 min that subjects were in the van (Table I). All devices confirmed negative for human IgG, thereby verifying that there was no contact with human oral fluid. These results are significant in comparison to observed concentrations of THC determined in oral fluid specimens collected from passively exposed subjects.

Screening and confirmation testing of passive subjects

EIA and GC–MS–MS results for bilateral oral fluid specimens collected from the four passive participants in Study 1 and 2 are shown in Tables II and III. Figure 1 illustrates mean THC concentrations for bilateral collections of passive subjects and active smokers in Study 1. For comparison, the U.S. Department Health and Human Services (DHHS) proposed a confirmation cutoff concentration of 2 ng/mL, which is shown as a dotted line in the figure (6). All passive subjects' oral fluid and urine specimens tested negative by EIA and GC–MS–MS prior to the start of the exposure session. Immediately at the end of exposure to active cannabis smoking (time = 0), all oral fluid specimens collected from the passive subjects screened positive for cannabis at an administrative cutoff concentration of 3 ng/mL and were confirmed positive for THC by GC–MS–MS. At the end of cannabis smoking (0 h), oral fluid specimens of passive subjects in Study 1 contained THC concentrations ranging from 3.6 ng/mL to 7.5 ng/mL. At 0.25 h after exposure, two subjects (Subjects A and D) continued to screen and confirm positive for THC, whereas two subjects (Subjects B and C) screened negative and had THC concentrations ranging from 1.3 ng/mL to 2.8 ng/mL. At 0.5 h, Subjects A, C, and D had one bilateral collected specimen that screened positive, whereas the second specimen screened negative. THC concentrations for the specimens which screened positive ranged from 2.8 ng/mL to 4.8 ng/mL, whereas negative speci-

Table I. Results from Study 1 of Intercept Collectors Analyzed for THC after Exposure to Environmental Cannabis Smoke While Subjects Were in the Van*

Collection (min)	THC ng/mL (GC–MS–MS)	IgG Result
Pre-study baseline	0	Negative
0	14	Negative
15	9.9	Negative
30	4.5	Negative
45	3.0	Negative

* Samples were exposed for 3 min at each time point and later analyzed for THC content and human IgG.

mens had concentrations from 1.3 ng/mL to 3.3 ng/mL. Peak THC concentrations ranged from 4.5 ng/mL to 7.5 ng/mL with a mean (\pm SEM) of 6.2 ± 0.6 ng/mL. Peak concentrations occurred at zero time (end of smoking) for three of four subjects. Subject A's peak concentration occurred at 0.25 h. After 0.5 h, all oral fluid specimens screened and confirmed negative with the exception of a single specimen collected from Subject C at 2.5 h, which screened and confirmed positive for THC (3 ng/mL). The accompanying bilateral collection from this subject screened and confirmed negative. The positive result at 2.5 h for Subject C, who sorted and packaged specimens from active smokers, was attributed to contamination based on the negative results for his other specimen collected at the same time.

Study 2 included the precaution of collecting all specimens from passive subjects outside the van after the cessation of smoking. As a result of this change in procedure, dramatic differences in results were obtained for oral fluid concentrations of THC (Table III). Unlike Study 1, all samples collected from passively exposed individuals following smoking cessation were negative by EIA and showed only trace amounts of THC using GC-MS-MS with a range of 0.0 to 1.2 ng/mL. None of the oral fluid specimens collected from passive subjects exceeded the recommended DHHS confirmation cutoff concentration of 2 ng/mL for THC. By 2 h all specimens were completely negative for THC using GC-MS-MS. No differences were seen for bilateral samples from any subject by immunoassay.

EIA and GC-MS-MS results for urine specimens collected from the four passive participants in both Study 1 and Study 2 are shown in Tables IV and V. Although all urine specimens collected from the four passive subjects tested negative for cannabinoids by EIA (cutoff concentration = 50 ng/mL) and GC-MS-MS (cutoff concentration

Table II. GC-MS-MS and EIA Results for THC in Bilateral Oral Fluid Specimens of Four Passive Subjects Seated Alongside Four Cannabis Smokers (Study 1)*

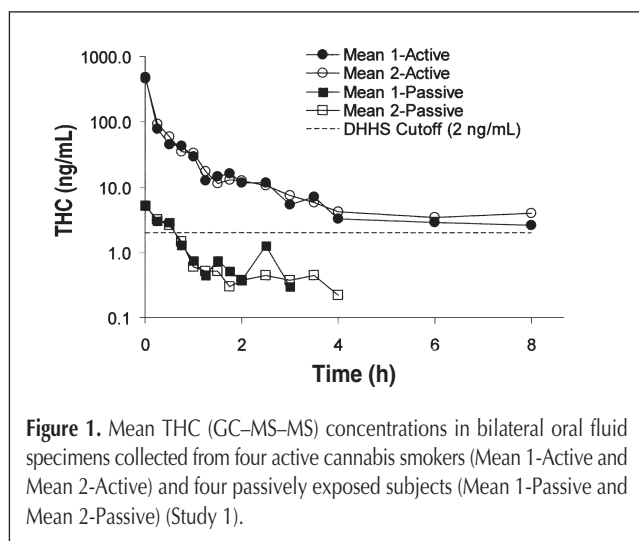
Time (h)	Subject				Mean THC GC-MS-MS, ng/mL (SEM)
	A THC GC-MS-MS, ng/mL (Screen)	B THC GC-MS-MS, ng/mL (Screen)	C THC GC-MS-MS, ng/mL (Screen)	D THC GC-MS-MS, ng/mL (Screen)	
-0.5	0/0 (-/-)	0/0 (-/-)	0/0 (-/-)	0/0 (-/-)	0/0 (0/0)
0	4.8/3.6 (++)	6.0/7.5 (++)	6.6/5.1 (++)	3.9/4.5 (++)	5.3/5.2 (0.6/0.8)
0.25	4.2/6.0 (++)	2.7/2.8 (-/-)	1.3/1.8 (-/-)	3.9/2.3 (++)	3.0/3.2 (0.7/1.0)
0.5	3.3/4.8 (-/+)	2.4/1.6 (-/-)	3.0/1.3 (+/-)	2.8/2.9 (+/-)	2.9/2.7 (0.2/0.8)
0.75	2.0/1.7 (-/-)	0.9/1.1 (-/-)	0.9/0.6 (-/-)	1.4/2.6 (-/-)	1.3/1.5 (0.3/0.4)
1	1.2/0.9 (-/-)	0.6/0.6 (-/-)	0.3/0.3 (-/-)	0.9/0.6 (-/-)	0.8/0.6 (0.2/0.1)
1.25	0.9/0.3 (-/-)	0.3/0.9 (-/-)	0.3/0.3 (-/-)	0.3/0.6 (-/-)	0.5/0.5 (0.2/0.1)
1.5	0.9/0.6 (-/-)	0.3/0.3 (-/-)	0.6/0.6 (-/-)	1.2/0.6 (-/-)	0.8/0.5 (0.2/0.1)
1.75	0.6/0.6 (-/-)	0.6/0.3 (-/-)	0/0 (-/-)	0.9/0.3 (-/-)	0.5/0.3 (0.2/0.1)
2	0.6/0.6 (-/-)	0.6/0.6 (-/-)	0/0 (-/-)	0.3/0.3 (-/-)	0.4/0.4 (0.1/0.1)
2.5	0.9/0.6 (-/-)	0.6/0.9 (-/-)	3.0/0 (+/-)	0.6/0.3 (-/-)	1.3/0.5 (0.6/0.2)
3	0.6/0.3 (-/-)	0.3/0.6 (-/-)	0/0 (-/-)	0.3/0.6 (-/-)	0.3/0.4 (0.1/0.1)
3.5	0/0 (-/-)	0/0 (-/-)	0/0.6 (-/-)	0/1.2 (-/-)	0/0.5 (0/0.3)
4	0/0 (-/-)	0/0 (-/-)	0/0 (-/-)	0/0.9 (-/-)	0/0.2 (0/0.2)
6	0/0 (-/-)	0/0 (-/-)	0/0 (-/-)	0/0 (-/-)	0/0 (0/0)
8	0/0 (-/-)	0.7/0 (-/-)	0/0 (-/-)	0/0 (-/-)	0.2/0 (0.2/0)

* All results from 12 to 72 h were negative. EIA results for bilateral collections are shown in parentheses. The EIA cutoff concentrations were 3 ng/mL. The GC-MS-MS LOD/LOQ for THC was 0.3/0.75 ng/mL. Oral fluid concentrations are multiplied by 3 to correct to neat oral fluid. Abbreviations: SEM, standard error of the mean.

Table III. GC-MS-MS and EIA Results for THC in Bilateral Oral Fluid Specimens of Four Passive Subjects Seated Alongside Four Cannabis Smokers (Study 2)*

Time (h)	Subject				Mean THC GC-MS-MS, ng/mL (SEM)
	A THC GC-MS-MS, ng/mL (Screen)	B THC GC-MS-MS, ng/mL (Screen)	C THC GC-MS-MS, ng/mL (Screen)	D THC GC-MS-MS, ng/mL (Screen)	
-0.5	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (0)
0	0.7 (-/-)	0.6 (-/-)	1.1 (-/-)	0.6 (-/-)	0.7 (0.1)
0.25	0.3 (-/-)	0 (-/-)	0.4 (-/-)	0 (-/-)	0.2 (0.1)
0.5	0.3 (-/-)	0 (-/-)	0.4 (-/-)	0 (-/-)	0.2 (0.1)
0.75	0 (-/-)	0.4 (-/-)	0.6 (-/-)	0 (-/-)	0.3 (0.2)
1	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)
1.25	0.9 (-/-)	0.6 (-/-)	0.9 (-/-)	0.6 (-/-)	0.8 (0.1)
1.5	0.9 (-/-)	1.2 (-/-)	1.2 (-/-)	0.6 (-/-)	1.0 (0.2)
1.75	0 (-/-)	0 (-/-)	0 (-/-)	0.4 (-/-)	0.1 (0.1)
2	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)
3	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)
4	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)
5	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)
6	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)
7	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)
8	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)	0 (-/-)

* EIA results for bilateral collections are shown in parentheses. The EIA cutoff concentrations were 3 ng/mL. The GC-MS-MS LOD/LOQ for THC was 0.3/0.75 ng/mL. Oral fluid concentrations are multiplied by 3 to correct to neat oral fluid. Abbreviation: SEM, standard error of the mean.



for THCCOOH = 15 ng/mL), measurable concentrations of THCCOOH by GC-MS-MS were generally present for as long as 72 h in Study 1 and 8 h (no collections were made beyond 8 h) in Study 2. In Study 1, peak THCCOOH concentrations observed at 6 to 8 h after cannabis smoke exposure ranged from 5.8 ng/mL to 14.7 ng/mL with a mean of 11.2 ± 2 ng/mL (Table IV). In Study 2, peak THCCOOH concentrations for three subjects ranged from 2.9 ng/mL to 11.6 ng/mL with a mean of 8.42 ng/mL (Table V). Passive subject #2 was negative over the entire 8-h collection period.

Screening and confirmation testing of cannabis smokers

EIA and GC-MS-MS results for oral fluid collected from the four cannabis smokers in both studies are shown in Tables VI and VII. For Study 1, all oral fluid specimens collected prior to the start of the exposure session tested negative by EIA and GC-MS-MS with the exception of Subject A, who screened

Table IV. GC-MS-MS, EIA, and Creatinine Results for THCCOOH in Urine of Four Passive Subjects Seated Alongside Four Cannabis Smokers (Study 1)*

Time (h)	Subject								Mean THCCOOH, GC-MS-MS, ng/mL (SEM)	Mean Creatinine, mg/dL (SEM)
	A THCCOOH, GC-MS-MS, ng/mL (Screen)	A Creatinine, mg/dL	B THCCOOH, GC-MS-MS, ng/mL (Screen)	B Creatinine, mg/dL	C THCCOOH, GC-MS-MS, ng/mL (Screen)	C Creatinine, mg/dL	D THCCOOH, GC-MS-MS, ng/mL (Screen)	D Creatinine, mg/dL		
-0.5	0 (-)	196	0 (-)	155	0 (-)	177	0 (-)	151	0.0 (0)	170 (10)
1	2.6 (-)	149	2.6 (-)	149	0 (-)	104	2.4 (-)	119	1.9 (0.6)	130 (11)
4	6.2 (-)	71	12.7 (-)	150	0 (-)	20	NS	NS	6.3 (3.2)	80 (33)
6	4.5 (-)	146	14.7 (-)	121	5.8 (-)	87	13.2 (-)	102	9.6 (3.0)	114 (13)
8	11.2 (-)	160	10.3 (-)	142	4 (-)	113	9.3 (-)	98	8.7 (1.6)	128 (14)
10	3.3 (-)	38	3.2 (-)	46	0 (-)	48	3 (-)	32	2.4 (0.8)	41 (4)
12	3.1 (-)	45	3.7 (-)	70	2.5 (-)	54	4.9 (-)	89	3.6 (0.5)	65 (10)
24	6.4 (-)	92	6.3 (-)	169	0 (-)	106	QNS	QNS	4.2 (2.1)	122 (21)
36	4.6 (-)	136	3.1 (-)	96	2.2 (-)	96	4.5 (-)	161	3.6 (0.6)	122 (16)
48	3.7 (-)	106	0 (-)	74	0 (-)	82	3.1 (-)	132	1.7 (1.0)	99 (13)
60	4.4 (-)	146	2.1 (-)	121	0 (-)	156	4.2 (-)	309	2.7 (1.0)	183 (43)
72	4.5 (-)	199	2.2 (-)	162	0 (-)	218	3.1 (-)	265	2.5 (0.9)	211 (21)

* EIA results are shown in parentheses. The EIA cutoff concentration for THCCOOH was 50 ng/mL. The GC-MS-MS LOD/LOQ for THCCOOH was 1.0 ng/mL. Abbreviations: SEM, standard error of the mean; NS, no specimen; QNS, quantity not sufficient.

Table V. GC-MS-MS, EIA, and Creatinine Results for THCCOOH in Urine of Four Passive Subjects Seated Alongside Four Cannabis Smokers (Study 2)*

Time (h)	Subject								Mean THCCOOH, GC-MS-MS, ng/mL (SEM)	Mean Creatinine, mg/dL (SEM)
	A THCCOOH, GC-MS-MS, ng/mL (Screen)	A Creatinine, mg/dL	B THCCOOH, GC-MS-MS, ng/mL (Screen)	B Creatinine, mg/dL	C THCCOOH, GC-MS-MS, ng/mL (Screen)	C Creatinine, mg/dL	D THCCOOH, GC-MS-MS, ng/mL (Screen)	D Creatinine, mg/dL		
-0.5	0 (-)	156	0 (-)	121	0 (-)	152	0 (-)	43	0.0 (0)	55 (31)
2	0 (-)	254	0 (-)	68	0 (-)	159	0 (-)	77	0.0 (0)	130 (11)
4	11.6 (-)	334	0 (-)	59	0 (-)	83	0 (-)	65	2.9 (2.9)	42 (17)
6	10.8 (-)	252	0 (-)	86	11 (-)	139	11	180	8.1 (2.7)	91 (43)
8	8.7 (-)	232	0 (-)	55	7 (-)	107	7.3 (-)	179	5.8 (2.0)	80 (45)

* EIA results are shown in parentheses. The EIA cutoff concentration for THCCOOH was 50 ng/mL. The GC-MS-MS LOD/LOQ for THCCOOH was 1.0 ng/mL. Abbreviations: SEM, standard error of the mean; NS, no specimen; QNS, quantity not sufficient.

and confirmed positive for THC. Mean peak concentrations were variable and ranged from 45 ng/mL to 1080 ng/mL with a mean of 596 ± 215 ng/mL. All peak concentrations occurred in the first specimen collected immediately after smoking. Following the initial peak, concentrations declined slowly over the remaining 8 h of collection. All subjects screened and confirmed positive through 2 h after active cannabis smoking with variable results thereafter.

In Study 2, subjects B, C, and D all tested and confirmed positive for THC prior to the start of the exposure session. Similar to Study 1, peak concentrations of THC were found immediately after smoking cessation with detectable THC for as long as 8 h. Peak concentrations ranged among subjects from 22 ng/mL to 384 ng/mL with a mean of 148 ± 84 ng/mL.

EIA and GC-MS-MS results for urine specimens collected from the four cannabis smokers in Study 1 and 2 are shown in Tables VIII and IX. In Study 1, Smoker A's urine specimen collected prior to the session confirmed positive for THCCOOH by GC-MS-MS at conventional cutoff concentrations, whereas Subjects B and C were negative. Subject D had insufficient specimen for analysis. Peak THCCOOH concentrations were observed at six to eight h after cannabis smoke exposure and ranged from 41 ng/mL to 136 ng/mL with a mean of 78 ± 21 ng/mL. In Study 2, all smokers' urine specimens were positive prior to the session. Peak concentrations of THCCOOH occurred at 4 to 8 h and ranged from 167 ng/mL to 443 ng/mL following smoking cessation.

Agreement between bilaterally collected oral fluid specimens (Study 1)

A total of 148 oral fluid specimens were collected in Study 1 from passive and active subjects by simultaneous insertion of

two Intercept® Oral Specimen Collection Devices into the mouth at the same time (left and right side; collection #1 and collection #2). All collections of oral fluid were made for a 3-min collection period. The overall mean THC concentration by GC-MS-MS for collection #1 was 21.2 ± 8.4 and for collection #2 was 21.4 ± 7.2 ng/mL. Good agreement was found between GC-MS-MS and immunoassay results for matching bilateral samples.

Discussion

Passive exposure of four drug-free individuals seated in an unventilated motor vehicle alongside four active cannabis smokers resulted in the initial appearance of THC in oral fluid specimens immediately after smoking. In Study 1, all subjects remained in the unventilated van for an additional hour after smoking. During this period, oral fluid specimens were collected inside the van. In addition, oral fluid collector devices were exposed to environmental air inside the van (without contact with oral fluid) and were found to be highly contaminated with THC. A different methodology was utilized in Study 2 to eliminate contamination of the collector devices. At the end of passive exposure inside the van, subjects emerged from the van, and all specimen collections were conducted in a clean area free of cannabis smoke. A substantial reduction in THC concentrations in oral fluid specimens collected from passive subjects was observed. Oral fluid concentrations for the two studies are illustrated in Figure 2 for both active and passive subjects. It is clearly evident from these data and the data for the exposed device (no oral fluid) that con-

Table VI. GC-MS-MS and EIA Results for THC in Oral Fluid of Four Cannabis Smokers (Study 1)*

Time (h)	Smoker#				Mean THC GC-MS-MS, ng/mL (SEM)
	1 THC GC-MS-MS, ng/mL (Screen)	2 THC GC-MS-MS, ng/mL (Screen)	3 THC GC-MS-MS, ng/mL (Screen)	4 THC GC-MS-MS, ng/mL (Screen)	
-0.5	12.4/5.4 (+/+)	0/0 (-/-)	0/0 (-/-)	0/0 (-/-)	3.1/1.4 (3.1/1.4)
0	408.0/720.0 (+/+)	420.0/540.0 (+/+)	1080.0/540.0 (+/+)	26.4/45.0 (+/+)	483.6/461.3 (218.8/145.1)
0.25	183.0/213.0 (+/+)	66.0/84.0 (+/+)	33.0/57.0 (+/+)	29.4/24.0 (+/+)	77.9/94.5 (36.0/41.4)
0.50	93.0/156.0 (+/+)	42.0/33.0 (+/+)	29.4/29.4 (+/+)	18.6/21.0 (+/+)	45.8/59.9 (16.5/32.1)
0.75	99.0/81.0 (+/+)	42.0/17.4 (+/+)	20.7/28.5 (+/+)	9.9/12.6 (+/+)	42.9/34.9 (19.9/15.7)
1.00	51.0/78.0 (+/+)	48.0/30.0 (+/+)	10.8/12.3 (+/+)	8.1/12.6 (+/+)	29.5/33.2 (11.6/15.5)
1.25	22.2/14.4 (+/+)	13.2/33.0 (+/+)	8.4/15.9 (+/+)	7.2/6.0 (+/+)	12.8/17.3 (3.4/5.7)
1.50	23.1/16.8 (+/+)	19.2/17.7 (+/+)	8.1/6.6 (+/+)	8.7/4.5 (+/+)	14.8/11.4 (3.8/3.4)
1.75	23.7/17.4 (+/+)	30.0/9.0 (+/+)	5.4/12.6 (+/+)	5.7/13.5 (+/+)	16.2/13.1 (6.3/1.7)
2.00	23.1/23.1 (+/+)	9.0/12.9 (+/+)	9.9/8.1 (+/+)	4.8/7.2 (+/+)	11.7/12.8 (4.0/3.6)
2.50	27.3/30.0 (+/+)	10.8/6.9 (+/+)	6.6/3.6 (+/+)	2.4/1.8 (-/-)	11.8/10.6 (5.5/6.6)
3.00	12.3/14.4 (+/+)	2.4/3.9 (-/-)	3.0/6.0 (-/-)	4.2/5.7 (+/+)	5.5/7.5 (2.3/2.3)
3.50	14.7/15.6 (+/+)	2.4/3.6 (-/+)	3.6/3.0 (-/-)	8.1/1.2 (+/-)	7.2/5.9 (2.8/3.3)
4.00	6.3/6.0 (+/+)	3.9/5.7 (-/+)	1.1/3.9 (-/-)	1.8/1.1 (-/-)	3.3/4.2 (1.2/1.1)
6.00	3.3/5.7 (+/+)	4.5/1.9 (+/-)	2.4/3.9 (-/+)	1.5/2.4 (-/-)	2.9/3.5 (0.6/0.9)
8.00	4.5/7.5 (-/+)	3.6/2.8 (+/+)	0.8/1.4 (-/-)	1.5/4.5 (-/-)	2.6/4.0 (0.9/1.3)

* No specimens were collected beyond 8 h. EIA results for bilateral collections are shown in parentheses. The EIA cutoff concentrations were 3 ng/mL. The GC-MS-MS LOD/LOQ for THC was 0.3/0.75 ng/mL. Oral fluid concentrations are multiplied by 3 to correct to neat oral fluid. Abbreviation: SEM, standard error of the mean.

tamination of the collector device occurred in Study 1, and it falsely elevated oral fluid concentrations for passive subjects. When oral fluid collections were made in the absence of cannabis contamination (Study 2), THC concentrations in oral fluid specimens collected from passive subjects were extremely minimal.

In Study 1, Peak THC concentrations for passive subjects were generally present in the first oral fluid specimen collected immediately following smoking (zero time) and ranged from 4.5 ng/mL to 7.5 ng/mL with a mean of 6.2 ± 0.6 ng/mL. In contrast, peak THC concentrations for active smokers were approximately 100-fold higher. THC concentrations declined rapidly for passive subjects and became negative within 30 to 45 min despite the residual cannabis smoke contaminating the Intercept collectors. Similar results were observed in an

earlier study by Niedbala et al. (8) in which four passive subjects were located in a sealed 36-m³ size room approximately 1.5 m from five active cannabis smokers. Given that this previous study used a similar methodology (collection inside a contaminated area), it is likely that the previous results were also influenced by environmental contamination. Peak THC concentrations in the earlier study ranged from 6.3 ng/mL to 26.4 ng/mL with a mean of 13.3 ± 4.5 ng/mL. The combined results of these studies strongly suggests that environmental cannabis smoke can contaminate collection devices unless specimens are collected outside the area of smoke contamination. Study 2 supports this assertion since none of the passive subjects produced a positive result after providing samples once outside the van following smoking cessation. Smokers, however, did produce positive results whether specimens were collected inside or outside the van.

Analyses of urine specimens collected from passive subjects in both studies are consistent with the interpretation that passive subjects inhaled a low dose of THC during cannabis smoke exposure. Although all specimens screened negative by EIA at a 50 ng/mL cutoff concentration for THCCOOH, detectable concentrations by GC-MS-MS were present for all passive subjects. Peak THCCOOH concentrations for passive subjects in Study 1 and Study 2 were observed at six to eight h and ranged from 5.8 ng/mL to 14.7 ng/mL. These data are of similar magnitude to THCCOOH concentrations measured in urine of five subjects passively exposed to sidestream smoke of four cannabis cigarettes (2.8% THC) by Cone et al. (2). Although three of the five subjects in the earlier study produced no detectable THCCOOH in urine (GC-MS, cutoff concentration = 5 ng/mL), two subjects produced maximum urine concentrations of 8 and 12 ng/mL.

In contrast to passive subjects, urine

Table VII. GC-MS-MS and EIA Results for THC in Oral Fluid of Four Cannabis Smokers (Study 2)*

Time (h)	Smoker #				Mean THC GC-MS-MS, ng/mL (SEM)
	1 THC GC-MS-MS, ng/mL (Screen)	2 THC GC-MS-MS, ng/mL (Screen)	3 THC GC-MS-MS, ng/mL (Screen)	4 THC GC-MS-MS, ng/mL (Screen)	
-0.5	0.93 (-/-)	33 (+/+)	1.6 (+/+)	2.8 (+/+)	9.6 (7.8)
0	18 (+/+)	384 (+/+)	156 (+/+)	36 (+/+)	148 (84)
0.50	22 (+/+)	46 (+/+)	35 (+/+)	24 (+/+)	32 (5.5)
1.00	3.9 (+/+)	42 (+/+)	5.4 (+/+)	3.9 (+/+)	13.8 (9.4)
1.50	5.4 (+/+)	17 (+/+)	2.5 (+/+)	5.1 (+/+)	7.6 (3.3)
2.00	6.6 (+/+)	5.1 (+/+)	8.1 (+/+)	5.1 (+/+)	6.2 (0.7)
3.00	2.2 (+/+)	4.5 (+/+)	5.4 (+/+)	3.3 (+/+)	3.8 (0.7)
4.00	1.3 (-/+)	7.8 (+/+)	3.6 (+/+)	1.7 (-/-)	3.6 (1.5)
5.00	0.8 (+/+)	3 (+/+)	0.6 (-/-)	1.6 (-/-)	1.5 (0.5)
6.00	0.3 (+/+)	2 (+/+)	1.6 (+/+)	0.9 (-/-)	0.8 (0.4)
7.00	0.9 (+/+)	2.9 (+/+)	1.7 (+/+)	0.8 (-/-)	1.0 (0.5)
8.00	0.9 (+/+)	1.8 (+/+)	2.2 (+/+)	3.3 (+/+)	1.0 (0.5)

* No specimens were collected beyond 8 h. EIA results for bilateral collections are shown in parentheses. The EIA cutoff concentrations were 3 ng/mL. The GC-MS-MS LOD/LOQ for THC was 0.3/0.75 ng/mL. Oral fluid concentrations are multiplied by 3 to correct to neat oral fluid. Abbreviation: SEM, standard error of the mean.

Table VIII. GC-MS-MS, EIA, and Creatinine Results for THCCOOH in Urine of Four Cannabis Smokers (Study 1)*

Time (h)	Smoker #								Mean THCCOOH, GC-MS-MS, ng/mL (SEM)	Mean Creatinine, mg/dL (SEM)
	1 THCCOOH, GC-MS-MS, ng/mL (Screen)	1 Creatinine, mg/dL	2 THCCOOH, GC-MS-MS, ng/mL (Screen)	2 Creatinine, mg/dL	3 THCCOOH, GC-MS-MS, ng/mL (Screen)	3 Creatinine, mg/dL	4 THCCOOH, GC-MS-MS, ng/mL (Screen)	4 Creatinine, mg/dL		
-0.5	57 (QNS)	QNS	0 (-)	267	0 (-)	157	QNS	QNS	19.0 (19.0)	212 (55)
1	73 (+)	136	19 (+)	272	4.1 (-)	42	4.4 (-)	107	25.1 (16.3)	139 (48)
4	121 (+)	100	76 (+)	195	26 (-)	63	14 (-)	65	59.3 (24.6)	106 (31)
6	136 (+)	105	80 (+)	188	26 (-)	175	55 (+)	134	74.3 (23.4)	151 (19)
8	120 (+)	139	42 (+)	134	41 (+)	204	42 (+)	171	61.3 (19.6)	162 (16)

* EIA results are shown in parenthesis. The EIA cutoff concentration for THCCOOH was 50 ng/mL. The GC-MS-MS LOD/LOQ for THCCOOH was 1.0 ng/mL. Abbreviations: SEM, standard error of the mean and QNS, quantity not sufficient.

specimens collected from active smokers screened positive by EIA within the 8-h collection period in Study 1 and Study 2. Peak THCCOOH concentrations within the 8-h period were observed at 6 to 8 h and ranged from 41 to 443 ng/mL. Although no urine collections were obtained after 8 h, it is quite possible that higher THCCOOH concentrations were excreted by the active subjects at later times. In the Niedbala et al. (8) study, urine specimens were collected from active smokers for 4 h after smoking. Peak THCCOOH concentrations within the 4-h period ranged from 22 to 168 ng/mL with a mean of 75 ± 30 ng/mL. It is highly unlikely that THCCOOH excretion had reached maximal concentrations within the 4-h sampling period utilized in that study. For comparison, Huestis et al. (10) reported detailed urinary excretion data for six subjects following active smoking of cannabis cigarettes of two different strengths (1.75% and 3.55% THC) in which all urine specimens were collected over a seven-day period. Peak THCCOOH concentrations following the low strength cannabis cigarette were observed at a mean of 7.0 h (range 6.0–9.8 h); peak THCCOOH concentrations ranged from 20.6

to 234.2 ng/mL with a mean of 89.8 ± 31.9 ng/mL. Peak THCCOOH concentrations following the high strength cannabis cigarette were observed at a mean of 14.7 h (range 5.6–28.0 h); peak THCCOOH concentrations ranged from 29.9 to 355.2 ng/mL with a mean of 153.5 ± 49.2 ng/mL. If one considers only the data for urine specimens collected over the first 8 h in the Huestis et al. (10) study, the mean concentrations for THCCOOH were 82.2 ng/mL (range 20.6–234.2) and 115.9 ng/mL (range 29.9–318.0), respectively for the low and high doses.

In these study comparisons, it is important to compare cannabis potency and total THC content of the administered cannabis doses. In the present study, cannabis cigarettes mixed with tobacco contained 5.4% THC in Study 1 and 10.9% THC (no tobacco) in Study 2 as compared to the 1.75% and 3.55% THC cannabis utilized in the Huestis et al. (10) study. However, total available THC content to the smoker is of greater importance because of differences in the weight of cannabis cigarettes. The most important unknown element in these considerations are the amounts of THC delivered to the smoker in mainstream smoke and to passive subjects exposed to sidestream smoke. The cannabis cigarettes utilized in the Huestis et al. (10) study contained approximately 15.8 mg and 33.8 mg of THC, respectively, for the low and high doses. In the present study, the cannabis cigarettes contained THC content of 39.5 mg in Study 1 and 83.2 mg in Study 2. Consequently, the cannabis cigarettes consumed in the present study appear to be roughly equivalent in Study 1 and significantly higher in Study 2 when compared to the high dose cannabis utilized by Huestis et al. (10). However, THC delivery to both mainstream and sidestream smoke in Study 1 could have been reduced somewhat by the presence of tobacco. Fehr and Kalant (11) reported that tobacco cigarettes injected with pure THC and burned in a smoking machine with a continuous air flow yielded only 32.2% recovery of original THC content in condensed smoke compared to a recovery of 53% for cannabis cigarettes without tobacco. However, both urine and oral fluid data from this study support the interpretation that a substantial portion of the THC dose was delivered to smokers via mainstream smoke. In addition, it is clear that passive subjects inhaled a dose of THC of similar

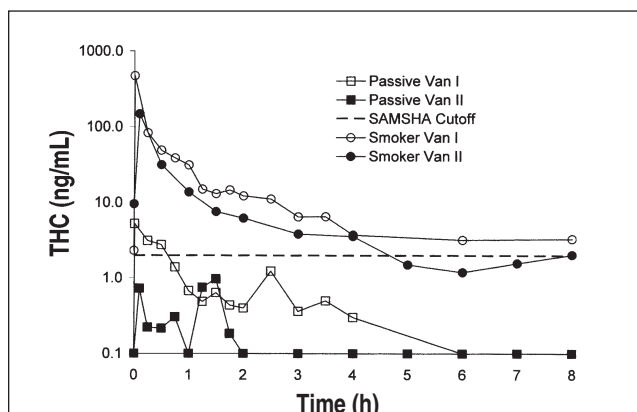


Figure 2. Comparison of THC oral fluid concentrations found in smokers and passively exposed individuals from Study 1 and Study 2. The results are shown as the average of four individuals from each group within the studies. The results are normalized to whole oral fluid concentrations. The solid line indicates the proposed SAMSHA cutoff for THC.

Table IX. GC–MS–MS, EIA, and Creatinine Results for THCCOOH in Urine of Four Cannabis Smokers (Study 2)*

Time (h)	Smoker #								Mean THCCOOH, GC–MS–MS, ng/mL (SEM)	Creatinine, mg/dL (SEM)
	1 THCCOOH, GC–MS–MS, ng/mL (Screen)	2 Creatinine, mg/dL	2 THCCOOH, GC–MS–MS, ng/mL (Screen)	3 Creatinine, mg/dL	3 THCCOOH, GC–MS–MS, ng/mL (Screen)	4 Creatinine, mg/dL	4 THCCOOH, GC–MS–MS, ng/mL (Screen)	Mean Creatinine, mg/dL		
–0.5	73 (+)	129	66 (+)	260	282 (+)	453	74 (+)	205	118 (45.3)	186 (50.4)
1	182 (+)	109	61 (+)	68	276 (+)	108	180 (+)	207	156 (24.4)	158 (45.5)
4	260 (+)	158	82 (+)	66	443 (+)	203	255 (+)	178	174 (21.9)	231 (80.7)
6	263 (+)	210	129 (+)	135	421 (+)	221	251 (+)	185	165 (35.1)	254 (60.5)
8	106 (+)	83	167 (+)	219	359 (+)	202	135 (+)	135	135 (25)	199 (60.3)

* EIA results are shown in parenthesis. The EIA cutoff concentration for THCCOOH was 50 ng/mL. The GC–MS–MS LOD/LOQ for THCCOOH was 1.0 ng/mL. Abbreviations: SEM, standard error of the mean.

magnitude to cannabis exposures reported in earlier passive inhalation studies (2–4,12,13).

What is interesting from the current studies is that even when the THC dose was doubled and the tobacco removed, there was no significant increase in THC concentrations in oral fluid. In fact, the results of Study 1 and Study 2 strongly suggest that environmental contamination in the field should be carefully avoided. When properly collected, passively exposed subjects produced samples that never exceeded the screening or confirmation thresholds to be considered positive.

Conclusions

Arrestees and defendants have long ago stopped using passive exposure to explain a positive urine marijuana test because study data and court debate have supported the position that confirmed positive measurements in urine are sufficient evidence to substantiate active smoking. Oral fluid, however, has not yet undergone such scrutiny. The results from the studies presented provide data to support that the careful collection of oral fluid specimens can exclude passive exposure as a defense.

Study 1 appears to extend earlier findings of passive cannabis exposure by evaluating higher potency cannabis and the effect of close proximity of passive subjects to smokers. Passive cannabis smoke exposure of four drug-free individuals seated in an unventilated motor vehicle alongside four cannabis cigarette smokers produced transient positive (screening and confirmation) results for THC in oral fluid specimens if specimens were collected in the presence of THC smoke. Study 2, however, introduces evidence that even when the THC content was doubled in comparison to Study 1, collection of samples outside the area of environmental contamination produced no positive results among those passively exposed.

In both Study 1 and 2, peak THC concentrations in oral fluid specimens of active cannabis smokers exceeded those observed in passive subjects approximately 100-fold. Urine testing for THCCOOH confirmed observations from oral fluid tests that passive subjects had inhaled a small dose of THC during exposure similar to those observed in earlier passive cannabis inhalation studies.

Overall, these two studies indicate that collection of specimens outside an area of possible smoke contamination is necessary for accurate determination of passive exposure effects on oral fluid testing. Even after extreme conditions employed in

these studies, the results suggest that passive cannabis smoke exposure is not of concern in the use of oral fluid testing in the workplace.

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