RESEARCH BRIEF

Detection Windows for Drugs in Oral Fluid: Cannabinoids, Stimulants, and Opioids

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In impaired driving enforcement, blood has traditionally been the preferred biological specimen in determining the presence of drugs in drivers. However, collecting blood specimens from drivers can be challenging, often resulting in delays impacting test results and noncompliance. The use of oral fluid as a matrix for the analysis of drugs is gaining popularity and an increasing number of research studies substantiate the correlation between drug concentrations in oral fluid and blood (Bosker & Huestis, 2009; Busardo et al., 2018). Drugs may be deposited in oral fluid via ingestion (e.g., smoked or oral) and passive diffusion from blood into saliva (Lee & Huestis, 2014). As a detection matrix, oral fluid has several advantages over blood and urine: collection is easy, noninvasive, and can be observed, limiting opportunities for adulteration. Oral fluid also can be collected at the roadside, close to the time of a suspected impaired driving offense. However, there is still much to be learned about the use of oral fluid especially as a detection matrix at the roadside. The objective of this research brief is to assess the literature on oral fluid detection times to address how long after a person uses a drug it can be detected in oral fluid, and what factors may influence detection times. As drug prevalence does not imply impairment, efforts to understand the proximity of drivers' drug use in time may assist in better understanding and properly enforcing drug-impaired driving laws.

METHOD

A comprehensive search was carried out using the PubMed, Web of Science, Transport Research International Documentation, and Toxicology Literature Online (TOXLINE) databases for relevant scientific literature. The search targeted papers that combined certain key words related to (1) oral fluid (and variations thereof); (2) detection times or windows; and (3) particular drug types, classes or related metabolites. Articles were also required to be written in English and employ human subjects (vs. animals).

The initial search was conducted during the months of June to August 2018 and yielded over 1,800 articles. All titles and abstracts were reviewed for inclusion by three independent reviewers, based on the above criteria. Training on a subset of titles and articles was conducted to assess and improve inter-rater reliability. Manual filtering of the article list reduced the number of potentially relevant papers to approximately 150. A significant number of studies were omitted as they were not directly relevant to detection windows. Full text copies were obtained for those articles deemed relevant. Upon full text review, articles that did not contain information on detection times were excluded. Backward searching was also employed to identify additional relevant articles. Finally, articles were restricted to publication in the past 10 years in order to better reflect oral fluid technology currently in use.

For the final set of 29 articles, key information was distilled and entered into Detection Window Summary Tables by drug class. This information included drug type; route of administration; dose; analyte(s) and limit(s) of detection; collection device; analysis method; duration of oral fluid collection; minimum last detection time; median last detection time; maximum last detection time; participants' frequency of use inclusion criteria; number of participants; and citation (source).

RESULTS

Twenty-one relevant articles were identified for cannabis and derivatives, four for opioids, and four for stimulants. Insufficient literature was found on last detection times for other drug classes, including benzodiazepines, sedative hypnotics, and hallucinogens.

Detection Window Summary Tables

As noted, key information was summarized in a series of Detection Window Summary Tables. These are available in Excel format as a resource to accompany this research brief. Individuals can sort and filter the information in the Summary Tables according to their needs or interests and are encouraged to consult the original references for further details.

In the following sections, some key findings and patterns are highlighted. It is important to note that the sections below are not intended to offer a comprehensive treatment of the very rich and complex data included in the Detection Window Summary Tables. Critical factors that can impact detection times are also described. In many cases, these factors vary across studies and so synthesizing the outcomes remains a challenge.

Last Detection Times

In the discussion below, results from studies with similar dosing and routes of administration were grouped where possible. The results are presented in terms of the median last detection time and the range (i.e., minimum and maximum) of last detection times among study participants with at least one positive result for the analyte(s) and limit(s) of detection of interest. In instances where the results of multiple studies are grouped, or where a given study provided more than one median last detection time (e.g., for multiple dosing conditions), the range of median last detection times are also presented. Importantly, in some studies the last detection times coincided with the last oral fluid sampling; in such cases, the result is denoted by a "≥," indicating that the true detection time could be longer than the observation period of the study. Oral fluid testing methods were based on immunoassay, chromatography, and/or mass spectrometry techniques.

Cannabis and cannabinoids

A common approach to dosing was to have subjects smoke a 6.8% THC cigarette ad libitum, typically for up to 10 minutes. The median and range of last detection times across relevant studies are summarized in Table 1. In these studies, the median last detection time for Δ^9-tetrahydrocannabinol (THC), the main psychoactive component in cannabis, in oral fluid ranged from six to ≥30 hours, while the last detection time ranged from a minimum of two hours to a maximum of ≥30 hours (see Table 1). The median last detection time for 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH), the secondary and non-psychoactive metabolite of THC, ranged from 0.25 to ≥30 hours, while the range of last detection times was the same. The last detection times for THC and THCCOOH were greater for frequent smokers than occasional smokers (Newmeyer et al., 2014).

Table 1. Median and range of last detection times for cannabis and cannabinoids for select studies with dosing through smoking a 6.8% THC cigarette.

Analyte	Median Last Detection Times	Range of Last Detection Times	Sources
Δ^9-tetrahydrocannabinol (THC)	6 to ≥30 hours	2 to ≥30 hours	Anizan et al., 2013 Cone, Bigelow, et al., 2015 Lee et al., 2012 Milman et al., 2012 Newmeyer et al., 2014
11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH)	0.25 to ≥30 hours	0.25 to ≥30 hours	Anizan et al., 2013 Cone, Bigelow, et al., 2015 Lee et al., 2012 Milman et al., 2012 Newmeyer et al., 2014
Cannabidiol (CBD)	2 to 5 hours	1 to ≥22 hours	Anizan et al., 2013 Lee et al., 2012 Milman et al., 2012 Newmeyer et al., 2014
Cannabinol (CBN)	3.5 to 8 hours	1 to 13.5 hours	Anizan et al., 2013 Lee et al., 2012 Milman et al., 2012 Newmeyer et al., 2014

Note: See *cannabis and cannabinoids* in the Detection Window Summary Tables for information on dosing, detection concentrations, and analysis methods.

The detection times for the metabolites cannabidiol (CBD) and cannabinol (CBN) were shorter than those for THC and THCCOOH. The median last detection time for CBD ranged from two to five hours, while the last detection time ranged from one to ≥22 hours. The median last detection time for CBN ranged from 3.5 to eight hours, while the last detection time ranged from one to 13.5 hours. Most studies considered alternative cutoffs for combinations of analytes. For example, when THC and CBD were both considered at detection limits of 1 microgram per liter (μg/L), the median last detection time was three hours for frequent smokers and 2.5 hours for occasional smokers (range of last detection times 1 – 6 hours for both) (Newmeyer et al., 2014). When the cutoff for THC was 1 – 2 μg/L and that for THCCOOH was 50 ng/L, the median last detection time was 6 hours (range of last detection times 0.25 – 6 h) (Lee et al., 2012).

Two of the identified studies utilized 6.8% THC cigarettes and the Draeger DrugTest® 5000 on-site oral fluid screening device. Huestis et al. (2013) tested subjects for up to 30 hours after smoking, yielding a median last detection time for THC of 12 hours for occasional smokers and 21 hours for frequent smokers. Desrosiers et al. (2012) combined the results of the DrugTest 5000 with those of two dimensional gas chromatography mass spectrometry (2D-GC-MS) using various combinations of analytes and cutoffs. For example, when the cutoff for the DrugTest 5000 was set at 5 μg/L for THC and combined with a cutoff of 2 μg/L for THC via 2D-GC-MS, the median detection time was 6 hours (range of last detection times 3 – ≥22 h). When a cutoff of 20 ng/L for THCCOOH was added to this combination, the median last detection time was 6 hours (range of last detection times 4 – ≥22 h). Two additional studies utilized on-site screening devices for testing after alternative smoked doses (i.e., other than 6.8% THC cigarettes). Mansson and colleagues (2013) used the Biosens® on-site system to test the oral fluid of eight subjects for 6 hours after smoking a cannabis cigarette containing 0.3 mg THC per kilogram body weight. The median last detection time for THC at a cutoff of 20 ng/mL was 3.5 hours (range of last detection times <1 – 4 h). Lee et al. (2015) tested the oral fluid of 11 subjects for up to 17.1 hours after last smoking a 5.9% THC cigarette. When cutoffs of 1 or 2 μg/L for THC were combined with a cutoff of 0.5 μg/L for CBD, the last detection time ranged from 0.5 to 12.4 hours.

Several studies tested subjects' oral fluid after oral administration of various forms and doses of THC and other cannabinoids, including brownies, Sativex® oromucosal spray, and Marinol® (dronabinol). These are summarized in Table 2. In some studies, multiple doses were administered over a series of days (see *cannabis and cannabinoids* in the Detection Window Summary Tables for details). For these studies, last detection times are reported from the final dose. The median last detection time for THC ranged from 1.75 to 44 hours, while the last detection time ranged from a minimum of one hour to a maximum of ≥48 hours. The median last detection time for THCCOOH ranged from eight to ≥48 hours, while the last detection time ranged from three to 122 hours. After Sativex dosing, CBD was detected in all subjects ≥10.5 hours after dosing (Lee et al., 2013). Similarly, the median last detection time for CBN after Sativex dosing ranged from 7.5 to ≥10.5 hours, depending on the dose, while the last detection time ranged from 4.5 to ≥10.5 hours (Lee et al., 2013). Hayley et al. (2018) used the on-site Securetec Drugwipe® II Twin device to test the oral fluid of subjects after dosing with a low or high dose of THC oil. THC was not detected by the device in any subjects for either dose condition.

Table 2. Median and range of last detection times for cannabis and cannabinoids with oral dosing (brownies, Sativex, Marinol).

Analyte	Median Last Detection Times	Range of Last Detection Times	Sources
Δ^9-tetrahydrocannabinol (THC)	1.75 to 44 hours	1 to ≥48 hours	Lee et al., 2013 Milman et al., 2011 Newmeyer et al., 2017 Vandrey et al., 2017
11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH)	8 to ≥48 hours	3 to 122 hours	Lee et al., 2013 Milman et al., 2011 Newmeyer et al., 2017 Vandrey et al., 2017

Note: See *cannabis and cannabinoids* in the Detection Window Summary Tables for information on dosing, detection concentrations, and analysis methods.

Two studies were identified that tested the oral fluid of subjects undergoing monitored abstinence from cannabis. In one study, the last detection time for THC ranged from 0 to 8 days (median not reported) (Andås et al., 2014). In the other study, the median last detection time for THC was 24 hours after admission, while the last detection time ranged from 0 to 28 days (Lee et al., 2011). The median last detection time for THCCOOH ranged from 4 to 13 days, while the last detection time ranged from 0 to 29 days (Lee et al., 2011). CBD and CBN had much shorter detection times. Both were last detected 0 days after admission in all subjects (Lee et al., 2011). Lee et al. also considered combinations of analytes and alternative cutoffs. For example, the median last detection time for THC ≥ 2 μg/L and THCCOOH ≥ 20 ng/L was 0 days (range of last detection times 0 – 1 day). In both monitored abstinence studies, positives were interspersed with negative specimens (Andås et al., 2014; Lee et al., 2011).

Stimulants

For subjects dosed intravenously with 25 mg cocaine, the median last detection time for cocaine ranged from four to 12.5 hours, while the last detection time ranged from two to ≥69 hours (Ellefsen et al., 2016a, 2016b). In the same two studies, the median last detection time for benzoylecgonine, a metabolite of cocaine, ranged from 12.5 to 30.5 hours, while the last detection time ranged from a minimum of 3 hours to a maximum of ≥69 hours, depending on the cutoff considered.

When subjects were dosed subcutaneously with cocaine, the median last detection time for cocaine ranged from eight to 17.7 hours, while the last detection time ranged from four to 28.5 hours (Scheidweiler et al., 2010). The median last detection time for benzoylecgonine ranged from 28.0 to 47.0 hours, while the last detection time ranged from 4.1 to 72.0[1] hours. The median last detection time for the metabolite ecgonine methyl ester ranged from 24.1 to 32.0 hours, while the last detection time ranged from a minimum of 4.1 hours to a maximum of 72.0[1] hours. Detection times were greater for a high dose of cocaine (150 mg per 70 kg body weight) compared to a low dose (75 mg per 70 kg body weight).

One study was identified in which the oral fluid of subjects undergoing drug detoxification was collected twice daily for up to 10 days (Andås et al., 2016). The median last detection times for amphetamine and methamphetamine were two and three days, respectively (range of last detection times 0 – 8 days for both), with negative results interspersed with positive results for some subjects. The authors noted that these were minimum estimates since actual times of last ingestion were not known.

Opioids

After oral dosing with 20 mg of controlled release oxycodone, the median last detection time for oxycodone in oral fluid ranged from 12 to 32 hours, while the last detection time ranged from 6 to ≥52 hours (Cone, DePriest, et al., 2015a). The median last detection time for noroxycodone, the major metabolite of oxycodone, ranged from 6 to 32 hours, while the last detection time ranged from 4 to ≥52 hours (Cone, DePriest, et al., 2015a). Last detection times decreased as the cutoffs for oxycodone and noroxycodone increased. For example, at the lowest cutoff examined, 1 ng/mL, oxycodone was last detected between 28 and ≥52 hours after dosing, while at the highest cutoff examined, 40 ng/mL, the last detection time ranged from 6 to 24 hours.

Among subjects dosed orally with 20 mg of hydrocodone, the median last detection time for hydrocodone ranged from 7 to 28 hours after dosing, while the last detection time ranged from three to 48 hours (Cone, DePriest, et al., 2015b). For norhydrocodone, a primary metabolite of hydrocodone, the median last detection time ranged from 1.5 to 19 hours, while the last detection time ranged from 1 to 28 hours after dosing.

Tramadol and *O*-desmethyltramadol were last detected at ≥48 and 32 hours, respectively, after oral dosing with 50 mg tramadol (only maximum last detection times were provided) (Meyer et al., 2015). Dihydrocodeine was detected in oral fluid after 8 mg of oral dihydrocodeine phosphate administration for one day in three dosed subjects (Kuwayama et al., 2016).

Factors Influencing Detection Times

It is important to underscore that many factors can influence drug detection times in oral fluid. These include cutoffs, analytes, dose, route of administration, time since use, the amount of drug initially deposited in the mouth, oral fluid collection method, and collection device (e.g., Andås et al., 2016; Anizan & Huestis, 2014; Ellefsen et al., 2016b; Lee & Huestis, 2014; Lee et al., 2015). Findings

[1] The reported maximum detection time exceeded the reported observation period.

regarding frequency and duration of use have been mixed. While several studies demonstrated an association between frequency and duration of use and detection times, one study involving monitored abstinence from cannabis did not (Ellefsen et al., 2016b; Lee & Huestis, 2014; Lee et al., 2011, 2015; Newmeyer et al., 2014). Ingestion of food or drink, or rinsing of the mouth, may impact detection times (Bosker & Huestis, 2009; de Castro et al., 2014). Because the pH of oral fluid is more basic than that of blood, basic drugs (e.g., cocaine) diffuse more readily into oral fluid than acidic drugs (e.g., benzodiazepines) (Cone, DePriest, et al., 2015a; Kuwayama et al., 2016). One study investigated the relationship between chemical structures of analytes and detection times and did not find an association (Kuwayama et al., 2016). Factors influencing detection times should be considered when interpreting test results and synthesizing across different studies.

DISCUSSION

An important consideration for oral fluid testing in the context of drug-impaired driving is how drug detection windows in oral fluid relate to the duration of drug effects, particularly given that the presence of a drug analyte or metabolite in a bodily fluid is not necessarily an indication of impairment. At some of the cutoffs considered in the examined studies, various analytes and metabolites were detectable in oral fluid for days and even weeks, long after the acute effects and impairment extend. For example, in the studies considered, THC was last detected 28 days after smoking of cannabis, while acute impairment from smoking cannabis typically lasts between two and 3.5 hours, and up to six hours (Compton, 2017; Couper & Logan, 2004; Desrosiers et al., 2015; Lee et al., 2011; Ramaekers et al., 2006). However, while research has been mixed, there is some evidence that residual cognitive impairment due to heavy cannabis use may persist between seven and 28 days after cessation of use (Bolla et al., 2002; Pope et al., 2001). It is unclear whether this residual impairment manifests in driving performance. Additional research is needed to investigate the duration and magnitude of acute and residual effects of drug use and their relationship to detection in oral fluid, including as they relate to driving impairment.

In order for windows of detection in oral fluid to be relevant to drug-impaired driving, many have suggested utilizing the confirmation of multiple analytes and/or metabolites, ratios of metabolites to parent drug, as well as higher cutoffs (Lee & Huestis, 2014; Lee et al., 2011, 2012; Milman et al., 2012; Newmeyer et al., 2014; Scheidweiler et al., 2010; Schwope et al., 2012). This may help distinguish recent drug use and reduce misconception of residual excretion, especially for cannabis. Including THCCOOH in addition to THC would also help differentiate use from passive exposure (Cone, Bigelow, et al., 2015; Lee et al., 2011, 2012; Milman et al., 2011). A possible barrier to using multiple analytes and metabolites to improve test interpretation is the potential increased costs for running multiple tests.

Information presented in this research brief is subject to several limitations. In real-world settings, individuals may self-administer more and higher doses than those permitted in an experimental laboratory setting, potentially yielding detection times greater than those seen in controlled administration studies. The results of multiple dosing and monitored abstinence studies may help mitigate this issue. Many of the studies examined had few participants, which may have limited the generalizability of the results. Many of the studies had relatively short periods of oral fluid collection following dosing, and often subjects were still positive at the last oral fluid collection time. In some studies, there were relatively long intervals between oral fluid specimen collection. Therefore, detection times in such studies may be underestimated (Cone, DePriest, et al., 2015a, 2015b; Meyer et al., 2015). It was not possible to present all of the specifics of each study in this brief; readers are encouraged to consult the Detection Window Summary Tables for details. While this work assessed oral fluid detection windows, real-world application of oral fluid testing needs to be ultimately weighed against other matrices, taking into account practical considerations, strengths, and limitations.

Several ongoing research needs were identified in the course of the present investigation. Additional research is needed regarding:

- detection windows associated with chronic drug use and abuse;
- best practices, and potentially standards for, oral fluid collection;
- appropriate cutoffs for specific drugs in the context of drug-impaired driving enforcement;

- factors that influence detection times as well as their potential interactions;
- substances and routes of administration for which oral fluid testing may present significant limitations;
- and, as noted above, the relationship between drug detection in oral fluid and driving impairment (Anizan & Huestis, 2014).

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The AAA Foundation for Traffic Safety is a 501(c)(3) nonprofit, publicly supported charitable research and education organization. It was founded in 1947 by the American Automobile Association to conduct research to address growing highway safety issues. The organization's mission is to identify traffic safety problems, foster research that seeks solutions and disseminate information and educational materials. AAA Foundation funding comes from voluntary, tax-deductible contributions from motor clubs associated with the American Automobile Association and the Canadian Automobile Association, individual AAA club members, insurance companies and other individuals or groups.

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