# Blood & Urine Drug Testing for Cannabinoids

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## 1. General

1.1 In the light of the serious consequences for the individual, and liabilities which can be incurred in the event of a positive or incorrect test result, Simpson et al[1] discussed the need for established procedures covering storage, chain of custody, confirmation of results and appropriate legal standards for 'library' matching of spectra from unknown substances (e.g. designer drugs) requiring identification.

1.2 Most blood and urine tests for the presence of cannabinoids differ from alcohol test results as these measure inactive metabolites of cannabis, and not the active drug itself. Alcohol produces clear dose-related impairment as measured by breath, blood or urine tests. The presence of cannabinoids in urine merely signifies that the person had used or been exposed to cannabis at some point prior to the test[2].

## 2. Cannabis Pharmacokinetics

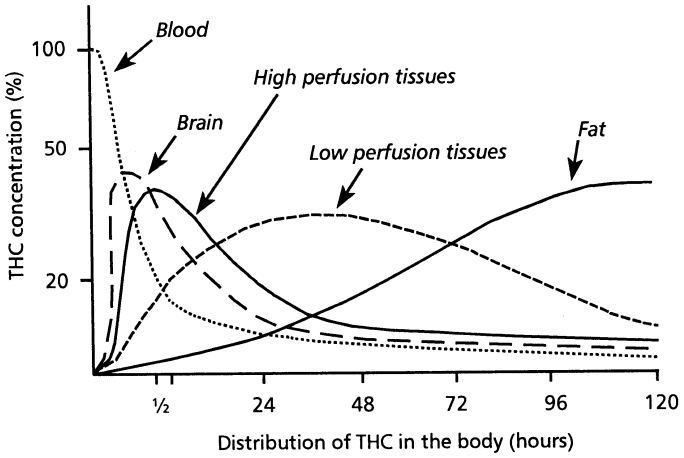
2.1 Pharmacokinetics is the study of the time course of how drugs are distributed in the body, how long the effects last and how such effects relate to drug tests.

2.2 The major problem with measurement of metabolites is the very long detection times, owing the the rapid deposition of cannabinoids in inert fatty tissue following administration. Johannson et al[3] reported that total amount of THC metabolites and the levels of delta THC-acid could be followed up to 25 days after abstinence using EMIT cannabinoid assay and HPLC.

2.3 The residual level of THC in the bloodstream occurs when THC is released from the adipose (fatty) tissues, where it is deposited shortly after smoking. THC is also converted to its inert acid form within minutes of ingestion[4]. The half-life of THC in fatty tissue is approximately 8 days[56]. There is little evidence that clearance rates for THC differ significantly between naive and experienced cannabis users.

2.4 The distribution of THC in body tissues is shown in fig 1 below. Plasma levels drop dramatically following cessation of use, with increased absorption in the brain and high perfusion tissues, but after 1 hour residual levels fall much more gradually. Levels in body fat increase over a period of hours or days, and slowly release metabolites into the bloodstream thereafter. The slow clearance rate from body fat is the main reason why cannabinoids can be detected in blood or urine for many days or weeks following cessation of use.

**Fig 1 - Distribution of THC in the Body (Kreutz & Axelrod (1973)**[7]




2.5 Harder & Rietbrock[8] noted the effects on plasma levels and intoxication produced by smoking different strengths of 'joint' at different intervals, finding that the effect of a strong (9mg) reefer would last around 45min, or if smoked continuously a recovery within 100 minutes, with a continuous high if smoked hourly with a recovery after 150 minutes. Weak (3mg) and hemp (1mg) reefers produced lower levels of intoxication and more rapid recovery times.

2.6 Chesher[9] summarised that.the inactive metabolite THC acid, formed in the liver from metabolism of THC, appears after THC in blood, and if present when the a subsequent dose is smoked, higher concentrations would ensue. Unmetabolised THC may be stored, and gradually released, from body fat for up to 28 days in chronic users. He commented: 'analytical data that provides a value only for the metabolite can only be validly interpreted as indicating recent consumption of cannabis ... a matter of hours or days. For this reason quantitative determination of only the metabolite is of no value to determine possible impairment.'

2.7 McBurney *et al* [10]describe a study of plasma concentrations of THC in users where one subject was rejected as having a concentration of 37ng/ml prior to the test. It is not stated when the subject had last smoked marijuana. Perez-Reyes *et al*[11] tested concentrations in experienced marijuana smokers who had refrained for 6 days prior to the experiment. Two cigarettes, with an average of 882mg cannabis at 1% THC (8.82mg THC), were smoked two hours apart, blood samples being taken every 5 minutes for the first 20 minutes after smoking, and at 10 minute intervals thereafter. The first cigarette produced a level of 70ng/ml at 10 minutes roughly 17ng/ml at 20 min, and roughly 3ng/ml at 2 hours. The second produced respective levels of 90, 17 and 5ng/ml at similar intervals after smoking. There is a rapid rise in THC concentration during smoking, and then an equally rapid fall which levels off at roughly 30 min post-smoking and falls gradually thereafter.

2.8 Sticht & Kaferstein[12] estimated that the blood THC concentrations produced in a 70kg person smoking 15mg THC would peak at 7-8 minutes, after 30 minutes between 14-42ng/ml, and at 60 minutes between 7.5-14ng/ml. Rosencranz[13] reported that blood levels of THC peak at 5 minutes, with a distribution half-life of 30 minutes, and elimination half-life of 18-36 hours. For THC-acid, levels peaked at 20 minutes, with distribution and elimination half-lives of 15-30 minutes and 24-72 hours respectively.

2.9 Agurell et al[14] studied THC levels in one "heavy marijuana user". His plasma THC was measured each day for four days before and one hour after smoking one cigarette laced with 10mg radioactively labelled THC, and for 8 days after ceasing all use. Prior to the experiment his plasma THC was roughly 20ng/ml. The levels of labelled and unlabelled THC both rose after smoking each cigarette, indicating that existing THC may be displaced from the fatty tissues as fresh THC is absorbed. The pre-smoking unlabelled (i.e. residual) THC level fell steadily over the period of the experiment (20ng to 9ng to 8ng to 2ng/ml on successive days), still exceeding ten-fold the labelled (i.e. fresh) THC concentration. After 8 days abstinence the levels were 1ng/ml unlabelled, and 0.1ng/ml labelled. The decline during the first period of the experiment, when the subject was smoking 10mg THC per day, indicates that his normal consumption may have exceeded this level, possibly by ten-fold or more, i.e. 100mg THC per day.

2.10 Cone & Huestis[15] postulated a model for predicting the time of marijuana exposure from relative plasma concentrations of THC and THC-carboxy acid metabolite (THCCOOH). These models were based on data from a controlled clinical study of marijuana smoking. Such models allow prediction of the elapsed time since marijuana use based on analysis for cannabinoids from a single plasma sample and provide accompanying 95% confidence intervals around the prediction. They noted that concentration estimates in the range of 7-29 ng/ml for amount of THC in blood is necessary for production of 50% of the maximal subjective high effect. Their models were based on either THC concentration, or on the ratio of 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (THCCOOH) to THC in plasma[16], noting that their predicted times of exposure were generally accurate but tended to overestimate time immediately after smoking and tended to underestimate later times..

2.11 Cami et al[17] studied the effects of expectancy on intoxication, noting a tendency toward more marked subjective effects in subjects who expected and received the drug, and that positive expectancy induced powerful subjective effects in the absence of active THC.

## 3. Metabolite or active drug?

3.1 It has been postulated, on the basis of experimental studies, that levels of 11-hydroxy THC (a psychoactive metabolite) in excess of 20ng/ml may be indicative of recent use[18], however this study used single doses, or a short series of doses, of THC (150$\mu$g/kg) on volunteers, and would not measure residual cannabinoid levels in longer-term users. There was a substantial variation in clearance rates, with several subjects showing total cannabinoids in urine samples (measured by EMIT) to be higher 18-22 hours after ingestion than 0-6 hours after consumption.

3.2 Reeve et al[19] compared plasma THC levels with performance on the roadside sobriety test, finding that failures were associated with levels over 25-30ng/ml. Sticht & Kaferstein[20] estimated that the blood THC concentrations produced in a 70kg person smoking 15mg THC would peak at 7-8 minutes, after 30 minutes between 14-42ng/ml, and at 60 minutes between 7.5-14ng/ml.

3.3 McBay[21] compared THC and THC-COOH levels in a study involving smoked marijuana cigarettes. THC-acid levels increased steadily following smoking, but were still detectable long after intoxication would have ceased. Plasma THC levels declined rapidly following cessation of smoking, but were almost all still over 10ng/ml one hour later, and in the range of 1ng to 10ng/ml 2-4 hours after cessation of smoking.

3.4 Although there are many papers reporting plasma THC levels, there are no papers which unequivocally relate plasma THC levels with overall consumption. Most have been experimental studies matching short-term THC levels with perceived psychotropic effects.

## 4. False Positives and Passive Smoking

4.1 Screening tests need to be confirmed by GCMS analysis, as positives may be obtained by consumption on non-psychoactive substances such as hemp-seed bars[22], or milk from cattle grazing on wild cannabis[23] (which could include hemp silage).

4.2 Positive tests for cannabinoids in urine may also occur as a result of passive smoking, with cannabinoid (THC-acid) levels of over 20ng/ml detectable in one case 4 days after passive exposure[24]. It was concluded that presence of cannabinoids in urine or blood is not unequivocal proof of active cannabis smoking. Giardino[25] reported that poor air quality could lead to THC-acid positives (>15ng/ml) arising from passive inhalation of cannabis smoke. Magerl et al[26] found THC-acid levels of up to 30-50ng/ml from passive-exposed subjects, and recommended a threshold of 65ng/ml to differentiate between active and passive smoking of cannabis.

4.3 Mason et al[27] produced plasma THC levels of 2.0-2.2ng/ml in passive smokers in a confined space, whereas plasma THC was not detected in a study by Law et al[28] in a separate closed-space study where the smokers developed THC of 7.5ng/ml.

4.4 In a review of passive inhalation studies, Hayden[29] reported that most studies support the proposition that passive inhalation should be seriously considered as a possible explanation for a positive urine test for marijuana, although he noted that passive inhalation does not have a major effect outside the laboratory.

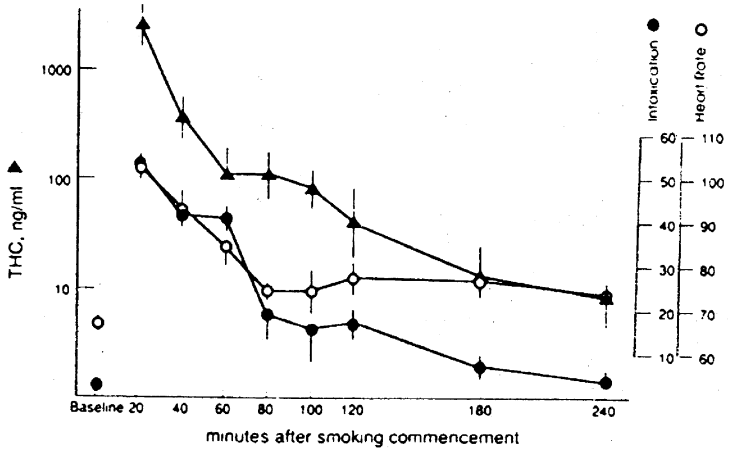
## 5 Determining Current Use - saliva testing?

5.1 Valentine & Psaltis[30] suggested use of fluorometic assay for detection of cannabinol in human saliva as a correlate of use, and also suggested detection mechanisms for breath[31] Kircher et al[32] describes the use of tandem immunoaffinity chromatography and HPLC for determination of $\Delta^9$ THC concentration in deproteinised human saliva.

5.2 Menkes et al[33] studied salivary THC levels, subjective intoxication and heart rate among 13 experienced volunteers abstinent for one week before the test. Baseline THC levels of up to 3.4ng/ml (nanograms per millilitre) were recorded (mean 0.36ng/ml). After smoking a single cigarette containing 11mg THC, salivary THC levels substantially exceeded 100ng/ml for the first hour after smoking, with levels over 10ng/ml persisting for up to 4 hours (fig 2).

5.3 Self-reported intoxication and heart rate were both substantially elevated for over 1hour, heart rate was close to baseline by 80min, and low levels of intoxication reported up to 3 hours after smoking. Salivary THC levels over 100ng/ml were associated with clear intoxication, and levels over 50ng/ml with mild intoxication.

**Fig 2. Salivary THC and subjective intoxication (Menkes et al)**



5.4 Four British police forces tested sweat or saliva testing devices in early 1998, however in December 1998 the DETR stated that '

> *the operating mechanisms in both devices sometimes failed or proved unreliable, and the notation by police of positive or negative readings from the devices simply cannot be regarded as meaningful. We cannot therefore use the data in any way that could be construed as indicative of drug use among drivers and it would be irresponsible if we were to attempt to do so'* and conceded that *'the incidence of drugs in road accident casualties...does not give us any help with accident causation'*[34]

## 6 Significance of test results - Policy & Practice

6.1 Most urine tests only detect an inactive metabolite - THC carboxylic acid. The results for cannabinoid metabolites in urine are of no significance whatsoever in determining intoxication or performance impairment, as the THC-acid is not an active compound, and can persist for many weeks after chronic use. Presence of active drug (i.e. THC - delta-9-tetrahydrocannabinol), or active metabolite 11-hydroxy THC - present in the period shortly following smoking of cannabis) would indicate recent use capable of causing intoxication or impairment.

6.2 A positive sample could easily be caused by passive smoking, or ingestion of non-psychoactive cannabis products (e.g. hemp seed bars). Such a sample could also have been produced days or weeks after taking the drug, long after any cannabis taken would have ceased to have any effect.

6.3 In many labs the cutoff threshold for 'cannabis' - a misleading term when metabolite is measured - is extremely low (15ng/ml), in comparison to other drugs. For instance amphetamine thresholds are commonly 1000ng/ml, or 1 microgram per millilitre, representing a relatively high dosage for the average individual, such as might be produced shortly after taking a gram of street 'speed'.

6.4 I note the cut off threshold used for urine testing by Home Office researchers[35] is 50ng/ml, when using the EMIT (immunoassay) technique. Magerl et al[36] recommended a threshold of 65ng/ml to differentiate between active and passive smoking.

6.5 I would consider the cut-off threshold currently in widespread use by drug testing laboratories to be unreasonably low, and highly susceptible to false-positive results. Testing for the THC-acid metabolite has no relevance to considerations of impairment or intoxication 'on the job'.

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