The Significance of Blood & Urine Test Results

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[i] 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.

Most blood and urine tests for the presence of cannabinoids differ from alcohol test results, as they 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 testii. The Department for Transport recognizes that "tests should take into account that the effect of cannabis on driving is probably limited to a few hours at most after it is taken and therefore set aside inactive metabolites of cannabis, which remain well after *it is taken by regular users*"[iii]

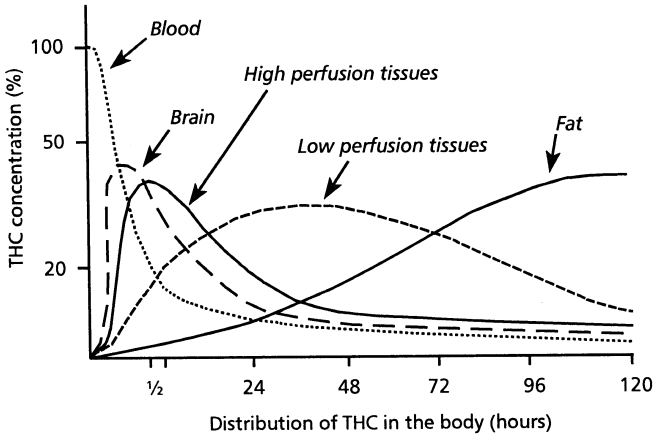
Cannabis Pharmacokinetics

The distribution of THC in body tissues is shown in fig 4 below. Plasma levels drop dramatically following cessation of use, with increased absorption in the brain and high perfusion tissues. 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.

The major problem with measurement of metabolites is the very long detection times, owing to the rapid deposition of cannabinoids in inert fatty tissue following administration. Johannson et al[iv] 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. Toennes & Kauert[v] noted that the nature of sample containers and preserving agents can affect test results for a variety of drugs.

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[vi]. The half-life of THC in fatty tissue is approximately 8 days[vii viii]. There is no evidence that clearance rates for THC differ between naive and experienced cannabis users. Chesher[ix] reported unmetabolised THC may be stored, and gradually released, from body fat for up to 28 days in chronic users.

Fig 4 - Distribution of THC in the Body
(Kreutz & Axelrod (1973)[x]



Harder & Rietbrock[xi] 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.

Chesher[xii] 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. 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."*

McBurney et al [xiii]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*[xiv] 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.

Giroud et al[xv] studied levels of THC, 11-hydroxy THC and THC-acid in whole blood, serum and plasma samples, finding a 2.4:1 ratio between serum and whole-blood concentrations, and 1.6:1 between plasma and whole blood.

Agurell et al[xvi] 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.

Cone & Huestis[xvii] 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[xviii], noting that their predicted times of exposure were generally accurate but tended to overestimate time immediately after smoking and tended to underestimate later times..

Sticht & Kaferstein[xix] 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[xx] 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.

Cami et al[xxi] 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.

Augsberger et al[xxii] studied quantitative results of drug tests in Switzerland, finding "*One or more psychoactive drugs were found in 89% of blood samples. Half of cases (223 of 440, 50.7%) involved consumption of mixtures (from 2 to 6) of psychoactive drugs. The most commonly detected drugs in whole blood were cannabinoids (59%), ethanol (46%), benzodiazepines (13%), cocaine (13%), amphetamines (9%), opiates (9%) and methadone (7%). Among these 440 cases, 11-carboxy-THC (THCCOOH) was found in 59% (median 25 ng/ml (1-215 ng/ml)), Delta(9)-tetrahydrocannabinol (THC) in 53% (median 3 ng/ml (1-35 ng/ml)), ethanol in 46% (median 1.19 g/kg (0.14-2.95 g/kg)), benzoylecgonine in 13% (median 250 ng/ml (29-2430 ng/ml)), free morphine in 7% (median 10 ng/ml (1-111 ng/ml)), methadone in 7% (median 110 ng/ml (27-850 ng/ml)), 3,4-methylenedioxymethamphetamine (MDMA) in 6% (median 218 ng/ml (10-2480 ng/ml)), nordiazepam in 5% (median 305 ng/ml (30-1560 ng/ml)), free codeine in 5% (median 5 ng/ml (1-13 ng/ml)), midazolam in 5% (median 44 ng/ml (20-250 ng/ml)), cocaine in 5% (median 50 ng/ml (15-560 ng/ml)), amphetamine in 4% (median 54 ng/ml (10-183 ng/ml)), diazepam in 2% (median 200 ng/ml (80-630 ng/ml)) and oxazepam in 2% (median 230 ng/ml (165-3830 ng/ml)). Other drugs, such as lorazepam, zolpidem, mirtazapine, methaqualone, were found in less than 1% of the cases*."

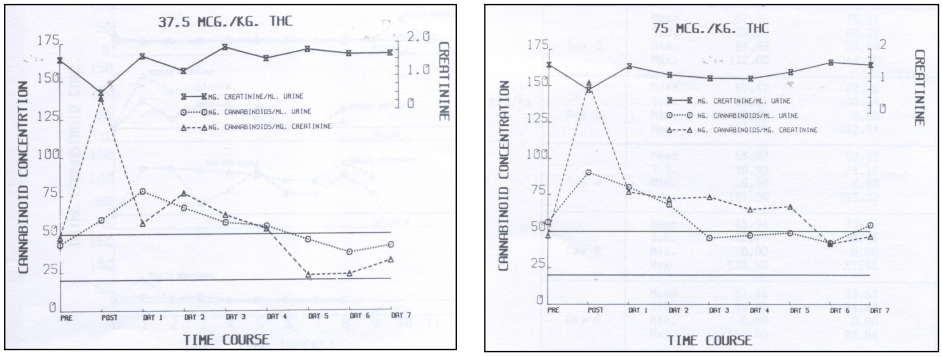
Jones et al[xxiii] reported that in Australia "*Over a 10-year period (1995-2004), between 18% and 30% of all DUID suspects had measurable amounts of THC in their blood (> 0.3 ng/ml) either alone or together with other drugs… The frequency distribution of THC concentrations (n = 8794) was skewed markedly to the right with mean, median and highest values of 2.1 ng/ml, 1.0 ng/ml and 67 ng/ml, respectively. The THC concentration was less than 1.0 ng/ml in 43% of cases and below 2.0 ng/ml in 61% of cases… THC concentrations in blood were higher when this was the only psychoactive substance present (n = 1276); mean 3.6 ng/ml, median 2.0 ng/ml compared with multi-drug users; mean 1.8 ng/ml, median 1.0 ng/ml (P < 0.001). In cases with THC as the only drug present the concentration was less than 1.0 ng/ml in 26% and below 2.0 ng/ml in 41% of cases… The concentration of THC in blood at the time of driving is probably a great deal higher than at the time of sampling (30-90 minutes later)*."

Metabolite or active drug?

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[xxiv], however this study used single doses, or a short series of doses, of THC (150μg/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.

The vast majority of workplace urine tests measure not THC but the inactive metabolite - 11-Nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-acid, or THC-COOH). Manno et al[xxv] criticised reliance on THC-acid levels in urine as evidence of recent usage as "*No accurate prediction of time of use is possible because THC-COOH has a half-life of 6 days*" and concluded that only free THC could establish recent use - "*Urinary concentrations of THC greater than 1.5 ng/mL suggests marijuana use during the previous 8-h time period*." In 1984 Manno et al[xxvi] examined the effect of doses of 37.5μg/kg and 75μg/kg THC, finding urine cannabinoid levels to exceed the 50ng/ml cut-off for 3-4 days after the lower dose (fig 5)

Fig 5 – Urine Cannabinoid Profiles (Manno et al 1984)



Johansson et al[xxvii] found "*An average elimination half-life (+/- SD) of 3.0 +/- 2.3 days was obtained for delta 1-THC-7-oic acid*." Fraser & Worth[xxviii] studied urinary cannabinoids in chronic cannabis users, finding "*The mean (range) of urinary Delta(9)-THC-COOH concentration was 1153ng/mL (78.7-2634) with a cut-off of 15ng/mL*". Studying oral doses of THC, Gustafson et al[xxix] found "*the terminal urinary elimination t(1/2) of THCCOOH following oral administration was approximately two to three days for doses ranging from 0.39 to 14.8 mg/d*."

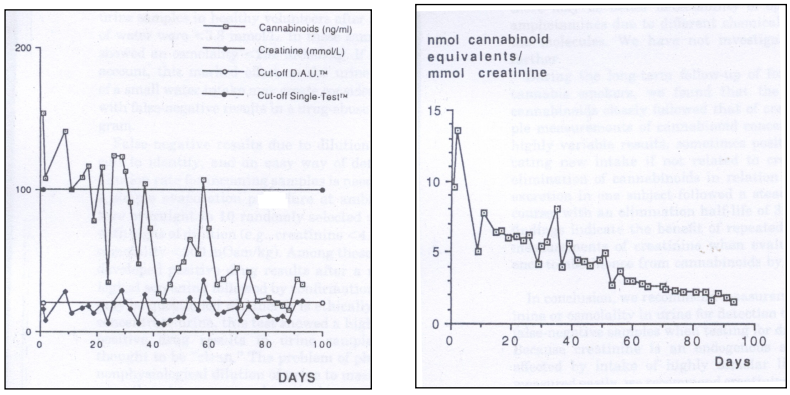
Skopp et al[xxx] studied serum cannabinoid levels of heavy (n = 12, > 1 joint/day), moderate (n = 11, < or = 1 joint/day) and light (n = 6, < 1 joint/week) smokers of cannabis for up to 48 hours after smoking cannabis, and found "*For heavy users of cannabis, THC was detectable in 8 samples, and in 5 cases both biologically active compounds, THC and 11-hydroxy-THC, were present (1.3-6.4 ng THC/mL serum, 0.5-2.4 ng 11-hydroxy-THC/mL serum). Among moderate users, in 1 sample 1.8 ng THC/mL serum and 1.3 ng 11-hydroxy-THC/mL serum were determined, and another sample was tested positive with low concentrations close to the limit of detection. In serum samples of light users both analytes could not be detected, indicating that in those persons a positive finding of THC and 11-hydroxy-THC may rather result from recent consumption than from cannabis use 1 or 2 days prior to blood sampling. The concentrations of THC-COOH and its glucuronide covered a wide range in all groups of cannabis users. However, there was a trend to higher concentrations in heavy users compared to moderate users, and the mean concentration was smaller in light smokers than in moderate smokers*."

In a study of prison inmates following most recent reported use, Smith-Kielland et al[xxxi] reported "*The plotting of THCCOOH/creatinine ratios (THCCOOH/C) versus time gave smoother excretion curves than THCCOOH concentrations alone. Based on THCCOOH/C the first 5 days after the last reported intake, the mean urinary excretion half-life was 1.3 days in infrequent users, and a median of 1.4 days was found in frequent users. In the latter group, apparent terminal urinary excretion half-lives up to 10.3 days were observed. The last positive specimens were found after 4 days for THCCOOH with cutoff 15.0 ng/mL (NIDA/SAMSHA), 5 days for THCCOOH with cutoff 10.3 ng/mL, and 12 days for cannabinoids (EMIT20) in infrequent users and after 17, 22, and 27 days, respectively, in frequent users*."

Lafolie et al[xxxii] established the importance of creatinine in normalising drug samples in urine of different dilutions, finding a near linear relationship between drug concentrations and urinary creatinine levels, with false negatives attributable to over-diluted urine samples. Following the effects of abstinence in a formerly chronic cannabis user, the cannabinoid-creatinine ratio showed a much steadier decline than the raw cannabinoid (THC-acid) data.

Fig 6 – Cannabinoid Elimination following chronic use

(a) Cannabinoids (ng/ml) **(b) Cannabinoid/creatinine Ratio**

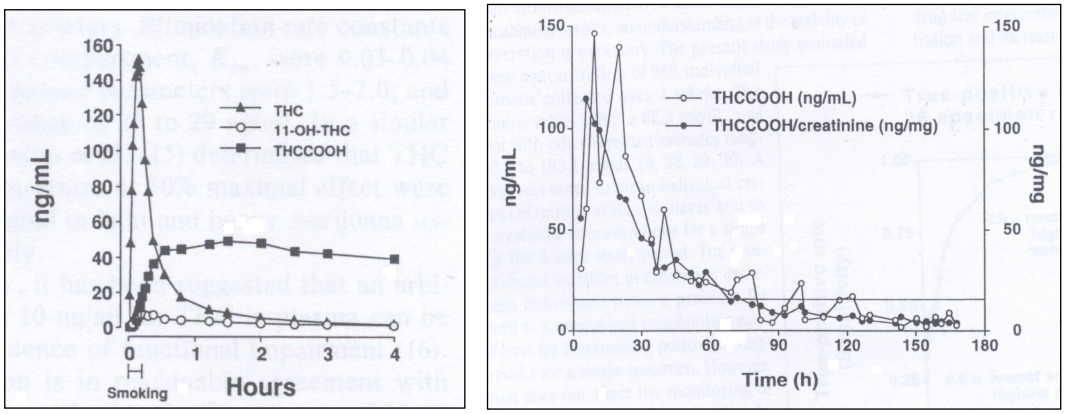


Source – Lafolie et al [1991]

Leading researchers in this field include Cone and Huestis, who have undertaken a wide range of studies into cannabinoid excretion profiles and detection times in body fluids. In 1998[xxxiii] they conducted a controlled clinical study "*Subjects smoked a single marijuana cigarette (placebo, 1.75% or 3.55% THC) each week. Urine specimens (N=953) were analyzed under blind conditions for THCCOOH by gas chromatography-mass spectrometry. Mean+/-SEM half-lives calculated by the amount remaining to be excreted method after the low and high doses were 31.5+/-1.0 hours (range, 28.4 to 35.3 hours) and 28.6+/-1.5 hours (range, 24.9 to 34.5 hours), respectively, when a 7-day monitoring period was used. The amounts of THCCOOH excreted over a 7-day period were 93.9 +/-24.5 microg (range, 34.6 to 171.6 microg) and 197.4+/-33.6 microg after the low- and high-dose sessions. Longer half-lives, 44.3 to 59.9 hours, were obtained with a 14-day sample collection*".

Cannabinoid Levels after smoking single reefer cigarette of 3.55% potency (15.8mg THC)

(a) Plasma - Huestis et al [1992][xxxiv] **(b) Urine – Huestis & Cone [1998]** [xxxv]



In a further study[xxxvi] Huestis & Cone monitored urine cannabinoids for up to 8 days following similar exposure. In 1996[xxxvii] they reported "*Mean peak urine THCCOOH concentrations averaged 89.8 +/- 31.9 ng/mL and 153.4 +/- 49.2 ng/mL after smoking of approximately 15.8 mg and 33.8 mg THC, respectively. The mean times of peak urine concentration were 7.7 +/- 0.8 h after the 1.75% THC and 13.9 +/- 3.5 h after the 3.55% THC dose. Mean GC-MS THCCOOH detection times for the last positive urine sample after the smoking of a single 1.75 or 3.55% THC cigarette were 33.7 +/- 9.2 h and 88.6 +/- 9.5 h, respectively, when a 15-ng/mL cutoff concentration was used*", and in 1995[xxxviii] studying effects of cut-off levels, found "*Mean detection times increased from a maximum of 0.5 days after the low dose to 1.5 days after the high dose using the 100-ng/mL cutoff. Mean detection times were less than 1 day following the low dose and less than 2 days following high-dose exposure using the 50-ng/mL cutoff. Mean detection times ranged from 1 to 5 days after the low dose and from 3 to 6 days after the high dose using the 20-ng/mL cutoff immunoassay*."

Ellis et al[xxxix] monitored urine cannabinoids in abstinent chronic users, and reported "*under very strictly supervised abstinence, chronic users can have positive results for cannabinoids in urine at 20 ng/ml or above on the EMIT-d.a.u. assay for as many as 46 consecutive days from admission, and can take as many as 77 days to drop below the cutoff calibrator for 10 consecutive days. For all subjects, the mean excretion time was 27 days*." Law et al[xl] noted "*delta 9-THC metabolites were detected in blood for up to 5 days and in urine for up to 12 days following a single oral dose of delta 9-THC (20 mg)*."

McBay[xli] 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.

Reeve et al[xlii] compared plasma THC levels with performance on the roadside sobriety test, finding that failures were associated with levels over 25-30ng/ml. Sticht & Kaferstein[xliii] 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.

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.

Menetrey et al[xliv] proposed a 'cannabis influence factor' (CIF) value, which relies on the molar ratio of main active to inactive cannabinoids, finding a CIF "*greater than 10 was found to correlate with a strong feeling of intoxication. It also matched with a significant decrease in the willingness to drive, and it matched also with a significant impairment in tracking performances.*" Giroud et al[xlv] concluded "*The cannabis influence factor (CIF) was demonstrated as a better tool to interpret the concentrations of THC and its metabolites in blood in forensic cases and therefore it was proposed to assume absolute driving inability because of cannabis intoxication from a CIF > or = 10. Additionally, a higher CIF is indicative of a recent cannabis abuse*."

False Positives and Passive Smoking

The first documented report of passive exposure to cannabis smoke as in 1977 by Zeidenberg et al[xlvi] During the course of a laboratory study of heavy cannabis use, one of the placebo subjects and staff members complained of dizziness, nausea, conjunctivitis and tachycardia, the placebo subject was found to have cannabis metabolites in urine. The authors warned "*The detection of cannabinoids in the urine of this nonsmoker documents the previously anecdotal concept of the "contact high" and has implications for marijuana research and for precautions that may be necessary should marijuana become legal*." Perez-Reyes et al[xlvii] noted a further case of urinary cannabinoids following passive exposure, and followed up with 3 studies[xlviii] each involving 4 persons smoking marijuana and two non-smoking subjects confined in the same room for 1 hour. Two samples exceeded a 20ng/ml threshold for active THC using EMIT immunoassay, with 'minute but detectable' plasma levels found.

Positive tests for cannabinoids in urine may occur as a result of passive smoking[xlix], with cannabinoid levels of over 20ng/ml detectable in one case 4 days after passive exposure. It was concluded that presence of cannabinoids in urine or blood is not unequivocal proof of active cannabis smoking. Giardino[l] reported the effects of air quality on THC-acid positives arising from passive inhalation of cannabis smoke. Skopp & Potsch[li] cautioned "*the discrimination between active and passive inhalation may cause severe problems*"

Mason et al[lii] 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[liii] in a separate closed-space study where the smokers developed THC of 7.5ng/ml. Law et al[liv] placed 4 nonsmoking subjects in a small unventilated room (volume 27950 litres) for 3 hours with 6 'smoking' subjects who each smoked a cigarette containing 17mg

THC at the start of the experiment. Plasma samples taken during the experimental period showed no detectable cannabinoids, although urine samples taken 6 hours after exposure showed 'significant' concentrations of metabolites (≤6.8ng/ml) THC-acid.

Morland et al[lv] tested 5 healthy volunteers exposed to cannabis (hashish) smoke in a small car (650 litres) for 30 minutes, finding "*delta 9-Tetrahydrocannabinol (THC) could be detected in the blood of all passive smokers immediately after exposure in concentrations ranging from 1.3 to 6.3 ng/mL. At the same time total blood cannabinoid levels (assayed by radioimmunoassay [RIA]) were higher than 13 ng/mL in four of the volunteers. Both THC and cannabinoid blood concentrations fell close to the cutoff limits of the respective assays during the following 2 h. Passive inhalation also resulted in the detection of cannabinoids in the urine by RIA and enzyme multiple immunoassay technique (EMIT) assays (above 13 and 20 ng/mL, respectively). It is concluded that the demonstration of cannabinoids in blood or urine is no unequivocal proof of active Cannabis smoking*."

Cone & Johnson[lvi] exposed 5 healthy men to the side-smoke of 4 or 16 'standard' (2.8% THC) marijuana cigarettes for 1 hour per day over 6 days, finding "*Daily mean plasma levels of delta-9-THC ranged from 2.4 to 7.4 ng/ml with an individual high of 18.8 ng/ml for the 16-cigarette condition. With the use of EMIT cannabinoid assays with 20 ng/ml (EMIT 20) and 100 ng/ml (EMIT 100) cutoffs, urines positive per subject under the four- and 16-cigarette passive exposure conditions were 4.6 +/- 2.2 and 35.2 +/- 3.8, respectively, for the EMIT 20 and 0.0 and 1.0 +/- 0.8, respectively, for the EMIT 100 assay*." In a further study, Cone et al[lvii] found peak THC-acid urine concentrations in the 16 cigarette condition exceeded a 15ng/ml cut-off using RIA in all five subjects (range 38ng/ml to over 100ng/ml) and confirmatory testing (GCMS) exceeded the 15ng/ml cutoff in 5 out of 7 passive subjects (range 10-87ng/ml). In the four cigarette condition four out of 5 RIA screens exceeded 15ng/ml (range 10.5-34.5ng/ml), although only two out of 5 showed detectable cannabinoids using GCMS (8 and 12ng/ml). They concluded "*The studies show that significant amounts of THC were absorbed by all subjects at the higher level of passive smoke exposure (eg., smoke from 16 marijuana cigarettes), resulting in urinary excretion of significant amounts of cannabinoid metabolites… Room air levels of THC during passive smoke exposure appeared to be the most critical factor in determining whether a subject produced cannabinoid-positive urine specimens*."

Mulé et al[lviii] exposed 3 nonsmoking volunteers to smoke from 4x 27mg THC cigarettes in a 21600ltr room for 1 hour. Urine samples taken 20-24 hours post-exposure showed cannabinoid levels of less than 6ng/ml, the authors concluded "*Passive inhalation experiments under conditions likely to reflect realistic exposure resulted consistently in less than 10 ng/mL of cannabinoids. The 10-100-ng/mL cannabinoid concentration range essential for detection of occasional and moderate marijuana users is thus unaffected by realistic passive inhalation*."

Busuttil et al[lix], reviewing cases where passive exposure was claimed as a defence to positive urine tests, concluded "*It remains impossible to define objectively an upper limit for blood and urine levels in cases of passive inhalation of cannabis from the environment*." The authors suggested a solution: "*making it an offence to place oneself in a position of being 'concerned' in the use of the drug. The onus should be on the defendant to prove that he had not attempted to extricate himself from the situation, being aware of the smoking of cannabis in his immediate vicinity*" Giardino[lx] reviewed a case of a serving soldier claiming a test result in excess of the US Department of Defense cut-off of 15ng/ml was caused by passive exposure, with reference to an air-quality simulation.

In a 1991 review of passive inhalation studies, Hayden[lxi] (working for a testing company rather than an academic institution) noted "*most of these studies appear to support the proposition that passive inhalation should be seriously considered as a possible explanation for a positive urine test for marijuana*" but concluded: "*Examination of the experimental conditions that are required to produce positive test results indicates that passive inhalation does not have a major effect outside the laboratory and should not affect drug test results in the workplace*."

In 1987, Magerl et al[lxii] recommended a cut-off level of 65ng/ml to distinguish between active use of, and passive exposure to, cannabis, after finding "*Under extreme conditions concentrations between 40 to 50 ng/ml of cannabinoids had been found in the urine*" Skopp & Potsch[lxiii] warned "*Whenever small amounts of drugs are present in blood or urine samples, especially of substances that are preferentially smoked such as cannabinoids, the discrimination between active and passive inhalation may cause severe problems*."

Non-smoke passive exposure: Screening tests need to be confirmed by GCMS analysis, as positives may be obtained by consumption of non-psychoactive substances such as hemp-seed bars[lxiv] Ahmad & Ahmad[lxv] found that consumption of milk from buffalo grazing on cannabis could produce detectable levels of cannabinoids in urine specimens from 29% of exposed children. Rosenberg et al[lxvi] screened urine from children suspected of cocaine exposure in the home for metabolites of cocaine and cannabis, but found no cannabinoids present although benzoylecgonine was found in 8 samples.

Saliva testing: Niedbala et al[lxvii] compared urine and saliva samples of individuals exposed to 5x 1.75% THC cigarettes in a 36000ltr room over a period of 4 hours. Passive subjects generated peak THC saliva levels of 26ng/ml during exposure, and remained detectable for one hour post-exposure, falling below the limit of detection thereafter. In a second study conducted in a van[lxviii], using stronger cigarettes (40 and 83mg THC) the authors concluded that positive results in passive subjects may have been a result of environmental contamination from sampling in the presence of cannabis smoke. Moore et al[lxix] proposed use of simultaneous saliva and urine samples, with presence of THC- acid in saliva considered indicative of active use. Pil & Verstraete[lxx] noted "*Recent studies (eg, the discovery of the presence of THC-COOH in oral fluid) can contribute to solve the issue of false-positive results caused by passive exposure to marijuana*."

Comment on realism of experiments. The 'room' experiments involved volumes between 20 and 36 cubic metres, equivalent to a typical sitting room, whereas the vehicle experiments would produce much higher air concentrations of THC.

I note the maximum THC content of any cigarette used in the above experiments was approximately 83mg (range 17mg to 83mg), with the maximum total THC release in any experiment being approximately 330mg, with most being in the region of 100mg (e.g. 6x 17mg). Most of the studies have involved cannabis which would be considered poor or very poor quality, compared to the premium 'skunk' varieties in common usage since the late 1990s, although this is to some extent compensated for by the general use of neat cannabis cigarettes of approximately 800mg total weight rather than cannabis-tobacco mixtures. Potential levels of exposure with high-grade skunk reefers (table 11) could significantly exceed the levels of exposure reported in the scientific literature.

Table 11 - THC content of reefer cigarettes

Type/size of cannabis/reefer	Weight of cannabis (mg)	Potency (% THC)	THC content (mg)
Soap-Bar Resin			
Typical	200	4%	8
Large	350	4%	14
Low-grade skunk			
Typical	150	8%	12
Large	400	8%	32
Neat	700	8%	56
High-Grade Skunk			
Typical	150	16%	24
Large	400	16%	64
Neat	700	16%	112

Saliva/Sweat testing for recent use

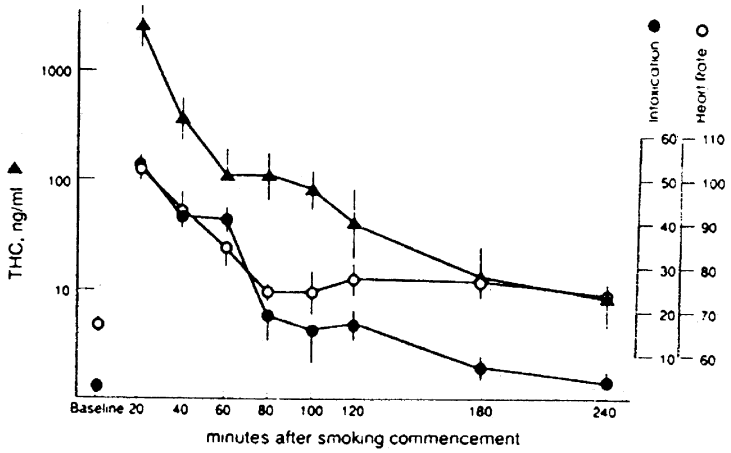
Valentine & Psaltis[lxxi] suggested use of fluorometic assay for detection of cannabinol in human saliva as a correlate of use, and also suggested detection mechanisms for breath[lxxii] Kircher et al[lxxiii] described the use of tandem immunoaffinity chromatography and HPLC for determination of Δ^9 THC concentration in deproteinised human saliva.

Studying cannabinoid detection in saliva and sweat samples, Kintz et al[lxxiv] noted "*Two main limitations of saliva and sweat are apparent: the amount of matrix collected is smaller when compared to urine, and the levels of drugs are higher in urine than in saliva and sweat. A current limitation in the use of these specimens for roadside testing is the absence of a suitable immunoassay that detects the parent compound in sufficiently low concentrations*." Investigating Drugwipe sweat and saliva testing systems, Samyn & van Haeren[lxxv] reported "*For cannabinoids…false negatives and even some false positives were observed*."

In comparative studies of drug levels in sweat, saliva and plasma, Samyn et al[lxxvi] noted "*The positive predictive value of sweat wipe analysis with GC-MS was over 90% for cocaine and amphetamines and 80% for cannabis. The accuracy of Drugwipe was assessed by comparing the electronic read-out values obtained on-site after wiping the tongue and the forehead, with the corresponding GC-MS results in plasma, oral fluid, and sweat. The accuracy was always less than 90% except for the amphetamine-group in sweat*." Mura[lxxvii] reported "*Among biological media easily accessible, saliva is considered as the most suitable medium for revealing a recent use whereas blood is undoubtedly the only medium which can be used for confirmation and quantification*".

Menkes et al[lxxviii] 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 8.

Fig 8. - Salivary THC and subjective intoxication (Menkes et al 1991)



Self-reported intoxication and heart rate were both substantially elevated for over 1 hour, heart rate was close to baseline by 80min, and low levels of intoxication were 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.

Gronholm & Lillesunde[lxxix] noted "*It was possible to detect amphetamines and opiates in oral fluid by the used on-site devices, but the benzodiazepines and cannabinoids did not fulfil the needs of sensitivity*."

Steinmeyer et al[lxxx], testing (unspecified) roadside sweat, saliva and urine-testing devices, found "*The roadside tests gave 97.6% correct assistance to the police officers in the right direction*"

Saliva and sweat testing kits are being experimented with in several US and Australian states. Four British police forces tested sweat or saliva testing devices in early 1998. 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."* They conceded that *"the incidence of drugs in road accident casualties... does not give us any help with accident causation"*[lxxxi]

Gronholm & Lilsunde tested the accuracy of on-site testing devices to GCMS analysis of urine and saliva samples, and noted "*Good results were obtained for the urine on-site devices, with accuracies of 93-99% for amphetamines, 97-99% for cannabinoids, 94-98% for opiates and 90-98% for benzodiazepines. However, differences in the ease of performance and interpretation of test result were observed. It was possible to detect amphetamines and opiates in oral fluid by the used on-site devices, but the benzodiazepines and cannabinoids did not fulfil the needs of sensitivity*."

Kintz et al[lxxxii], comparing blood, urine, saliva and sweat samples from 198 injured drivers, found "*Of the 22 subjects positive for 11-nor-9-carboxy-THC (THCCOOH) in urine, 14 and 16 were positive for THC in oral fluid (1 to 103 ng/Salivette) and forehead wipe (4 to 152 ng/pad), respectively. 11-Hydroxy-THC and THCCOOH were not detected in these body fluids*", noting "*the presence of certain analytes in saliva is a better indication of recent use than when the drug is detected in urine, so there is a higher probability that the subject is experiencing pharmacological effects at the time of sampling*" and concluding: "*Two main limitations of saliva and sweat are apparent: the amount of matrix collected is smaller when compared to urine, and the levels of drugs are higher in urine than in saliva and sweat. A current limitation in the use of these specimens for roadside testing is the absence of a suitable immunoassay that detects the parent compound in sufficiently low concentrations*."

Crouch et al[lxxxiii] evaluated different saliva-testing devices (Oratect, Uplink and Drugwipe (sweat)) and reported "*In general, the Branan and OraSure devices detected amphetamine, methamphetamine, opiates, and cannabinoid metabolite (THC-COOH) well in the concentration ranges approximating those proposed by the Substance Abuse and Mental Health Services Administration (SAMHSA), but all three devices performed poorly in detecting Delta9-tetrahydrocannabinol (THC) at the proposed SAMHSA cutoff*." Crouch et al[lxxxiv] later investigated Drugwipe sweat-testing devices, finding "*Drugwipe sensitivities were 36.4%, 35.9%, 42.9%, and 7.7%, respectively, for amphetamine(s), cocaine, opiates, and cannabinoids. The Drugwipe specificities were 99.2%, 97.4%, 99.6%, and 99.6%, respectively, for amphetamine(s), cocaine, opiates, and cannabinoids. Drugwipe failed to meet the study criteria for acceptable device performance, required performance sensitivities, and specificities 90% or greater*." Comparing the results of saliva and sweat testing devices, Kintz et al[lxxxv] reported "*the presence of delta9-tetrahydrocannabinol (THC) in oral fluid is a better indication of recent use than when the drug is detected in urine, so there is a higher probability that the subject is experiencing pharmacological effects at the time of sampling. At 3 check points organized by the Swiss police in Bern, 61 drivers were tested for the presence of drugs of abuse using the Drugwipe 5 device. In parallel, oral fluid was collected with the Intercept DOA Oral Specimen Collection device and tested by gas chromatography-mass spectrometry (GC-MS) after methylation of THC (limit of quantitation 1 ng/mL). The Drugwipe device identified 1 exposed driver, but with GC-MS, 18 drivers tested positive. THC concentrations in the Intercept buffer ranged from 2.1 to 205.1 ng/mL. These concentrations represent about 1/2 to 1/3 the authentic THC concentrations in oral fluid because of the dilution by the blue liquid of the device. Two main limitations of oral fluid were 1. the amount of matrix collected is smaller when compared to urine and 2. the levels of drugs in urine are higher than in oral fluid*."

Pehrsson et al[lxxxvi] compared results of the Drugwipe tests with laboratory GC-MS confirmation results of oral fluid or whole blood, finding "*The results of the performance evaluations were: for oral fluid*

(sensitivity; specificity; accuracy) amphetamines (95.5%; 92.9%; 95.3%), cannabis (52.2%; 91.2%; 85.1%), cocaine (50.0%; 99.3%; 98.6%), opiates (100%; 95.8%; 95.9%), benzodiazepines (74.4%; 84.2%; 79.2%) and for whole blood accordingly, amphetamines (97.7%; 86.7%; 95.9%), cannabis (68.3%; 87.9%; 84.9%), cocaine (50.0%; 98.5%; 97.7%), opiates (87.5%; 96.9%; 96.6%) and benzodiazepines (66.7%; 87.0%; 74.4%). Although the Drugwipe 5 successfully detected amphetamine-type stimulant drugs and the police officers were quite pleased with the current features of the Drugwipe tests, improvements must still be made regarding the detection of cannabis and benzodiazepines." Speedy et al[lxxxvii] concluded *"The Cozart DDS oral fluid collector provides a reliable mechanism for the collection of oral fluid at the roadside that achieves the rapid collection times required*" Drummer et al[lxxxviii] compared sweat and saliva tests for random drivers in Australia, noting "*These roadside tests gave 313 positive cases following GC-MS confirmation. These comprised 87 cases positive to… THC... The median oral concentrations (undiluted) of …THC was… 81 ng/mL. The overall drug positive rate was 2.4% of the screened population*."

Cirimele et al[lxxxix] studied the response or oral fluid over time after smoking a cigarette containing 25mg THC "*two male subjects were screened in saliva using the OraLine and Intercept devices after consumption of a single cannabis cigarette containing 25mg of THC. Saliva was first tested with the OraLine device and then collected with the Intercept device for GC/MS confirmation. In one subject, the OraLine on-site test was positive for THC for 2 h following drug intake with THC concentrations decreasing from 196 to 16 ng/mL, while the test remained positive for 1.5 h for the second subject (THC concentrations ranging from 199 to 11 ng/mL).*" Texeira et al[xc] report methodology for recovery of active THC from oral fluid samples for detection and quantitation using LC-MS, claiming their system to be "*sensitive, accurate and reproducible and may be utilized in ongoing controlled cannabinoid administration studies and in roadside studies*"

In a critical review of saliva testing protocols, Verstraete[xci] warned "*more work needs to be done, principally in the areas of the sensitivity and reliability of on-site screening devices, particularly for cannabis and benzodiazepines, knowledge about passive contamination and more generalised proficiency testing before oral fluid testing for DUID will have the reliability needed to be used forensically*." Dierich & Soyka[xcii], reviewing saliva-testing methods, concluded "*For cannabinoids and benzodiazepines, results were unsatisfactory*."

Hair Testing: Hair testing is generally used to detect longer-term usage patterns and is of no value in detecting recent use of any drug. However for cannabis there are further problems with this technique. Musshof & Madea[xciii] criticised the effectiveness of hair analysis to detect cannabinoids, concluding "*In contrast to other illicit drugs, hair analysis lacks the sensitivity to act as a detector for cannabinoids. THC and especially the main metabolite THC-COOH have a very low incorporation rate into hair and THC is not highly bound to melanin, resulting in much lower concentrations in hair compared with other drugs. Additionally, THC is present in cannabis smoke and also can be incorporated into the hair only by contamination*"

Field Impairment Testing

UK police traffic officers are now being trained in the use of roadside sobriety tests as used in parts of the USA to detect drug-induced impairment.[xciv] These are reported as including:

(a) '*The Pupil Test*. An examination of the suspect's eyes. Such drugs as cannabis tend to make pupils enlarge, while opiates like heroin make them contract.'

(b) '*The Romburg Test*. The suspect is asked to stand with his/her feet together, close their eyes with their head tipped back and decide when 30 seconds have elapsed.'

(c) *The Walk and Turn*. This involves the suspect trying to walk in a straight line, turn round heel to toe, and walk back counting each step aloud.

(d) *The One-Legged Stand*. The suspect stands with one leg straight and the toes pointing forward. The other leg is raised into the air, then held in position for a set period of time. This exercise is repeated using the other leg.

(e) *Finger to Nose*. Here the suspect is told to tilt his/her head back, then touch his/her nose with whichever index finger is indicated by the police officer.

Cannabis does not usually dilate pupils, this is a common example of inaccuracy in police information, as officers often report 'dilated pupils' as evidence of impairment. Cannabis intoxication is indicated by increased blood flow to the conjunctivae, giving the user the appearance of red or bloodshot eyes, which is one of the most reliable indicators of contemporaneous intoxication. Dilated pupils can result from a number of factors other than drug intoxication, including darkness and the after-effects of shock (e.g. following an accident).

In an evaluation of field sobriety tests among drug-using drivers, Papafotiu et al[xcv] reported "*The results revealed that there was a positive relationship between the dose of THC administered and the number of participants classified as impaired based on the SFSTs. Results also revealed that the percentage of participants classified as impaired decreased from Time 1 to Time 3 and that the addition of a new sign, head movements or jerks (HMJ), increased the percentage of participants classified as impaired in both the low and high THC conditions. These findings suggest that impaired performance on the SFSTs is positively related to the dose of THC administered and that the inclusion of HMJ as a scored sign in the SFSTs improves their predictive validity when testing for THC intoxication*." In a more detailed study, the same team[xcvi] reported "*In a repeated measures design, 40 participants consumed cigarettes that contained either 0% THC (placebo), 1.74% THC (low dose) or 2.93% THC (high dose). For each condition, after smoking a cigarette, participants performed the SFSTs on three occasions (5, 55 and 105 min after the smoking procedure had been completed) as well as a simulated driving test on two occasions (30 and 80 min after the smoking procedure had been completed). The results revealed that driving performance was not significantly impaired 30 min after the consumption of THC but was significantly impaired 80 min after the consumption of THC in both the low and high dose conditions. The percentage of participants whose driving performance was correctly classified as either impaired or not impaired based on the SFSTs ranged between 65.8 and 76.3%, across the two THC conditions. The results suggest that performance on the SFSTs provides a moderate predictor of driving impairment following the consumption of THC and as such, the SFSTs may provide an appropriate screening tool for authorities that wish to assess the driving capabilities of individuals suspected of being under the influence of a drug other than alcohol*."

Shinar & Schechtman[xcvii] investigated the efficacy of police methods for detecting drug impairment, based on objective or observable criteria, and noted "*with this partial information, the officers are able to detect drug impairment at better-than-chance levels with a sensitivity (correct detection of impairments) of 72%, but with a specificity of 43% (false alarm rate of 57%). Furthermore, the association between drug ingestion and identification of the specific impairing drug category was not very high, with sensitivities ranging from a low of 10% for amphetamine to a high of 49% for cannabis*." In a separate paper the same authors[xcviii] reported "*A formal model, based on data collected by police officers trained to detect and identify drug impairments, yielded sensitivity levels greater than 60% and specificity levels greater than 90% for impairments caused by cannabis, alprazolam, and amphetamine*."

Toennes et al[xcix] compared oral fluid and blood (serum) test results from roadside tests, and reported "*Cannabis was most prevalent (78%), and 70% of these individuals were also positive for tetrahydrocannabinol in serum. Overall, 97% of oral fluid samples positive for any substance were also positive in serum. Comparing data of oral fluid and serum for amphetamine, MDMA, morphine, benzoylecgonine, and tetrahydrocannabinol, the sensitivities were 100%, 97%, 87%, 87%, and 92%, respectively. Overall specificity and accuracy were in the range of 91-98%. Discrepancies between a negative oral fluid sample and a positive serum sample could be explained by analytical insensitivity in the lower volume of oral fluid analyzed (estimated for 0.1 mL confirmation vs. 1 mL of serum) or a shorter detection window in oral fluid. The low prevalence of discrepancies with positive oral fluid and negative serum results (2-9% of the cases) may be explained by persistent oral contamination especially for orally consumed drugs, like MDMA and cannabis. It is concluded that the detection of a psychoactive substance in oral fluid taken at the roadside is highly predictive for the detection of the corresponding drug or its*

metabolite in serum. Oral fluid testing is therefore suitable for the efficient confirmation of drug use of drivers suspected of being under the influence of drugs."

In a study correlating test results to impairment symptoms, Toennes et al[c] reported "*Accuracy in correlating drug detection in oral fluid and serum were >90% for all substances and also >90% in urine and serum except for THC (71.0%). Of the cases with oral fluid positive for any drug 97.1% of corresponding serum samples were also positive for at least one drug; of drug-positive urine samples this were only 82.4%. In 119 of 146 cases, impairment symptoms above threshold were observed (81.5%). Of the cases with drugs detected in serum, 19.1% appeared not impaired which were the same with drug-positive oral fluid while more persons with drug-positive urine samples appeared uninfluenced (32.7%). The data demonstrate that oral fluid is superior to urine in correlating with serum analytical data and impairment symptoms of drivers under the influence of drugs of abuse*."

Towards a legal limit for cannabinoids?

Laloup et al[ci] noted the legal limit for THC in plasma in Belgium to be 2ng/ml, after testing the Dräger on-site test device they concluded "*Since the accuracy was always less than 66%, we do not recommend this Dräger DrugTest system for the on-site screening of THC in oral fluid.*" Comparing oral fluid with blood they reported "*a good accuracy when comparing THC detection in oral fluid and plasma (84.9-95.7% depending on the cut-off used for plasma analysis)… an optimal cut-off value of 5.2 ng/mL THC in oral fluid (sensitivity, 91.6%; specificity, 88.6%) was observed*."

Grotenhermen et al[cii] considered evidence to justify a 'legal limit' for THC in blood, reporting "*In analogy to alcohol, finite (non-zero) per se limits for delta-9-tetrahydrocannabinol (THC) in blood appear to be the most effective approach to separating drivers who are impaired by cannabis use from those who are no longer under the influence. Limited epidemiological studies indicate that serum concentrations of THC below 10 ng/ml are not associated with an elevated accident risk. A comparison of meta-analyses of experimental studies on the impairment of driving-relevant skills by alcohol or cannabis suggests that a THC concentration in the serum of 7-10 ng/ml is correlated with an impairment comparable to that caused by a blood alcohol concentration (BAC) of 0.05%. Thus, a suitable numerical limit for THC in serum may fall in that range*."

Conclusion: drug testing

Tests for the presence of drugs in bodily fluids of drivers or accident victims may not provide scientifically or legally acceptable evidence that the person was unfit to drive or their actual driving ability was impaired by that drug.

Tests showing inactive metabolites of cannabis do not indicate a current level of intoxication or actual or potential impaired skills. No single test should be relied on as the sole basis for a prosecution.

To determine current intoxication, blood or saliva samples should be tested for unmetabolised THC, and/or the active metabolite 11-hydroxy-THC, with two or more samples taken at recorded intervals of 15 minutes or more to enable back-calculation of the likely levels at the relevant time.

There are major logistical problems with obtaining blood samples without delays which allow active THC levels to fall significantly. An increase in police powers is required to allow saliva samples to be taken at the roadside and then contemporaneously with a later blood sample, to enable back-calculation of blood THC levels to the time of any incident or accident.

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