

# Toxicology News

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*An AACC Educational Newsletter for Toxicology Laboratories*

## European Urine Drug Testing Contrasts with U.S. Practices

*By Olof Beck and Laurent Rivier*

**U**rine drug testing has been used for a long time in Europe for forensic and clinical applications. There is still substantial diversity in methodology and detection limits because there has been no standardization. For example, one survey covering 269 laboratories in nine countries found that the cutoff used for cannabis ranged from 10–500 ng/mL in the screening assay and from 1–400 ng/mL in the confirmation assay (1). A common practice in clinical testing was to report positive results without a confirmation assay.

The use of urine drug testing is widespread: In total 920 laboratories participated in 10 European proficiency testing (PT) programs (2). The further development of the European Union (EU) will of course affect the status of urine drug testing and perhaps lead to better uniformity in methodology, but this may take some time because many European countries have not yet become EU members.

### Methodology

The most common approach to screening among European laboratories is to use immunoassays (EMIT, Abbott, or Roche kits) (1,3). However, participants in the United Kingdom PT program reported frequent use of thin-layer chromatography (TLC) methods, although this technique demonstrated significantly lower sensitivity. For amphetamines, 31% of the test results were obtained using TLC, and for cannabis it was 7%. However, these rather high numbers might not be representative for the EU but rather due to the high rate of U.K. participants (72%), as U.K. and Denmark previously reported a higher use of TLC than others (1). In Sweden, for example, TLC methods are no longer in use for urine drug testing.

The most common methods used for confirma-

tion are high performance liquid chromatography, gas chromatography, and gas chromatography/mass spectrometry (GC/MS), although confirmation by a second immunoassay also occurs. Of these techniques, GC/MS is the most common; in the U.K. program, 63% of the confirmed positive results were obtained by GC/MS (3).

One important limitation of today's common approach of immunoassay screening and GC/MS confirmation is that the search is directed only at the drugs targeted by the screening test (4). An approach that might better meet the needs in many applications of urine drug testing would be to broaden the analytical approach to an undirected search by a systematic toxicological investigation. But such an approach would depend on the development of more effective methodologies than available today.

### Proficiency testing

A great number of PT programs are in use in Europe (2) and the results from these have been studied in a number of reports (see reference 3 for more information). A study at the start of the Swedish national PT program six years ago obtained very poor results (5). Similar to the situation in the United States in the mid 1980s, only a minority (27%) of participating laboratories correctly reported positive and negative results when challenged. However, performance has rapidly improved, and the rate of false results is now reduced to 1–2%.

In a major European survey reported in 1998

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## Ask the Experts

**Q** Can quantitative levels determined with a cannabinoid immunoassay be used to monitor compliance in a drug-treatment program? How quickly do levels decrease? How long does it take to go from positive (>50 ng/mL) to negative? (*Submitted by Dr. Clifford Group of Health-Productivity Systems in Kansas City, Missouri.*)

*Answered by Jimmie L. Valentine*

**A** An immunoassay used to screen for cannabinoids can provide a quantitative value, but the absolute value has little meaning because of cross-reactions. The antibody reacts not only with 9-carboxy-THC acid, the major urinary metabolite of marijuana typically assayed by GC/MS confirmation, but also with other cannabinoids in marijuana smoke and their metabolites.

There are more than 60 different terpenoids in marijuana (1), such as cannabidiol, cannabinol, and cannabichromene, that have the potential to cross-react with the antibodies used in immunoassays. For this reason a GC/MS confirmation test will always give a quantitative value less than that of an immunoassay screen.

Given the same cutoff value, the chance of obtaining a positive result with the immunoassay is greater for a longer period of time. This is part of the basis for having a value of 50 or 20 ng/mL as the cutoff for the initial immunoassay screen and 15 ng/mL as the GC/MS cutoff. One study (2) using GC/MS following smoking of a single marijuana cigarette provided data that 9-carboxy-THC acid, regardless of the two different doses given, was below 50 ng/mL in most subjects within about one day and below 20 ng/mL within two days. Some variation among subjects was observed, reasons for which I discuss below. Thus, in people who claim to be infrequent (occasional) users of marijuana, one might anticipate their urine to be negative by immunoassay within two days, depending on the cutoff used and the amount of marijuana used.

A recent study in prisoners in Norway (3) gave similar results for persons who by self-report were infrequent marijuana users. However, self-reported chronic (regular) users produced greater variation in the number of days required to obtain specimens below a 20 ng/mL cutoff. Thus, in practice, the immunoassay generally detects a larger window of time following use if the lower 20 ng/mL cutoff is used. If a laboratory wants to provide for a longer

window of detection using only immunoassay, the lower cutoff of 20 ng/mL should be considered.

### Physiological considerations

The above discussion considered only the analytical side of interpreting a determined level. However, the physiological side must also be considered. A number of studies have examined how long after the last marijuana cigarette has been smoked an immunoassay will be positive. Typically, such studies have been performed in individuals sequestered in drug-rehabilitation programs. For example, one oft-cited earlier study (4) suggested that marijuana use can be detected for up to 21 days following last use. But one must remember that this study was performed in the days when immunoassays were not as specific as those on the market today. For the above reasons, this study over-represented the time-course of the marijuana metabolite associated with the active constituent, THC.

A subsequent study in U.S. naval personnel undergoing detoxification demonstrated a difference in duration in time of marijuana metabolite detection based on whether the individual was by self-report a chronic or infrequent marijuana user (5). Schwartz, Hayden, and Riddile (6) were among the first workers to suggest that immunoassay results could distinguish between chronic and infrequent users. Later workers suggested that urine levels greater than 100 ng/mL of marijuana metabolites were usually associated with recent marijuana use by a chronic user (7, 8). The original U.S. Department of Transportation guidelines were based on this immunoassay screening level of 100 ng/mL. In 1994, the screening cutoff for marijuana metabolites was lowered by the Substance Abuse and Mental Health Services Administration to 50 ng/mL in an effort to "identify individuals who use illegal substances regardless of whether they are regular or occasional users" (9). This official statement recognized that lowering the screening detection level to 50 ng/mL made it possible to detect both chronic (regular) and infrequent (occasional) users.

Such information suggests that screening levels above 100 ng/mL could be interpreted as representing recent use by a chronic marijuana smoker, while levels moderately above 50 ng/mL would include infrequent users as well as chronic users who have not used in several days.

Pharmacokinetics studies of delta-9-THC have clearly demonstrated that multiple body compartment models must be used to describe its distribution. Its volume of distribution is very large, representing extensive extravascular distribution

(10). This is consistent with the 5000:1, lipid:water ratio observed with delta-9-THC and suggests that this physiologically active cannabinoid is stored in deep-body compartments (lipid storage sites) (11). Conceptually, these deep storage sites can act as repositories for delta-9-THC that is removed from the blood each time additional marijuana is smoked. Therefore, in theory, a person with a large, non-lean body mass might retain more delta-9-THC than a person with a lean body mass. Although this has not been demonstrated scientifically, it is possible that a person of lean body mass would have a shorter period of positive 20 ng/mL cutoff immunoassay tests following the start of marijuana abstinence.

### Multiple samples

All of this simply means that interpreting how long ago the last marijuana cigarette was smoked using a quantitative immunoassay of only one urine specimen is very difficult from a physiological standpoint. However, it might be possible to derive some useful information from multiple quantitative immunoassays.

For example, consider the question: Has a person in a drug rehabilitation program abstained from marijuana since entering the program one week ago? This question can be answered with two urine specimens, one collected upon entering and the next seven days later. Obviously, the initial urine specimen should be decidedly positive. In most cases, a chronic marijuana user will have a value >100 ng/mL. The specimen collected seven days later should be negative using a 50 ng/mL cutoff, but may be positive using a 20 ng/mL cutoff. To extend this further, if a quantitative value obtained on day seven is greater than that from day one, the person with high probability used marijuana in the intervening time. However, there is evidence that, using a 20 ng/mL cutoff, an individual can test negative one day and positive the next without having used additional marijuana. This phenomenon is most likely a result of redistribution of THC from deep storage sites and varying urinary excretion of water (3, 4).

A word of caution is appropriate. Immunoassays can produce false-positive results. New therapeutic drugs are constantly being introduced, and the use of herbal products is widespread. There is a potential for such drugs or herbs or their metabolites to cross-react with the immunoassay antibody.

Definitive interpretation of a positive urine result for marijuana metabolite should always be based on GC/MS confirmation. Retention of speci-

mens is recommended if the laboratory plans to provide any interpretive information regarding the immunoassay test result. Further testing, including identification and quantitation by GC/MS, would then be possible.

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## European Perspective

*Continued from page 1*

(6) with about 200 participating laboratories, the rate of false-positive results was about 1%, and the rate of false-negative results about 4%. In a more recent report from the ongoing U.K. program with about the same number of participants, the number of false-positive results was below 1% and the number of false-negative results about 7%. In directed challenges with samples spiked with interfering substances (ephedrine, phentermine, labetalol, and pholcodine), the rate of false-positive results increased substantially to 11–17%. Efforts to more closely link the different national programs are under way (2). In 1999, one set of test samples was distributed among several programs within Europe.

### Accreditation

A European standard for accreditation of testing laboratories, known as EN45001, has existed since 1989. A new standard document, ISO17025, is about to become effective. The different national bodies for issuing accreditation are organized in the 28-member EA (European co-operation for Accreditation; [www.european-accreditation.org](http://www.european-accreditation.org)). The status of accreditation of clinical and forensic laboratories performing urine drug testing is, however, very different in the different countries.

In 1996, a Toxicology Expert Working Group was formed to develop recommendations for drugs-of-abuse testing programs within the EU. Their report, published in 1997 (7), delineated the requirements for reliable detection of illicit drugs in urine. A major recommendation was that laboratories performing workplace testing should be accredited according to EN45001. Furthermore, the group recommended that workplace testing follow specific requirements laid out in their report and the EN45001 document. To date, the group's recommendations have not yet led to visible changes, but they are under continuing consideration. The group's recommended cutoff limits for screening and confirmation are presented in Table 1.

In Sweden, the accreditation of clinical labora-

tories has progressed during the 1990s to the point that most have now obtained accreditation. A special document on the requirements of urine drug testing was developed based on the Expert Group report and EN45001. According to this document, which came into effect in 1999, a laboratory can obtain accreditation in three categories:

1. Screening of clinical samples (subject to conditions on how positive screening results are reported and on the establishment of a relationship with a laboratory that performs confirmations when needed).
2. Screening and confirmation of clinical samples.
3. Workplace drug testing.

The document requires that confirmation be performed by GC/MS. It also requires labs that perform workplace testing to implement chain-of-custody procedures.

The College of American Pathologists has also inspected and accredited one European laboratory through its Forensic Urine Drug Testing program—the laboratory at Karolinska Hospital in Stockholm, Sweden, was accredited in 1997.

### Workplace drug testing

Workplace drug testing is far less common in Europe than in the United States. The first European conference on workplace testing was held in 1998, and the second will take place in October 2000. The attitude toward workplace drug testing is very different in different parts of Europe. While countries such as Sweden that are conservative regarding drug use have easily adopted the concept of workplace testing, countries such as Holland and Denmark have more liberal attitudes toward drug use and are therefore more resistant to such testing.

Updated information is available at the homepage of the European Workplace Drug Testing Society ([www.ewdts.org](http://www.ewdts.org)). A summary from the first conference has been published (8).

In Sweden, the number of workplace testing samples was estimated to be 24,000 in 1998, with an increasing trend. Most tests are performed pre-employment, and the frequency of positive samples in this testing was 2.3%. The rate of positive results in random testing was estimated to about 0.5%. The drug most commonly found was cannabis, followed by opiates, amphetamines, and benzodiazepines.

In the U.K., workplace testing is used in the trades of construction, transport, finance, catering, and police. The possible introduction of workplace testing among healthcare workers has created controversy, however, despite the reported high preva-

**Table 1. Cutoffs Recommended by European Expert Group**

	Screening (ng/mL)	Confirmation (ng/mL)
Opiates	300	200
Cocaine	300	150
Amphetamines	300	200
Cannabinoids	50	15

lence of cannabis (27%) and other drug use (9,10).

In Sweden, a number of court cases have examined various aspects of workplace drug testing. The conclusion of these trials is that testing can be performed as a valuable part of a drug policy at the workplace. Each workplace that implements testing must demonstrate a reasonable cause for its use, such as security, and must meet the requirements of reliable testing through accreditation.

### Abused drugs and trends

Drug abuse is considered a major problem in Europe. An EU institute based in Portugal, the European Monitoring Centre for Drugs and Drug Addiction, compiles information on the drug situation and publishes annual reports ([www.emcdda.org](http://www.emcdda.org)).

The drug that causes the most deaths is heroin. An estimated 3 to 5 million people in the EU have tried heroin. About 300,000 people are undergoing opiate substitution therapy, predominantly with methadone, but buprenorphine is already widely used in France.

Cannabis is the most common drug, followed by amphetamines. Cocaine is most prevalent in Spain and France. Heavy drug abuse is highest in Italy, Luxembourg, and Great Britain, and lowest in Germany, Austria, Finland, and Sweden, with frequency ranging from 2–10% in the population.

One recent trend is the increasing use of synthetic drugs, including new substances related to ecstasy that have not yet been classified. These drugs originate in clandestine laboratories in Holland, Poland, Spain, and Great Britain.

Recently, 4-methylthioamphetamine (4-MTA) has been associated with several deaths. 4-MTA has activity similar to MDMA (3,4-methylenedioxy-methamphetamine; ecstasy), and rat studies have shown it to increase serotonin release and inhibit uptake and in addition inhibit monoamine oxidase-a (MAO-A). Police and customs in all EU member states have repeatedly seized 4-MTA tablets. Other detected compounds are MBDB [2-methylamino-1-(3,4-methylenedioxyphenyl)-butane], 2-CB (4-bromo-2,5-dimethoxyphenylethylamine), DOB (2,5-dimethoxy-4-bromoamphetamine), and GHB (gamma-hydroxybutyrate).

Some aspects of drug use differ between Europe and the United States. In Europe, amphetamine is a more common stimulant than methamphetamine, and cocaine and PCP use are low. One benzodiazepine drug that has achieved attention in recent years is flunitrazepam. This compound has been a registered therapeutic drug in many countries since the 1980s.

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## Can Ecgonidine in Urine Be a Marker for Use of Cocaine?

By B.D. Paul

In many legal proceedings, defendants claim that unknowing ingestion caused the evidence of cocaine in their urine. These claims have some credence because the cocaine metabolite benzoylecgonine can be detected in urine up to 29 hours after ingestion of one cup of Health Inca Tea (1) ( $C_{\max}$  1274 ng/mL). Similar claims can be made about some soft drinks (2).

Stories of dermal absorption and passive smoke exposure have less credibility. The urine concentrations of benzoylecgonine produced through dermal absorption (3) and passive smoke (4) are far below the cutoff concentration mandated by the Department of Health and Human Services (5).

### Chemical marker for cocaine smoking

Over the past two decades, smoking has been the major route of cocaine administration. When cocaine is smoked, a pyrolytic product, methyl ecgonidine (MED), is also consumed. Therefore, detection of MED in urine can be related to cocaine smoking.

The analytical method used to detect MED is essentially the same as that used for cocaine and benzoylecgonine. However, because of rapid metabolism and instability at pH >8.0, the amount of MED in urine is generally low (5–27 ng/mL) (6).

The major metabolic and hydrolytic product of MED is ecgonidine (ED). ED has been studied as an alternative marker to use when MED is below the limit of detection (7). Like benzoylecgonine, ED is a zwitterion and is highly water-soluble. However, the compound could not be extracted under the conditions used for benzoylecgonine using mixed mode ( $C_{8-}/-SO_3H$ ) solid-phase extraction (SPE).

The compound's increased ionic characteristics and lack of a lipophilic group (as in the benzoyl group in benzoylecgonine) may be the reasons for the poor absorption of ED by solid-phase matrix. For extraction, it is necessary to convert the compound to the undissociated carboxylic acid by adjusting the pH to 2–3. At this pH, the extraction efficiency is 95%. ED was finally identified by GC/MS as a tert-butyl dimethylsilyl derivative.

### ED and MED as artifacts

The formation of ED and MED as artifacts during GC/MS analysis is a major concern (7). To avoid

this possibility, ED was separated from cocaine and benzoylecgonine before GC/MS analysis. Urine samples were adjusted to pH 5–6 and passed through SPE columns. The cocaine, benzoylecgonine, and MED were retained by the column, but the ED passed through the column unabsorbed.

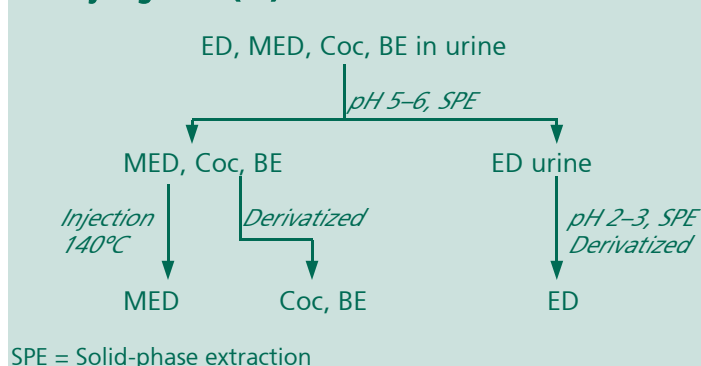
The solution containing ED was then readjusted to pH 2–3 and passed through another set of SPE columns for ED absorption (Figure 1). Because the MED fraction contained other thermally labile compounds, a high injection port temperature (>140°C) was avoided for MED analysis. The possibility that ED was an artifact was also ruled out because cocaine and benzoylecgonine were not detected in the ED fraction. As a check against formation of MED and ED during analysis, a control containing cocaine, benzoylecgonine, ecgonidine, and methyl ecgonine can be used in batch analysis.

### Oral ingestion

To study the possibility that urinary ED and MED could result from unknowing oral ingestion of cocaine, 368 samples of illicit cocaine were analyzed. The authors claimed that the samples contained 0.01–0.23% ED and 0.01–0.56% MED (8). In the procedure, ED and MED were analyzed at an injection port temperature of 230°C without separating the cocaine and benzoylecgonine. Later, it was demonstrated that similar conditions produced ED and MED as artifacts (7).

When six illicit cocaine samples were analyzed after separation of the cocaine and benzoylecgonine, ED was not detected. MED was also not detected in the samples when tested at an injection port temperature of 140°C (7). Therefore, appropriate experimental conditions to test for ED and MED are important.

**Figure 1. Flow Chart for Detection of Ecgonidine (ED), Methyl Ecgonidine (MED), Cocaine (Coc), and Benzoylecgonine (BE) in Urine**



### Passive smoke inhalation

A study that tested the effects of repeated passive exposure to side-stream cocaine smoke found that peak cocaine and benzoylecgonine concentrations in urine were 1 ng/mL and 6 ng/mL, respectively (9). But in most specimens, neither compound could be detected. These samples were not tested for MED or ED.

However, free-base cocaine was vaporized in a room and the air concentrations of cocaine and MED were measured. The MED air concentrations were similar to the cocaine concentrations, indicating that there could be a relationship between MED and ED urine concentrations and cocaine and benzoylecgonine concentrations. A systematic study is needed to evaluate the concentrations after passive exposure to MED.

### Specimen analysis

To find out how often smoking is the route of administration of cocaine, 23 benzoylecgonine-positive samples were analyzed (7). Surprisingly, 22 of these samples contained ED and 17 contained MED. The average concentration of ED ( $503 \pm 829$  ng/mL) was 42 times more than that of MED ( $12 \pm 28$  ng/mL). In three specimens, the concentration of ED was greater than that of benzoylecgonine. The results indicated that smoking is the major route of cocaine administration (96%), and ED is a useful marker for identifying active use of cocaine.

### Summary

When cocaine is smoked, a pyrolytic product MED is consumed. The major portion of the MED is metabolized or hydrolyzed to ED and can be detected in urine. To avoid artifact formation, appropriate analytical conditions are necessary to test samples. Illicit cocaine preparations contained either trace amounts or no detectable amount of ED or MED. The possibility of detecting ED or MED after passive exposure to side-stream cocaine smoke is extremely small. If detected at all, the concentrations are likely to be less than 6 ng/mL. Almost 96% of benzoylecgonine-positive specimens were positive for ED, indicating that smoking is the major route of cocaine administration. ED or MED in urine could be helpful markers for detecting active use of cocaine.

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## California Association of Toxicologists Meets Quarterly

The California Association of Toxicologists, one of the largest organizations of forensic and clinical toxicologists in the nation, meets quarterly to present current research and to discuss toxicology topics. Anyone interested in toxicology is invited to attend. For further information, contact the meeting host or visit the association's website at [www.cal-tox.org](http://www.cal-tox.org).

Upcoming meetings and contacts include:

August 3-4: Bill Phillips, California Department of Justice, 4949 Broadway, Room F249, Sacramento, CA 95820; (916) 227-3620.

November: Javier Vasquez, Poisonlab, Inc., 7272 Clairemont Mesa Blvd, San Diego, CA 92111; (858) 279-2600.

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The kits feature antibody pre-coated microplates with removable strips, room temperature incubations, and suitability for automation.

Contact: Neogen Corp., 628 Winchester Road, Lexington, KY 40505; (800) 477-8201; [www.neogen.com](http://www.neogen.com).

## NCCLS Circulates Proposed Standard on Confirmation

The National Commission on Clinical Laboratory Standards (NCCLS) has issued for review *Gas Chromatography/Mass Spectrometry (GC/MS) Confirmation of Drug; Proposed Guideline*.

### Have a Question?

Readers can send their questions to: *Clinical and Forensic Toxicology News*, AACC, 2101 L St., N.W., Suite 202, Washington, DC 20037; [CFTN@aacc.org](mailto:CFTN@aacc.org).

This document provides guidance for establishing uniform practices for producing quality data for quantitation and identification of a drug or drug metabolite using GC/MS. The document also presents quality assurance criteria for maintaining and documenting optimal instrument performance.

NCCLS is seeking comments on the proposal through Nov. 1.

For information or to order the document, contact NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898; (610) 688-1100; [www.nccls.org](http://www.nccls.org).

## Inspection Checklists Posted On-Line for Downloading

The College of American Pathologists has now posted a wide variety of information on the worldwide web in a form suitable for downloading, including laboratory improvement and inspection checklists.

The CAP homepage is [www.cap.org](http://www.cap.org), where users can click on "Download Library."

More specifically, for "Laboratory Accreditation Program Checklists" and "Laboratory Accreditation Program Manual," point your browser to [www.cap.org/html/ftpdirectory.html](http://www.cap.org/html/ftpdirectory.html).

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