NDCI COMMENTARY

THE USE OF CREATININE-NORMALIZED CANNABINOID RESULTS TO DETERMINE CONTINUED ABSTINENCE OR TO DIFFERENTIATE BETWEEN NEW MARIJUANA USE AND CONTINUING DRUG EXCRETION FROM PREVIOUS EXPOSURE

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The use of creatinine-normalization of marijuana drug test results by drug courts in order to establish either continued participant abstinence or to differentiate between new drug exposure and residual drug excretion appears widespread. However, confusion may exist regarding the application of this approach in a drug court setting. Based upon a review of the scientific and medical literature associated with creatinine-normalized cannabinoid results, this article provides guidance to drug courts on the use of this technique in a forensic environment.

A list of fundamental considerations necessary for the proper use of creatinine-normalized cannabinoid results is provided. Calculations for determining both continued participant abstinence and for differentiating between new drug exposure and residual drug excretion are reviewed, and examples given. It is recommended that if creatinine-normalized cannabinoid results are to be utilized in a forensic context (drug court case management), that a 1.5 specimen ratio threshold be employed for the determination of new drug exposure. A non-normalized method for making these differentiations, using only qualitative drug test results (positive/negative), is also presented.

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ARTICLE SUMMARIES

NON-NORMALIZED METHOD FOR DETECTING DRUG USE

[19] Drug urine concentrations are not a reliable method of detecting use.

CONSIDERATIONS IN CREATININE-NORMALIZED CANNABINOID DRUG TESTS

[20] Remember that only cannabinoid can be tested with this method; only identical, consecutive testing methods should be compared, establish elimination benchmarks, and do not dilute normalized samples.

CREATININE-NORMALIZED CALCULATIONS

[21] The test involves the quantitative results of the urine cannabinoid test and the urine creatinine test and a simple mathematical formula.

INTERPRETING CREATININE-NORMALIZED RATIOS

[22] Drug courts should use a specimen ratio of 1.5 when comparing periods of cannabinoid/creatinine ratios.

INTRODUCTION

There are numerous factors that influence both the concentration and the duration of detectability of marijuana metabolites in urine. These factors include the frequency and chronicity of use, potency of drug, individual physiological characteristics, timing of specimen collection, testing methodologies and degree of urine dilution (Schwartz and Hawks, 1985; Bell, et al., 1989). As a result of these variables, the monitoring of absolute cannabinoid concentrations in urine in an effort to establish continued abstinence (falling concentrations) or to determine new drug intake (rising concentrations) is inappropriate and can lead to incorrect result interpretations. Increases in absolute cannabinoid concentrations resulting from changes in urinary output are often mistakenly interpreted as new drug use rather than carryover from previous drug exposure. Decreases in absolute cannabinoid concentrations, which can also result from urine volume changes, may be misinterpreted as proof of continued abstinence. Consequently, the use of absolute drug concentrations produced by qualitative testing methods for determining a participant's drug use patterns is without scientific foundation and should be avoided (Chiang and Hawks, 1986). Nonetheless, many drug courts find it necessary to use the results of drug testing in determining either continued abstinence or to differentiate between new drug exposure and continuing excretion from previous drug use.

In the mid-1980's, toxicologists proposed the creatinine normalization of urine drug test results in an effort to correct for variations that occurred in urine volume (Bell, et al., 1989; J.E. Manno, 1986; J.E. Manno, Ferslew, and B.R. Manno, 1984). Quantitative manipulations using creatinine concentrations have been used for decades in the field of toxicology (Levine and Fahy, 1945). Creatinine is a waste product of muscle metabolism that is excreted into the urine at a relatively constant rate throughout the day in healthy individuals (Spencer, 1986; Narayanan and Appleton,

1980; Bingham and Cummings, 1985). Urine volume, on the other hand, is highly variable and is influenced by a variety of factors including; liquid, salt and protein intake, exercise and age (Huestis and Cone, 1998 October). The goal of normalization is to reduce the apparent variability of drug excretion due to changes in urine volume by creating a ratio of drug concentration to creatinine concentration (expressed as nanogram of drug per milligram of creatinine). Thus, drug/creatinine ratios of specimens collected over time can be compared to determine if new drug use has occurred or to validate continued participant abstinence (Huestis and Cone, 1998 October; Lafolie, et al., 1994 January; Smith-Kielland, Skuterud, and Morland, 1999 September; Fraser and Worth, 1999 October).

The guidance provided herein is designed neither to encourage nor discourage the use of the normalization technique as an aid in the interpretation of drug testing results. The purpose of this document is to describe the normalization method and to provide direction for its proper administration in a drug court setting. Scientific research indicates that even under the most controlled conditions creatinine-normalization of cannabinoid results accurately predicts new drug use in 83 percent of cases and can have a false-negative (predicting residual drug excretion when new marijuana use had occurred) rate of 24 percent (Huestis and Cone, 1998 October; Fraser and Worth, 1999 October). Therefore, it is essential for each drug court to evaluate the forensic acceptability of this technique prior to instituting its practice with participants.

THE NON-NORMALIZED METHOD

[19] While the primary focus of this guidance document is to discuss using creatinine-normalized cannabinoid results to make the differentiation between new marijuana use and continuing residual drug excretion, it is worthwhile nonetheless to review the non-normalized approach for accomplishing the same goal. The use of urine

drug concentrations, even under the best of circumstances, is not without risk and is by no means absolutely conclusive in all cases. Additionally, there are some drug courts that may not wish to employ mathematical formulas in the business of dispensing justice. Finally, the non-normalized method for distinguishing between re-use and continuing excretion can be used with all of the drugs of abuse, not just cannabinoids.

The non-normalized approach relies solely on the qualitative drug test results (positive or negative) to make the distinction between new drug use and continued excretion of drug from a previous exposure. A drug court participant is deemed "drug-free" following two consecutive drug tests both yielding negative results, where the two tests are separated by at least five days. Subsequent positive drug tests would be considered new use. In other words, the two negative drug tests – at least five days apart – establish a participant's abstinence baseline for the drugs being tested. Any positive drug test result following the establishment of this abstinence baseline indicates new/recent drug exposure. For cannabinoids, the non-normalized technique can be used with assays that test for marijuana at either the 20 or 50 ng/mL cutoff concentration.

If the design of qualitative drug testing methods is simply the determination of the presence or the absence of drugs and their metabolites in urine, then the non-normalized approach represents a simple, effective and reliable method for differentiating new drug use from residual drug excretion. This "two-negative test" approach is consistent with manufacturer's recommendations for the proper use of their products and results; and requires no arithmetic calculations.

FUNDAMENTAL CONSIDERATIONS

[20] Before discussing the specifics of using creatinine-normalized cannabinoid results to determine continued abstinence or to differentiate between new marijuana use and continuing residual excretion, it is necessary to review some essential rules for accomplishing these comparisons. Using a solid scientific foundation enables drug courts to employ normalization with the confidence that this approach will withstand legal scrutiny. Failure to follow the guidance detailed below can result in incorrect interpretation of testing results and inappropriate court decisions.

1. **Cannabinoids Only**. While the scientific community has researched the creatinine-normalization of drugs other than marijuana (Huestis and Cone, 1998 October), it is recommended that the technique of creatinine-normalization be applied only to cannabinoid results. Marijuana is ideally suited for normalization because the drug is more fat-soluble than most of the other drugs of abuse tested in drug court (J.E. Manno, 1986). In fact, it is the very extended excretion of marijuana metabolites in urine that has prompted the concept of creatinine-normalization of cannabinoid results. Attempts to creatinine-normalize drugs with more rapid elimination rates (i.e. cocaine) can be misleading and is generally ineffective in a drug court environment.

2. **Compare Only Identical Methods**. In order to correctly compare creatinine-normalized results, it is essential that cannabinoid values from identical drug testing methods be utilized. In other words, EMIT cannabinoid results must be compared with EMIT cannabinoid results; GC/MS cannabinoid concentrations must be compared with GC/MS cannabinoid concentrations, and so on. Never attempt to compare results obtained from dissimilar cannabinoid methodologies. This is also true for the

creatinine methods, which are used in calculating the ratios.

In addition, request the laboratory use only quantitative cannabinoid concentrations (i.e. GC/MS) or automated methods that produce "semi-quantitative" cannabinoid results (such as the Abbott TDx method). Semi-quantitative results are derived from assays that employ multiple calibrators to establish a standard curve. The comparison of results from different laboratories is not recommended. On-site (i.e. hand-held, point-of-care) testing devices are not appropriate for producing creatinine-normalized results.

NOTE: Only urine samples separated by a minimum of 24 hours between collections should be used for comparison purposes.

3. **Compare Consecutive Tests**. For creatinine normalization to be useful in the interpretation of urine cannabinoid results, it is important that comparisons be made on consecutive testing results. For example, if a participant has been drug tested on five separate days in the last two weeks (Days #2, 5, 8, 11 & 12) compare creatinine-normalized results consecutively, in the order in which the tests were collected – compare Day #2 with Day #5, compare Day #5 with Day #8, and so on. Comparing creatinine-normalized results from non-sequential tests such as comparing Day #2 with Day #11, for example, is problematic and should be avoided.

   It is however appropriate to make consecutive comparisons of creatinine-normalized results if there is a single intervening negative test result. Using the collection schedule in the example above, if on Day #8 that drug test produced a negative result and Days #5 and #11 produced positive results, it is legitimate

to compare the creatinine-normalized results of Day #5 with Day #11.

4. **Establish Elimination Benchmarks**. While it is true that the presence of marijuana metabolites persists in urine long after use (Huestis, Mitchell, and Cone, 1996 October; Kelly and Jones, 1992 July-August; Ellis, et al., 1985; Dackis, et al., 1982), it is inappropriate to attempt to use creatinine-normalized cannabinoid comparisons after the time period cannabinoids would have been expected to be eliminated from the body, assuming abstinence. In other words, programs must adopt elimination benchmarks that define the period after which a continued positive cannabinoid result is indicative of new use – regardless of the creatinine-normalized profile.

   Example: A drug court establishes an elimination benchmark for cannabinoids of 30 days (i.e. Regardless of past chronic or occasional marijuana use patterns, an abstinence participant's urine should drug test negative for cannabinoids after 30 days in the program.). A drug court participant has been in the program for 32 days and is continuing to test positive for cannabinoids. It is inappropriate to use creatinine-normalized cannabinoid comparisons beyond the 30-day period to determine new use versus continued elimination. New use is established based upon the elimination benchmark, not the creatinine-normalized results.

5. **Do Not Normalize Dilute Samples**. Dilute urines (with creatinine values of less than 20 mg/dL) most likely represent samples influenced by excessive participant hydration prior to specimen collection (Cook, et al., 2000 October). Dilute samples should be handled (sanctioned) as tampered specimens based upon existing drug court policies. Due to the

potential for inaccurate normalization and incorrect result interpretation, drug courts are advised not to use creatinine-normalized cannabinoid results that have been calculated from urine samples with creatinine measurements of less than 20 mg/dL or drug test samples that have been reported as "dilute".

THE CREATININE-NORMALIZED CALCULATIONS

[21] At first glance, the calculations detailed below may appear daunting. **Do not panic**! The calculations presented are quite simple and are described primarily for educational purposes only. The reference laboratory providing drug testing services to the drug court often performs the actual calculations. That said, understanding the basic principles outlined in this section will assist drug court teams in utilizing normalized urine cannabinoid results appropriately.

The calculation for normalizing (correcting) urine cannabinoid results for creatinine concentrations is relatively straightforward. Regardless of whether the creatinine-normalized calculation is determined by the laboratory or is performed by drug court staff, the mathematics involves the results of two analyses: the quantitative or semi-quantitative result from the urine cannabinoid test (usually expressed as urine cannabinoids or THC or THC-COOH in nanograms per milliliter – ng/mL) AND the quantitative result from the urine creatinine test (usually expressed as either creatinine in milligrams per deciliter – mg/dL or creatinine in milligrams per milliliter – mg/mL).

1. Normalization of urinary cannabinoid excretion to urine creatinine concentration (if creatinine is expressed in mg/dL) proceeds as follows:

$$\frac{\text{urine cannabinoid (ng/mL)}}{\text{creatinine (mg/dL)}} \times 100 = \text{"normalized" cannabinoid urine (ng/mg creatinine)}$$

EXAMPLE #1: urine cannabinoid result = 150 ng/mL
urine creatinine result = 200 mg/dL

150 ÷ 200 = 0.75 X 100 = 75 ng cannabinoid/mg of creatinine

2. Normalization of urinary cannabinoid excretion to urine creatinine concentration (<u>if creatinine is expressed in mg/mL</u>) proceeds as follows:

urine cannabinoid (ng/mL) / creatinine (mg/mL) = "normalized" cannabinoid urine (ng/mg creatinine)

EXAMPLE #2: urine cannabinoid result = 150 ng/mL
urine creatinine result = 2.0 mg/mL

150 ÷ 2.0 = 75 ng cannabinoid/mg of creatinine

The examples cited above represent the preferred approach to expressing the cannabinoid/creatinine ratio and the method used in most of the scientific research associated with this subject matter. However, it is not uncommon for laboratories to simply calculate the ratio without regard for the units of measure (i.e. ng/mL or mg/dL). In those circumstances the normalized test results may simply be expressed as a ratio.

EXAMPLE #3: urine cannabinoid result = 150 ng/mL
urine creatinine result = 200 mg/dL

150 ÷ 200 = 0.75 (cannabinoid/creatinine ratio)

NOTE: All of the examples presented to illustrate the calculations for normalizing urine cannabinoid results for creatinine concentrations demonstrate the necessity for

strictly adhering to Fundamental Consideration #2 – Compare Only Identical Methods. Do not attempt to compare creatinine-normalized results from different drug testing methods. Also, do not attempt to compare ratios from different laboratories.

INTERPRETING CREATININE-NORMALIZED RATIOS

[22] Determining continued participant abstinence using creatinine normalized ratios is quite simple. Following marijuana smoking, dividing the urinary cannabinoid excretion by creatinine concentration produces a cannabinoid/creatinine ratio that should continue to decrease until either a new episode of drug use occurs or the cannabinoid test becomes consistently negative. Example A provides such a participant scenario:

Example A.

Test	**Collection Date**	**Cannabinoid**	**Creatinine**	**THC/ CR ratio**	**THC/ CR ratio**
		Result (ng/mL)	**Result (mg/dL)**	**(in ng/mg)**	**(no units)**
Test #1	Day 1	450	193	233	2.33
Test #2	Day 3	264	254	104	1.04
Test #3	Day 6	107	171	63	0.63
Test #4	Day 7	115	267	43	0.43
Test #5	Day 9	32	186	17	0.17
Test #6	Day 13	negative	192	***	***
Test #7	Day 15	negative	215	***	***

A review of the cannabinoid/creatinine ratio from Day 1 through Day 9 indicates a steadily decreasing profile – what would be expected in a continuing abstinence participant. This conclusion is further supported by the two consecutive negative test results on Days 13 and 15. Note that on Day 7 (Test #4), the absolute cannabinoid

concentration (115) actually increases from the previous sample (Day 6). However, following normalization the continued abstinence pattern is established suggesting that the increase in absolute cannabinoid concentration on Day 7 is not indicative of new marijuana use.

Differentiating between new marijuana use and continuing residual drug excretion using creatinine-normalized cannabinoid results is somewhat more complicated than determining continued participant abstinence. The primary difference being that the cannabinoid/creatinine ratios must not only be compared to one another, but the change between two ratios must be calculated. The calculation of the ratio from two positive urine cannabinoid tests (defined as the specimen ratio) proceeds as follows:

cannabinoid/creatinine ratio ÷ cannabinoid/creatinine ratio of an earlier positive sample = the specimen ratio

Test	**Collection Date**	**Cannabinoid**	**Creatinine**	**THC/ CR ratio**	**THC/ CR ratio**
		Result (ng/mL)	**Result (mg/dL)**	**(in ng/mg)**	**(no units)**
Test #1	Day 1	410	253	162	1.62
Test #2	Day 3	219	217	101	1.01
Test #3	Day 6	158	189	84	0.84
Test #4	Day 7	217	227	96	0.96
Test #5	Day 9	95	183	52	0.52

Example B.

Using test results from Example B, the calculation of the specimen ratio for comparing Day 3 to Day 1 would be expressed as:

101 ÷ 162 = 0.62 (specimen ratio)

The calculation returns a value of less than 1.0 because the cannabinoid/creatinine ratio for Day 3 is lower than that of Day 1.

If we determined the specimen ratio for Day 7 compared to Day 6 the calculation would be:

$$96 \div 84 = 1.14 \text{ (specimen ratio)}$$

Since the cannabinoid/creatinine ratio for Day 7 is greater than that of Day 6, the specimen ratio is also greater than 1.0.

In differentiating between new drug use and continuing drug excretion from previous exposure, only those specimen ratios of greater than 1.0 are of interest; because in almost all cases the only time a specimen ratio will be calculated is when the most recent cannabinoid/creatinine ratio is greater than the cannabinoid/creatinine ratio from a preceding positive sample.

While scientific researchers have evaluated the use of a variety of specimen ratios for predicting new marijuana use (including specimen ratios of less than 1.0), forensic scientists are in general agreement that a specimen ratio of 1.5 is the most appropriate standard for legal applications (Huestis and Cone, 1998 October; Fraser and Worth, 1999 October)**. Therefore, in drug court proceedings an increase in the specimen ratio of equal to or greater than 1.5 for two consecutive positive urine samples is indicative of new marijuana intake. When using this 1.5 specimen ratio standard, research indicates that new marijuana usage will be accurately predicted approximately 75 percent of the time, with a false positive rate (falsely predicting a participant had smoked marijuana when continued elimination was the true reason for the positive test) of less than one percent** (Huestis and Cone, 1998 October; Fraser and Worth, 1999 October)**. Put another way, one in four participants will**

be able to avoid "new use" detection using the 1.5 specimen ratio threshold, but virtually no one will be falsely accused.

A variety of issues can be examined by reviewing the data in Example C, including the calculation for differentiating between new marijuana use and continuing residual drug excretion.

Example C.

Test	**Collection Date**	**Cannabinoid**	**Creatinine**	**THC/ CR ratio**	**THC/ CR ratio**
		Result (ng/mL)	**Result (mg/dL)**	**(in ng/mg)**	**(no units)**
Test #1	Day 1	507	243	209	2.09
Test #2	Day 3	314	187	168	1.68
Test #3	Day 5	258	244	106	1.06
Test #4	Day 6	217	162	134	1.34
Test #5	Day 9	228	191	119	1.19
Test #6	Day 11	183	138	133	1.33
Test #7	Day 13	149	50	298	2.98

On Day 6 the cannabinoid/creatinine ratio (134) increases from the previous positive sample (106). Determination of the specimen ratio,

$$134 \div 106 = 1.26 \text{ (specimen ratio)}$$

indicates a change of 1.26, which is insufficient to document new marijuana usage utilizing the 1.5 specimen ratio threshold.

On Day 9 the absolute cannabinoid concentration (228) increases from the previous positive sample, however the cannabinoid/creatinine ratio decreases from Day 6 (134) to Day 9 (119) which is indicative of continued drug excretion.

On Day 11 the cannabinoid/creatinine ratio (133) increases from the previous positive sample (119). Determination of the specimen ratio,

$$133 \div 119 = 1.11 \text{ (specimen ratio)}$$

verifies this change (1.11) is also not sufficient to make the determination of new marijuana use employing the 1.5 specimen ratio threshold.

On Day 13, the cannabinoid/creatinine ratio (298) increases significantly from Day 11 (133) even though the absolute concentration (149) decreased from the previous test. Calculation of the specimen ratio,

$$298 \div 133 = 2.24 \text{ (specimen ratio)}$$

indicates a change of 2.24 between these two consecutive positive urine samples and clearly indicates new marijuana exposure – specimen ratio greater than the 1.5 threshold. Also note the significant drop in creatinine concentration on Day 13 which may suggest increased fluid intake by the participant in an effort to dilute the urine sample.

While the calculation examples listed in this section were all performed using the cannabinoid/creatinine ratios expressed in ng/mg, the computations using the cannabinoid/creatinine ratio with no units of measure are performed in exactly the same manner and yield the same interpretations.

Some drug courts may regard the 1.5 specimen ratio standard as overly conservative (i.e. allows too many participants to engage in new drug use without being detected by creatinine-normalized cannabinoid result comparison). As noted earlier, researchers have used specimen ratio thresholds as low as 0.5 in an effort to differentiate new drug use from continuing excretion (Huestis and Cone, 1998 October).

Drug courts are cautioned about the consequences associated with utilizing lower specimen ratio criteria. For example, at a specimen ratio of 1.0 the scientific literature indicates that the ability to accurately discriminate new marijuana use only increases to 80 percent, while the false positive rate jumps ten fold (Huestis and Cone, 1998 October; Fraser and Worth, 1999 October). This research indicates the lower the specimen ratio, the greater the incidence of incorrectly identifying a participant of engaging in new drug use when none has occurred.

SUMMARY

The need for drug court teams to use drug test results to establish either continued participant abstinence or to differentiate between new drug exposure and residual drug excretion can be compelling. This is particularly true for marijuana because of its protracted elimination profile. A court's response to a second positive marijuana urine test varies by program and may result in vastly different consequences for drug court clients. Creatinine-normalization of cannabinoid results has been seen by some as an approach toward establishing objective criteria for this decision-making process. However, given the ramifications associated with such a determination, drug courts should move cautiously in employing the techniques of creatinine-normalized cannabinoid results. While the use of this method for determining continued participant abstinence is straightforward, the interpretation of creatinine-normalization data for the purposes of differentiation between new marijuana use and continuing drug elimination is more complex. If creatinine-normalized cannabinoid results are to be utilized in the drug court arena, it is recommended that the 1.5 specimen ratio standard be employed due to the legal nature of the proceedings.

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