

More Effective Drug Testing: Tools, Interpretation, and Challenges

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Palo Alto, California

Pharmacokinetics Pharmacodynamics

Dose → Blood → Receptors → Effects

Absorption

Distribution

Metabolism

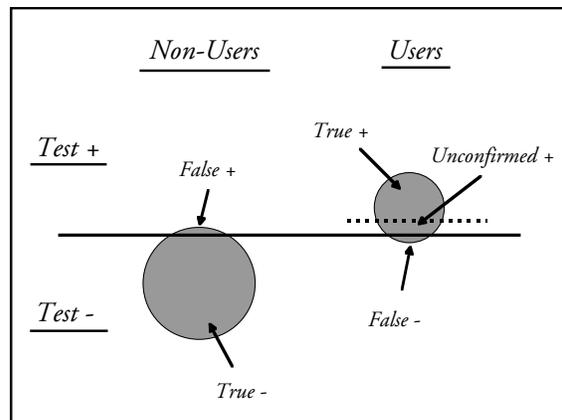
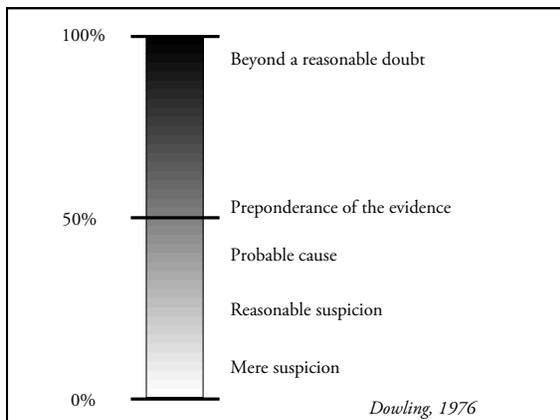
Elimination → Urine, sweat, oral fluid, hair, ...

Forensic Challenges: Specimens, Technologies

- ▶ Urine: Adulteration, substitution, dilution, interpretation
- ▶ Oral fluid: Adulteration, interpretation
- ▶ On-site: Subjectivity, performance
- ▶ Hair: Contamination, bias, ADA, standards
- ▶ Sweat: Contamination, tampering, standards
- ▶ Oculomotor: Science, standards

Forensic Issues for Laboratories / Toxicologists

- ▶ Admissibility of evidence
Legal standards: peer review, known error rate, standards, ...
- ▶ Evidentiary weight
Chain of custody, laboratory performance, interpretation, ...
- ▶ Legal requirements for decisionmaking
Beyond a reasonable doubt, preponderance, ...
- ▶ Laboratory liability
Duty owed, negligence, privacy of records/HIPAA ...
- ▶ Expert liability
Peer oversight



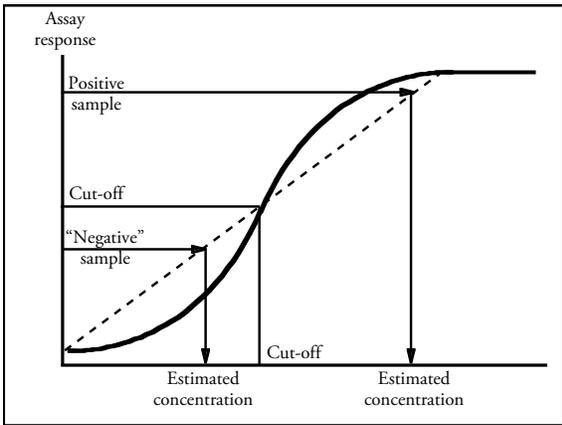
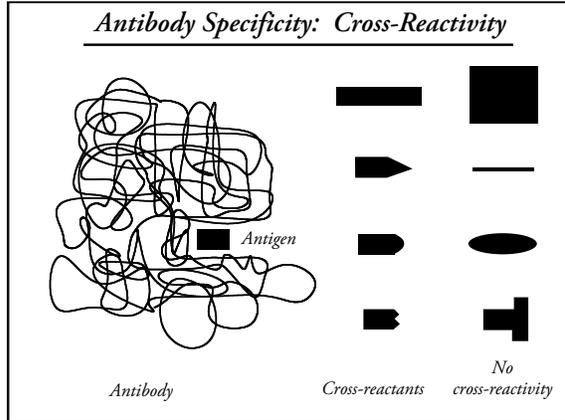
Qualitative
(positive, negative)

vs.

Quantitative
(ng/mL, immunoreactive equivalents, rate units)

vs.

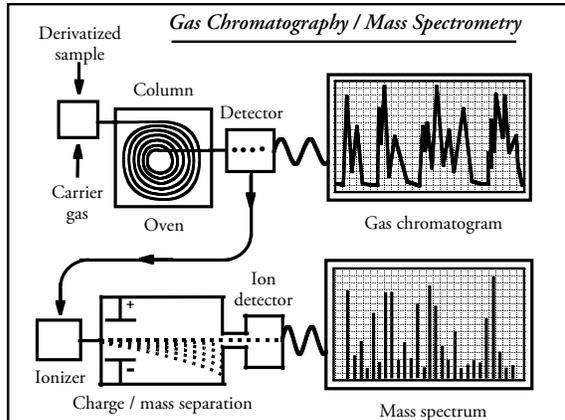
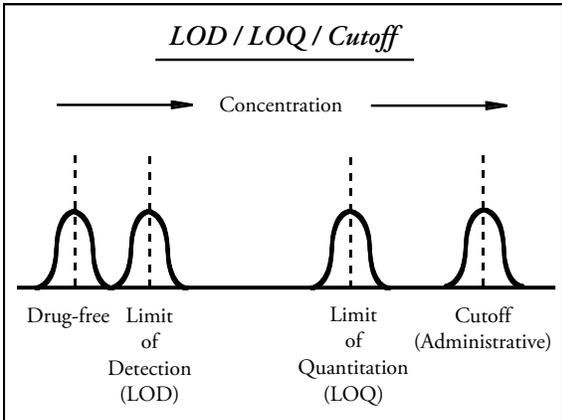
“Semi-quantitative”
(no such thing?)

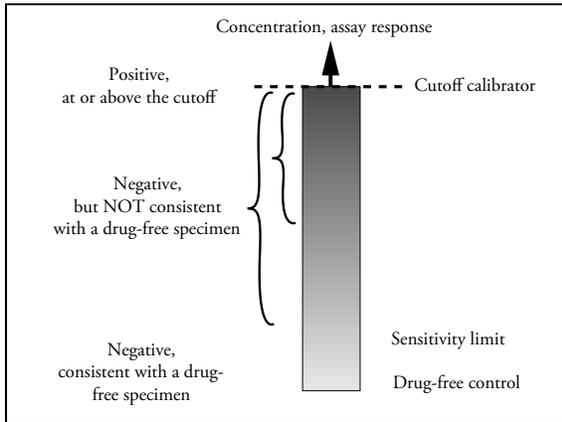


Cutoff
Level established administratively at or above which a result is reported as “positive” and below which is reported as “negative”

Limit of Quantitation (LOQ)
Level at which a result may be reported as a quantitative value (e.g. ng/mL) with acceptable accuracy (e.g. ±95%)

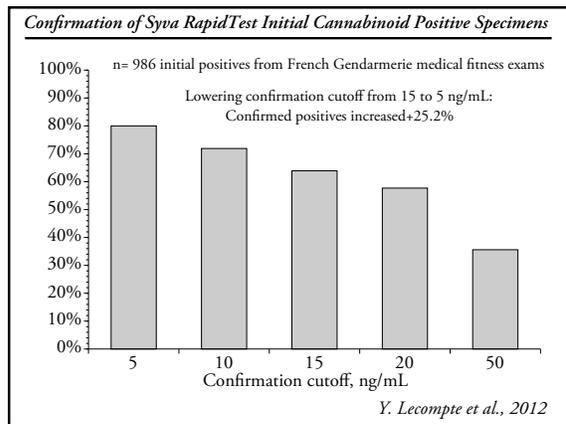
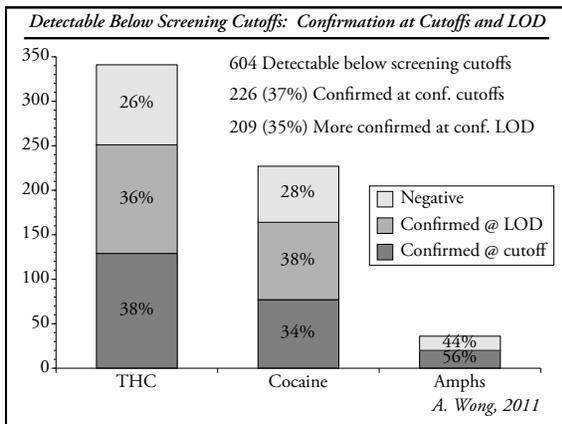
Limit of Detection (LOD)
Level at which a result can be clearly distinguished from the range of results for “drug-free” specimens



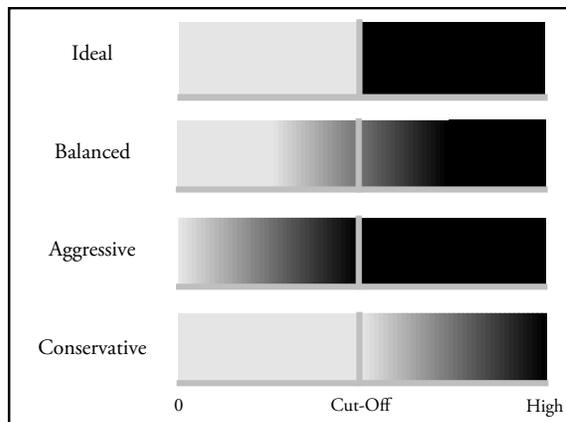


Sensitivity: Concentration above which a test result can be distinguished from a drug-free specimen with 95% confidence.

	Immunoassay Cutoff	Immunoassay Sensitivity
Amphetamines	500 ng/mL	150 ng/mL
Cocaine metabolite	150 ng/mL	<35 ng/mL
Cannabinoids	50 ng/mL	<15 ng/mL
Opiates	300 ng/mL	<16 ng/mL

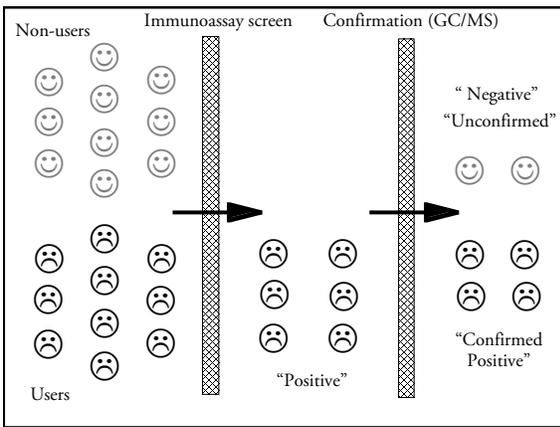
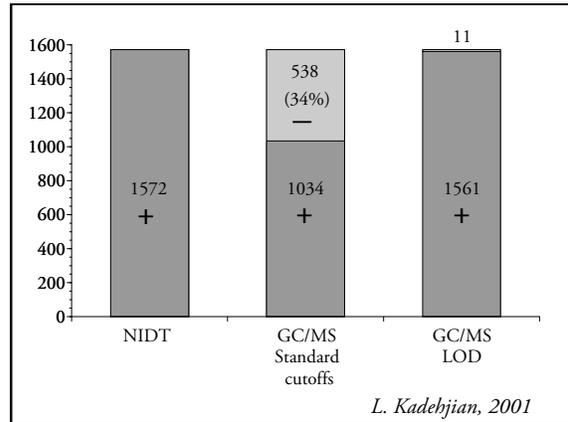


- San Mateo County "Truth in Testing"***
- ▶ Standard immunoassay screening cutoffs
 - ▶ FDA-cleared immunoassay screening device
 - ▶ Limit of quantitation GC/MS confirmation testing
 - ▶ Federally-certified (SAMHSA) laboratory
 - ▶ Established scientific methods and procedures
 - ▶ Regulatory recognition (SAMHSA policy)
 - ▶ Case law support



Non-Instrumented Drug Test Device Studies with Challenging Near Cut-off Specimens

	Accuracy vs. GC/MS
▶1997 Duo Research, U.S. Federal Courts	
15 devices	71% (52%–79%)
benchtop analyzer	78%, 82%
▶1998 Duo Research, SAMHSA	
15 devices	70% (61%–78%)
benchtop analyzer	76%
creatinine device	91%
▶1999 Kadehjian	
5 devices	70% (66%–74%)
benchtop analyzer	80%



SAMHSA “Drug Presence” Criteria

Mandatory Guidelines for Federal Workplace Drug Testing Programs

Subpart B--Scientific and Technical Requirements

Section 2.4 Laboratory Analysis Procedures

(j) Retesting a Specimen for Drugs.

(2) Because some drugs or drug metabolites may deteriorate during storage, the retest of an aliquot of a single specimen or the test of a split (Bottle B) specimen is not subject to a specific drug cutoff requirement, but must provide data sufficient to confirm the presence of the drug or metabolite.

SAMHSA, 69 FR 19644, 4/13/04

NRC: Dilute and Below Cutoff Results

§ 26.163 Cutoff levels for drugs and drug metabolites.

(a) Initial drug testing.

(2) At the licensee's or other entity's discretion, as documented in the FFD program policies and procedures, the licensee or other entity may require the HHS-certified laboratory to conduct special analyses of dilute specimens as follows:

(i) If initial validity testing indicates that a specimen is dilute, the HHS-certified laboratory shall compare the responses of the dilute specimen to the cutoff calibrator in each of the drug classes;

(ii) If any response is equal to or greater than 50 percent of the cutoff, the HHS-certified laboratory shall conduct confirmatory testing of the specimen down to the LOD for those drugs and/or drug metabolites;

(iii) The laboratory shall report the numerical values obtained from this special analysis to the MRO.

NRC, Final Rule, 73 FR 16966, 3/31/08

- U.S. v. Klimek (SDNY, 3/2/04)**
- ▶ Drug use violation of supervised release
 - ▶ “Positive” on-site immunoassay (300 ng/mL cut-off)
 - ▶ “Negative” laboratory screening immunoassay (181 ng/mL)
 - ▶ “Negative” GC/MS confirmation (118 ng/mL BE)
 - ▶ Creatinine 29.6 mg/dL
 - ▶ s.g. 1.003 = “diluted, invalid”

U.S. v. Klimek (SDNY, 3/2/04)

"The results of a drug test ... shall be subject to confirmation only if the results are positive, ..."

"A drug test confirmation shall be a urine drug test confirmed using gas chromatography/mass spectrometry techniques ..."

18 U.S.C. §3563(e) (probation)

18 U.S.C. §3583(d) (supervised release)

"The program shall include such standards and guidelines as the Director may determine necessary to ensure the reliability and accuracy of the drug testing programs ..."

18 U.S.C. §3608

P.L. 103-332 Violent Crime Control and Law Enforcement Act of 1994

U.S. v. Klimek (SDNY, 3/2/04)

"However, the test result did not mean that Klimek did not have cocaine in his system."

"Here, a GC/MS test was performed, and it confirmed that cocaine metabolite was present in Klimek's system."

"It should go without saying that it violates the terms of Klimek's supervised release to have ANY cocaine metabolite in his system."

"Even if I assume that the fixing of a 'cut-off' level for GC/MS represents the Director's conclusion that Klimek's test result is questionable, that is simply a factor going to the weight of the drug testing evidence before me."

U.S. v. Klimek (SDNY, 3/2/04)

"... there is nothing magical about the cut-off level selected by the AO; equally reputable organizations involved in drug testing specify lower cut-off levels."

"The results of the specimen validity test strongly suggest an effort to beat the test and are most persuasively interpreted in that way."

"And because I find that the results of the GC/MS test conducted on Klimek's urine sample satisfy the Congressionally-mandated requirement that a contested drug test be "confirmed" using GC/MS ..."

U.S. v. Klimek, 2nd Cir., 6/8/05

"Even more significantly, the confirmation test performed on defendant's sample—once it was "normalized" for dilution—would have evinced a cocaine metabolite concentration of 406 nanograms per milliliter, well above the cutoff level of 150 nanograms per milliliter."

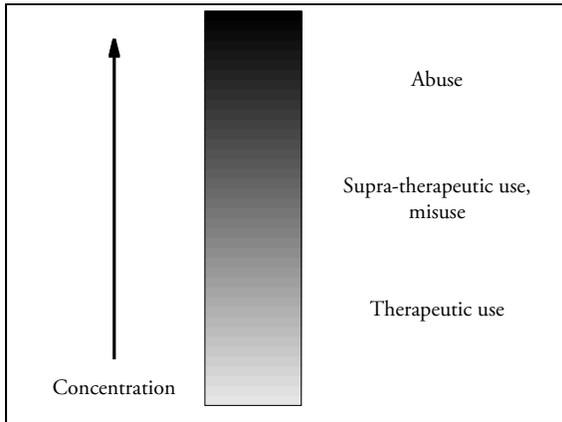
U.S. v. Klimek, 2nd Cir., 6/8/05

"We need not decide at this time whether Sections 3583(d) and 3608 preclude a district court from revoking a defendant's supervised release based solely on a test result that fell below the cutoff level."

"Negative"

does NOT mean

"No drug"



Urine Drug Concentrations (ng/mL): 10,922 Chronic Pain Patients

	Mean	Median	Range
Amphetamine	10,163	3,910	196–93,372
Methamphetamine	15,674	1,854	108–329,591
Oxycodone	7,599	2,690	100–341,009
Oxymorphone	4,930	1,637	100–188,306
Hydrocodone	2,953	1,380	100–405,020
Hydromorphone	1,062	476	100–64,526
Methadone	4,167	2,179	104–93,322
Meperidine	3,086	1,138	195–52,216
Normeperidine	3,490	1,375	124–19,908

E. Cone et al., 2008

- Utility of Urine Drug Levels*
- ▶ Evidence of use (“negative” vs. “no drug”)
 - ▶ “Unconfirmed positive” vs. “false positive”
 - ▶ Consistency of results with claims of donor
 - ▶ Renewed use vs. residual
 - ▶ Likelihood of dosing scenarios
 - ▶ Likelihood of impairment

New Testing Sites, Technologies, and Specimens

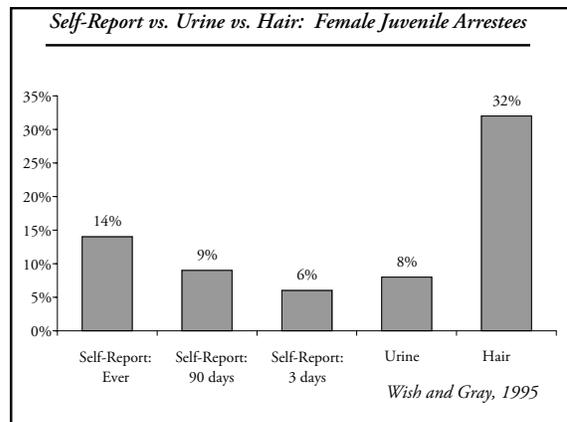
Department of Health and Human Services
 Substance Abuse and Mental Health Services Administration
 Mandatory Guidelines for Federal Workplace Drug Testing Programs

Notice of Proposed Revisions
 4/13/04
 69 FR 19673–19732

SAMHSA: Alternative Specimens

“Also, scientific advances in the use of head hair, sweat, and oral fluid in detecting drugs have made it possible for these specimens to be used in Federal programs with the same level of confidence that has been applied to the use of urine.”

SAMHSA, Federal Register, 4/13/04, 69 FR 19689



“It is FDA’s view that RIA hair analysis for the presence of drugs of abuse currently is an unproven procedure unsupported by the scientific literature or well-controlled studies or clinical trials. The consensus of scientific opinion is that hair analysis by RIA for the presence of drugs of abuse is unreliable and is not generally recognized by qualified experts as effective.”

FDA, Compliance Policy Guide, 1990

Hair

- ▶ Benefits
 - Long detection window (-3 mo.)
 - Easy collection / transport / storage
 - Lower infection risk
 - More difficult to adulterate
 - Detect at pg levels
- ▶ Mechanism
 - Passive diffusion from blood, sweat, sebum
 - Amount proportional to blood concentration
 - Can estimate time of use
- ▶ Concerns
 - Environmental contamination (use metabolites)
 - Hair color (racial) bias (limited studies, no significant association)

Consensus of the Society of Hair Testing on Hair Testing for Doping Agents

3. In case of positive urine results, the negative hair result cannot exclude the administration of the detected drug and cannot overrule the positive urine result.

www.sobt.org H. Sachs, President and P. Kintz, Secretary, 1999

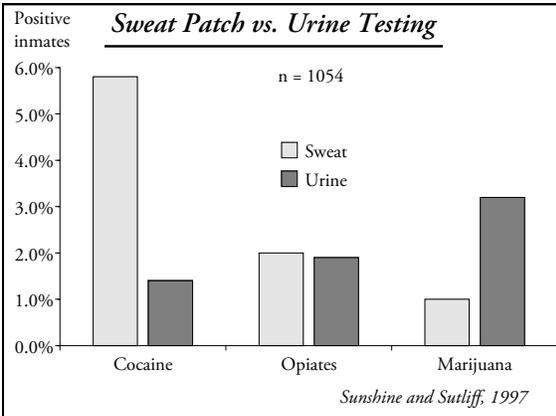
Society of Hair Testing Recommendations

“A negative result does not refute use or exposure to the drug.”

For. Sci. Int., (1997)

“The issue of external contamination must be addressed through multiple methodologies and cannot be solved through simple application of any single approach.”

For. Sci. Int., (2004)



Judicial Acceptance of Sweat Patch Testing

“ ..., this Court finds by a preponderance of the evidence that the PharmChem sweat patch drug testing device is a reliable scientific method for testing for the presence of controlled substances, ...”

U.S. v. Stumpf, 54 F.Supp.2d 972 (D.Nev. 1999)

Challenges to Sweat Patch Testing

- ▶ External contamination
 - Patch permeability
 - Distal exposure leading to patch positive results
- ▶ Internal contamination
 - Ineffective washing
 - Skin as a depot for cocaine
- ▶ Use benzoylecgonine (BE) as a marker of use
 - External sources of BE
 - Skin as a depot for BE
 - Conversion of cocaine to BE in/on skin

SAMHSA: External Contamination?

“Based on that information, the Department believes that external absorption of any drugs through the outer layer is not possible under normal circumstances.”

SAMHSA Proposed Rule, 4/13/04, 69 FR 19676

SAMHSA: Internal Contamination?

“With regard to contamination from a drug present on the skin before applying the sweat patch, the Department proposes that the skin area be washed with soap and cool water or with a disposable towelette. Then the collector must thoroughly clean the skin area where the patches will be worn with alcohol wipes prior to application. However, the Department encourages researchers to conduct further research in this area.”

SAMHSA, Proposed Rule, 4/13/04, 69 FR 19676-7

Sweat (patch)

- ▶ Benefits
 - Non-invasive
 - Extended wear
 - Generally accepted by patients
 - Tampering visible
- ▶ Mechanism
 - Poorly understood, passive diffusion from blood, transdermal migration
- ▶ Concerns
 - External contamination (believed not possible normally)
 - Skin contamination (wash soap/water, alcohol, further research)
 - Skin sensitivity
 - Stigma if visible

U.S. v. Meyer, 8th Cir., 4/25/07

“The presence of benzoylecgonine indicates that Meyer’s body had processed the cocaine.”

“Furthermore, Dr. Kadehjian noted that laboratories will not report a sweat patch as testing positive for cocaine unless a metabolite of cocaine is found, which indicates that the wearer’s body has broken down cocaine.”

“Today, we join the other courts that have previously determined that sweat patch results are a generally reliable method of determining whether an offender has violated a condition of his or her probation.”

“And while sweat patches have not been exhaustively studied by scholars, the peer-reviewed academic studies that have been conducted generally support the device’s reliability.”

U.S. v. Meyer, 8th Cir., 4/25/07

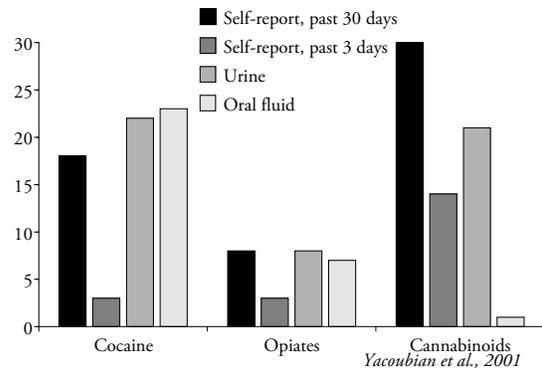
“Meyer’s effort to support an environmental explanation for his positive sweat patches is wholly unpersuasive. In order to test positive not only for cocaine but also for cocaine metabolite, Meyer would have needed to ingest cocaine residue inadvertently from the vehicles that he hauled. Moreover, Meyer returned eight consecutive sweat patches with positive results. And Meyer has proffered not one whit of evidence indicating that any of the cars that he worked with contained any amount of cocaine.”

“A negative urine test does not mean that Meyer did not take cocaine; it means only that the test did not reveal that Meyer had done so.”

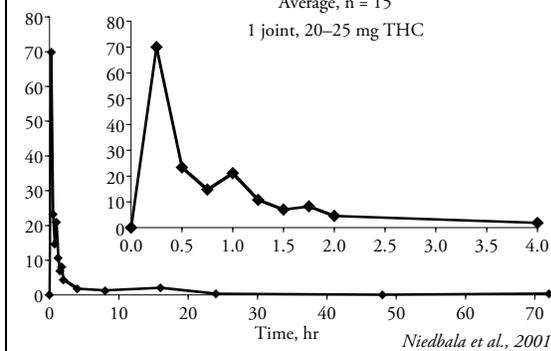
***Sweat Patch Drug Testing:
Admissibility and Evidentiary Weight***

- ▶ FDA cleared collection device and immunoassays (controlled-dosing, field, procedural integrity studies)
- ▶ Over 70 supporting publications in international peer-reviewed literature (only few challenges)
- ▶ Federal regulatory recognition (SAMHSA Proposed Rule 4/04)
- ▶ Majority of case law precedents supportive (especially recent)

Self-Report, Urine, and Oral Fluid Testing in Arrestees



Oral Fluid THC Levels after Smoking



Canada Labor Arbitration: THC in Oral Fluid Detects Impairment

“On the whole, we are satisfied that their evidence does confirm, beyond any real controversy, that the cheek swab test introduced by the Company as part of its random and unannounced drug testing policy does accurately detect actual impairment in the subject tested at the time the test is taken.”

“... as confirmed in the evidence of Dr. Willette and Dr. Kadehjian, there can be little doubt about the accuracy of the positive drug test and confirmation of impairment which is returned at that time.”

Imperial Oil Ltd. and Communications, Energy, and Paperworkers Union of Canada, Local 900, 12/06

Oral Fluid Drug Tests Upheld in Rockland County, NY, Family Court, 8/25/05

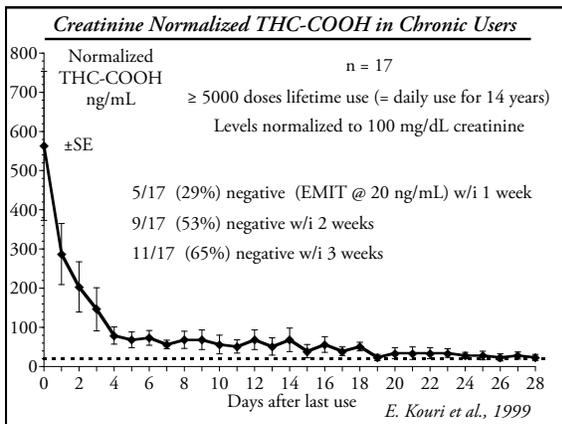
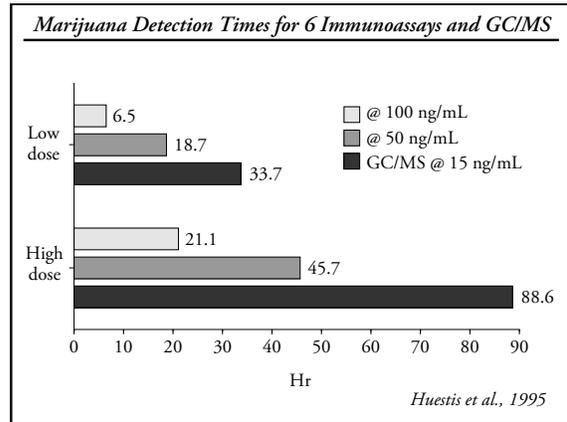
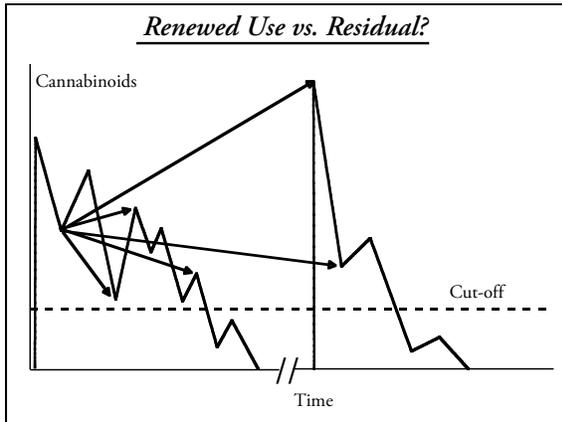
Oral fluid testing is “one of the most accurate tests available” and that it is “as good as or better” than urine testing. (Citing testimony of Dr. E. Cone)

The court noted that Dr. Cone testified that there are solid peer reviewed articles on oral fluid testing for drugs and oral fluid testing.

The court ruled that the allegations of drug use have been clearly established.

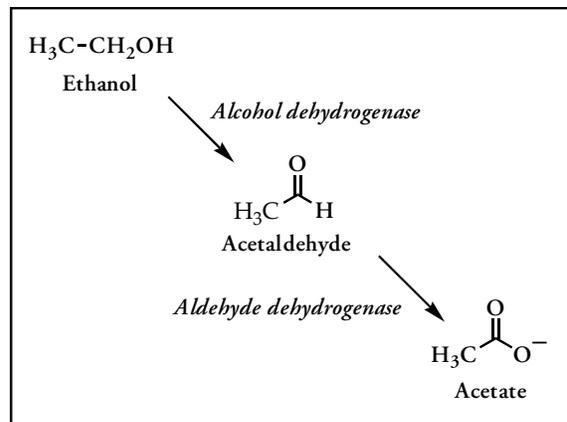
Oral Fluid: Benefits and Issues

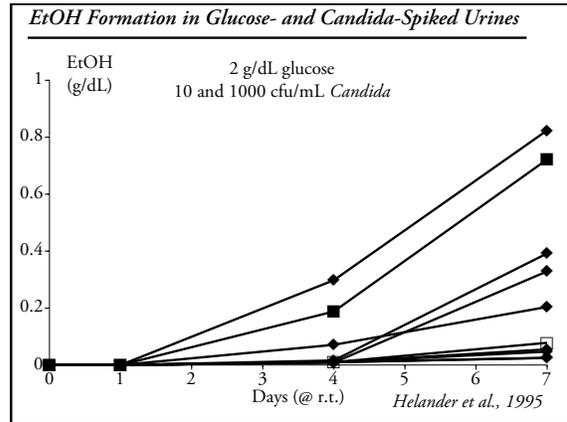
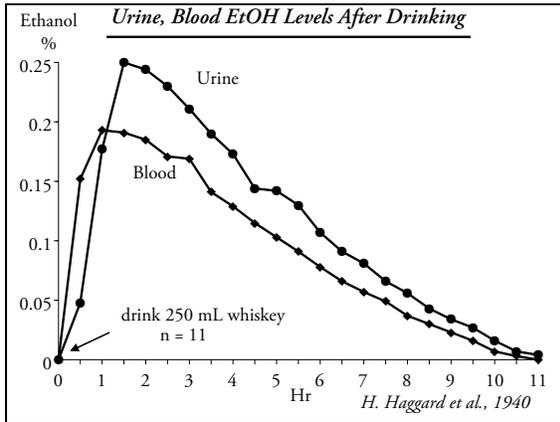
- | <u>Benefits</u> | <u>Issues</u> |
|---|---------------------------------|
| ▶ Ease of specimen collection | ▶ Low specimen volume |
| ▶ Difficult to adulterate | ▶ Low drug concentrations |
| ▶ Better correlation with effects | ▶ Shorter detection times |
| ▶ Established and growing scientific literature | ▶ On-site testing limited |
| ▶ Minimal biohazard risks | ▶ No formal regulatory scheme |
| ▶ Good specimen stability | ▶ No formal proficiency program |
| ▶ Accurate testing methods | ▶ Limited case law |



- Renewed Use or Residual?**
- With current immunoassays @ 50 ng/mL cut-off:
- ▶ Occasional users: positive for 1–2 days, rarely longer
 - ▶ Documented chronic users: positive for 2–3 weeks, rarely longer
 - ▶ Examine every positive, review intervening “negatives”
 - ▶ Positive after 1 month → Renewed use (conservative)
 - ▶ 50% increase in dilution-adjusted levels after 1 week → Renewed use (conservative)

- Renewed Use vs. Residual Levels from Prior Use?**
- Issues for consideration:
- ▶ Time: between test results, from claimed last use
 - ▶ Drug levels (normalized)
 - ▶ Pattern: levels (normalized), time, specimen ratios
 - ▶ Specimen validity: dilution, creatinine, normalization
 - ▶ Donor claims, history



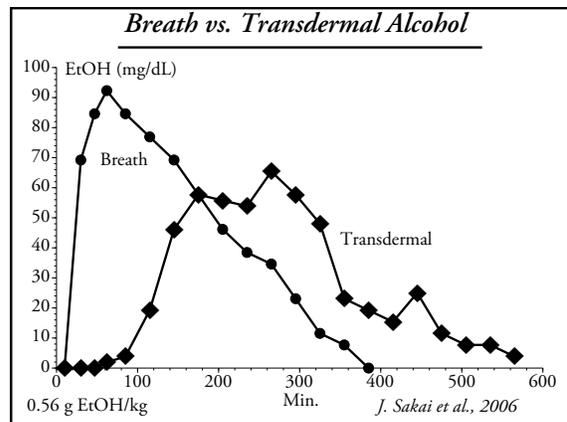


“ . . . the implied consent law is tantamount to governmental acknowledgment a urine test is functionally equivalent to a blood test for evidentiary purposes with respect to a blood alcohol level.”

People v. Fiscalini, Cal. App., 1991

Urine Alcohol Testing

- ▶ Specified by Congress in Omnibus Transportation Employee Testing Act
- ▶ Can reasonably accurately reflect blood levels
- ▶ Provides flexibility and cost savings
- ▶ Authorized in >1/2 of states' implied consent laws
- ▶ Has withstood legal challenge as a valid specimen

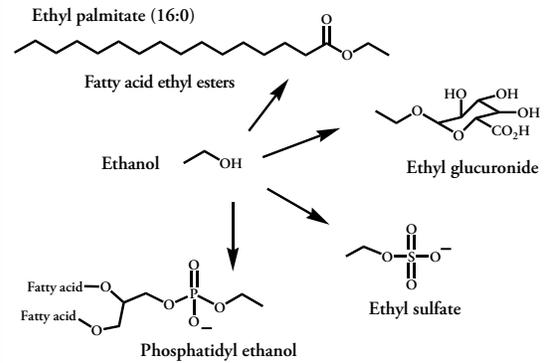


SCRAM Controlled Dosing / Field Study

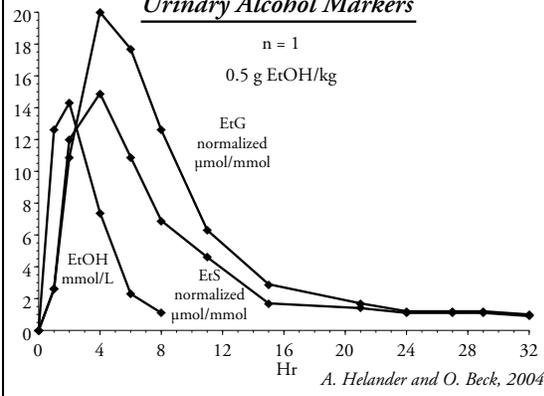
- ▶ Controlled dosing study (n=24):
No false negatives, no false positives
- ▶ Field study (n= 20):
Distinguished EtOH dependent from non-dependent
All self-reported users had positive SCRAM results
- ▶ Reasonable correlation between SCRAM and breath testing
- ▶ Not very comfortable to wear, but not very uncomfortable

J. Sakai et al., 2006

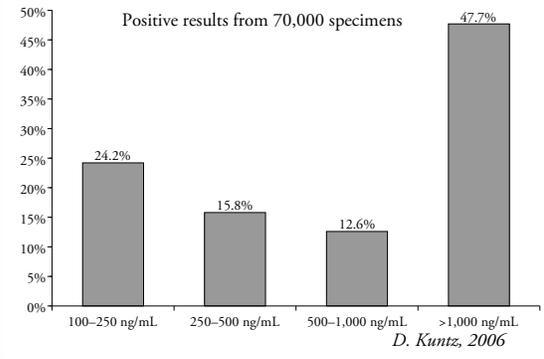
Markers of Ethanol Ingestion



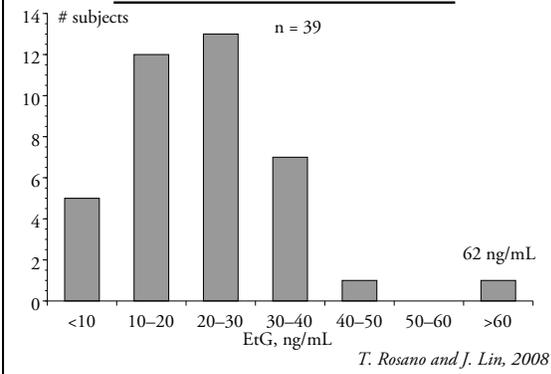
Urinary Alcohol Markers



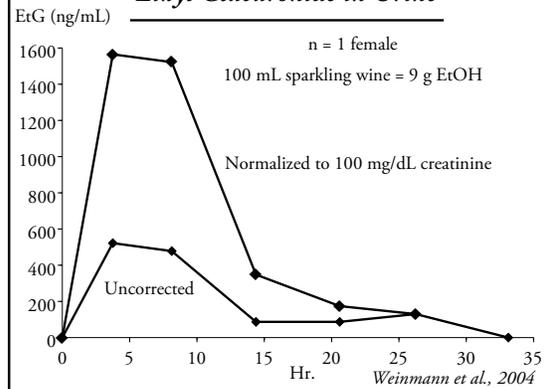
Distribution of Urine EtG Levels



Urine EtG in Adult Abstainers



Ethyl Glucuronide in Urine



“Currently, the use of an EtG test in determining abstinence lacks sufficient proven specificity for use as primary or sole evidence that an individual prohibited from drinking, in a criminal justice or regulatory compliance context, has truly been drinking. Legal or disciplinary action based solely on a positive EtG, or other test discussed in this Advisory, is inappropriate and scientifically unsupported at this time. These tests should currently be considered as potential valuable clinical tools, but their use in forensic settings is premature.”

SAMHSA, *Substance Abuse Treatment Advisory*, 5 (4), September 2006.

EtG: Passive Exposure: Hand Sanitizer

n = 9	1 mL @ 60% EtOH, 20 x/d, x 5 d	<10 – 114 ng/mL	Rosano and Lin, 2008
n = 3–4	62% EtOH, every 30, 60 min	neg @ 50 ng/mL	Robrig, 2006
n = 2	every 15 min for 8 hr	1/2 pos, 62 ng/mL	Robrig, 2006
n = 24	conditions not specified	pos, cutoff not specified	ASAM, 2006 (Wall St. J.)
n = 1	repeated throughout day	770 ng/mL	Wall St. J., 2006
	62% EtOH, throughout day	≤47 ng/mL	AACC / Quest, 2006
n = 11	every 5 min, 10 hr, x 3 d	max. 2001 ng/mL	Reisfield, 2011

EtG: “Innocent” Oral Exposure

	2 x 12 oz non-alcoholic beer	93 ng/mL	AACC / Quest, 2006
	1 tsp communion wine (9% EtOH)	77 ng/mL	AACC / Quest, 2006
	Nyquil (25% EtOH), 3 x 1 oz	≤246 ng/mL	AACC / Quest, 2006
n = 9	4 oz mouthwash (12% EtOH), gargle every 30 sec, 5 min	20/39 >50 ng/mL 8/20 <100 ng/mL 17/20 <250 ng/mL 1 <350 ng/mL	Costantino, 2005, 2006
n = 11	gargle 3 x d, 5 d	1/55 >50 ng/mL all <100 ng/mL	Costantino, 2005, 2006
n = 10	4 x d, 3 d	max. 173 ng/mL	Reisfield, 2011

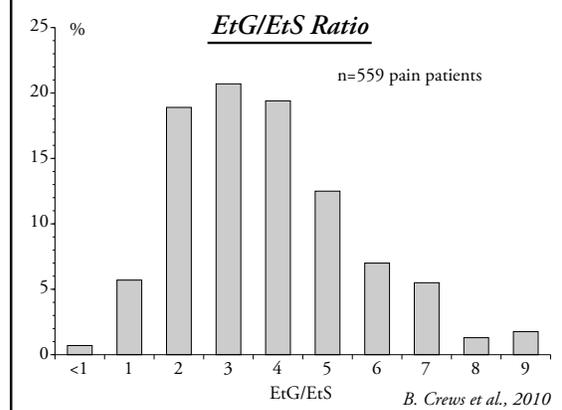
EtG: “Innocent” Oral Exposure

n = 3	2.5 L “non-alcoholic” beer	300–870 ng/mL	Thierauf et al., 2010
n = 2	baker’s yeast/sugar	120, 500 ng/mL	
n = 4	brewer’s yeast /sugar	ND	Thierauf et al., 2010

Although further research is needed before firm cutoffs for EtG can be established, sufficient research has been completed to reach the following conclusions:

- ▶ A “high” positive (e.g., >1,000 ng/mL) may indicate:
 - Heavy drinking on the same day or previously (e.g., previous day or two).
 - Light drinking the same day.
- ▶ A “low” positive (e.g., 500–1,000 ng/mL) may indicate:
 - Previous heavy drinking (previous 1–3 days).
 - Recent light drinking (e.g., past 24 hours).
 - Recent intense “extraneous” exposure (within 24 hours or less).
- ▶ A “very low” positive (100–500 ng/mL) may indicate:
 - Previous heavy drinking (1–3 days).
 - Previous light drinking (12–36 hours).
 - Recent “extraneous” exposure.

SAMHSA, *The Role of Biomarkers in the Treatment of Alcohol Use Disorders, Advisory*, 11 (2), 2012 Revision.



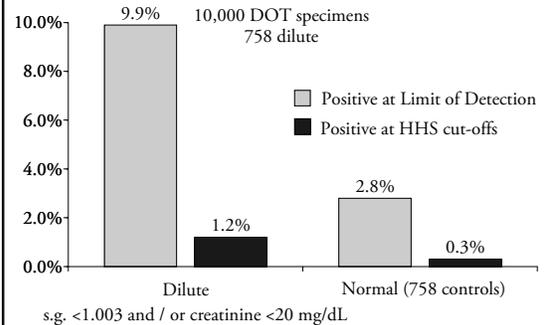
Urine Specimen Validity Tests

Department of Health and Human Services
 Substance Abuse and Mental Health Services Administration
 Mandatory Guidelines for Federal Workplace Drug Testing Programs

Revised Mandatory Guidelines
 4/13/04
 69 FR 19644-19673

Effective 11/1/04

Drug Use, Dilution, and Detection



National Laboratory Certification Program, Program Document #25, 1993

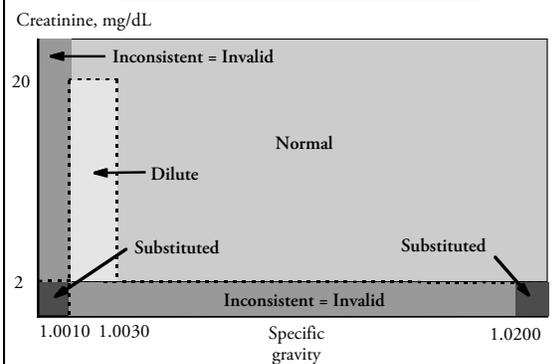
Required Specimen Validity Tests: Urine

- ▶ Creatinine
- ▶ Specific gravity if creatinine <20 mg/dL
- ▶ pH
- ▶ Oxidizing adulterants (≥1)
 Nitrites, pyridinium chlorochromate, chromium (VI), bleach, iodine, halogens, peroxidase, peroxide, others
- ▶ Additional as needed

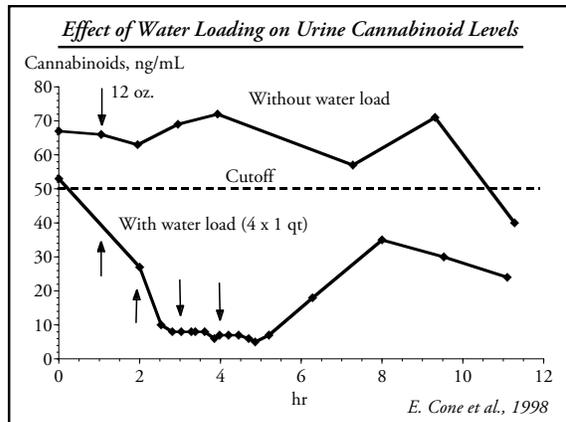
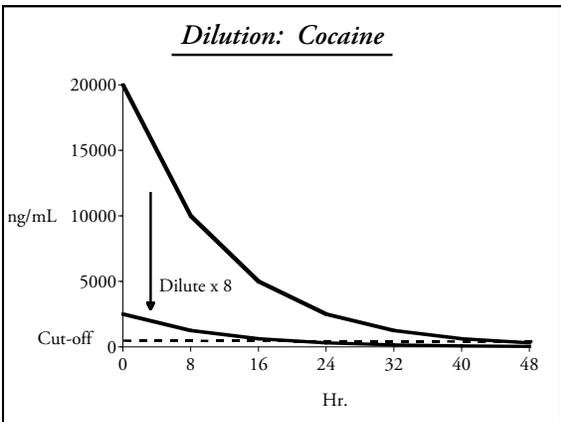
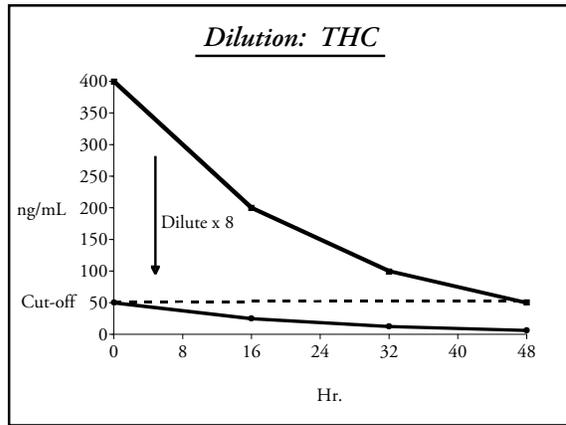
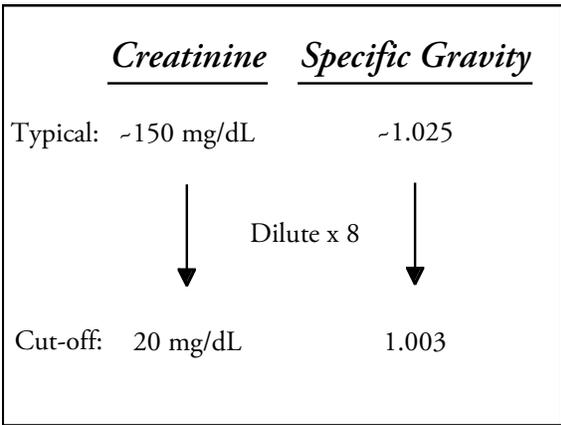
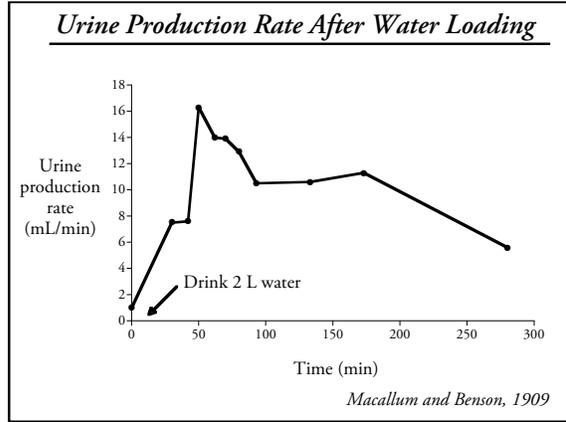
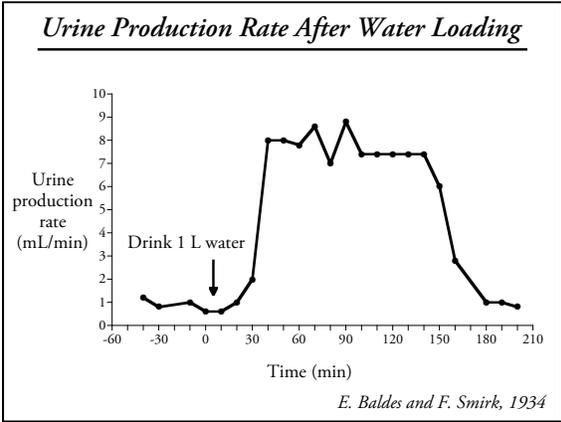
Urine Specimen Validity Testing

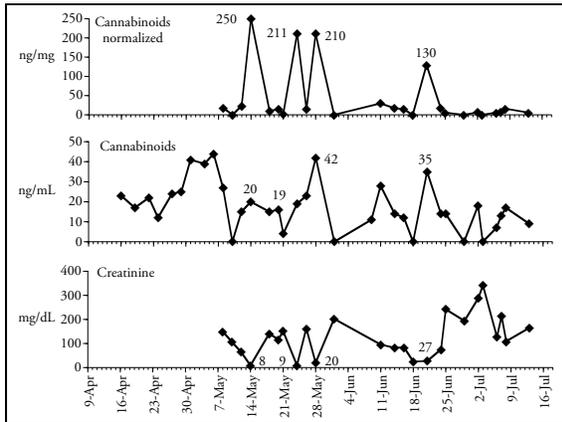
- ▶ Adulterated
 Non-normal constituent
 Endogenous constituent at non-normal concentration
- ▶ Substituted
 Creatinine <2 mg/dL AND s.g. ≤1.0010 or ≥1.0200
- ▶ Invalid
 Inconsistent creatinine, specific gravity
 Nitrite, pH, possible presence of other adulterants
 Interference
 Appearance
- ▶ Dilute
 Creatinine ≥2 mg/dL but <20 mg/dL AND s.g. >1.0010 but <1.0030

Validity Testing Criteria: Urine



	<u>SAMHSA</u>	<u>U.S. Courts</u>
▶ Dilute	creat ≥2 but <20 and s.g. >1.0010 but <1.0030	creat ≥2 but <15 or s.g. 1.002 or 1.003
▶ Invalid	creat <2 and s.g. >1.0010 but <1.0200	creat ≥2 and s.g. ≤1.001 or ≥1.045
▶ Substituted	creat <2 and s.g. ≤1.0010 or ≥1.0200	creat <2
▶ Adulterated	pH <3 or ≥11 Non-normal substance Non-normal level	pH ≤4 or >10 Non-normal substance Non-normal level





Adjusting Cannabinoid Levels for Dilution / Concentration

$$\frac{\text{ng Cannabinoids} / \text{mL}}{\text{mg Creatinine} / \text{dL}} \times 100 = \frac{\text{ng Cannabinoids}}{\text{mg Creatinine}}$$

$$\frac{50 \text{ ng Cannabinoids} / \text{mL}}{150 \text{ mg Creatinine} / \text{dL (normal)}} \times 100 = \frac{33 \text{ ng Cannabinoids}}{\text{mg Creatinine}}$$

$$\frac{50 \text{ ng Cannabinoids} / \text{mL}}{15 \text{ mg Creatinine} / \text{dL (dilute)}} \times 100 = \frac{333 \text{ ng Cannabinoids}}{\text{mg Creatinine}}$$