

Review of SAMHSA's Clinical Initiatives (Published Studies)

Edward J. Cone, Ph.D., DABFT
Johns Hopkins University
School of Medicine
Baltimore, MD
July 26, 2016

Outline

- Review of SAMHSA clinical studies
- Highlights of study designs
- Study execution
- Study results

Anatomy of the Design and Conduct of a SAMHSA Clinical Study

- Identify areas of concern
- Outline study
- How can study be implemented?
 - Identify clinical site and capabilities
 - Start approval process
- Funding
- Execution of study
- Analytical support
- Data and publications

Collaborative Teams

- SAMHSA
- Scientists with clinical and tox experience
- RTI
- Aegis Sciences Corporation
- JHU
- Contract CROs
- Paid subjects (anonymous)

SAMHSA's Need of Scientific Data: Clinical Studies

- Characterize the time course of appearance and disappearance of drugs and metabolites
 - Urine
 - Oral fluid
 - Blood
 - Hair

Drugs of Concern

- Pharmaceutical opioids
 - Oxycodone
 - Hydrocodone
 - Oxymorphone
 - Hydromorphone
- Cannabis
 - Exposure to smoked cannabis
 - Cannabis edibles
 - Vaped/volcano cannabis

Pharmaceutical Opioid Dosing Info

- Oxycodone
 - Single dose, one 20 mg OxyContin[®] CR tablet
- Hydrocodone
 - Single dose, two Norco[®] tablets, each containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen
- Oxymorphone
 - Single dose, one 10 mg oxymorphone CR tablet
- Hydromorphone
 - Single dose, one 8 mg hydromorphone CR tablets

Study Design

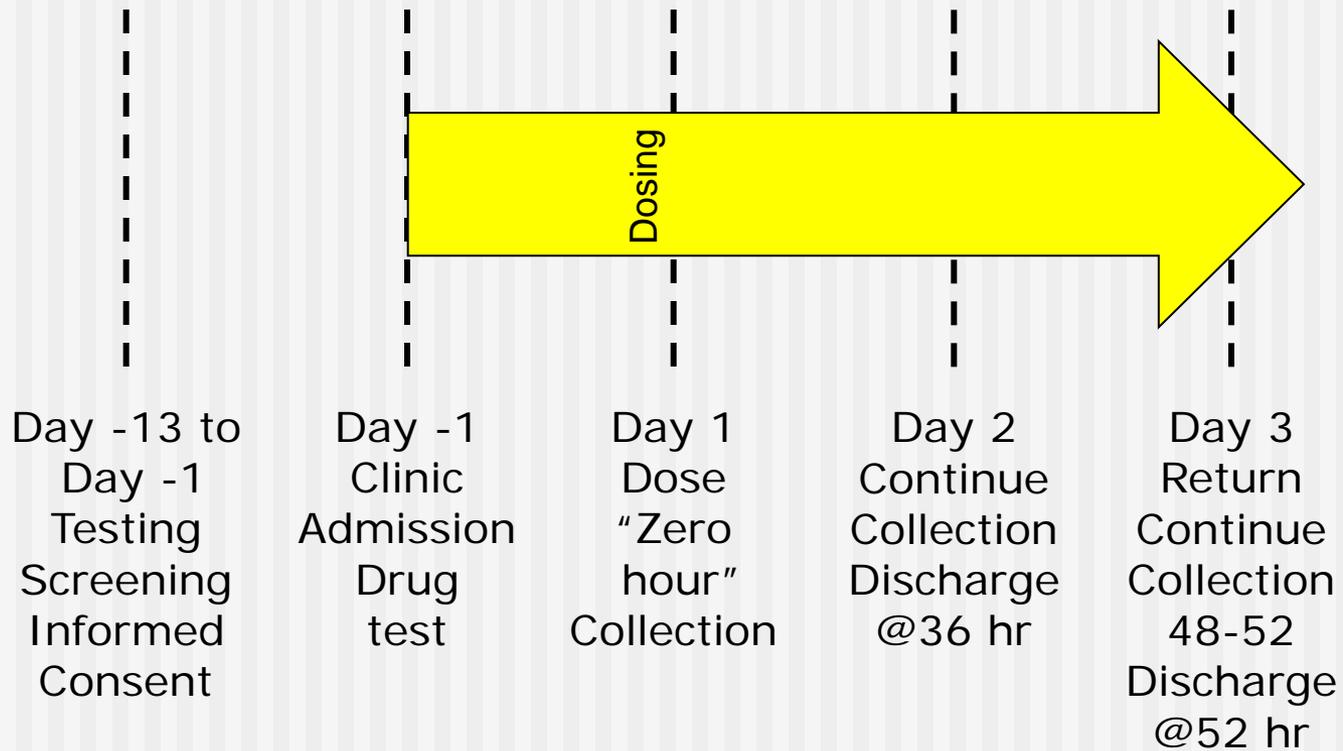
- Single center, randomized, parallel group, open-label, single dose study
- 12 Subjects per group
- Healthy adult volunteers
- Drug-free
- Timed oral fluid and blood collections
- Pooled urine specimens
- Overnight residence on controlled clinical ward (0-36 hr, discharge, 48-52, discharge)

Study Timeline & Specimen Collection

OF: -1, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 24, 28, 32, 36, 48, 49, 50, 52

BL: -1, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 24, 28, 32, 36, 48, 52

UR: -1, 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-24, 24-28, 28-32, 32-36, 48-52



Specimens

■ Urine

- Pooled specimens, empty bladder at timed intervals, measure total volume, save two 30 mL aliquots in separate bottles, stored frozen

■ Oral fluid

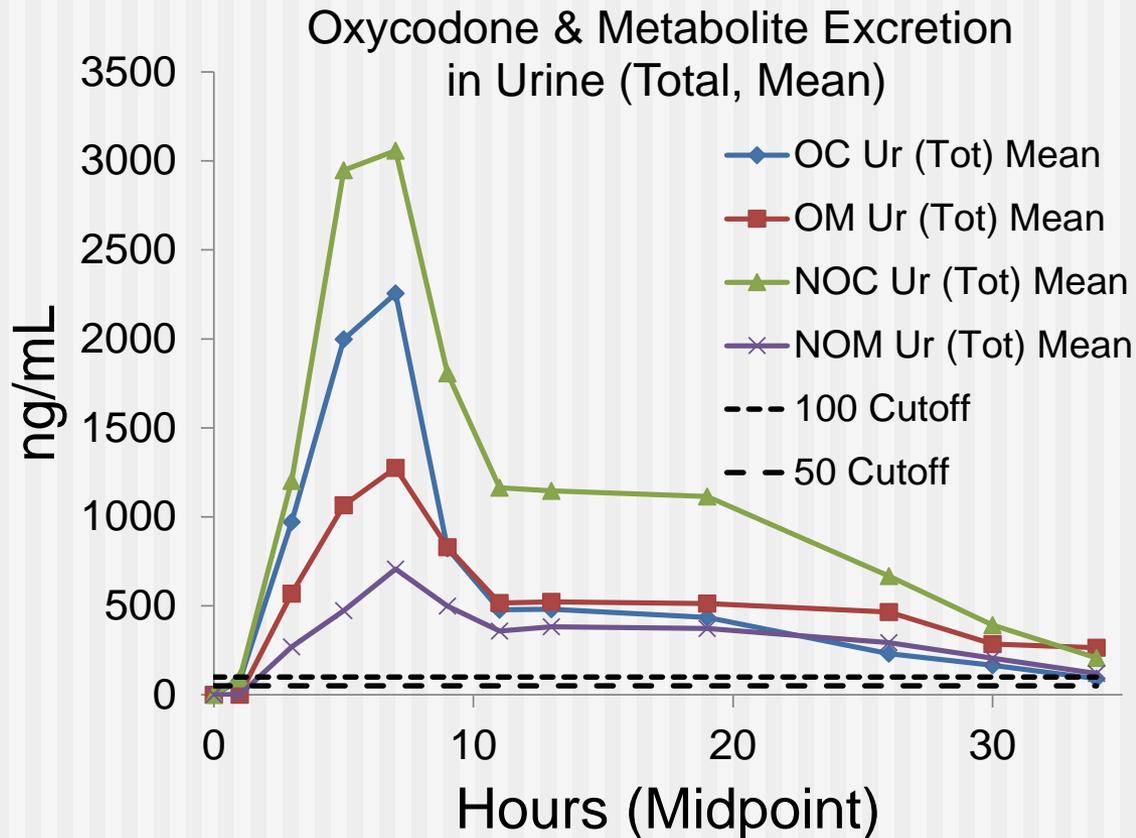
- Expectoration, up to 5 min, 15 mL plastic cent tubes, stored frozen

■ Whole blood

- 10 mL by venipuncture, vacutainer (gray top), separated into two aliquots, cryotubes, stored frozen

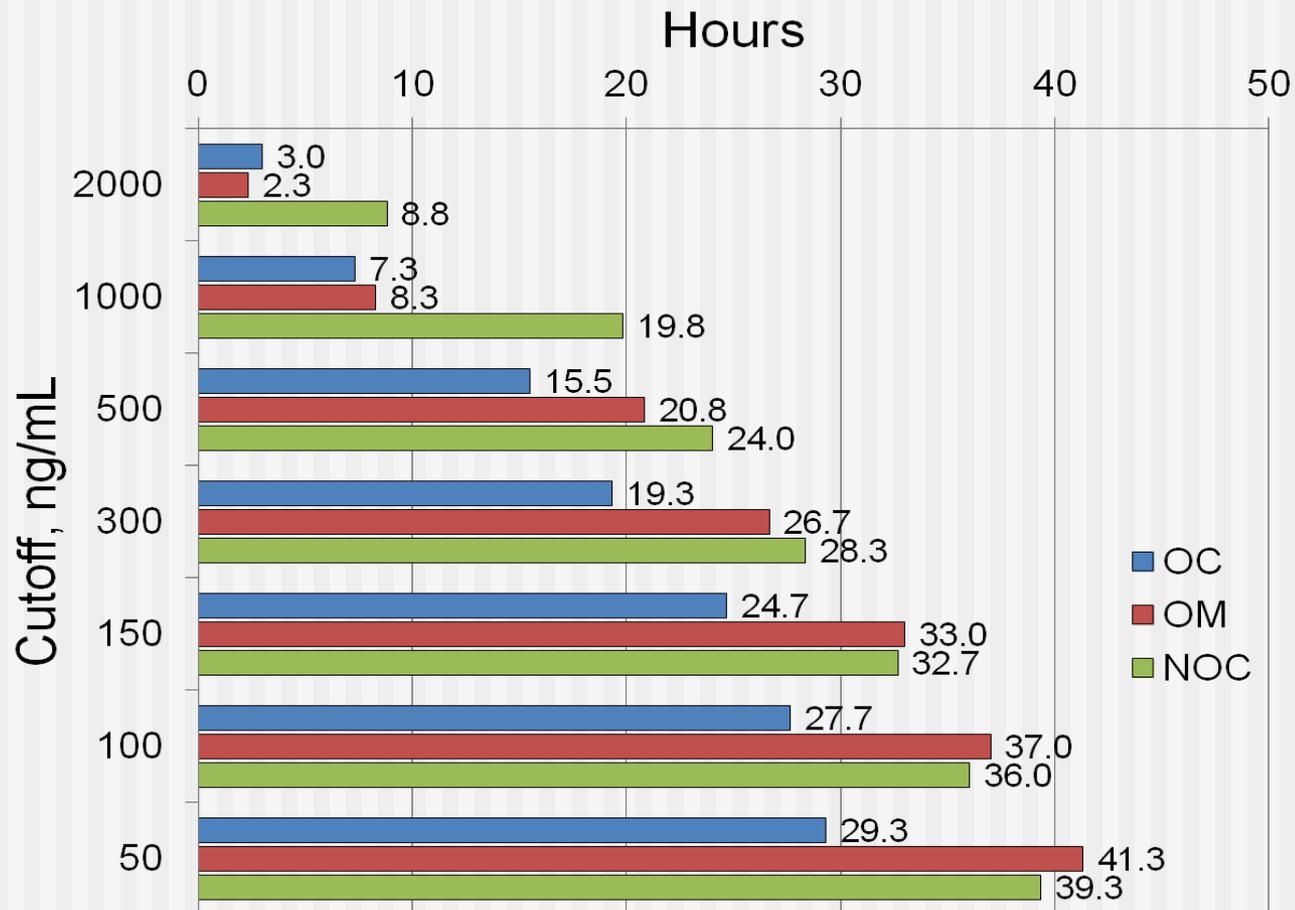
Oxycodone Excretion in Urine

■ Synthetic opioids...some highlights

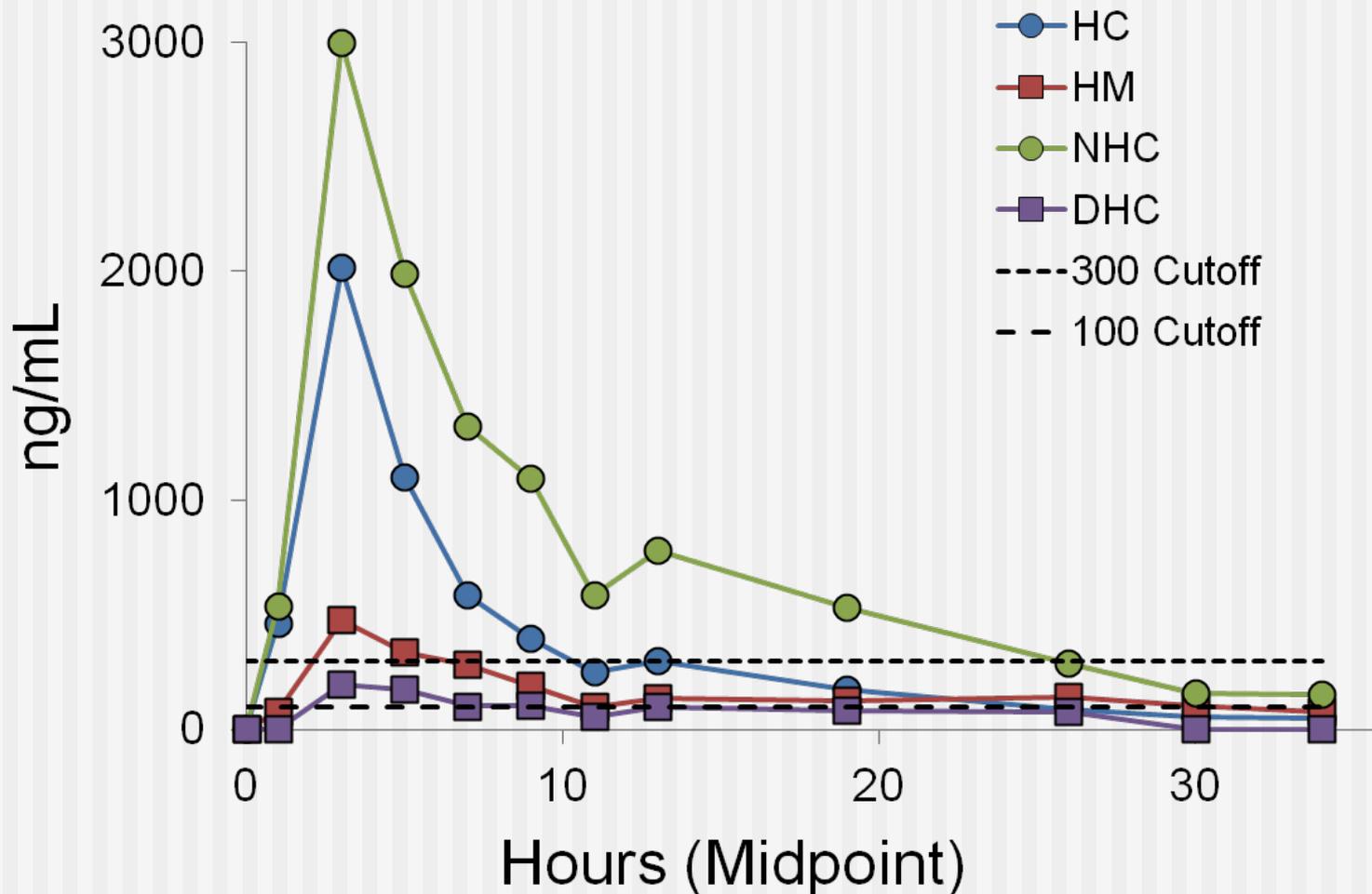


Oxycodone Detection Times in Urine by Selected Cutoff Concentrations

(Data represent mean of individual "time to last positive")

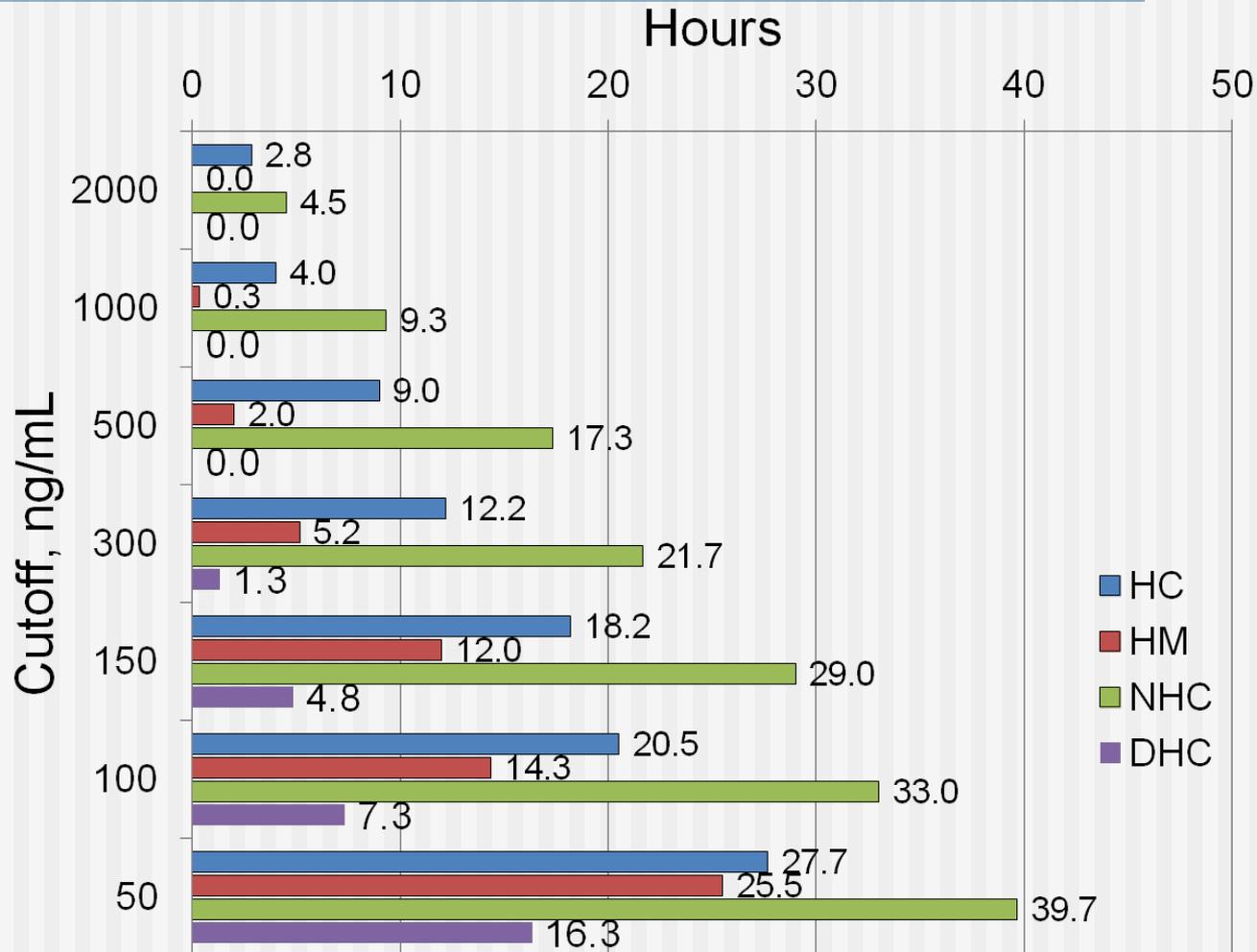


Hydrocodone Excretion in Urine

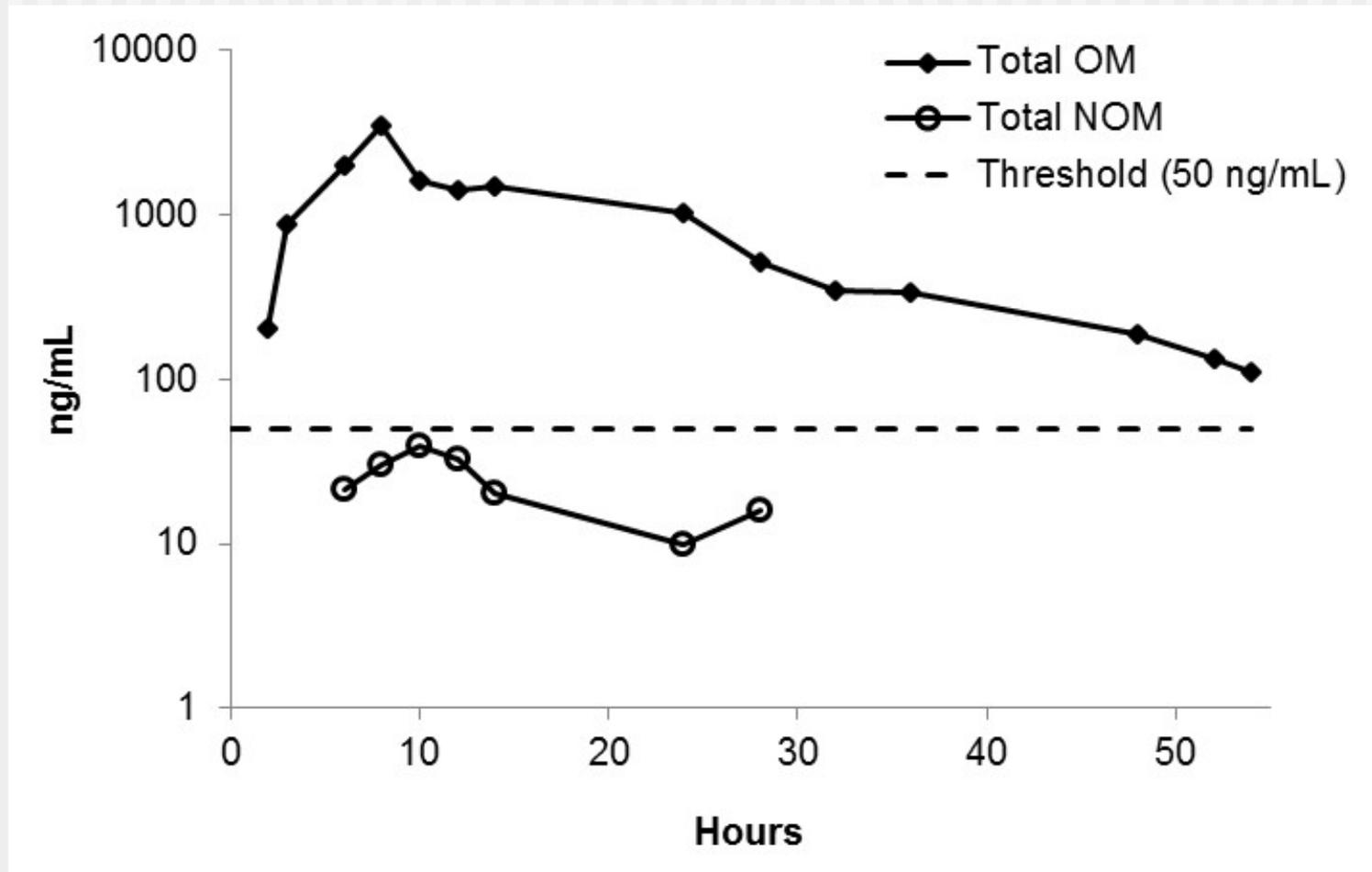


Hydrocodone Detection Times in Urine by Cutoff Concentrations

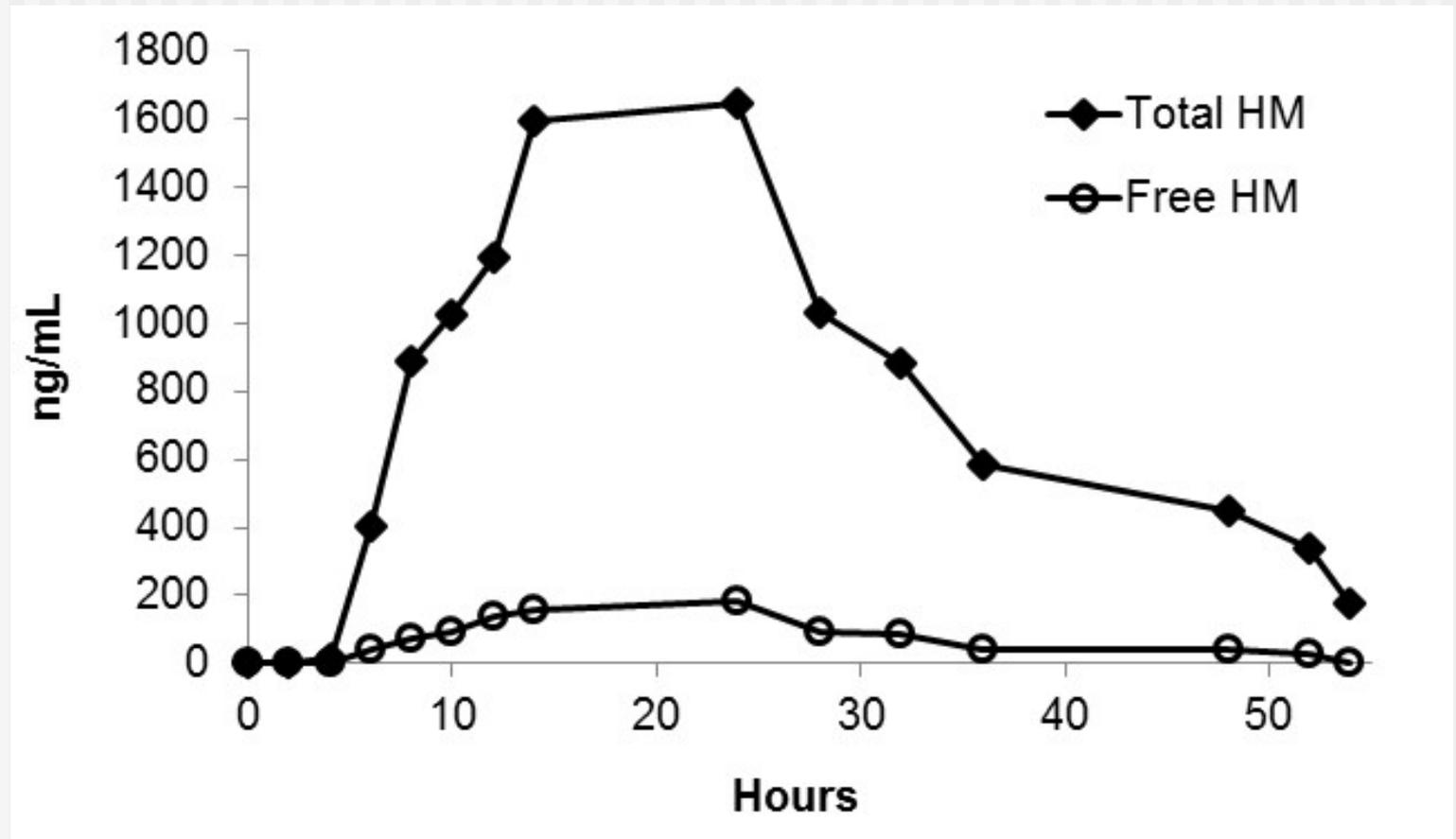
(Data represent mean of individual "time to last positive")



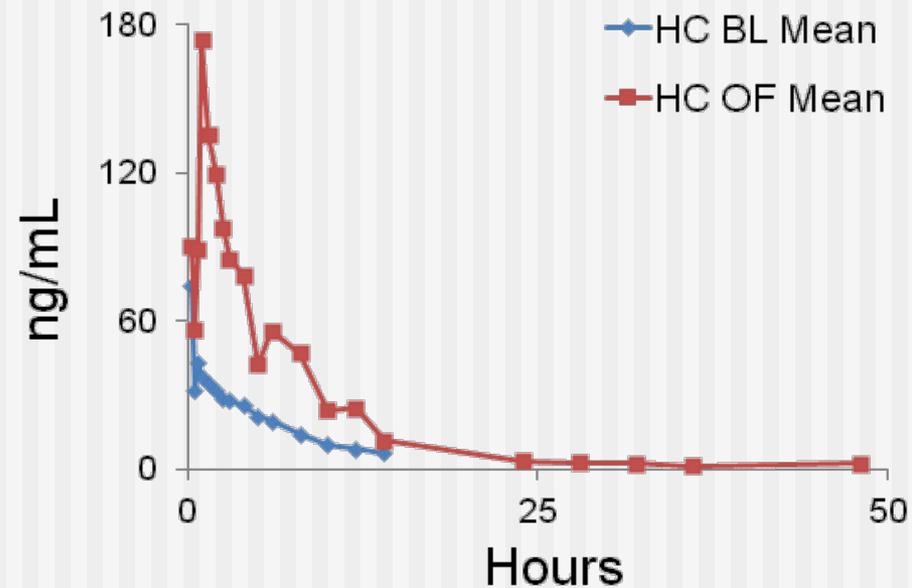
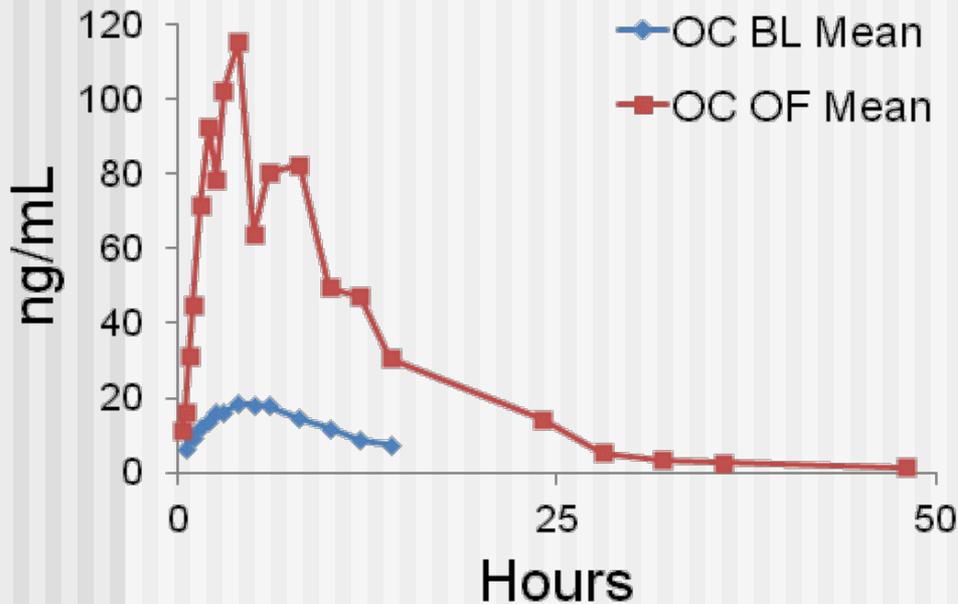
Mean Excretion of Oxymorphone in Urine Following a Single 10 mg Dose



Mean Excretion of Hydromorphone in Urine Following a Single 8 mg Dose



Oxycodone and Hydrocodone in Oral Fluid and Blood



Pharmaceutical Opioid Highlights

- Time course of urinary excretion of parent and metabolites and detection times defined at different cutoffs
- Nor-metabolites of OC (NOC) and HC (NHC) were often in higher concentrations in urine than the parent compound
- OC and HC appeared in oral fluid and blood within 15-30 minutes after oral administration
- OC and HC were in considerably higher concentrations in oral fluid compared to blood
- In contrast to urine, nor-metabolites of OC and HC were in lower concentration than parent in oral fluid
- Oral fluid detection times were identified at different cutoffs
- Oxymorphone and hydromorphone were excreted in oral fluid in low concentrations compared to oxycodone and hydrocodone

Aegis & SAMHSA

■ Synthetic opioids...JAT Publications

Prescription Opioids. I. Metabolism and Excretion Patterns of Oxycodone in Urine Following Controlled Single Dose Administration

Prescription Opioids. II. Metabolism and Excretion Patterns of Hydrocodone in Urine Following Controlled Single-Dose Administration

Prescription Opioids. III. Disposition of Oxycodone in Oral Fluid and Blood Following Controlled Single-Dose Administration

Prescription Opioids. IV: Disposition of Hydrocodone in Oral Fluid and Blood Following Single-Dose Administration

Prescription Opioids. V. Metabolism and Excretion of Oxymorphone in Urine Following Controlled Single Dose Administration (in press)

Prescription Opioids. VI. Metabolism and Excretion of Hydromorphone in Urine Following Controlled Single Dose Administration (in press)

Cannabis Studies: Complex Approval Process

- JHU IRB approval
- IND approval
- DEA approval
- FDA approval
- NIDA approval
- SAMHSA approval

Cannabis Studies

- Passive cannabis smoke exposure (completed)
- Oral ("edibles") (in progress)
- Smoked/vaped/volcano comparisons (in progress)

Passive Cannabis Smoke: Study Design



- Six active smokers, six non-smokers per session
- Enclosed room with air flow control, Plexiglas walls for observation
- Alternate seating of smokers and passives
- Three Sessions:
 - Session 1: smokers each smoke ad lib MJ cigarettes (5.3% THC) for one hour, no active air flow
 - Session 2: smokers each smoke ad lib MJ cigarettes (11.3% THC) for one hour, no active air flow
 - Session 3: smokers each smoke MJ ad lib MJ cigarettes (11.3% THC) for one hour, with active air flow simulating room air conditioning

JHU Exposure Chamber



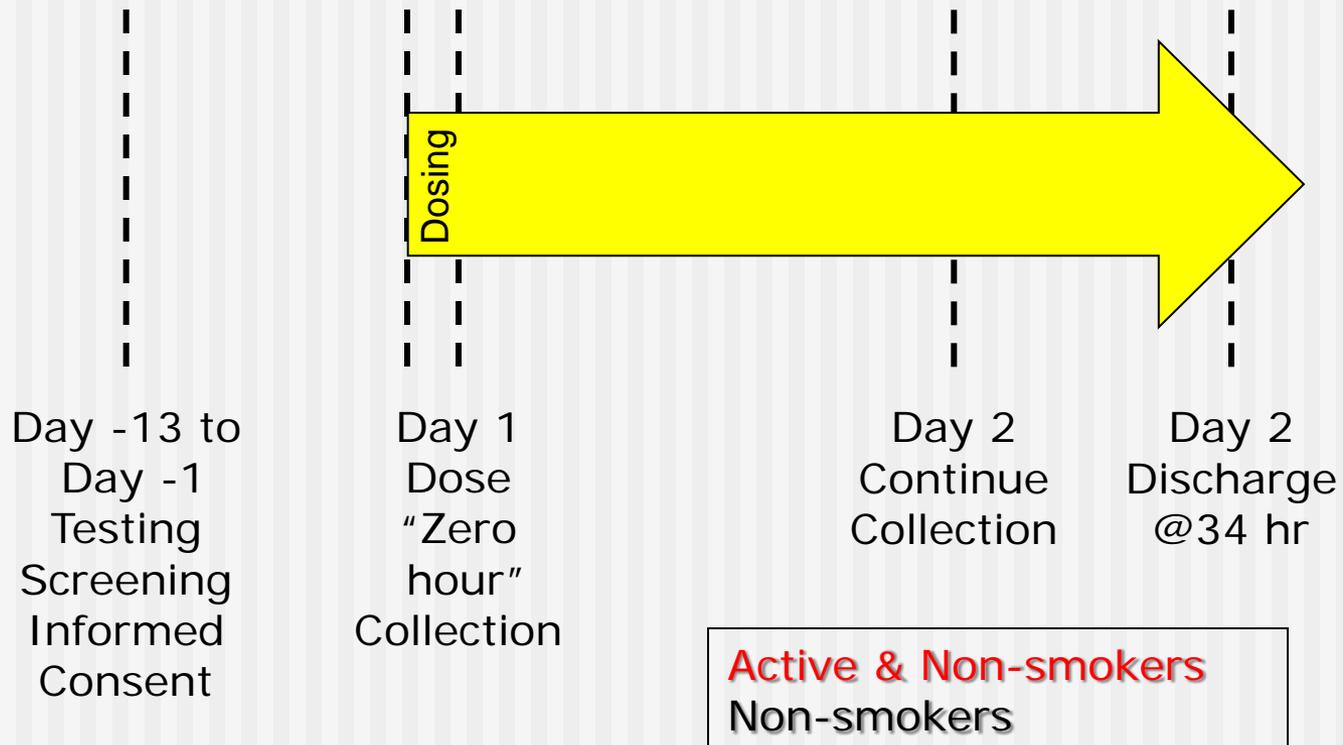
- Constructed of plexiglass and aluminum
- Dimensions: 10' x 13' x 7' (W x L x H), 910 cu ft (25.73 m³)
- Sealed door closure
- Optional no ventilation/ventilation comparable to A/C in home

Session Timeline & Specimen Collection

Oral Fluid (OF): -1, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 22, 26, 30, 34 h

Blood (BL): -1, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 22, 26, 30, 34 h

Urine (UR): -1, 1, 2, 3, 4, 4-6, 6-8, 8-10, 10-12, 12-22, 22-26, 26-30, 30-34 h



Specimens

■ Urine

- Individual voids through 4 hours; pooled specimens thereafter, empty bladder at timed intervals, measure total volume, save two 30 mL aliquots in separate bottles, stored frozen

■ Oral fluid

- Expectoration, up to 5 min, silanized glass tubes, stored refrigerated

■ Whole blood

- Venipuncture, vacutainer (gray top), separated into two aliquots, cryotubes, stored frozen

Analytical (Specimens)

■ Urine (CRL)

- Multiple IA screens (DRI, KIMS, Siemens, CEDIA)
- THCCOOH (GC/MS), 15 ng/mL (0.75 ng/mL LOQ)
- Volume, creatinine, SG, pH, uric acid

■ Oral Fluid (Immunoanalysis)

- THC screen (ELISA), 4 ng/mL
- THCCOOH screen (ELISA), 0.05 ng/mL (50 pg/mL)
- THC confirmation (LC/MS/MS), 2 ng/mL (1 ng/mL LOQ)
- THCCOOH confirmation (LC/MS/MS), 0.02 ng/mL (0.02 ng/mL LOQ) (note: 0.02 ng/mL = 20 pg/mL)

■ Whole Blood (Immunoanalysis)

- THC (LC/MS/MS), 0.5 ng/mL
- 11-HO-THC (LC/MS/MS), 0.5 ng/mL
- THCCOOH (LC/MS/MS), 0.5 ng/mL

Amount of Marijuana Smoked Per Session

Session	%THC	Conditions	Total grams Marijuana smoked	% Smoked based on Session 1
1	5.3	No ventilation	10.30	100
2	10.4	No ventilation	14.36	139.5
3	10.4	Ventilation	16.5	160.2

Session 1 Start-Up: 5.3% MJ, no Ventilation



Confidential

Session 1: 5.3% MJ, no Ventilation



Confidential

Session 1: 5.3% MJ, no Ventilation



Confidential

Session 2: 11.3% MJ, no Ventilation



Confidential

Session 2: 11.3% MJ, no Ventilation



Confidential

Session 2: 11.3% MJ, no Ventilation



Confidential

Session 3: 11.3% MJ, With Ventilation



Confidential

Session 3: 11.3% MJ, With Ventilation



Confidential

Session 3: 11.3% MJ, With Ventilation



Confidential

Urine Data



Urine: Immunoassay Screening Results (50 ng/mL cutoff) Non-Smoker Subjects

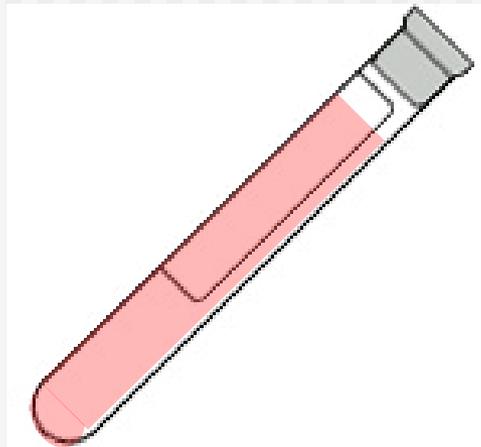
	Med Tox KIMS 50		Metrolab Siemens 50		CRL DRI 50		One Source Tox CEDIA 50		LabCorp RTP Siemens 50	
	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
Session 1	0	84	0	84	0	84	0	84	0	84
Session 2	0	82	0	82	0	82	0	82	1*	81
Session 3	0	84	0	84	0	84	0	84	0	84

*Confirmed by GC/MS, 46.3 ng/mL
 *Subject #37 @ 4 hours, the urine specimen had 149.7 mg/dL creatinine, 1.0218 SG, 6.9 pH, and 40 mL vol. The baseline CR was 42.3 mg/dL. The subject was a 24 yo female who weighed approximately 180 pounds.

Program Impact: One Confirmed Positive Urine Specimen @ 50/15

- One of 1250 urine tests (0.08%) from 6 non-smokers tested positive @ SAMHSA 50/15 cutoffs
- The positive came from S#37, Session 2 (12.5%, no ventilation) @ 4 hours following exposure. Confirmed by GC/MS for THCCOOH with a result of 46.3 ng/mL
- Oral fluid specimen from same subject at 4 hours screened negative (4 ng/mL) and had 1.3 ng/mL THC by LC/MS/MS
- Under identical test conditions to Session 2, no screening positives occurred in Session 3

Blood Data

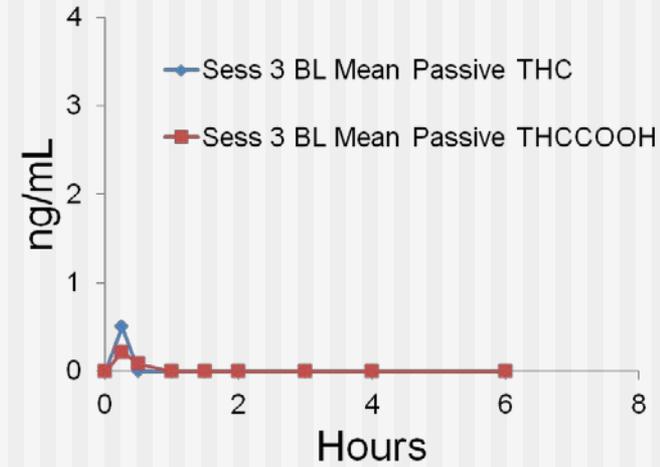
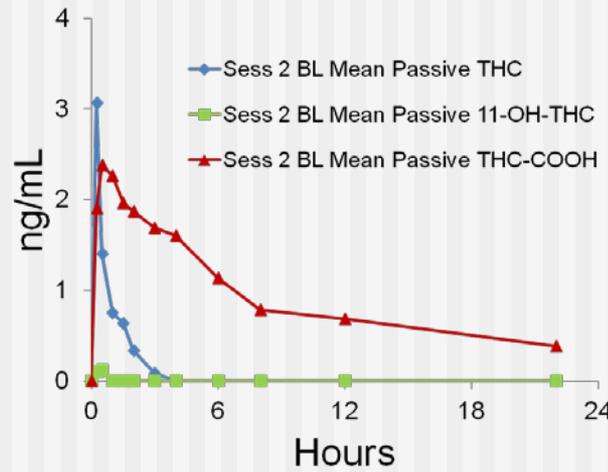
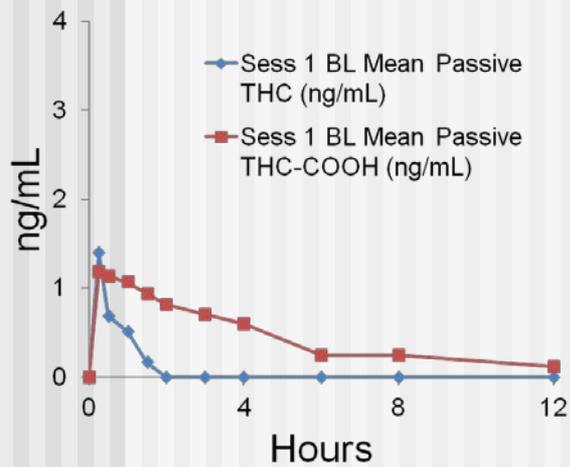


Non-Smoker Blood Concentrations (LCMSMS)

Ventilation Effect

No A/C

With A/C



5.3%

11.3%

11.3%

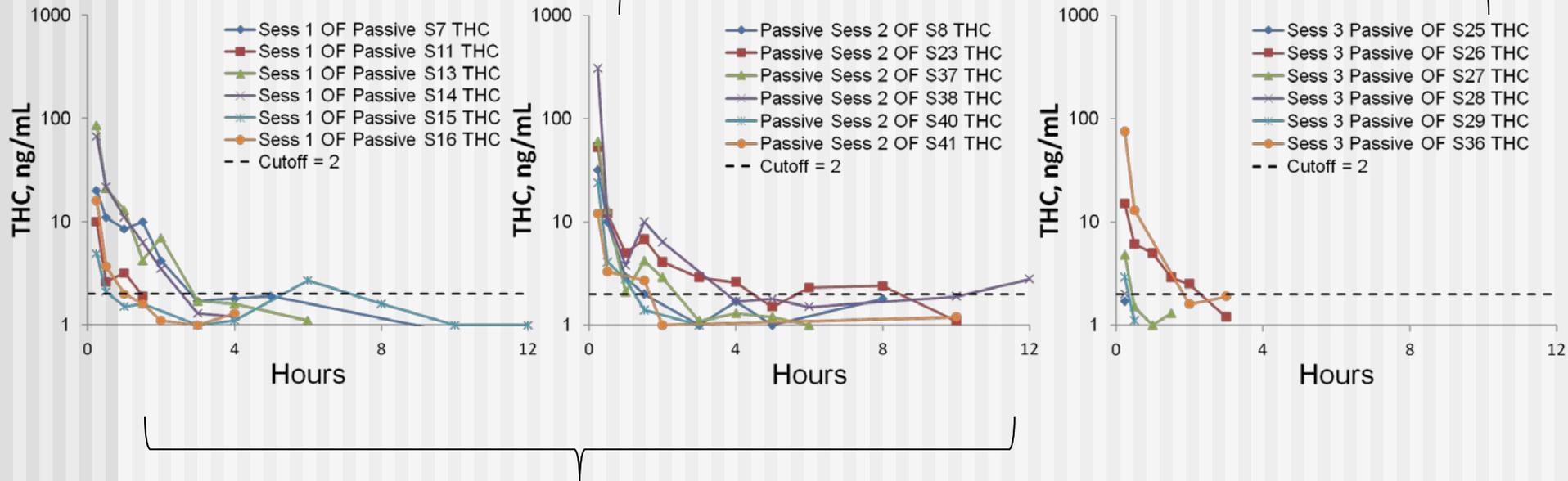
THC Potency Effect

Oral Fluid Data



Non-Smokers' Oral Fluid Results (LCMSMS, THC)

Ventilation Effect

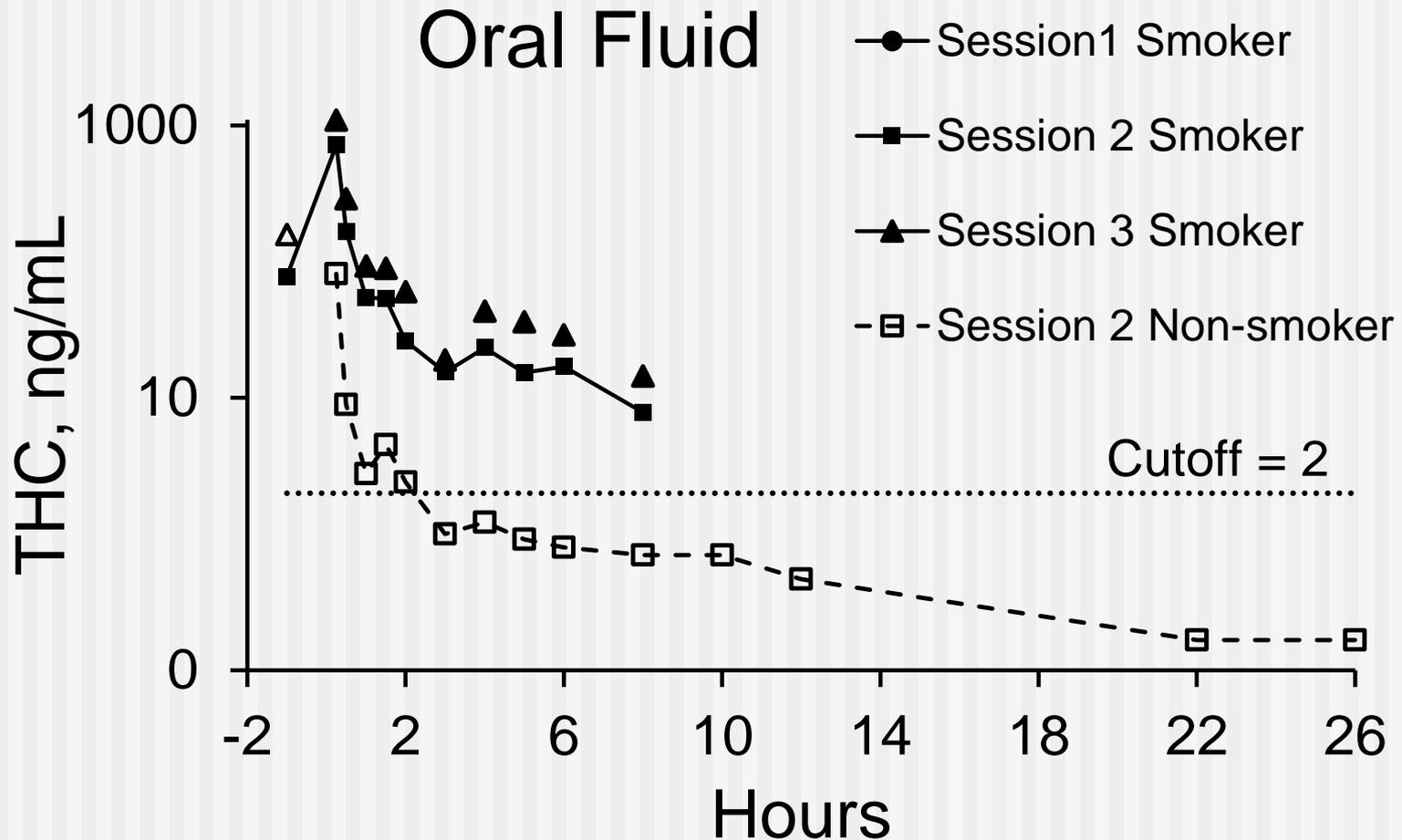


THC Concentration Effect

Program Impact: Multiple Confirmed Positive Oral Fluid Specimens @ 4/2

- Session 1: 17/96 positives (17.7%), 6/6 subjects, range 0.25 to 2 hours
- Session 2: 18/96 positives (18.8%), 6/6 subjects, range 0.25 to 3 hours
- Session 3: 6/96 positives (6.3%), 3/6 subjects, range 0.25 to 1.5 hours
- THC only, no THCA present (0.02 ng/mL)
- Ventilation reduced exposure
- All positives within 3 hours of exposure

Contrasting Passive to Active Use



Effects of Cannabis

Approved in treatment of migraines and epileptic seizures

Feeling of well-being, distortion of time, increased appetite, increased depression and anxiety, euphoria, increased perception, enhanced recollection, decreased problem solving

Reddening of eyes, decrease in intra-ocular pressure, helpful with glaucoma symptoms

Dryness of mouth

Alleviates asthma symptoms, relaxes muscles in chest and lungs

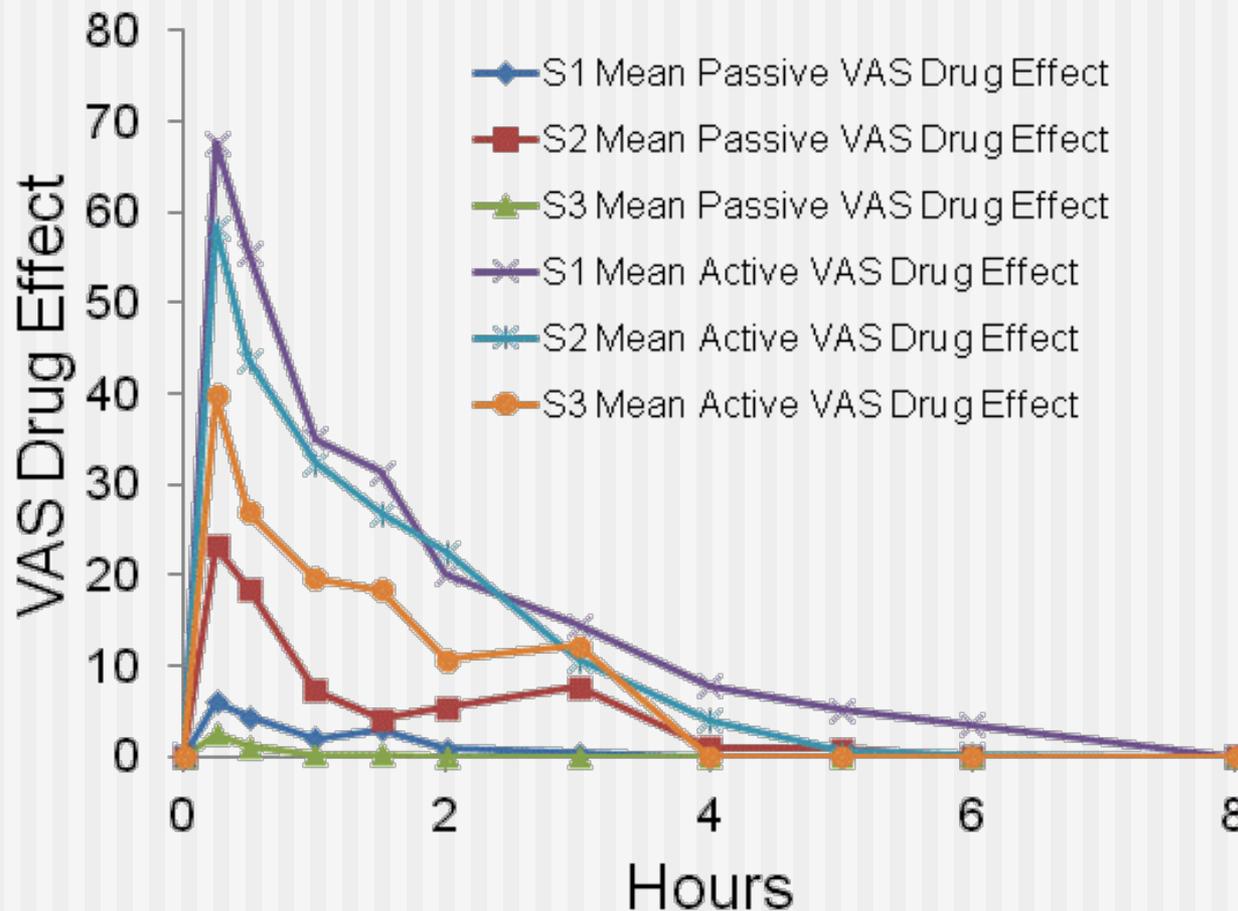
Increased heart rate

Relaxes muscles, reduces spasticity, approved for treatment of joint pain arthritis pain, and stiffness and spasticity in ALS and in multiple sclerosis

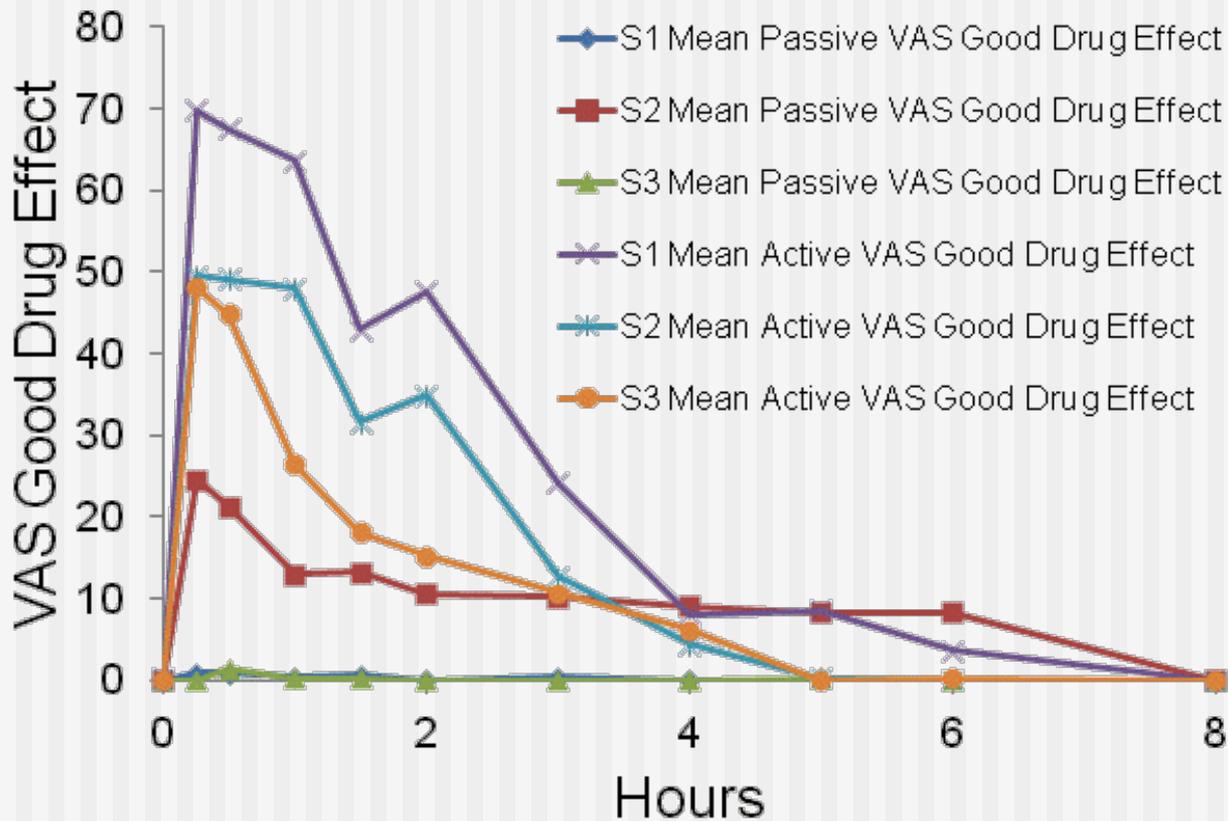
Relief of nausea, increases appetite resulting in weight gain, approved for treatment of severe nausea, and anorexia

www.facebook.com/montereybayholistic

Drug Effect: VAS Drug Effect (VAS = Visual Analog Scale)



Drug Effect: VAS Good Drug Effect (VAS = Visual Analog Scale)



Conclusions

- Severe exposure such as produced in these studies was irritating to mucous membranes especially eyes
- Such exposure would not be tolerated unknowingly; more appropriately termed “tolerated exposure”
- Severe exposure within 2-4 hours of specimen collection resulted in positive urine/oral fluid/blood results
- More sensitive cutoffs increased positivity rates
- THCCOOH was not detected in OF non-smokers and would serve to distinguish active use versus “tolerated use”
- All outcomes were related to severity of exposure; e.g., duration of exposure, THC potency, number of joints smoked, environmental conditions