Drug Recognition & Impairment Research
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NIDA's Current Drugged Driving Research

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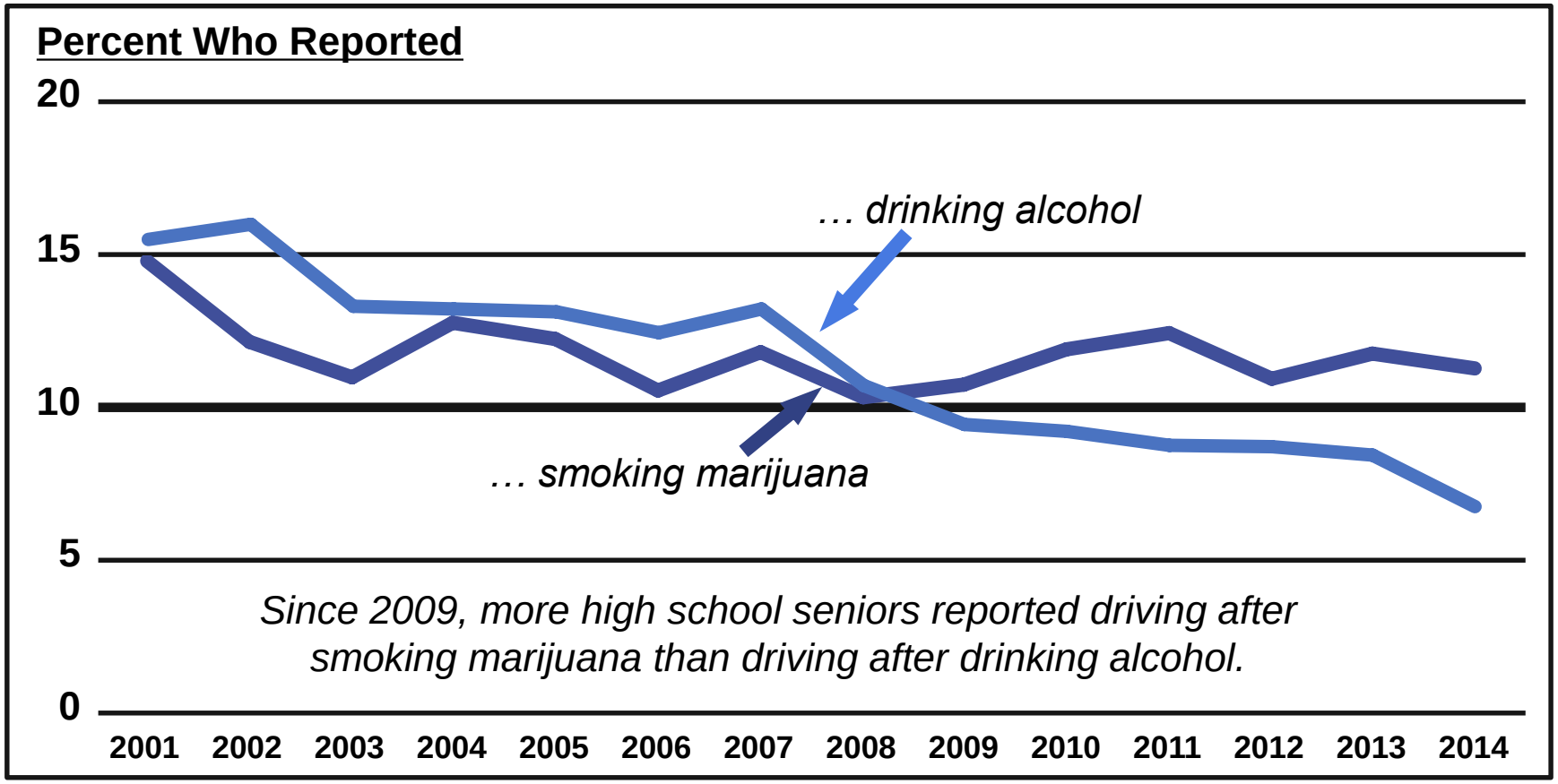
NIDA's Mission & Current Extramural Grants on Drug Recognition & Impairment Research

- To lead the Nation in bringing the power of science to bear on drug abuse & addiction
- Monitoring the Future Study
  - Annual survey of nationally representative samples of high school 8th, 10th & 12th graders since 1975
  - Questions related to licit & illicit drug use
  - Driving under the influence & riding with someone who's under the influence
  - Demographic & lifestyle questions

12th Graders Who Drove After Smoking Marijuana or Drinking Alcohol, 2001-2014

During the LAST TWO WEEKS, have you driven a car, truck, or motorcycle after ...



Source: University of Michigan, 2014 Monitoring the Future study. Unpublished special tabulations (December 2014)

NIDA's Current Extramural Grants on Drug Recognition & Impairment Research

- Medical marijuana implementation & impact on health
  - Accidents, drug driving, laws, improved policies
- In vivo driving impairment research method: A new methodology for examining drug & alcohol impaired driving
- Drugged driving resources website for prevention of drugged driving
- NIDA International Program support of ICADTS Illegal Drugs & Driving Workgroup

NIDA's Current Extramural Grants on Drug Recognition & Impairment Research

- Effects of drug treatment courts on outcomes of adults & their children
  - Driving While Intoxicated; drug driving; laws
- Drinking, driving & drugs: trajectories of DWI recidivism & how to intervene
  - Merge Texas driving record & treatment data to identify & evaluate risk & protective factors for DWI/DUI recidivism among individuals who received alcohol &/or drug treatment & successful interventions

NIDA's Current Extramural Grants on Drug Recognition & Impairment Research

- Drinking & driving among recent Latino immigrants
  - Latinos consistently overinvolved in alcohol-related motor-vehicle fatal crashes but do not drink more than Whites
  - Evaluate level of understanding by recent immigrants about alcohol-related traffic laws & policies, & their level of compliance & an estimation of prevalence of problem crucial to assessing need for designing efficient countermeasures

Chemistry & Drug Metabolism NIDA Intramural Research Program

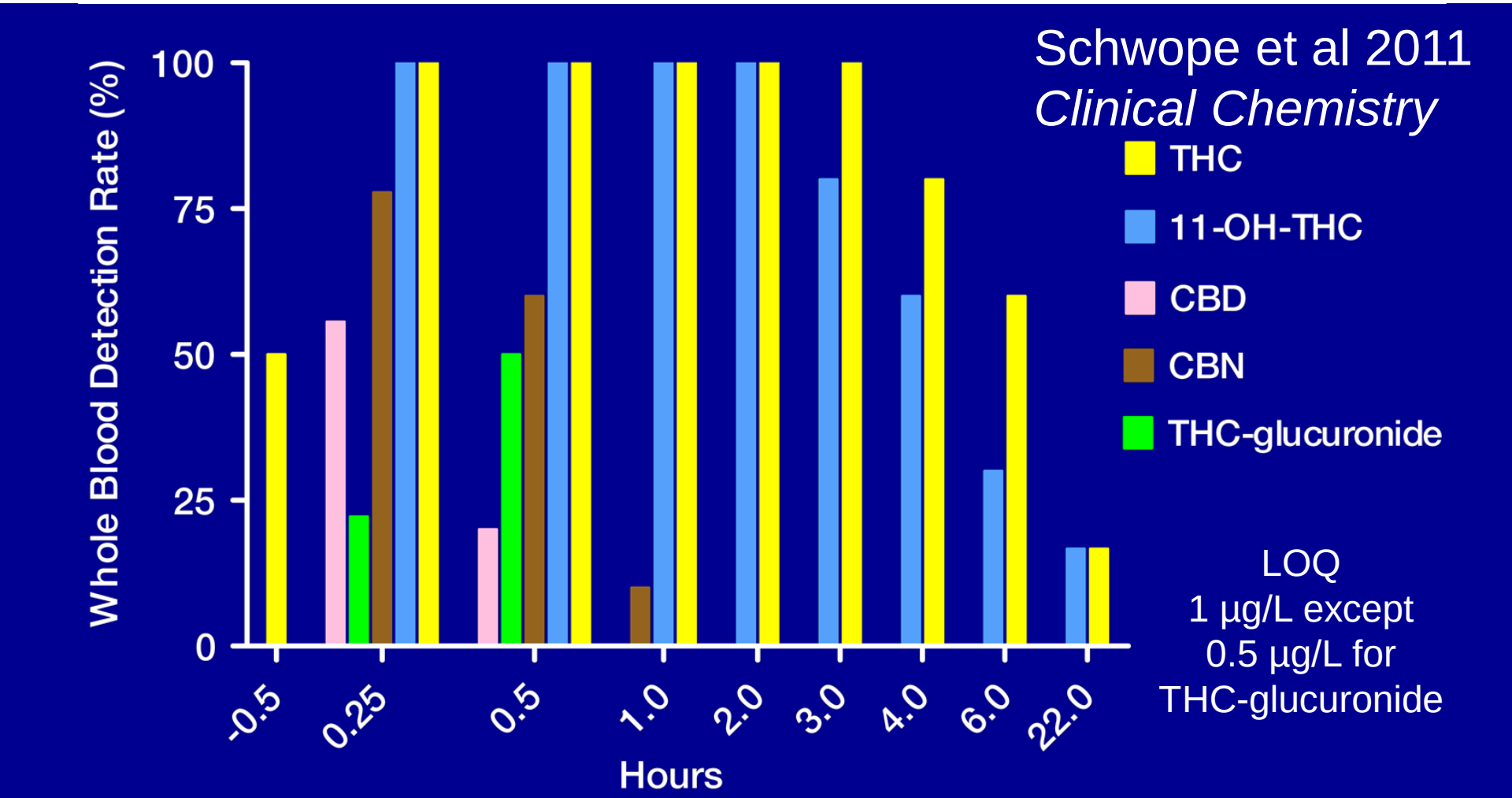
- Conduct controlled drug administration studies on pharmacodynamic & pharmacokinetic effects of drugs
  - Opioids, cocaine, methamphetamine, cannabis, MDMA, tobacco & alcohol
  - Onset, peak & duration of cognitive, psychomotor, subjective, hormone & physiological effects
  - Initial, peak & duration of drug concentrations in blood, plasma, oral fluid, urine, hair & sweat

Chemistry & Drug Metabolism NIDA Intramural Research Program

- Effects of cannabis with & without low dose alcohol on driving
  - National Advanced Driving Simulator- U of Iowa
- Novel psychoactive substances (NPS)
  - Screening &confirmation of synthetic cannabinoids, synthetic cathinones, piperazines
  - Identification of best urinary NPS targets by incubation with human hepatocytes & high resolution mass spectrometry HRMS
  - Non-targeted HRMS to identify urinary NPS, LC-MS/MS for targeted qualitative & quantitative NPS analysis

Are There Markers of Recent Cannabis Intake in Blood?

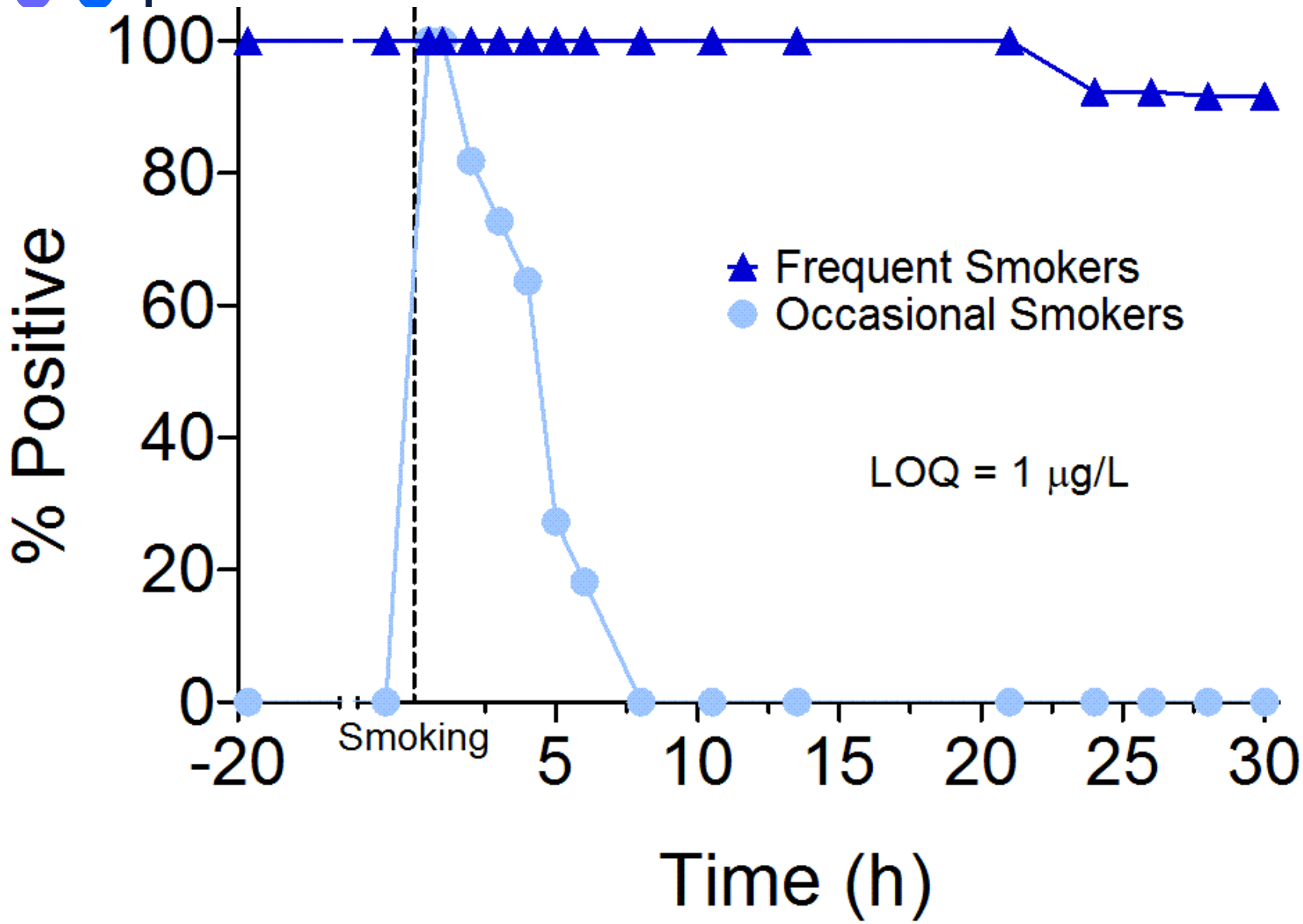
THCCOOH & THCCOOH-glucuronide present in all samples



What Is Best THC Blood Concentration To Indicate Driving Impairment? 1, 2 or 5 µg/L?

Desrosiers et al 2014 *Clinical Chemistry*

Blood THC After Smoking 6.8% THC



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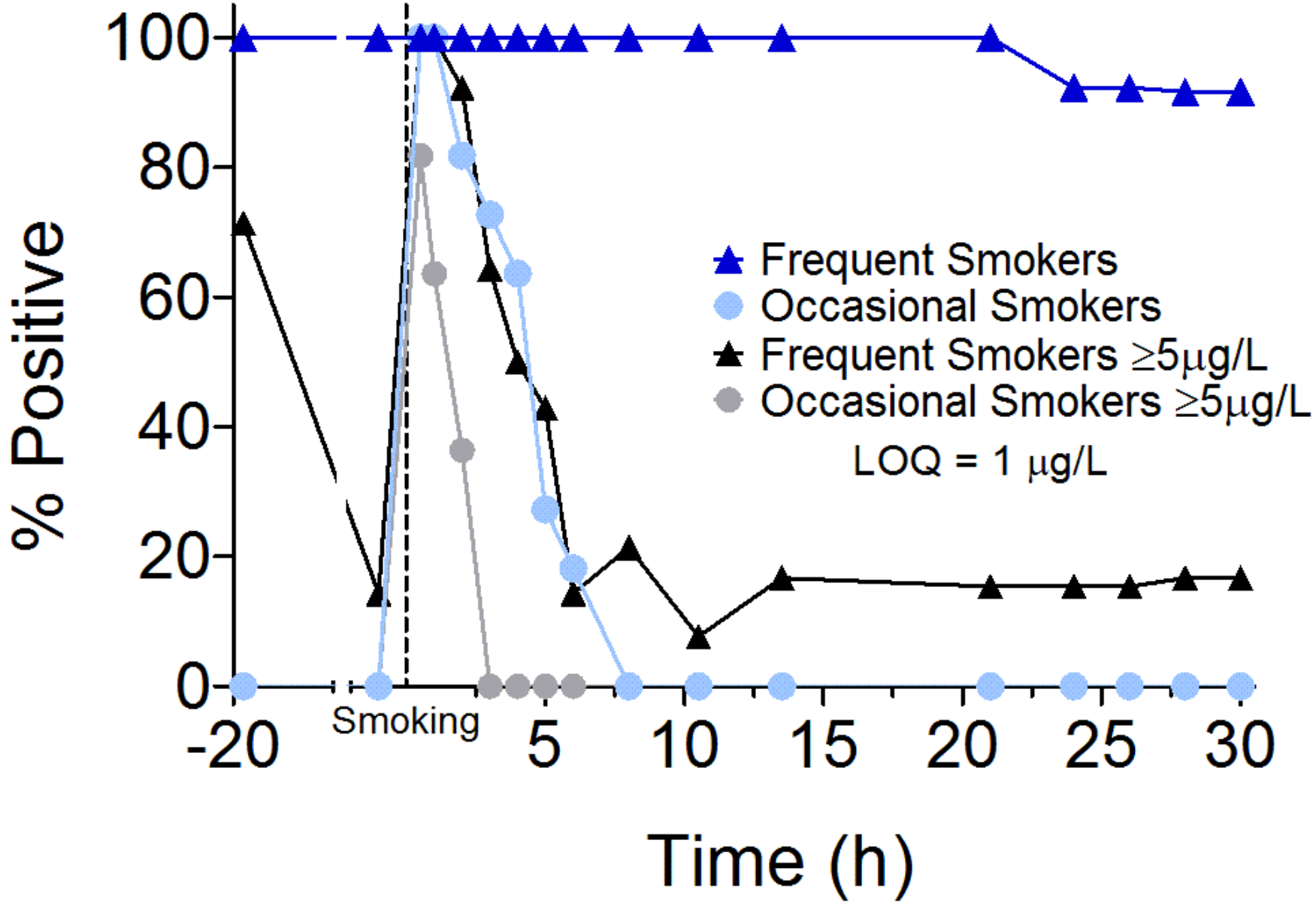
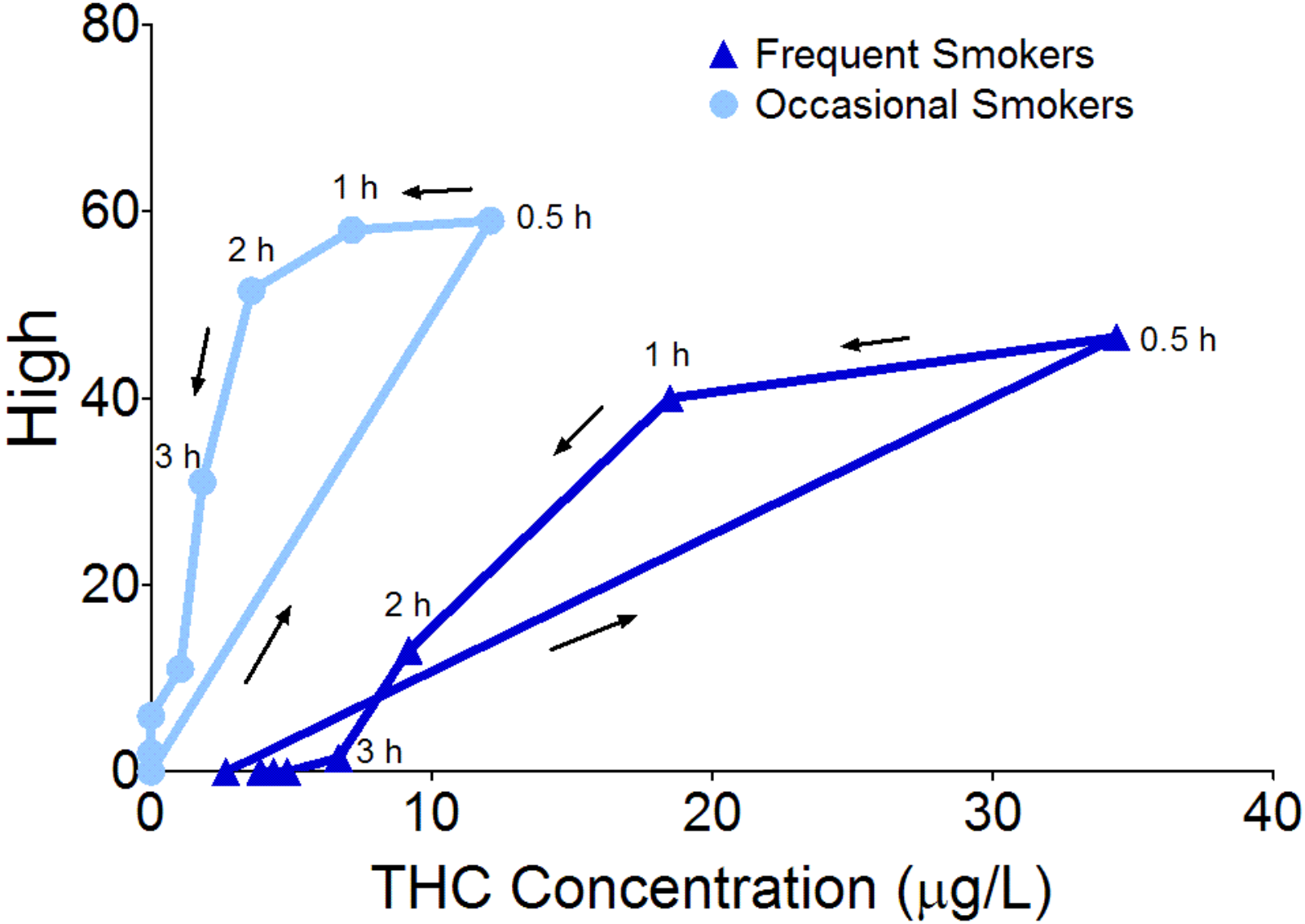


Legal Limits for Blood THC Concentrations & Driving

- In our research, occasional use = less than daily smoking & frequent smoking as daily cannabis smoking (varies by author)
- CO & WA state use ≥ 5 µg/L THC cutoffs
- Only 81.2% occasional smokers ≥ 5 µg/L at 30 min; all < 5 µg/L by 2 h
- <20% frequent smokers ≥ 5 µg/L by 5 h; 16.7% still ≥ 5 µg/L after 30 h

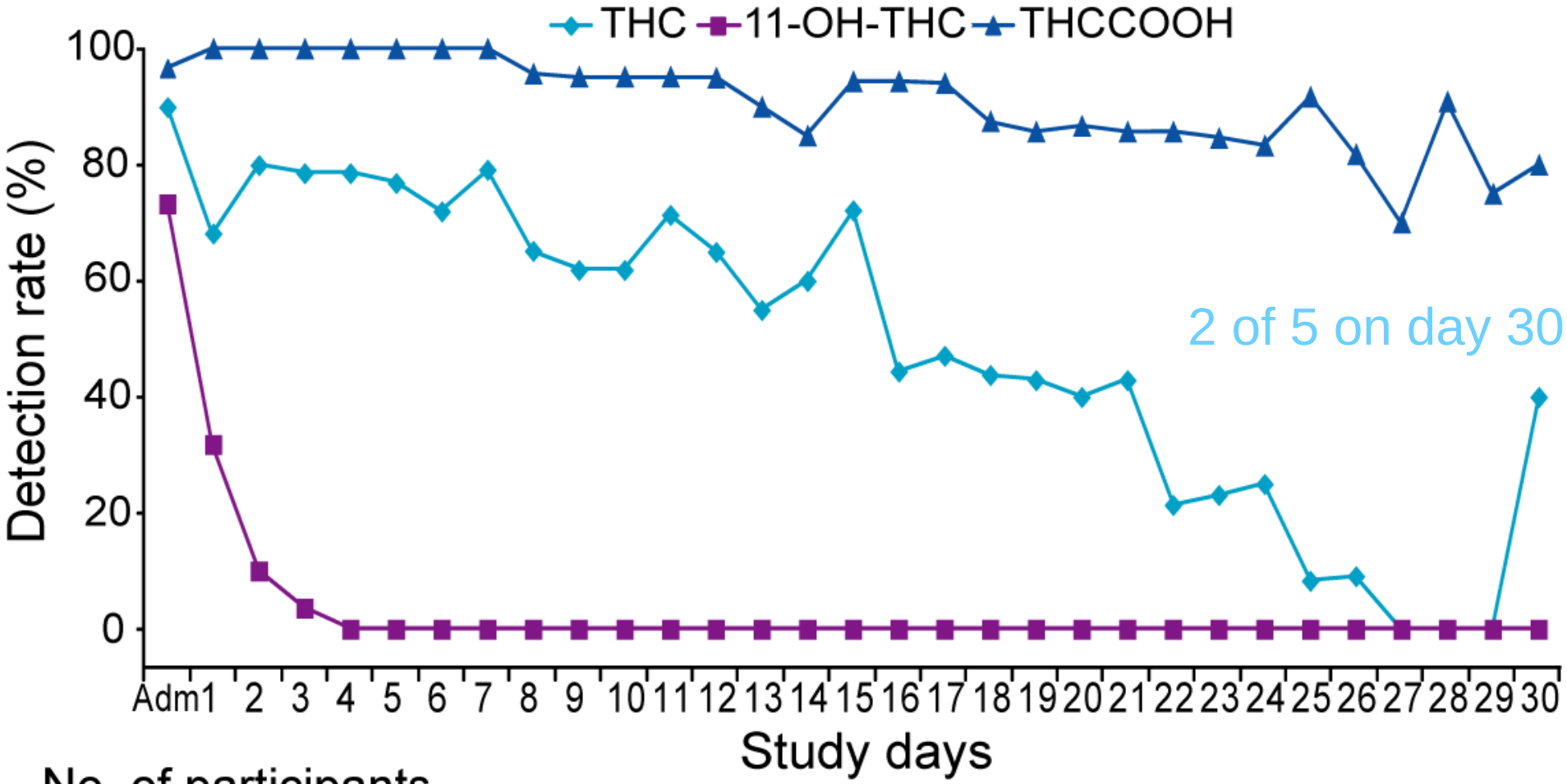
Hysteresis in Subjective "High"



Residual Blood Cannabinoids Excretion in Chronic Frequent Cannabis Smokers Over 30 Days Sustained Abstinence

Bergamaschi et al *Clinical Chemistry* 2013

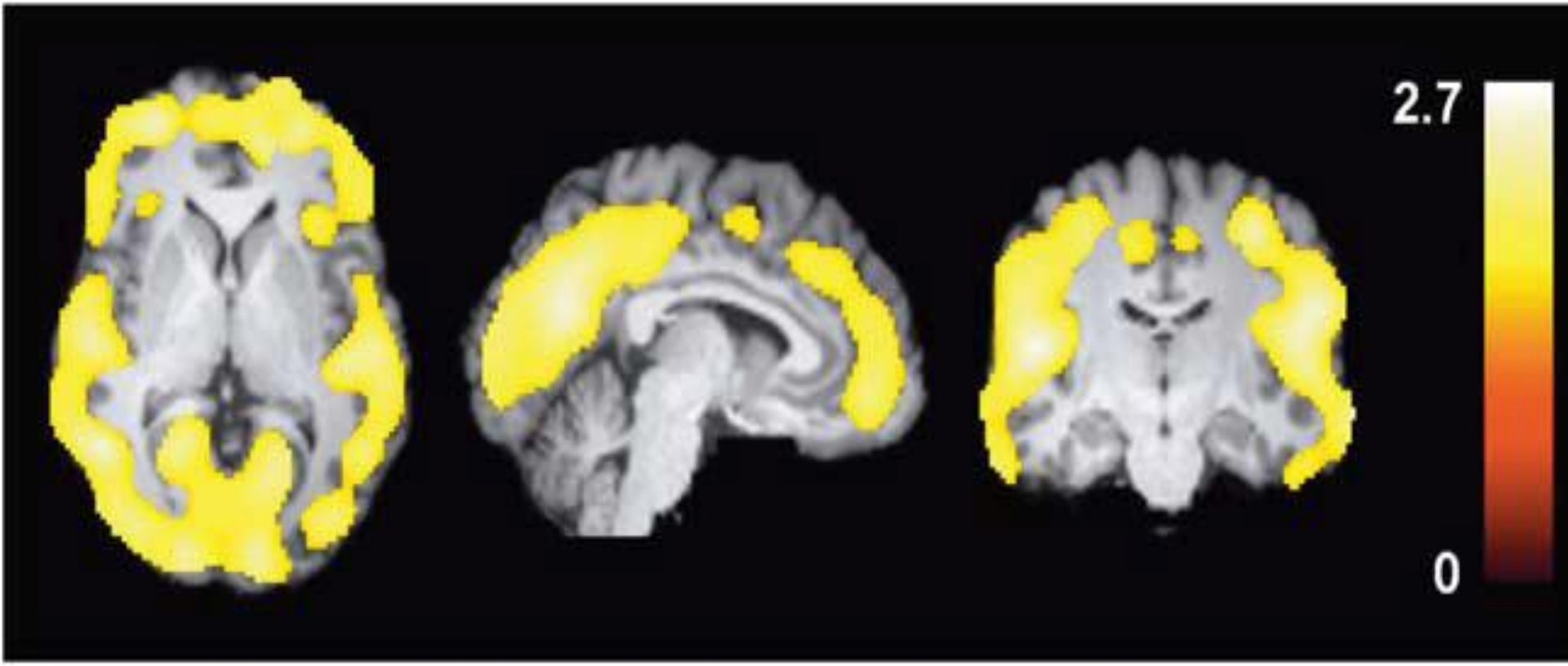
Median Cannabinoid Excretion in Chronic Frequent Cannabis Smokers Blood over 30 Days Sustained Abstinence (0.25 µg/L)



No. of participants

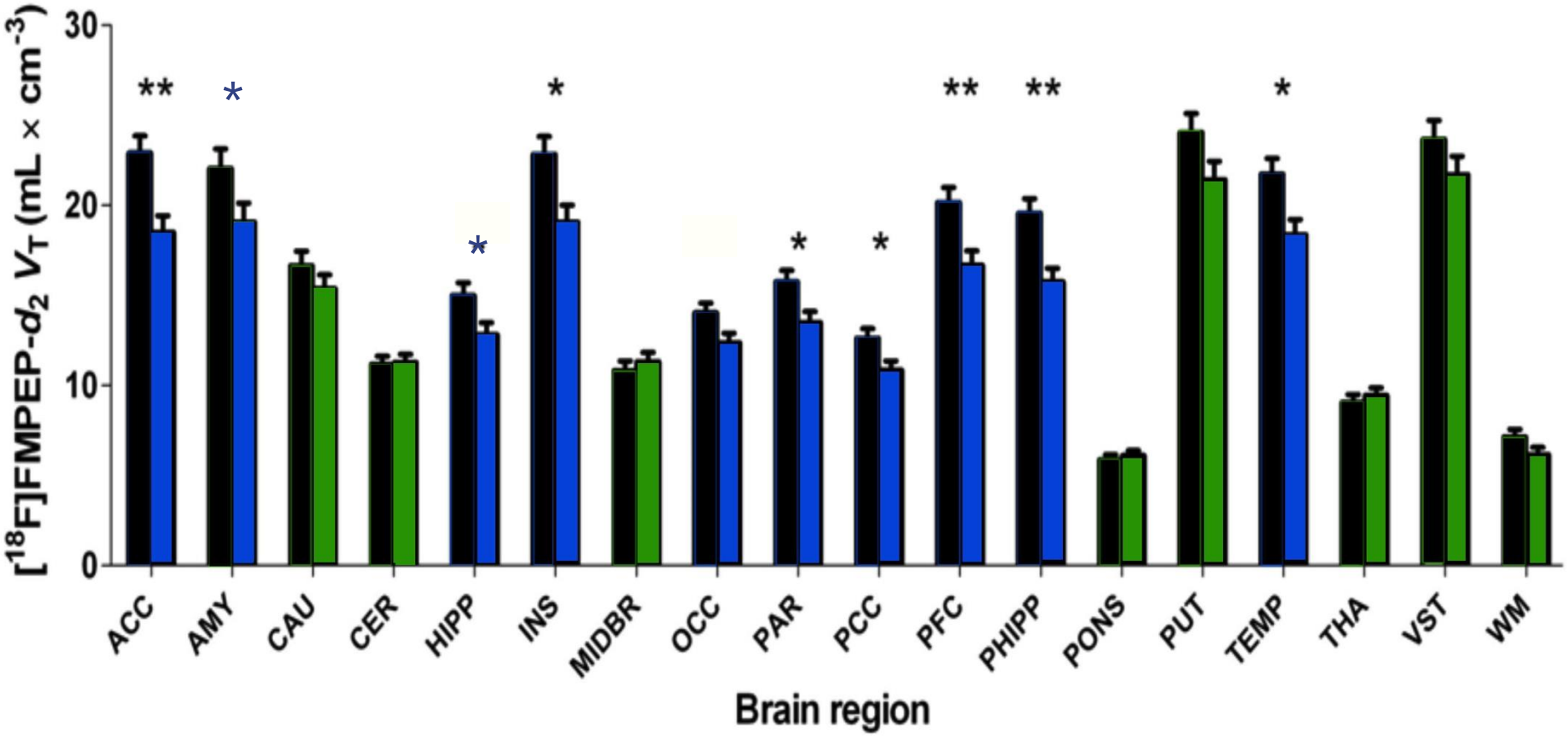
30 22 30 28 28 26 25 24 23 21 21 21 20 20 20 18 18 17 16 14 15 14 14 13 12 12 11 10 11 8 5

[^{18}F]FMPEP-d_2 Labels CB1 Cannabinoid Receptors in Brain of Chronic Daily Cannabis Smokers

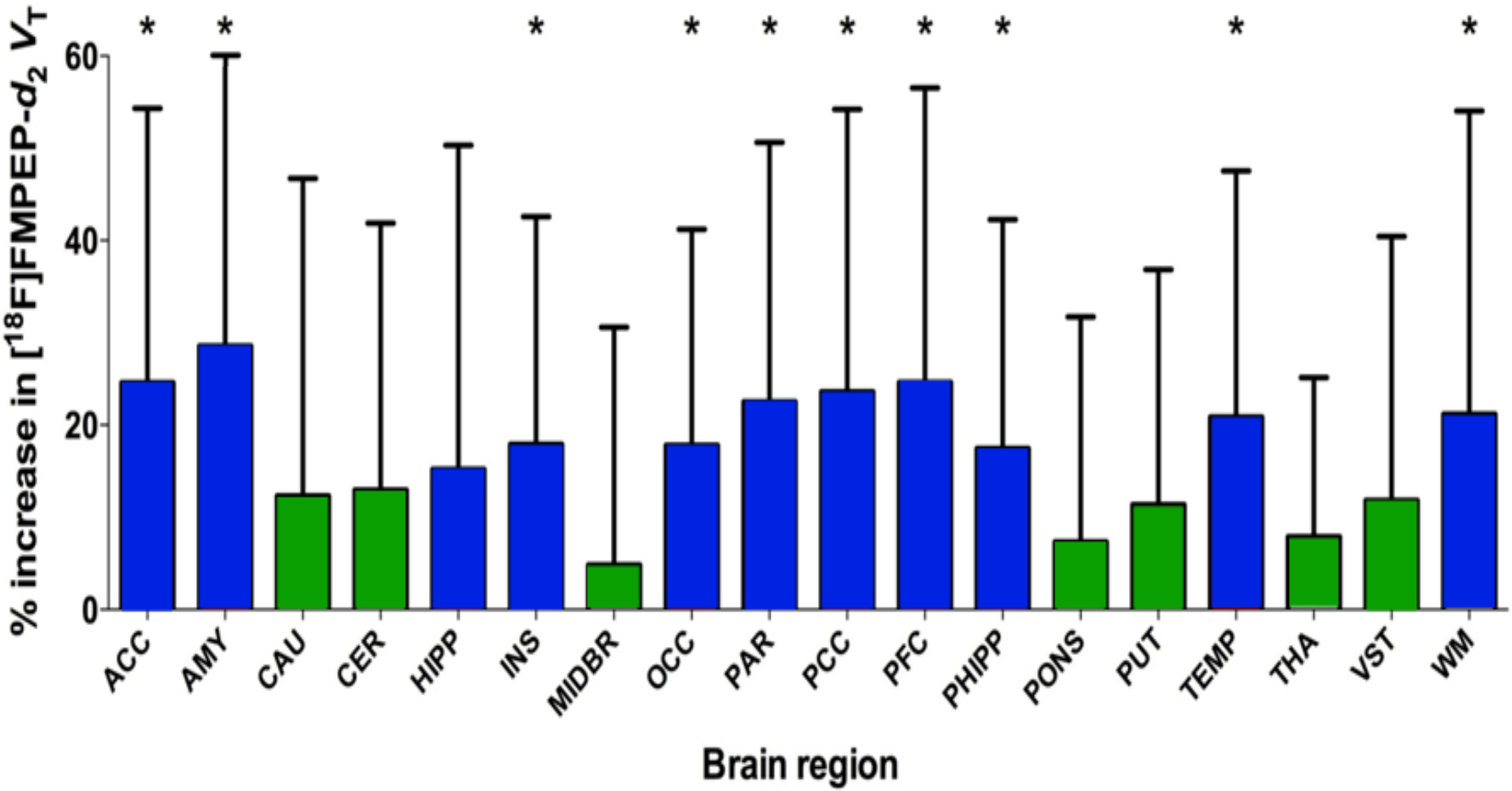


Hirvonen & Innis et al. *Molecular Psychiatry* 2012

CB_1-Cannabinoid Receptors Specifically Downregulated in Cortical Regions of Chronic Daily Cannabis Smokers (N=30) as Compared to Controls (N=28)



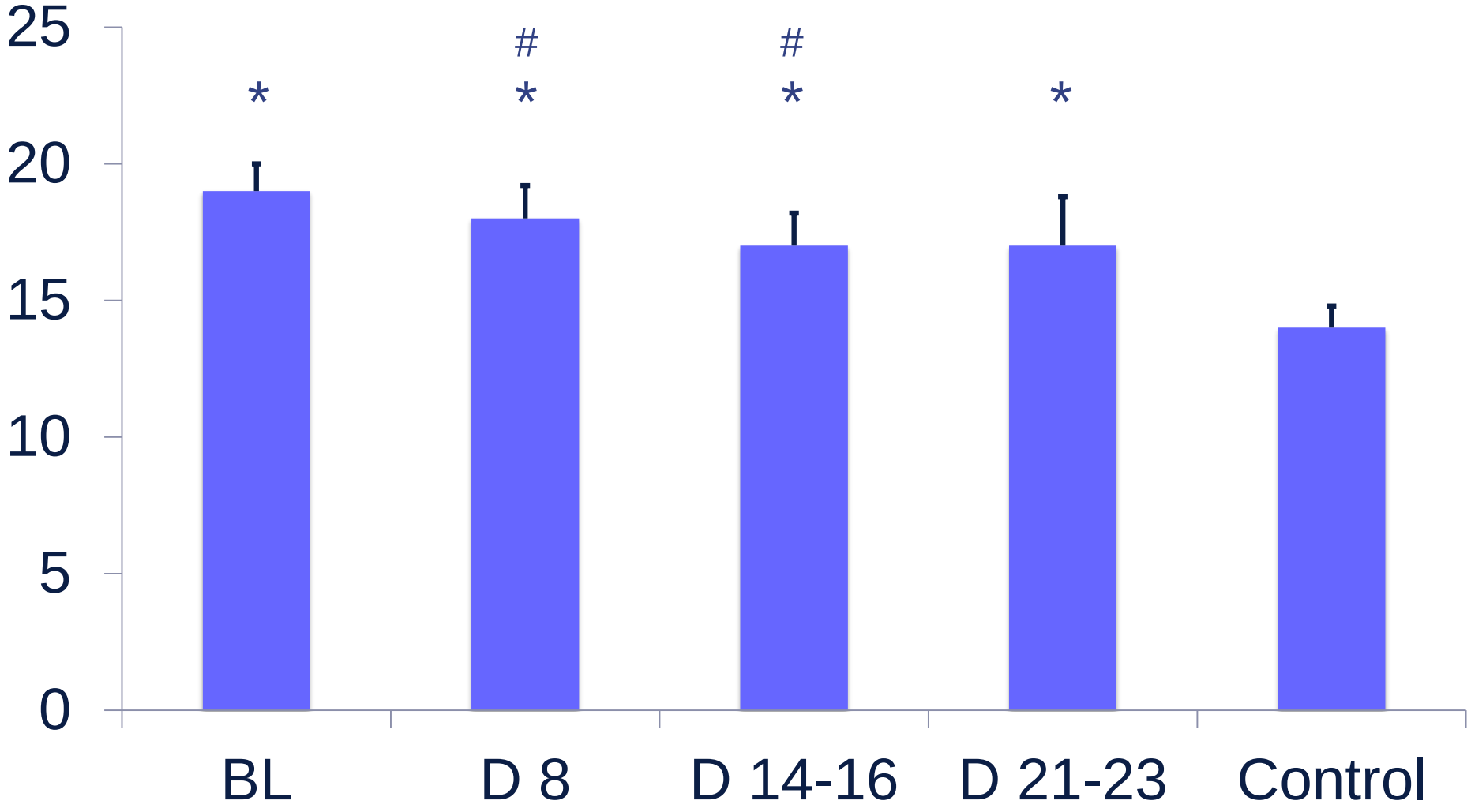
CB_1 Cannabinoid Receptors Significantly Increased after Sustained Cannabis Abstinence (N=14)



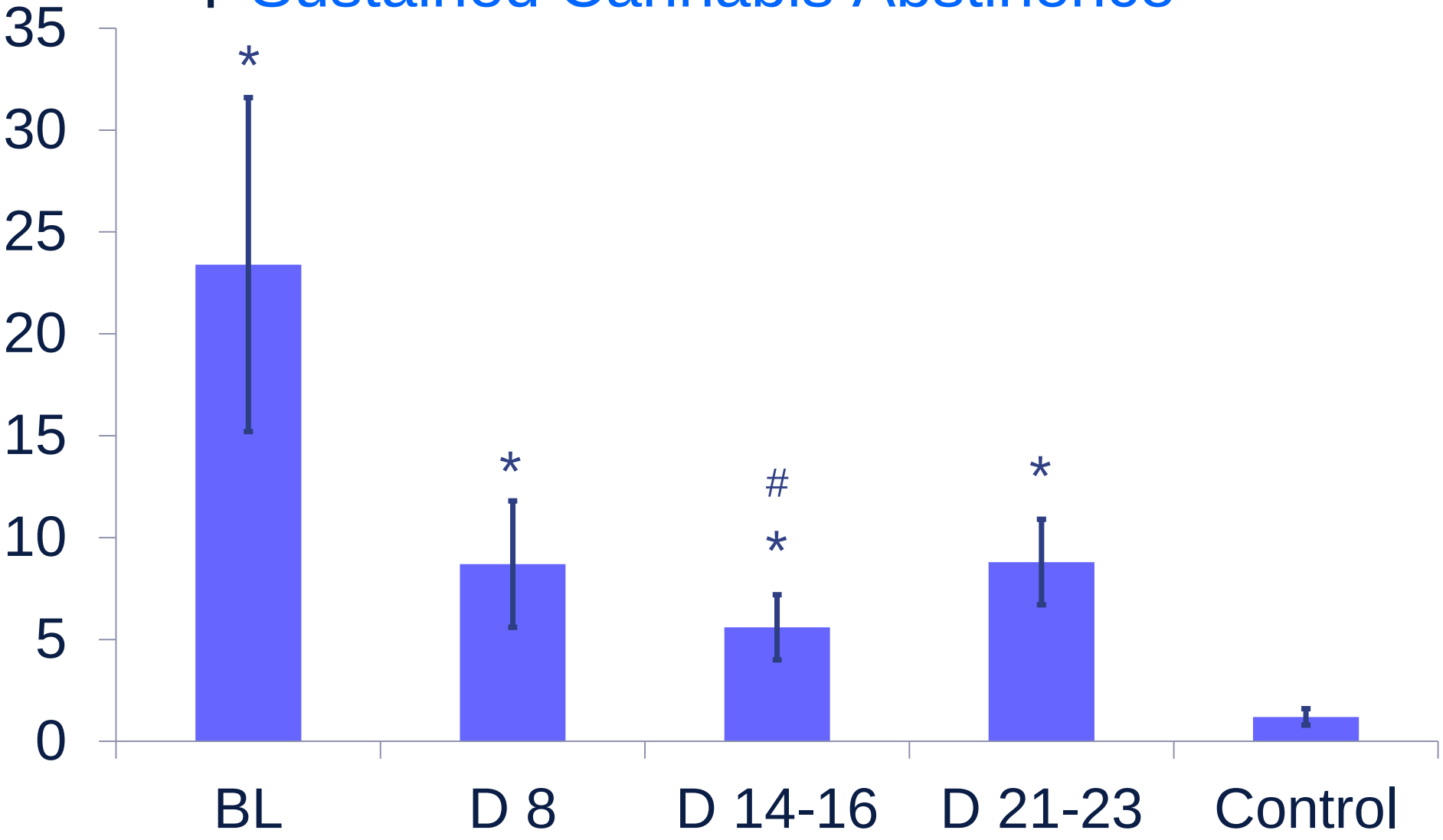
Psychomotor Impairment & Chronic Frequent Cannabis Smoking

Bosker et al *PLoS One* 2012

Mean±SE Tracking Error (mm) in Chronic Daily Cannabis Smokers During Sustained Cannabis Abstinence

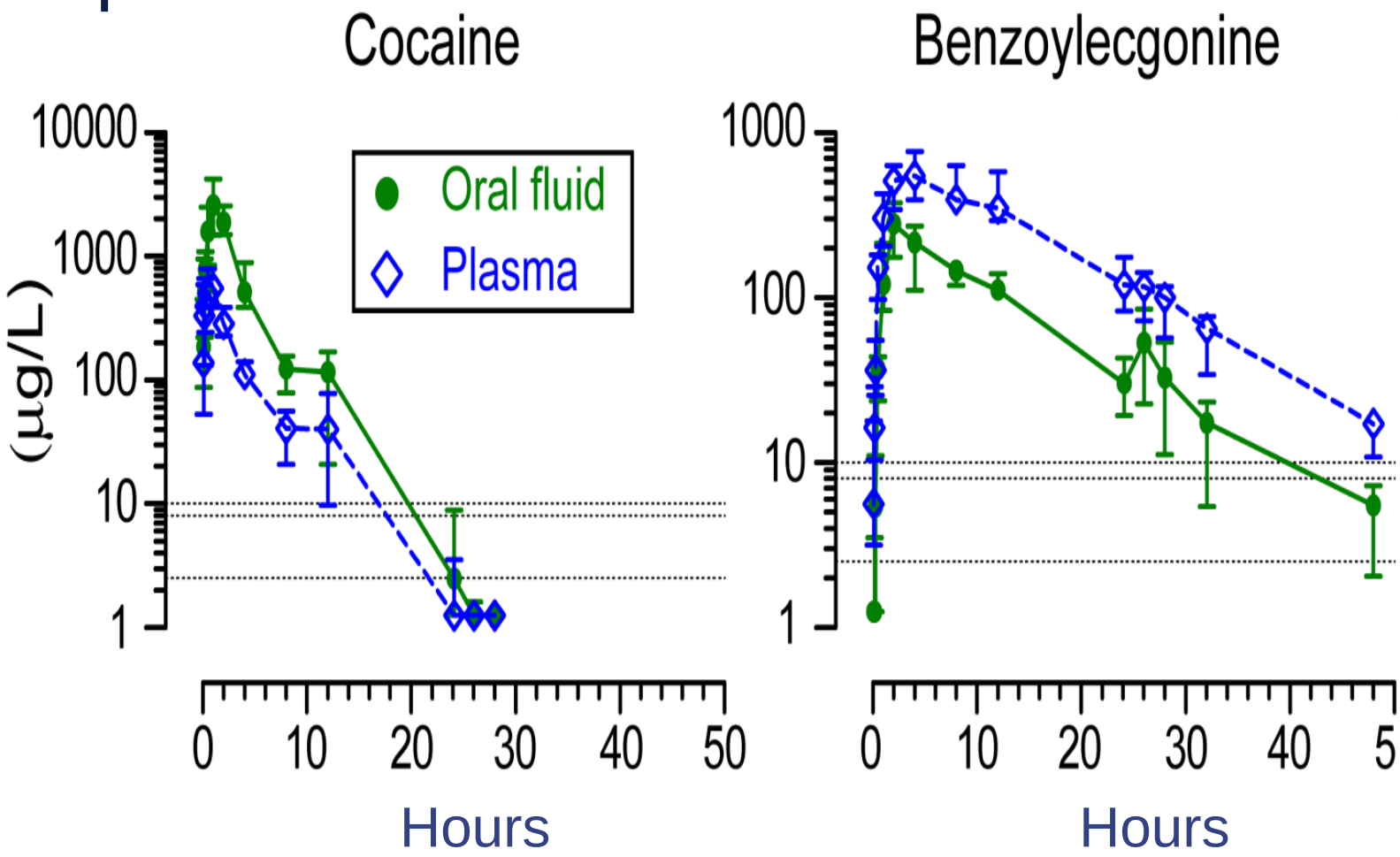


Mean±SE DAT Control Losses in Chronic Cannabis Smokers During Sustained Cannabis Abstinence



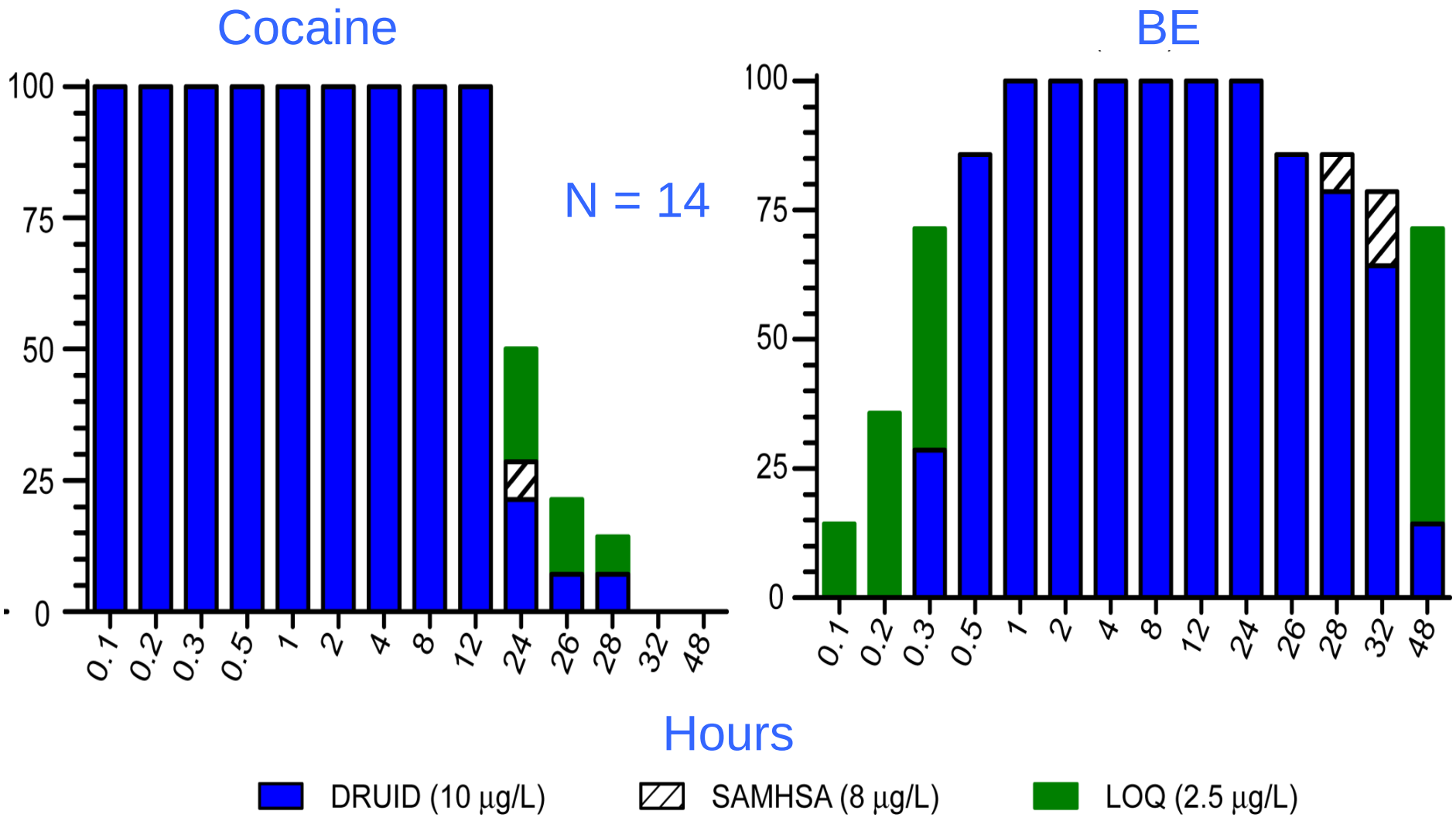
Is There A Better Biological Matrix for Monitoring for Driving Impairment?

Cocaine, BE & EME in Oral Fluid
150 mg/70 kg sc cocaine



(N=14 oral fluid) (N=13 plasma)

% Positive Expectorated OF Samples After 150 mg/70 kg Cocaine

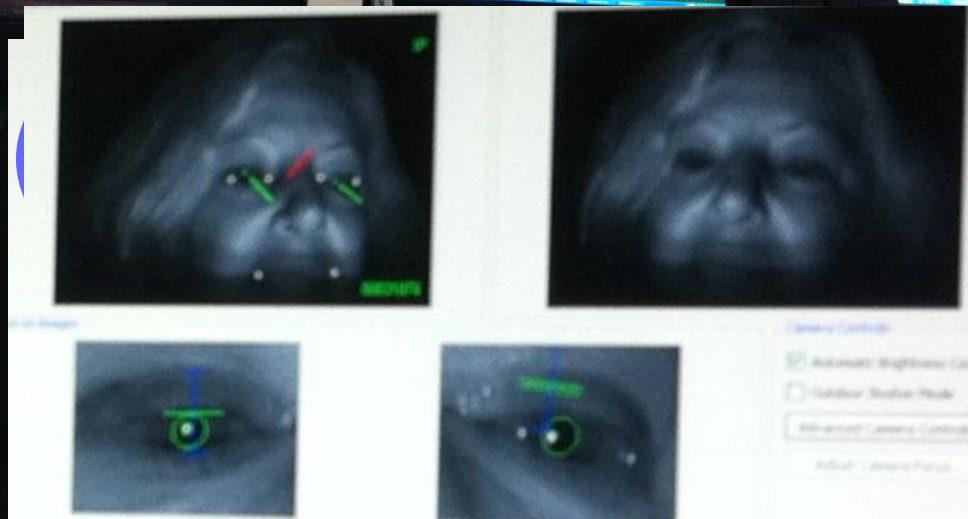


Breath Cannabinoid Concentrations After Acute Cannabis Smoking in Occasional & Chronic Frequent Smokers

THC-Positive Breath Specimens

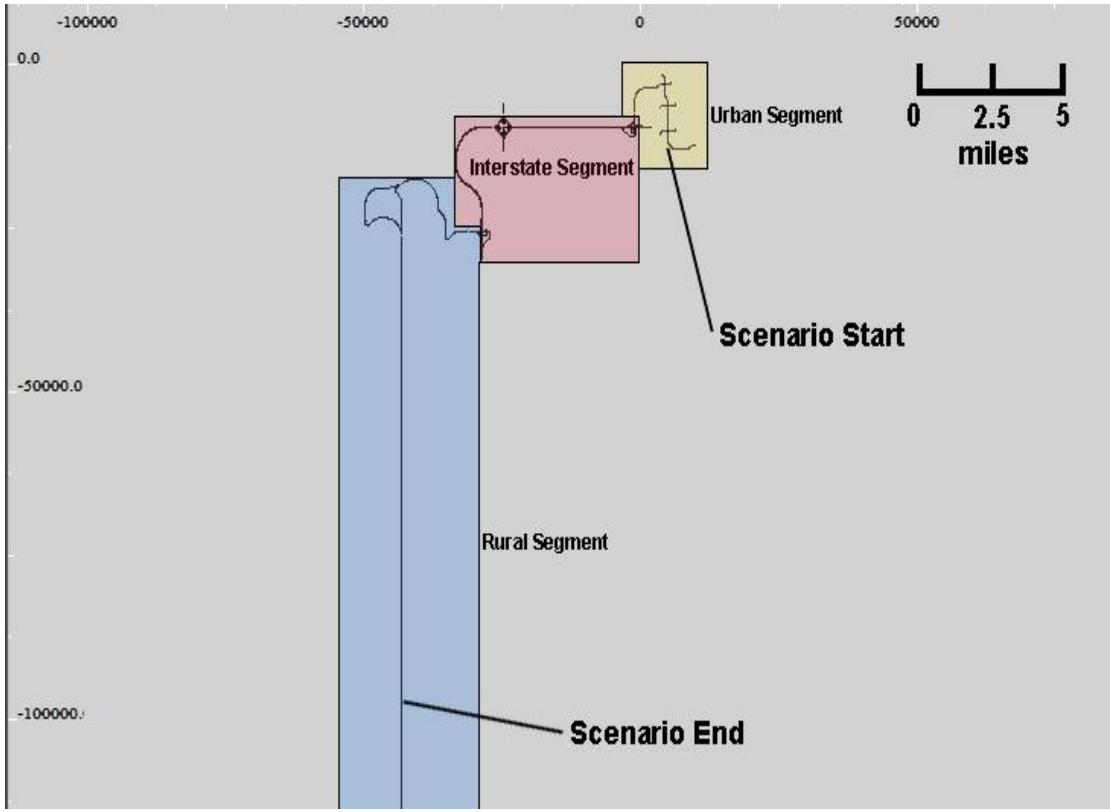
Time after smoking (h)	Chronic Users N=13	Occasional Users N=11
Admission	15.4%	0
-1.0	0	0
0.5	100%	90.9%
1.0	76.9%	63.6%
2.0	53.8%	0
3.0	0	0
4.0	7.7%	0

National Advanced Driving Simulator
University of Iowa



Iowa Study Simulations

- Nighttime driving
- 3 segments:
  - Urban
  - Interstate
  - Rural
- Each segment contains subtasks
- Drive time ~45 min



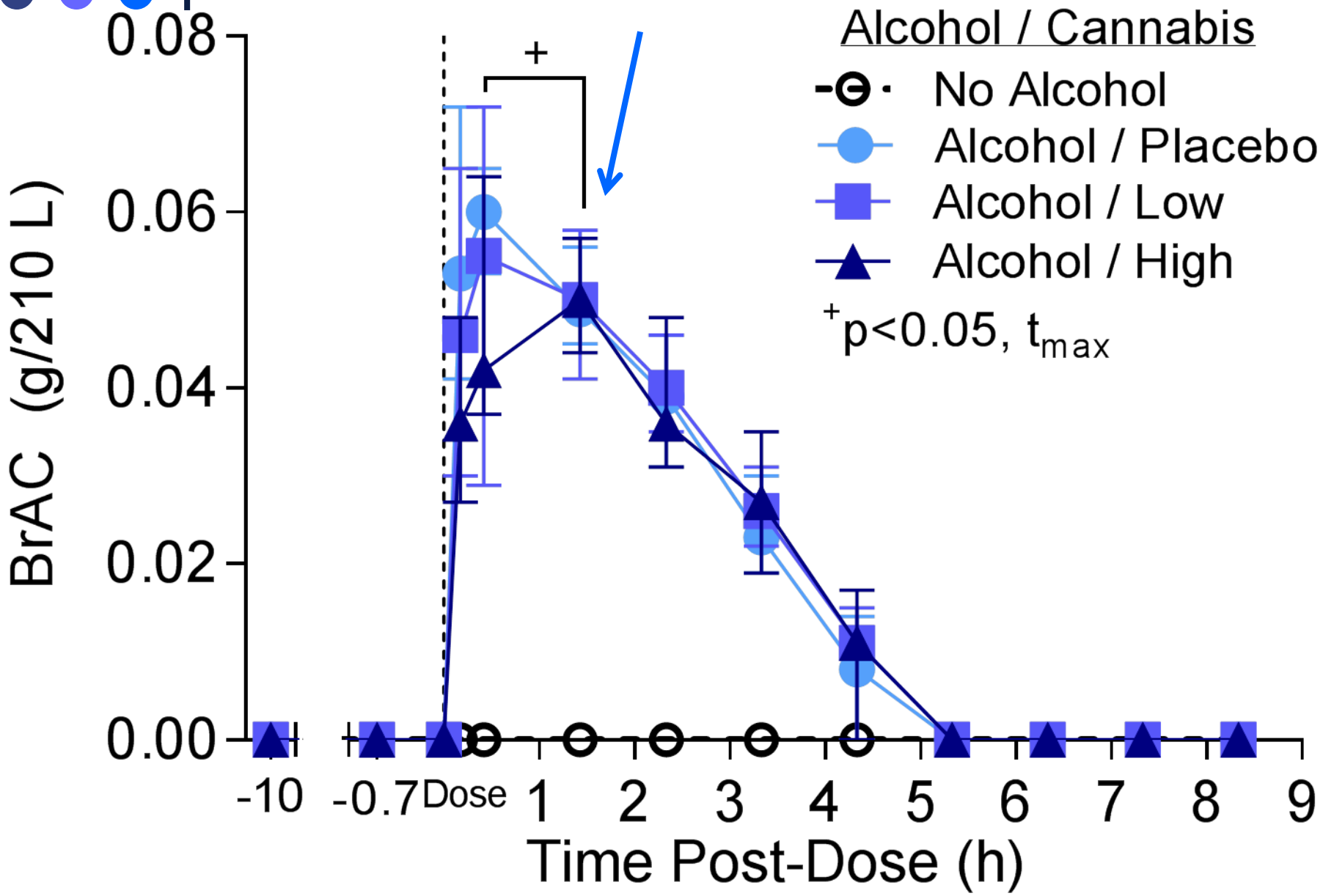
Cannabis Effects on Driving

- Decision-making
- Divided attention
- Visual search
- Focus, concentration
- Process changes
- Reaction Time
- Road tracking, vehicle control

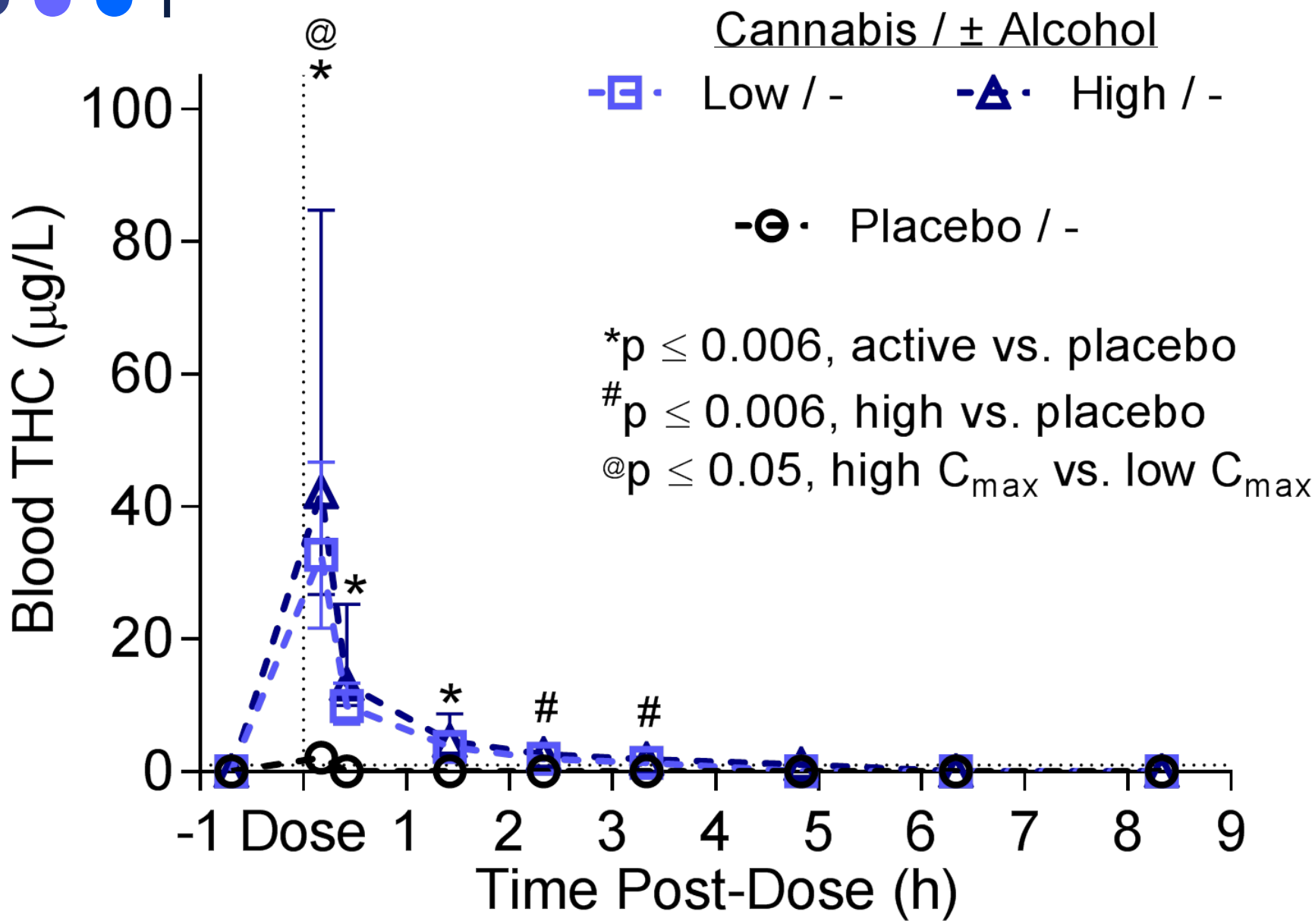
Drug Administration

- Placebo or low-dose alcohol
  - Calculated to produce ~0.065% peak BrAC (≥ 0.05% during driving)
- 0.5 g cannabis
  - Placebo, Low (2.9% THC), High (6.7% THC)
- Volcano® Medic vaporizer, inhale over 10 min

Median [Interquartile Range] Alcohol



Median [Interquartile Range] Blood THC



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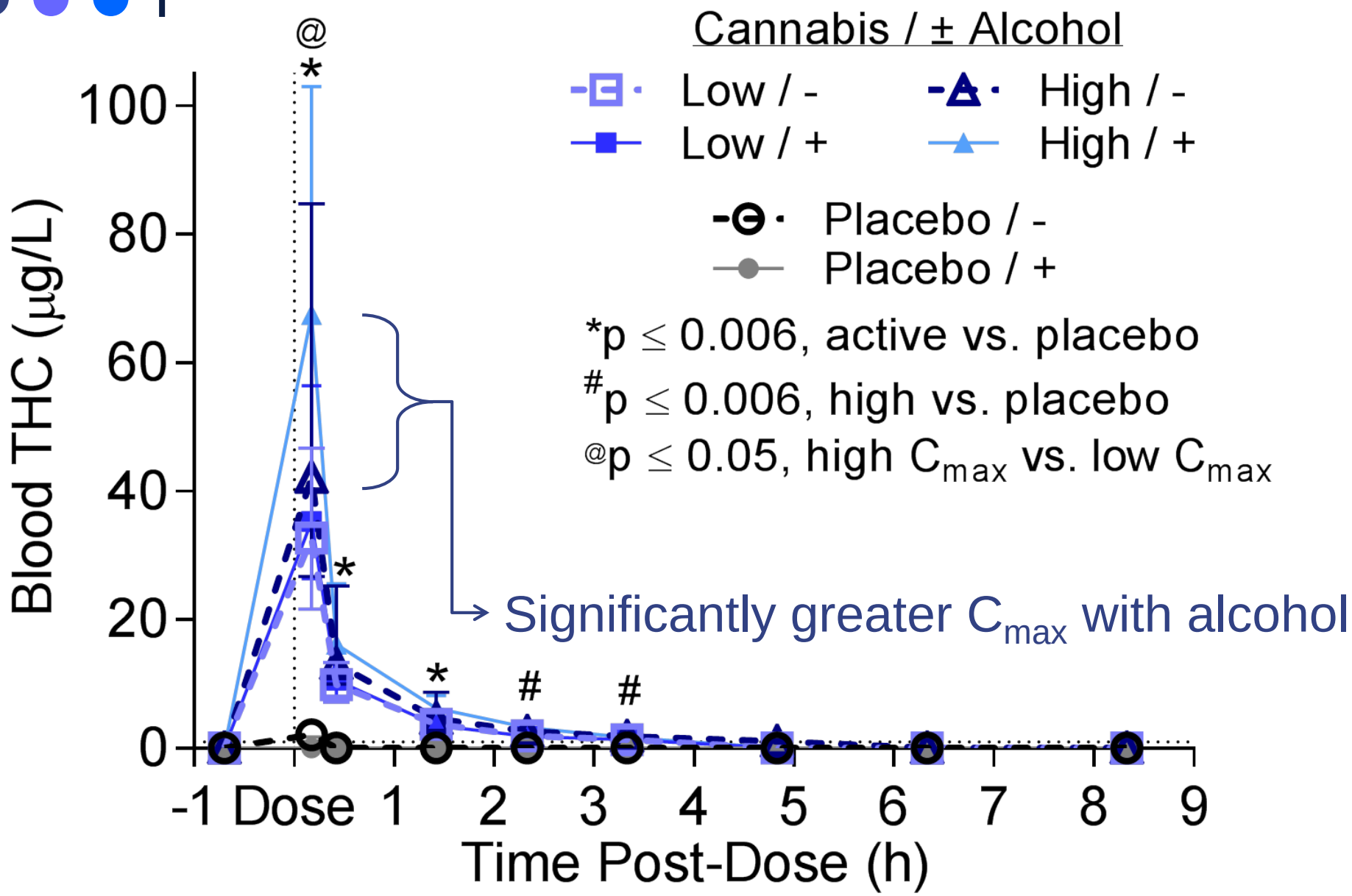
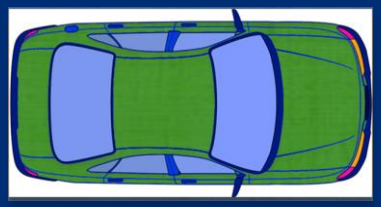
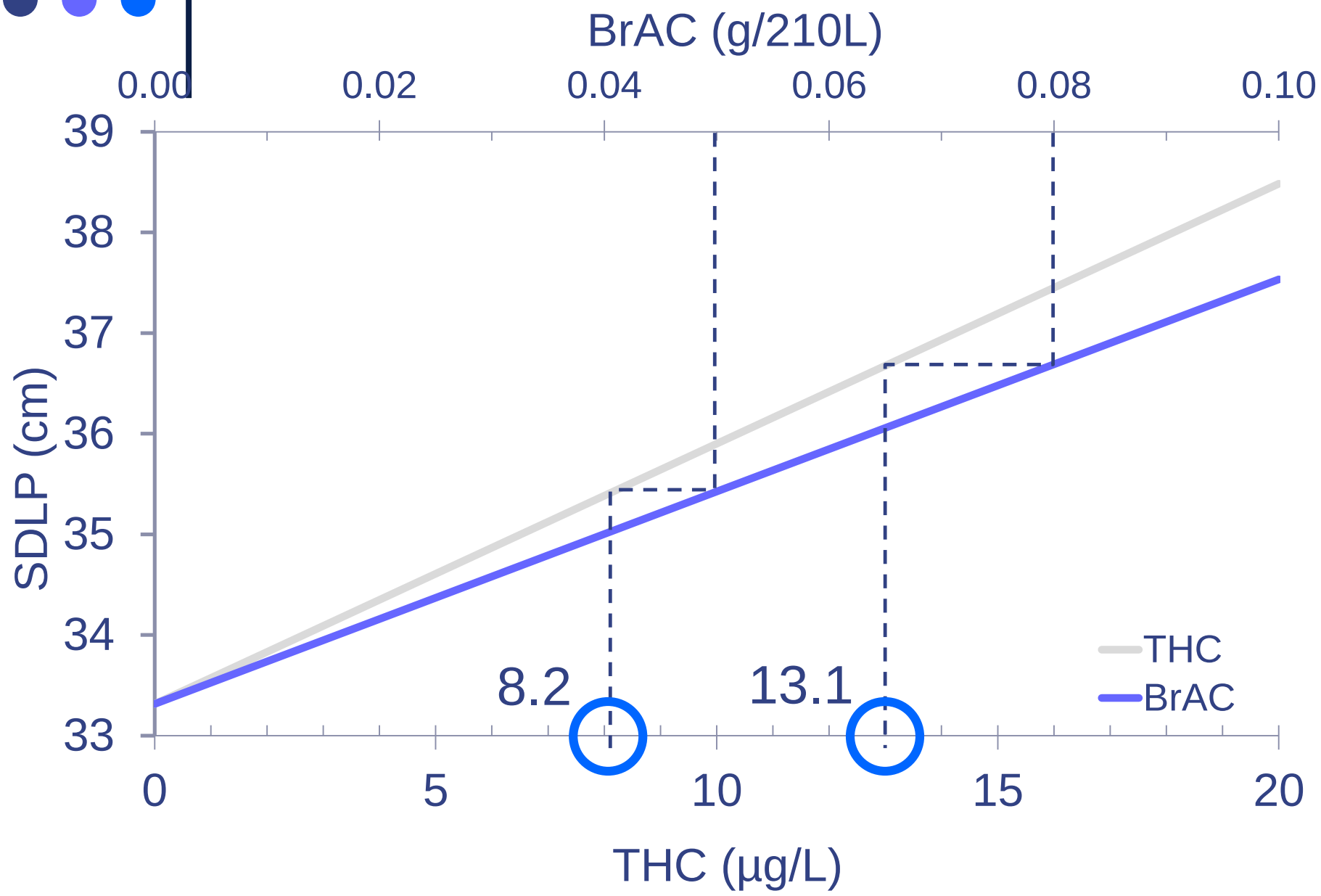


Cannabis & Alcohol Effects: Driving Lateral Control



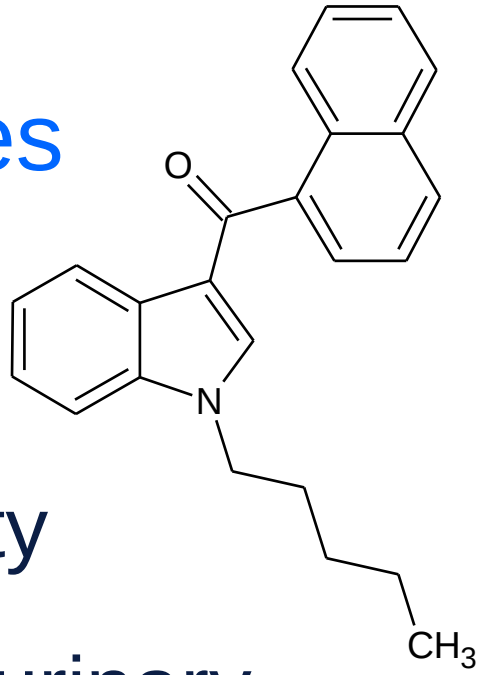
SDLP vs. THC & SDLP vs. BrAC



Driving Lateral Control

- Cannabis & alcohol affected SDLP, concentration dependent
  - ~8.2 & ~13.1 µg/L THC during driving produced impairment ~ [illegal] 0.05 & 0.08 g/210L
  - Due to blood draw delays, measured concentrations in authentic cases will be lower
- Additive effect with alcohol (not synergistic)
- No cannabis effect on other lateral control measures

NPS Analytical Challenges



- Vast array of target analytes
- Changing target analyte availability
- Lack of information about human urinary metabolites of new cannabimimetics
- Highly potent compounds produce lower metabolite concentrations
- Common metabolites for different targets

Challenges for Monitoring Synthetic Cannabinoid Intake

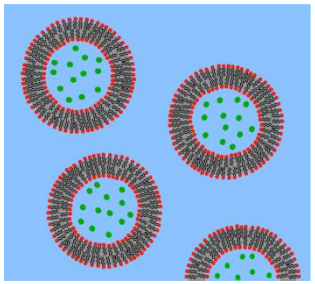
- Compounds closely related chemically, making chromatographic separation difficult
- Constantly need to add new compounds & metabolites

NPS: New Face of Drug Abuse

- Essential to identify NPS markers in biological samples
  - Short detection windows for parent NPS in blood & oral fluid
  - Urine markers provide longer detection times
  - Essential to document SC intake to link adverse outcomes with specific NPS & to educate public about potential SC toxicity

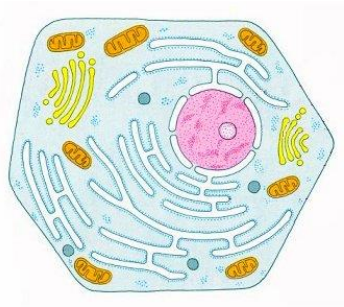
Identifying Human Metabolites with Human Liver Microsomes & Hepatic Cell Cultures & High-Resolution Mass Spectrometry

HLM Preparation
$T_{1/2}$ determination



1

Incubation with human hepatocytes

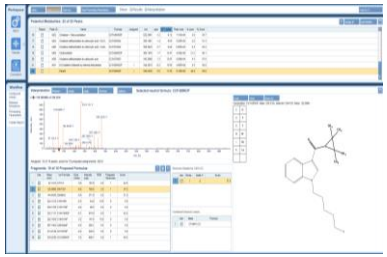


2

Analysis by LC-HRMS

3

Software-assisted data analysis



Compounds Evaluated to Date

- AKB48
- STS-135
- RCS-8
- RCS-4
- PB-22 & 5F-PB-22
- AB-PINACA & 5F-AB-PINACA
- AB-FUBINACA
- THJ-018 & THJ-2201
- AMB & 5F-AMB
- MDMB-FUBINACA
- FUBIMINA
- 5F-SDB-005-INDOLE
- FDU-PB-22
- FUB-PB-22
- AH-7921
- PV8
- Alpha-PVT
- 4MeO-alpha-PVP

Thank You!