Pharmacokinetics and Detection of THC Impairment
Traffic Safety Considerations in Canada

CCMTA/CCATM Annual Meeting

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Alcohol Countermeasure Systems (ACS)
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life saving innovations

AGENDA

1. Marijuana
   - chemistry and composition
   - cannabinoids pharmacokinetics (absorption, metabolism, excretion)
   - route of administration (smoking vs. ingestion)
2. Driving Impairment
   - correlation between THC (and metabolite) content and driving impairment
   - technologies for roadside drug detection
   - Legislative approaches for dealing with drug impaired driving
3. Roadside Screening
   - screening vs. evidential analysis
4. Legal challenges in DUID prosecution and possible solutions
5. Recommendations

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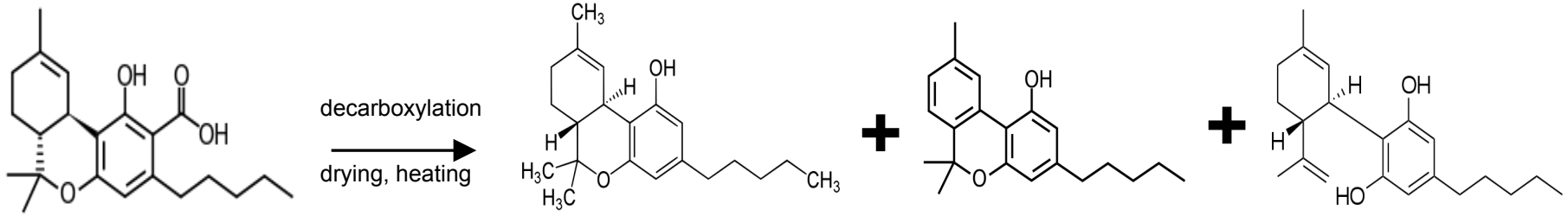
Marijuana – Chemistry and Composition



THC-Acid (living plant)
358.5 g/mol, **non-psychoactive**

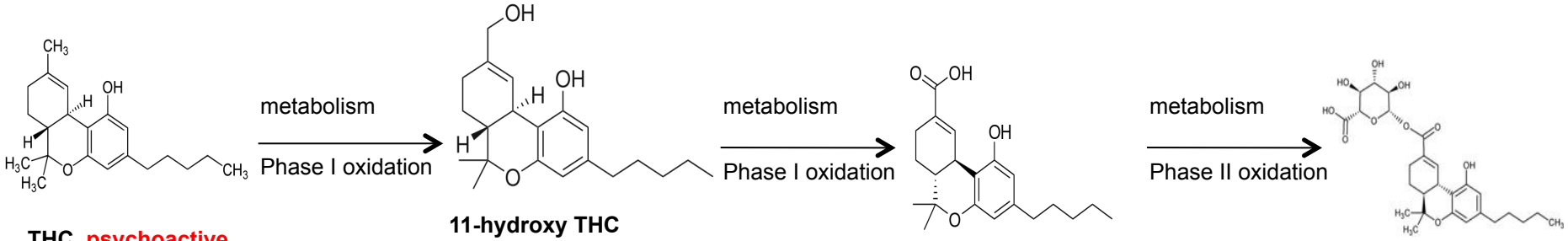
THC (Δ-9-tetrahydrocannabinol)
314.5 g/mol, **psychoactive**

CBN Cannabinol
310.4 g/mol
(~10% THC psychoactivity)

CBD Cannabidiol
314.4 g/mol **non-psychoactive**

- **Marijuana**: dried flowers and leaves of the ***Cannabis*** plant
- **Contains** over 420 chemical compounds
- including over 60 belonging to chemical group of **cannabinoids** with psychoactive (mood changing) properties
- **Cannabinoids:** primarily concentrated in flowers (less concentrated in leaves and stems)
- **Amount and mixtures of cannabinoids** vary with species of the plant, growing practices, timing of the harvest
- **Most psychoactive** component of marijuana is **THC** (delta-9-tetrahydrocannabinol)
- **THC in living plant** occurs in non-psychoactive form **THC-A(cid)** or tetrahydrocannabinolic acid

Marijuana – Metabolism



THC, **psychoactive**
314.5 g/mol

11-hydroxy THC
or 11-OH-THC psychoactive
330.5 g/mol,

11-nor-9-Carboxy-THC
or THC-COOH non-psychoactive
344.4 g/mol

11-norTHC-9-carboxylic acid glucuronide
or THC-COO-glu
520.6 g/mol, **non-psychoactive**

SUMMARY

THC → 11-OH-THC → THC-COOH → THC-COO-glu

psychoactive **psychoactive** **non-psychoactive** **non-psychoactive**

Physical

- Pronounced body sway
- Eyelid and body tremors
- Slow, deliberate speech
- Dilated pupils
- Watery, red eyes
- Increased Blood Pressure (new users)
- Increased pulse rate

Psychophysical

- Relaxed inhibitions
- Sharpened sense of humor
- Difficulty with concentration
- Disorientation
- Short-term memory problems
- Fatigue, lethargic
- Altered time and space perception

THC level in blood or saliva not indicative of what's in the brain

Marijuana – Psychoactive Symptoms & Route of Administration

Marijuana administration

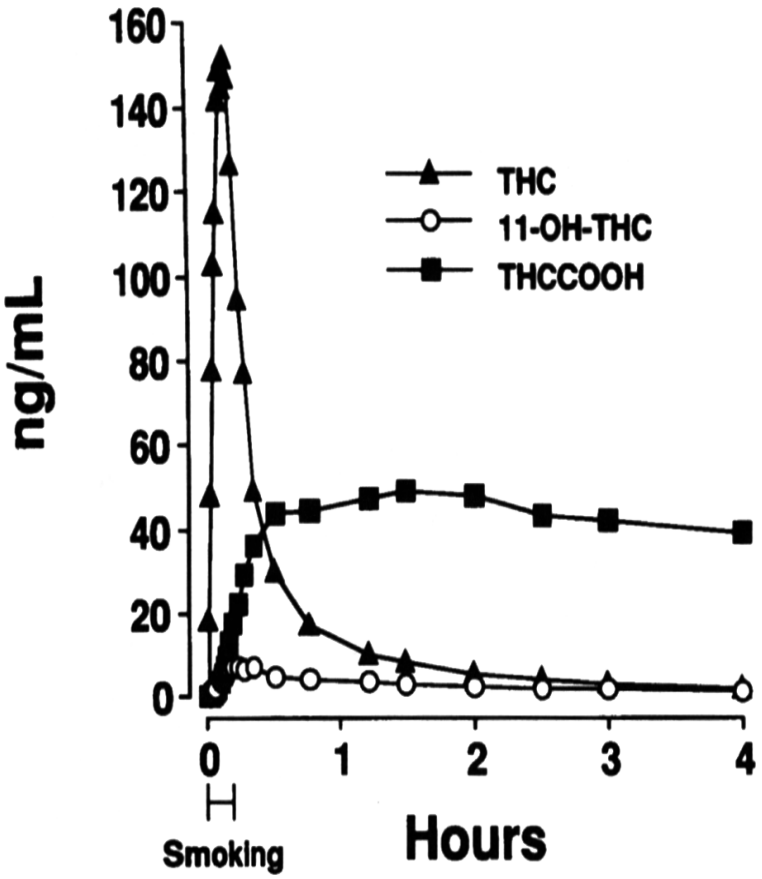
Smoking

Vaping

Ingestion

Most efficient drug delivery by smoking or vaping – affects CNS within seconds

Marijuana – Pharmacokinetics of cannabinoids – smoking – blood profiles

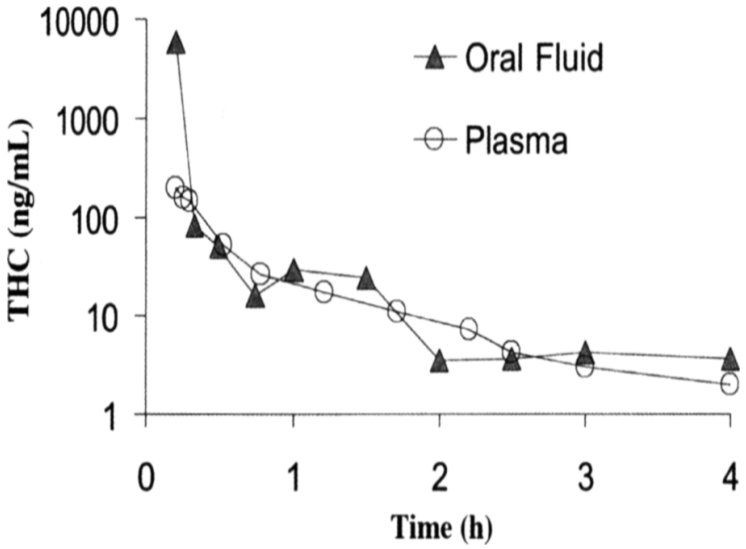


Mean **plasma** levels of THC, 11-OH-THC, and THCCOOH during and after smoking a single 3.55% THC marijuana cigarette (M. Huestis et al., J. Analytical Toxicology, Vol. 16, September/ October 1992.

- Peak THC level in blood ~3x greater than THC-COOH and ~20 time greater than 11-OH-THC
- Time-to-peak concentrations very rapid for THC and 11-OH-THC (after first puff) with short time courses of detection
- THC-COOH reaches plateau after ~1 hour and slowly declines over the period of ~160 hrs (at cut-off 0.5 ng/mL)
- Wide inter-individual variations in THC level despite controlled smoking protocol and dosing

Marijuana – Pharmacokinetics of cannabinoids – smoking – blood/saliva ratio

Controlled laboratory conditions:

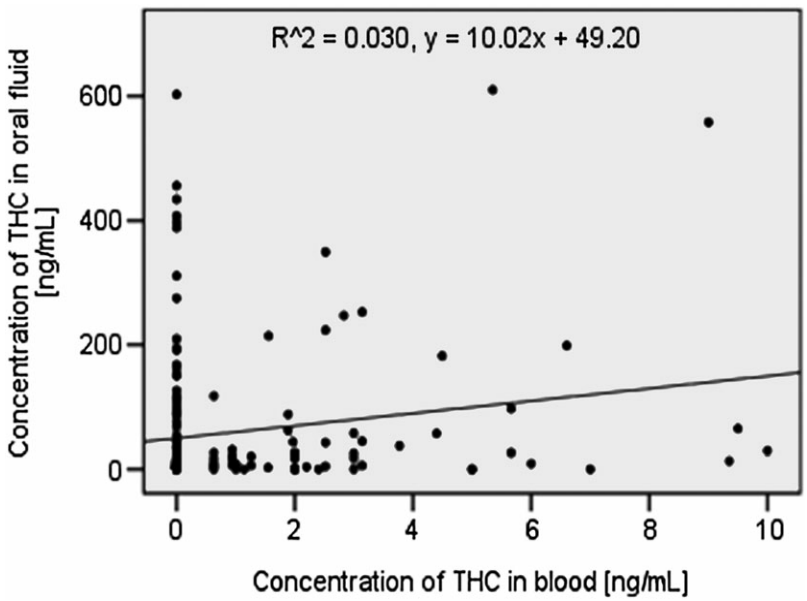


Simultaneous measurement of THC in oral fluid and plasma by GC-MS analysis (cutoff concentrations = 0.5 ng/mL) in a human subject over 4 h following smoking of a single cannabis cigarette (3.55%), Huestis & Cone, J. Analytical Toxicology, Vol. 28, September 2004

- Good correlation between THC content in blood and oral fluid in clinical, controlled setting due to transmucosal absorption of THC into blood
- Very high initial THC concentration in oral fluid caused by contamination of oral fluid during smoking and dissipated within ~30 min after smoking
- THC-COOH concentration in saliva ~1000 x lower than THC from THC metabolism

Marijuana – Pharmacokinetics of cannabinoids – smoking – blood/saliva ratio

Roadside test:



The oral fluid vs. whole blood concentration scatter plot for cannabis (delta-tetrahydrocannabinol, THC, N=173),

Langel et al, Drug Testing & Anal., 6(2014)461

- High variability of THC_{OF}/THC_{blood} in real roadside settings while both samples taken simultaneously caused by:
  - unknown dosage
  - time frame between consumption and sampling
  - oral contamination after smoking
  - THC removal by eating, drinking, saliva swallowing
- Physiological causes of THC_{OF}/THC_{blood} variablity saliva pH, drug molecular weight, drug pK_a, lipid solubility, saliva flow rate, elimination kinetics

Recreational

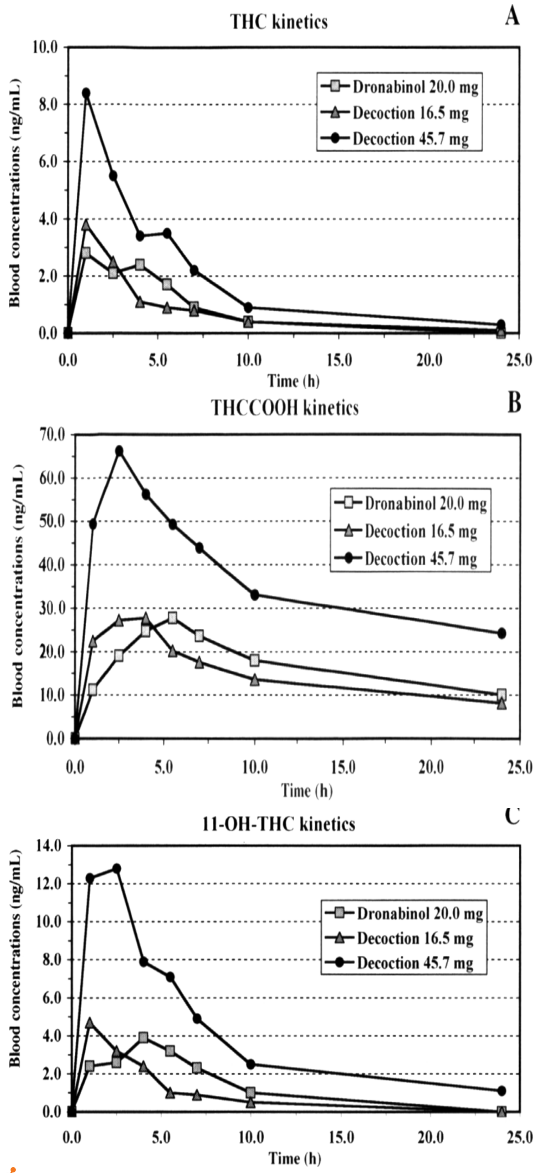
- cookies, gummies, cakes, hard candies, chocolate bars and more
- high potency extract-based concentrates (oil, “wax”, “shatter”- 80-90% THC) leads to over-intoxication
- Cannabis decoction obtained from hemp milk – liquid

Medical

- Marinol & Syndros contains dronabinol (synthetic THC)
- Cesamet contains nabilone (synthetic similar to THC)
- Sativex® (plant-derived, 50% THC & 50% CBD) used as sublingual spray
- Epidiolex (plant-derived CBD) – in clinical trial phase for pediatric epilepsy

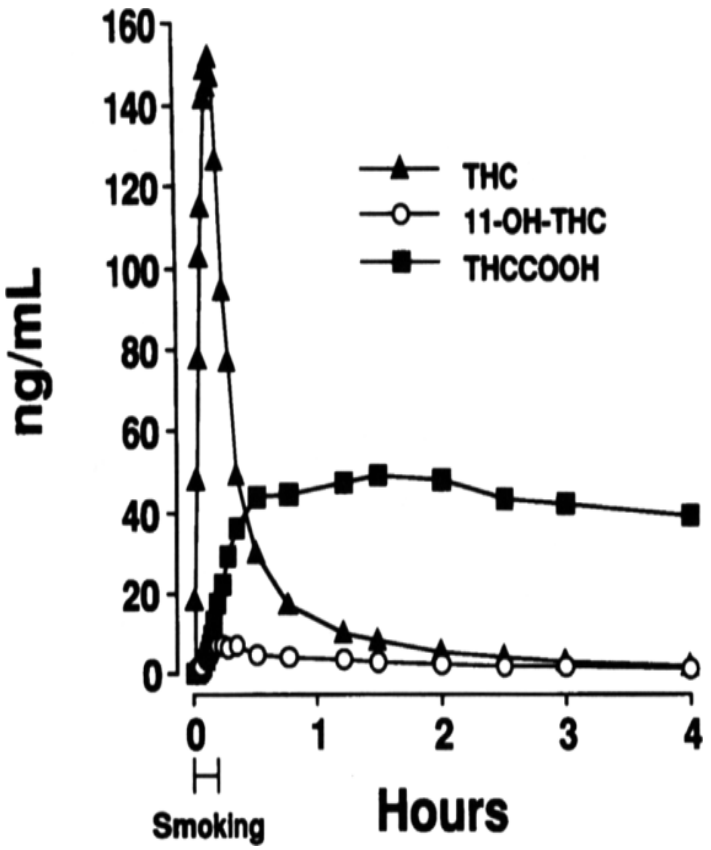
Marijuana – Pharmacokinetics of cannabinoids – smoked vs. edibles effects – blood profiles

Edible



Whole blood levels of mean THC (A), THCCOOH (B) and11-OH-THC (C) for 8 subjects, Ménétrey et al., J. Anal. Toxicology, 29(2005)327-338

Smoked



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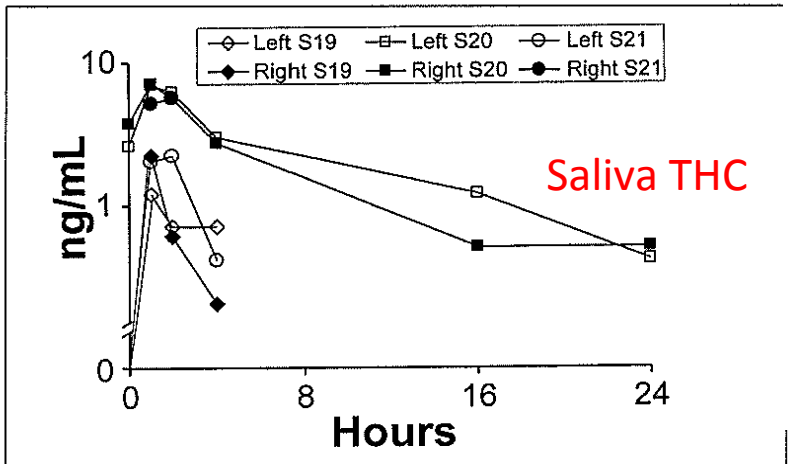
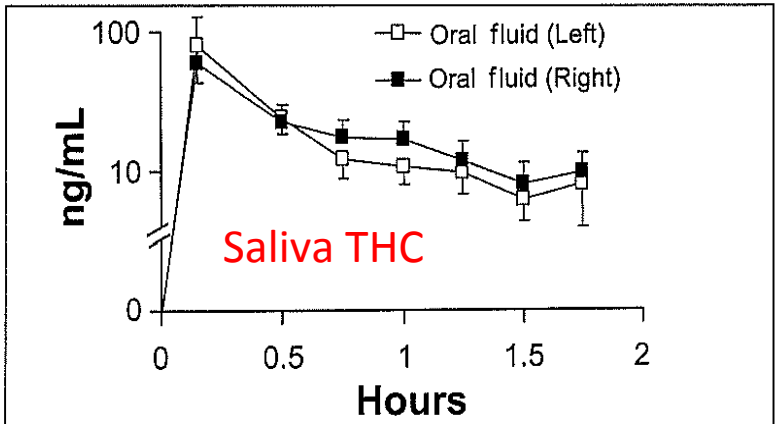
Marijuana – Pharmacokinetics of cannabinoids – smoked vs. edibles effects – saliva

Ingested ~ 25 mg



Smoked ~ 25 mg



Niedbala et al., J. Anal. Toxicology, 25(2001)289-303

THC concentrations in saliva after edibles are ~10x lower vs. smoking

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Marijuana – Correlation between THC content and driving impairment

Alcohol impairment – good correlation between BAC and impairment, BAC can be back-extrapolated, simple metabolism

THC impairment - no simple and direct correlation between THC concentration in blood and impairment

Lack of correlation between THC concentration and impairment due to:

- THC lipid solubility and thus its retention
- various individual metabolic profile
- administration frequency (chronic vs. casual users)
- driving experience
- health, age and other physiological factors
- THC concentration cannot be back-extrapolated due to unknown intake time, method of administration, inter-subject variability in metabolic rate
- little evidence of relation between crash risk and THC concentration

Marijuana – Correlation between THC content and driving impairment

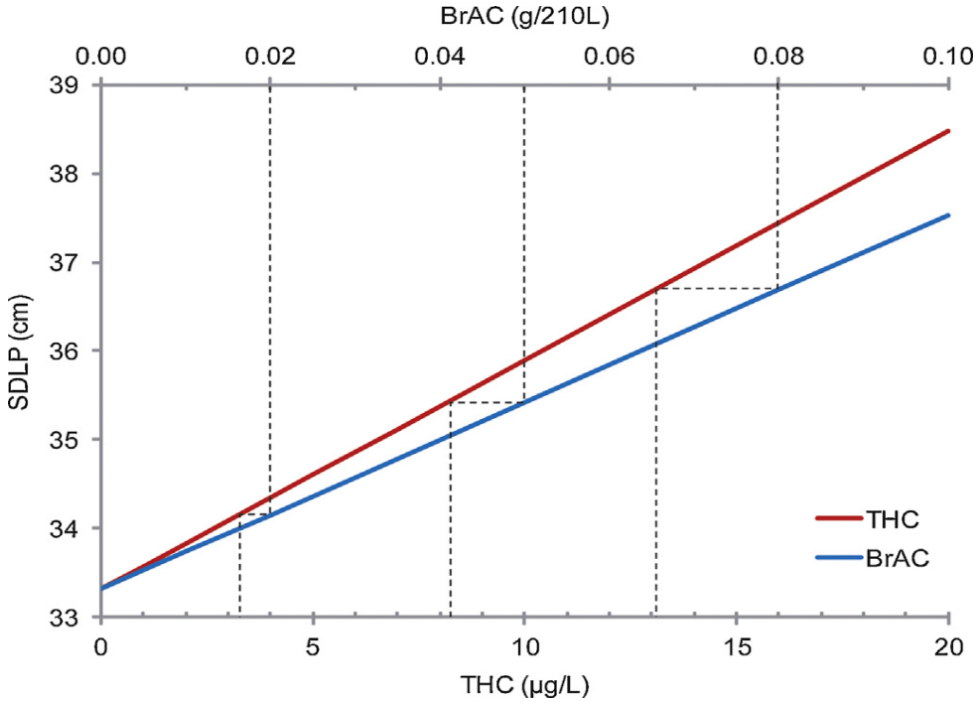
Effect of Cannabis on driving:

- Decision-making
- Divided attention
- Visual search
- Focus, concentration
- Reaction time
- Road tracking, vehicle control (e.g. SDLP)

SDLP – clinically controlled studies with simulator - marijuana vs. alcohol:

SDLP for alcohol vs. cannabis:
• BAC=50 equivalent to 8.2 ng/mL THC
• BAC=80 equivalent to 13.1 mg/mL THC

Hartman et al., Drug & Alcohol Dependence, 154(2015)25-37



Effect of drugs on driving performance – methodologies:

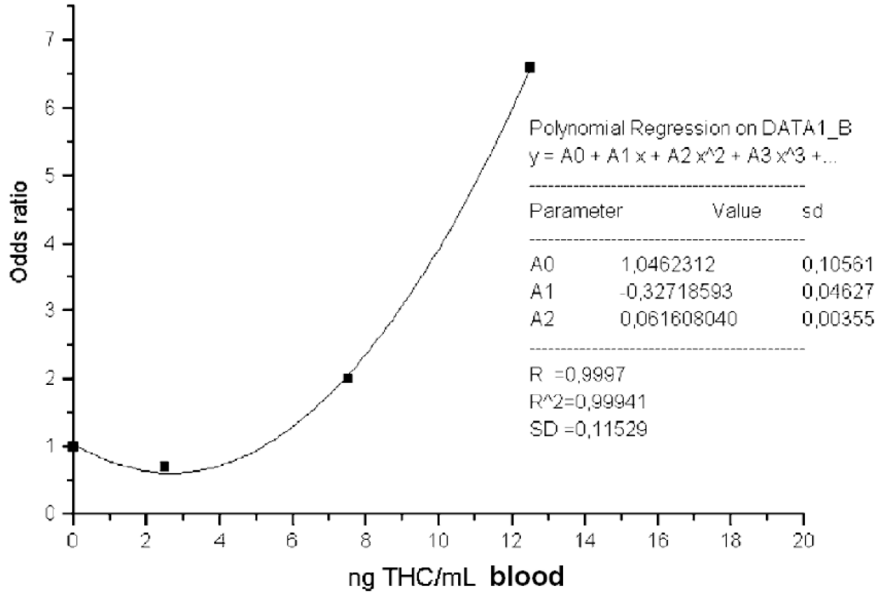
- Epidemiological studies: drug incidence in fatal and non-fatal accidents, causal drugs effects, culpability & responsibility analyses
- Performance impairment studies: effect of drugs on cognitive and/or psychomotor tasks
- Driving simulator and open road driving studies: effects of drugs in situations closely resembling real driving

Marijuana – Correlation between THC content and driving impairment

Summary of experimental and epidemiological studies:

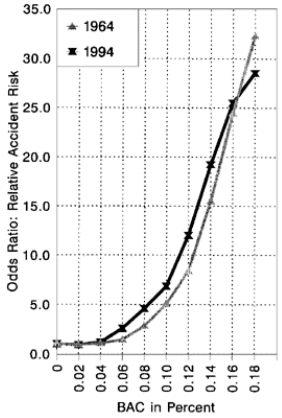
- Statistical association between traffic crashes and risk factor after drug consumption expressed as “odds ratio” (OR)
- OR>1 – increased accident risk
- OR=1 – control group
- Blood THC=6-8 ng/mL equivalent to OR=1.5 – 2 or BAC~50

- flaw: most studies investigate association between crash and traces of cannabinoids instead of crash risk vs. acute intoxication
- impairment expected to rise with dose but is also dependent on tolerance, driving experience and “baseline” THC level for chronic users



Grotenhermen et al., Addiction, 102(2007)1910

Grand Rapids Study for alcohol



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Marijuana – Correlation between THC content and driving impairment

Fundamental Challenges:

- THC presence vs. impairment – no correlation
- Establishing *per se* THC limit similarly as for alcohol and proof of impairment has no scientific basis
- Delays between roadside screening test and confirmatory blood testing may miss the impaired drivers due to fast THC decay below cut-off level, particularly for casual users
- Habitual users have elevated THC level and likely above typical *per se* levels and being charged even though may not be impaired
- Necessity of science-based performance and driving ability measures

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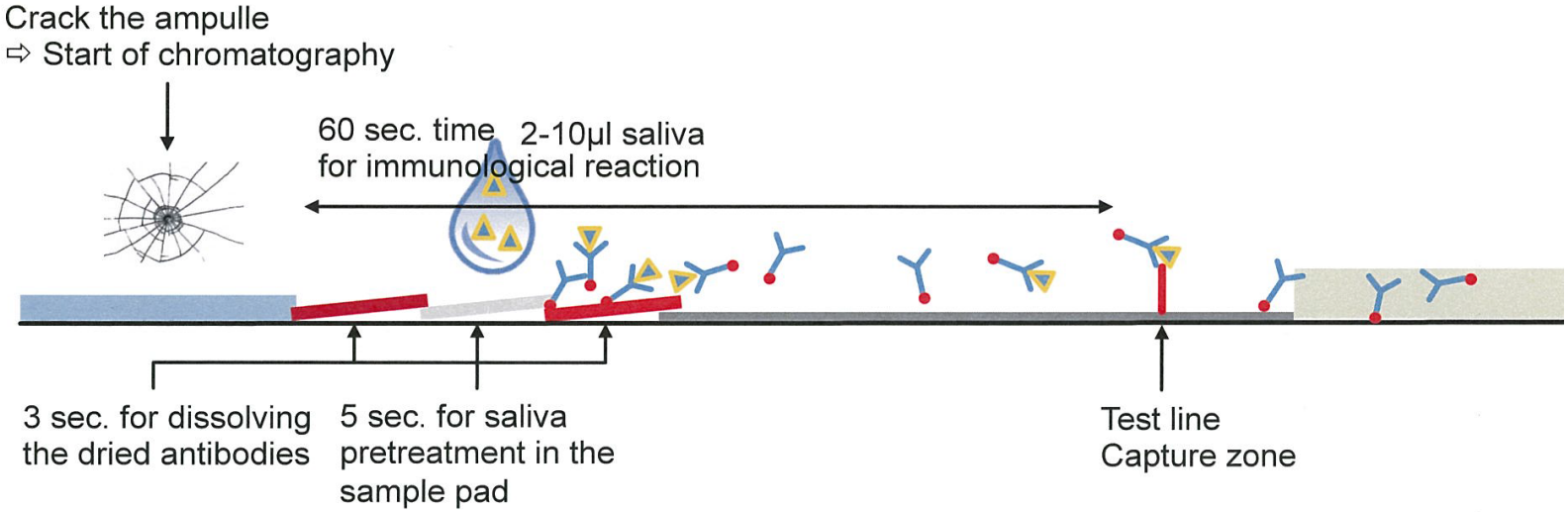
Screening by lateral flow immunoassay:

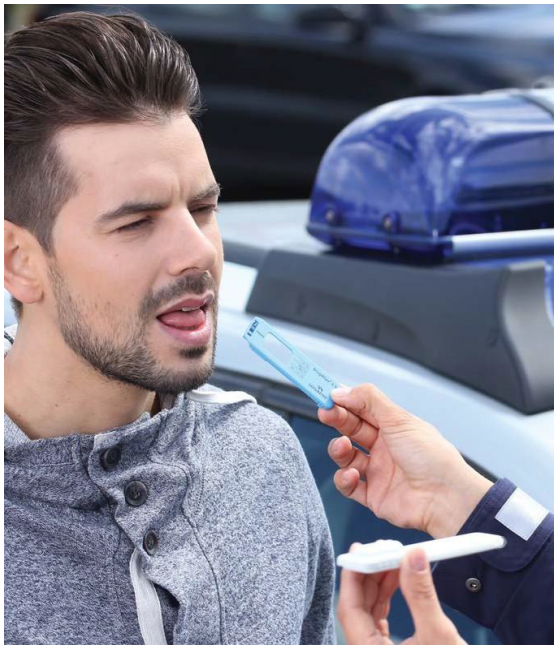
- Saliva collection followed by lateral flow immunoassay technique
- Extraction with buffer and deposition on cellulose test strip containing antibodies
- Sample fluid moves by capillary action to colorimetric marker conjugated with antibodies



- Fast, noninvasive, saliva multiple sampling
- Good indication of recent use (2 to 4 hours)
- Good correlation of THC concentration with blood
- Primary THC deposition in oral mucosa followed by transmucosal absorption into blood

Recent devices (DrugWipe®, Securetec)

- 95-97% in sensitivity, specificity & accuracy
- 5 ng/mL detection limit for THC
- 5 minute testing time for THC



Marijuana in breath

- Principle: breath contains bio-aerozol drug micro-particles measurable by GC/MS methodology in picogram level
- Drug can be inhaled or administered orally
- Several groups are working on “marijuana breathalyzer” for drug screening purpose, results are inconclusive or not available
- Detection principle: Ion Mobility Spectrometry (IMS), fluorimetry or polymer resistive sensors
- Designed for detection of very recent marijuana use
- Limitations: low detection limit and potentially low specificity

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Marijuana – Legislative approaches to impaired driving challenges

Regulatory options vary dramatically in various countries:

- Zero tolerance – driver prosecuted for a minimum detectable level of drug or metabolite in the body fluids

- Per se limit - driver prosecuted for having a level of drug at or above a preset limit in body fluids (e.g. 5 mg/mL THC). No impairment need be shown

- Hybrid system - driver prosecuted if there are measurable signs of impairment and minimum detectable level of drug in body fluids

- Two-tier penalty - driver prosecuted with lower (non-criminal) offence if there is a minimum detectable level of drug in the body fluids or is prosecuted with an impairing driving offence if there is a measurable signs of impairment

Marijuana – Legislative approaches to impaired driving challenges

Zero Tolerance

- Present in countries / states where possession of marijuana is illegal – prohibitionist approach
- Not workable option in view of global trend in cannabis decriminalization and legalization
- Incrimination of drivers whose bodily fluid contain any amount of drug or metabolite and not being impaired (e.g. chronic users)
- Risk of convict drivers with heavy passive exposure to marijuana smoke in closed area (e.g. car cabin)

Per se Limits

- Promoted by strong advocacy groups in developed countries who are willing to provide law enforcement with a number in exchange for legalization and treating cannabis like alcohol (supported by voters in Montana, Pennsylvania, Washington, Colorado)
- Typical per se limit of THC in blood varies between 1 and 5 ng/mL depending on country / state
- There is no scientific evidence of relationship between THC concentration in blood and degree of impairment (as for alcohol) or scientifically proven connection between THC psychoactive effect to its level in bodily fluids

Hybrid

- Hybrid system – likely suitable in legislations with decriminalized marijuana possession / use
- Two-tier penalty system – likely suitable in legislations with legal access to recreational and/or medical marijuana
- Based on complex THC metabolism including drug tolerance and individual metabolic profile criminal charges should be imposed on drivers who are measurably impaired but not having certain level of drug in the body fluids

Law Enforcement – General Facts

- Prosecution of DUID offence requires unequivocal evidence of driver impairment
- Poor understanding of substance use vs. driving under influence and impairment
- Train law enforcement officers on the signs and symptoms of impairment and reinforce existing training for drug impaired drivers for nearly every police officer
- Roadside saliva test combined with testimony of arresting officer may not be sufficient for prosecution
- Evidential chemical blood test flawed with significant delay between roadside check and sample collection:
  - no THC detection due to fast THC metabolism, particularly occasional users
  - no THC detection (even by roadside screening) while still impaired by the THC presence in brain

Roadside drug screening vs. evidential analysis

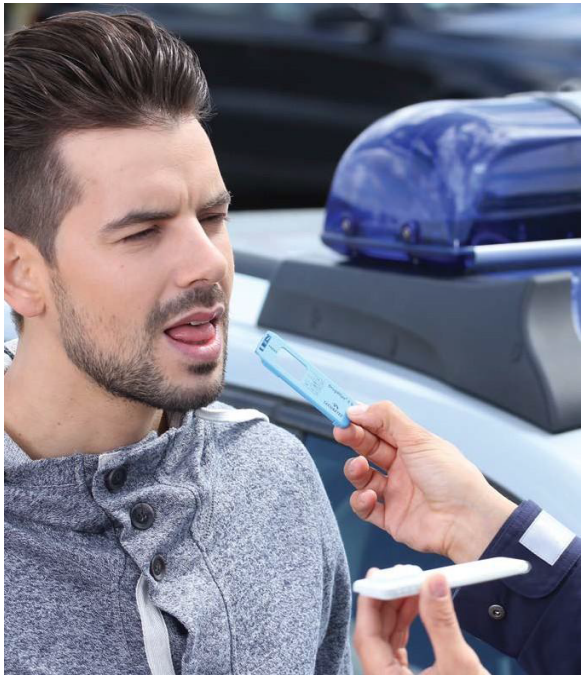
Steps:

1. Observed driving behavior: speeding, unable to maintain lane position, ran red light or stop sign, unsafe lane change, going to slow, collision – obvious initial observation
2. Physical indicators: green tongue, dilated pupils, red eyes – obvious initial observation
3. Standard Field Sobriety Test (SFST) – 2 to 5 cues
4. Drug screening test by existing oral fluid drug screening devices
5. Confirmatory / evidential analysis - collection body fluid (blood, saliva, urine) – lab analysis

Roadside drug screening vs. evidential analysis

Step 4: Drug Screening Test

- Good correlation in the concentration of THC in oral fluid and blood
- Positive test - strong indication of marijuana use over the last ~2 hours



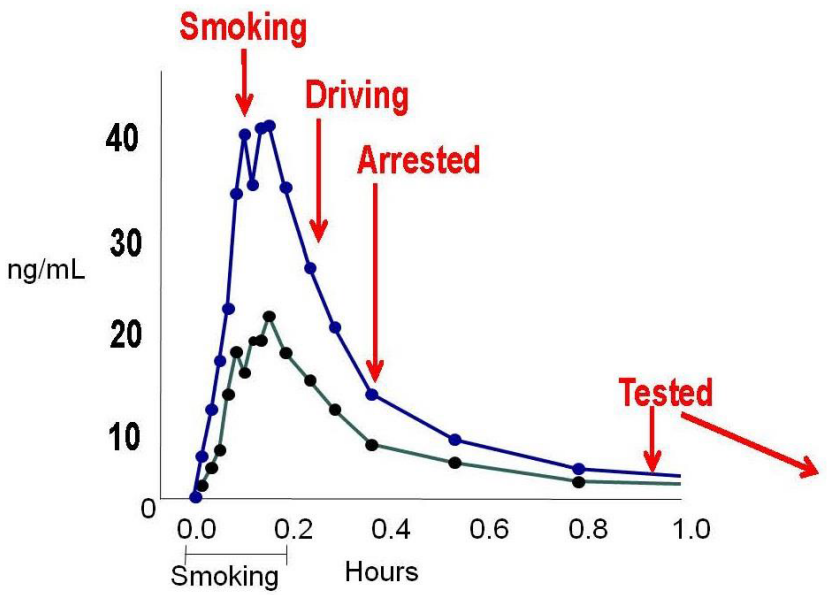
- State-of art drug screening devices based on classical immunoassay capable to detect THC with high sensitivity / accuracy /specificity in 5 minutes and low detection limit 5 ng/mL
- Methodology adopted successfully in Australia, Europe, Scandinavia and UK for mandatory roadside drug & alcohol screening
- High deterrence effect in view of growing worldwide trend in marijuana legalization

Roadside drug screening vs. evidential analysis

Step 5: Confirmatory / Evidential Analysis

- Confirmatory test required in case of failed SFST and / or oral fluid screening test
- Blood test always significant delayed (up to 1-2 hours) since sampling performed in medical facility
- Oral fluid test for evidential purpose collected at the time of roadside check is fast and convenient methodology for potential prosecution

- Challenges:
  - sample storage and transportation
  - sufficient number of certified / qualified labs



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Marijuana – Legal challenges in DUID prosecution and potential solutions

Main goal: <u>Presenting evidence of impairment</u> regardless of the results of roadside drug screening test

No devices can measure drug impairment at roadside!!

Challenges of current approaches:

- chronic users including medical marijuana users may have residual but measurable THC in the body without showing obvious signs of impairment
- occasional & "first time" users (adolescents) may show impairment with little dose not measurable by roadside screening devices
- bias related to "evidential" blood analysis due to delay in sample collection – current procedure

In view of lack scientifically proven correlation between THC level and impairment:

The most reliable & efficient approach for identifying THC impaired drivers:

1. Oral fluid screening test
2. Scores on SFST
3. Confirmatory test
   - If 1 and/or 2 fails:
   - Evidential / confirmatory test by collecting secondary oral fluid sample at the time of stop check followed by laboratory analysis

Marijuana – Legal challenges in DUID prosecution and potential solutions

Proposed legal code in Canada in view of cannabis legalization:

- Two-tier penalty:
  - driver prosecuted with lower (non-criminal) offence if there is a minimum detectable level of drug in the body fluids

  or

  - driver is prosecuted with an impairing driving offence if there is a measurable signs of impairment

- If prosecuted: same penalties as driving under influence of alcohol including administrative and criminal suspension

- Zero tolerance policy for THC for young drivers (under age 21)

- No legal THC limit recommended because:
  - No scientific basis similarly as for alcohol
  - Growing problem with poly drug use including alcohol & Rx medicines – need to prove impairment instead of drug presence

- Distinguishing policies on medical marijuana from social policies related to decriminalization / legalization

- Need to train police officers to identify drug impairment using SFST – DRE are excellent but not required

- Aggressive public awareness campaign with strong message: drugs impair driving skills regardless of their legal status and purpose of use (medical vs. recreational)

Marijuana – Conclusions

- Marijuana metabolism different from alcohol
- Smoking vs. edibles – different metabolism and detectability window
- No direct correlation between THC content in the body and impairment
- No scientific basis for *per se* THC limit in blood / saliva
- Hybrid- or Two-tier penalty system suitable for countries with decriminalized / legalized marijuana use
- Current roadside screening devices – a good indication of recent cannabis use
- Delay in "evidential" blood sampling has a little value due to fast THC metabolism

Most efficient methodology to identify and fine and / or prosecute drug impaired drivers:

- **Drug screening test – oral fluid**
- **SFST by any police officer**
- **Evidential saliva (or blood) collection at the time of stop check**

Marijuana – Conclusions

Thank you!

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Q & A

Matt Goledzinowski
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