Standards Australia Forum

Drugs in Oral Fluid
AS4760

Olaf H. Drummer

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AS 4760:2006

- The increasing awareness and use of oral fluid for drug detection led to the initiation of a committee to produce an Australian Standard in 2005
  - “procedures for the collection, detection and quantitation of drugs in oral fluid”
- Recognition that oral fluid drug testing would not be a replacement for urine testing (AS4308), rather
  - Enable detection of drugs used more recently
  - When a person is more likely to be impaired and unsafe at a workplace, or even driving a motorised vehicle
Limiting issues considered by first committee

- Recognition that technology for collection of oral fluid and devices used to screen for drugs still evolving
  - Did not have enough evidence to set cut-offs
  - Limited number of drugs being targeted
  - No POCT able to meet these targets at time
  - Required users to justify the approach for fitness for purpose if deviated away from targets

- Need to ensure that on-site testing did not have significantly less standards and controls than laboratory based initial testing
  - Hence requirement to have quality controls
Applications of oral fluid testing

- Australia has seen a huge increase in the use of this fluid for drug detection for illicit drugs
  - All States and Territories screen oral fluid at roadside for methamphetamine, MDMA and THC
    - Over 100,000 tests per year
    - Positive rate 2-4% drugs and 1% alcohol
  - In workplaces, such as aviation, mining, petrochemical and logistic industries (e.g., major trucking firms)
    - Many unions prefer oral fluid to urine testing to focus on safety rather than what worker does in their private time
Europe and USA

- Oral fluid testing is widely used in Europe now
  - Primarily for traffic safety applications as in Australia
  - Cut-offs used for THC
    - Belgium and France 15 ng/mL
- In the UK testing in oral fluid is used, but targeted to likely drug users in custody
  - 280,000 tests – 26% THC, 30% opiates, 21% cocaine
- In the USA Alere toxicology 600,000 tests in oral fluid in 2012/13
  - 7.4% THC, 6.3% amphetamines, 4.2% opiates
What’s New in Oral Fluid Drug Testing?

- Increased application
  - Particularly by workplaces only look for drugs used more recently when impairment is most likely
  - but also by police – large increases in roadside testing
- More information on the disposition of drugs in OF
  - Particularly for illicits
  - Use in Europe (DRUID project etc) and USA
- On-site devices common
  - several now available and many more coming
- Laboratory confirmation available by many labs
Largest controversy is cannabis

- Most frequently used illicit
- Rapid distribution but long terminal elimination half-life – days
- Measureable intoxication usually only lasts for hours, not days
- Many unions arguing for detection when a worker is likely to be impaired rather than detecting previous (safe!) use
- High dose chronic users have higher residual levels and will also show longer period of measureable impairment
Prolonged Excretion in Chronic Users

Box plots of plasma THC during week-long abstinence

○ = >1.5 x IQR
● = > 3 x IQR

Note: plasma THC is almost twice blood concentration

Karshner et al, JAT 33 (2009) 469-77

1 ng/mL blood
Controlled pharmacokinetic studies in OF

- There are not many studies that have examined OF concentrations under controlled conditions
  - see Drummer et al FSI 150 (2005) 133-42
    - Mainly for cannabis and methamphetamine
- How can we define cut-off concentrations in oral fluid that have any meaning?
  - Essentially using this fluid to show if “recent” drug use has occurred
Regular vs Occasional Smokers

Anizan et al ABC 405 (2013) 8451

- Subjects smoked 6.8% THC joint – controlled clinic
  - 10 occasional smokers (<twice weekly)
  - 11 frequent smokers (4 or more weekly, range 21-147)

- Detection times
  - Using 1 ng/mL cut-off THC
    - Occasional smokers ~24 h
    - Frequent smokers >30 h
  - Using 10 ng/mL cut-off
    - Both about 6 hours
### Oral fluid/blood ratio (dependent on various factors)

<table>
<thead>
<tr>
<th>Substance</th>
<th>n</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>158</td>
<td>16</td>
</tr>
<tr>
<td>Cocaine</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Codeine</td>
<td>26</td>
<td>6.8</td>
</tr>
<tr>
<td>MDMA</td>
<td>54</td>
<td>3.3</td>
</tr>
<tr>
<td>Morphine</td>
<td>17</td>
<td>2.7</td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>65</td>
<td>0.02</td>
</tr>
<tr>
<td>THC</td>
<td>323</td>
<td>16-20</td>
</tr>
</tbody>
</table>

For THC 1 ng/mL blood ≈ 16-20 ng/mL oral fluid

So 10 ng/mL oral fluid is actually (on average) < 1 ng/mL
Table 1

<table>
<thead>
<tr>
<th>Time relative to smoking (min)</th>
<th>Serum (GC–MS)</th>
<th>Oral fluid (GC–MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>THC 500</td>
<td>THC 250</td>
</tr>
<tr>
<td></td>
<td>THC</td>
<td>OH–THC</td>
</tr>
<tr>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>120</td>
<td>5.9 (2.7)</td>
<td>2.2 (1.6)</td>
</tr>
<tr>
<td>180</td>
<td>3.0 (1.7)</td>
<td>1.4 (0.9)</td>
</tr>
<tr>
<td>240</td>
<td>1.8 (0.9)</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td>300</td>
<td>1.2 (0.8)</td>
<td>0.7 (0.5)</td>
</tr>
<tr>
<td>360</td>
<td>0.9 (0.5)</td>
<td>0.5 (0.4)</td>
</tr>
</tbody>
</table>

Ramaekers et al, 2006 [DAD, vol 85, p114]

4-6 h
Toennes et al, 2010 [JAT v34, p216]

- Standard cannabis joint smoked by volunteers under controlled conditions
  - 500 μg per kg body weight, 22-48 mg, Intercept collection device
- THC was detectable in all samples with medians in the last samples (8 h) of 6 and 11 ng/mL in occasional and chronic users
- Oral fluid-to-serum median ratio was 16 with no difference between chronic and occasional users
  - Ratio confirmed by Kauert et al JAT 31 (2005) 288
Correlation between oral fluid and blood concentrations

Vindenes et al, FSI 219 (2012) 165
Correlation between oral fluid and blood concentrations

Langel et al, DTA 2013
E-pub September 9
N=5

Huestis & Cone Ann NY Acad Sci. 2007; 1098:104
## Screening Cut-offs

<table>
<thead>
<tr>
<th></th>
<th>AS4760</th>
<th>SAMSHA</th>
<th>DRUID</th>
<th>Talloires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis (THC)</td>
<td>25</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MA/Amp</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Opiates ¹</td>
<td>50(10)</td>
<td>40(4)</td>
<td>20(5)</td>
<td>20(5)</td>
</tr>
</tbody>
</table>

¹ 6-acetylmorphine in brackets

**Belgium** use 25 ng/mL for THC screen and 15 for confirmation

**France** use 15 ng/mL THC to confirm
Recent or Past Use?

- Current target concentrations if applied as cut-offs are more useful to detect “recent” use when impairment is more likely
  - i.e. THC 10 ng/mL (confirmation)

- If we lower cut-offs to SAMSHA concentrations then oral fluid would become quite similar to urine to detect past use of drugs (usually within 2-3 days)
  - i.e. THC 2 ng/mL, but
  - POCT devices unlikely to be useful – oral fluids would have to be taken to laboratory for testing
Cut-offs for Selected Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>THC</th>
<th>Amp/MA</th>
<th>Opiates ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Stat</td>
<td>15</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>DrugWipe5</td>
<td>30</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>DrugTest 5000</td>
<td>20(5)</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>DDS</td>
<td>31</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>OrALert</td>
<td>100</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Oratect III</td>
<td>40</td>
<td>25</td>
<td>10</td>
</tr>
</tbody>
</table>

For most devices no clear information of performance at (and near) cut-off, hence may not necessarily represent concentrations that can be detected reliably

¹ morphine and codeine
Benzodiazepines

- Some cut-offs have been applied to this drug group and some devices have claimed detectability, but
  - Very low [OF] compared with blood/plasma (1/20th)
  - Large variation in potency of benzodiazepines
  - Almost no pharmacokinetic studies described – only 3 ever

- Smink (2008) BJCP 66;556
  - Oxazepam 15/30 mg p.o. to 8 volunteers, Cmax 13/24 ng/mL

- Link (2008) BJCP 66;473
  - Midazolam 7.5 mg p.o. to 8 volunteers, Cmax ~1ng/mL

- Samyn (2002) JAT 26;211
  - Flunitrazepam 1 mg p.o., Cmax < 1ng/mL
Benzodiazepines …

- Gjerde 2013 *Ther Drug Monit.* ePub Sep 20
  - Unlikely to have justifiable cut-offs for these drugs
    - Concentrations very low in oral fluid
    - ELISA cut-off typically 10 ng/mL
  - On-site devices struggle to detect these drugs at anything but very high concentrations

- Will have difficulty to distinguish prescribed use from non-prescribed use – if subject abusing drug
- Most benzodiazepine abusers also abuse illicit drugs
Other (New) Drugs

- There is a large influx of synthetic cannabinoids and designer stimulants
  - Not covered by AS4760 (or even AS4308)

- Standard immunoassay screening tests are unlikely to cover many of these, let alone laboratory based mass spectroscopic methods
  - Almost no information on oral fluid levels (or urine)

- Will be difficult to include specific examples in a revision
  - Perhaps some generic comment - ? Cut-offs ?
The Future

- There is no doubt (by me at least!) that drug testing in oral fluid has a future.
- Still confusion over differences between OF and urine testing:
  - OF is not a replacement for urine, rather may compliment urine or used primarily for detection of "recent' use.
- Nevertheless it is clear that a revision of the standard is needed 8 years later.
FACTA workshop

- Comments made through presentations and/or question time were included generically in this talk
- Membership, and later at AGM, supported:
  - Revision of AS4760 as soon as possible
  - FACTA establish an expert technical group to advise on drug detection in oral fluid, and if possible
  - Make this an advisory expert committee for a AS4760 committee revising the standard
  - A summary of this workshop has been prepared by me and was sent to registrants and members of FACTA
Most Important Changes That Could Relatively Easily be Achieved

1. Replacement of target concentrations with cut-offs
2. Revision of cut-off concentrations
3. Establishing specifications and verification of performance of on-site detection devices
   - Including recovery of drug from collectors
   - Set performance at (e.g.) 90% detectability at cut-off ± 50% with fortified oral fluid with parent drug (i.e., THC)
4. Use and type of quality controls
   - Make minor amendments – but shelf-life of controls limited, or
   - No longer require use of daily QCs at POCT if performance of device is known and validation performed
Cont...

5. Uncertainty issues in reporting levels since volume of oral fluid collected is not known accurately for collectors that dilute absorbed drug with diluent
   - Use dye in diluent to quantify dilution, or
   - Set cut-offs for diluted oral fluid and perhaps lower cut-offs

6. Reference sample
   - Now require authorisation by subject for testing of B sample

7. Revise requirements for mass spectrometry ID using tandem MS
   - Requirements recently established by toxicology Special Advisory group (forensic labs in A&NZ)
   - Use of many international published guidelines
Thank you Standards Australia for this forum and to attendees for listening

Any questions?