



SUMMARY OF PULSE TESTING STUDIES FOR FENTANYL IN OPIOIDS INITIAL TEST POSITIVE AND Δ 8-THC IN THCA INITIAL TEST POSITIVE SPECIMENS

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PULSE TESTING FOR OPIOIDS

Impact of proposed changes to morphine cutoff?

Is fentanyl a better marker than 6-AM for “Heroin”?



PROPOSED RULE FOR MORPHINE

CURRENT RULE

- *Morphine cutoff at 2,000 ng/mL*
- *Only reported positive by the MRO if $\geq 15,000$ ng/mL and no legit medical explanation*
(OR clinical evidence of illegal opioid use)

PROPOSED RULE [2022, Federal Register 87(67)20560-605]

- *Morphine cutoff at 4,000 ng/mL and no legit medical explanation*
- *Supported by evidence from studies of poppy seed ingestion*

WHY FENTANYL?

Impairing and public health threat

- Potent opioid
- Overdose deaths

Mixed into heroin supply

- Better marker for heroin use than 6-AM?

Technology is ready

- Immunoassays targeting fentanyl and/or norfentanyl
- Included in many panels for non-regulated testing



STUDY DESIGN

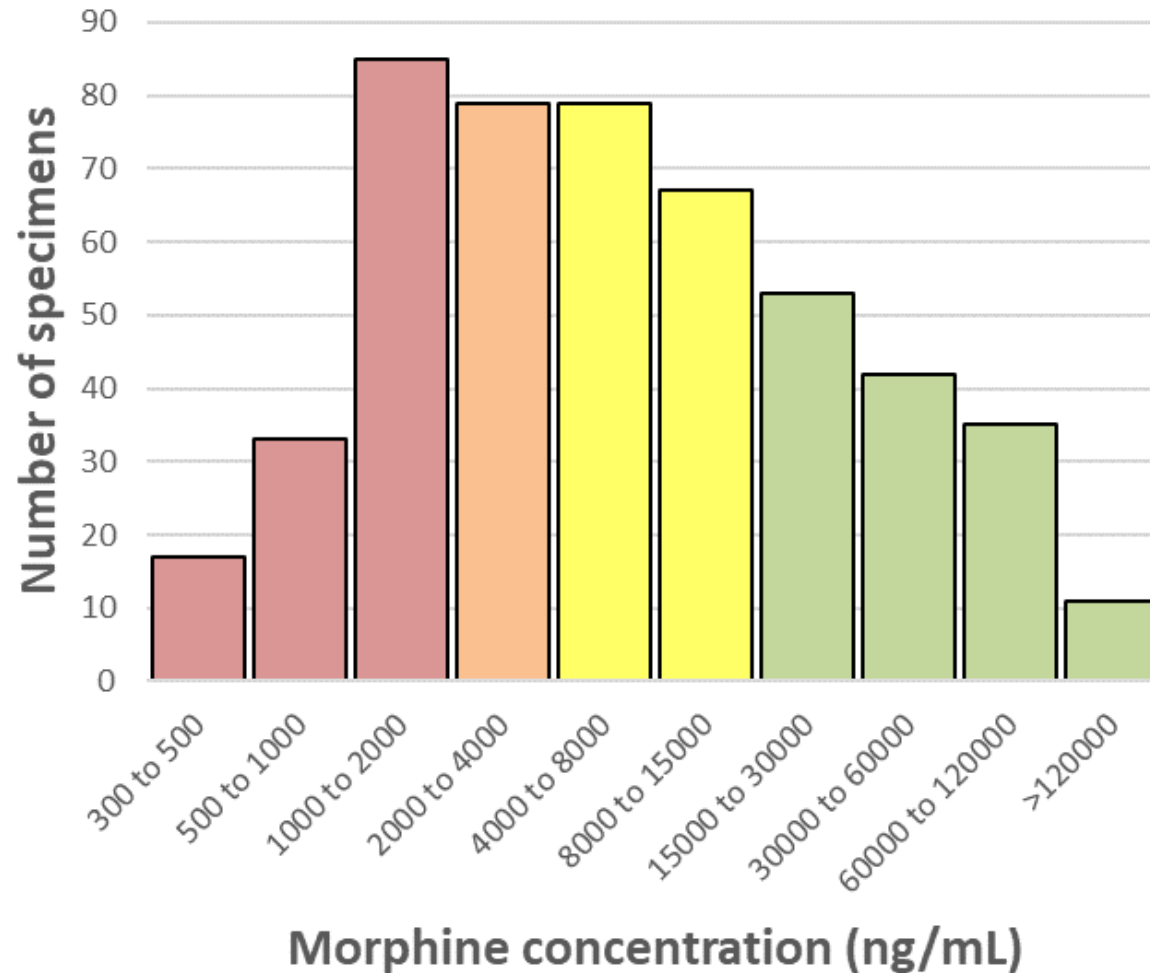
504 specimens initial test positive for morphine.

- Deidentified
- IA fentanyl (1 ng/mL)
- IA 6-AM (10 ng/mL)

LC-MS/MS assay confirmation

- Morphine 300 ng/mL
- Fentanyl/norfentanyl (1 ng/mL)
- 6-AM (10 ng/mL)

OBSERVED MORPHINE CONCENTRATIONS



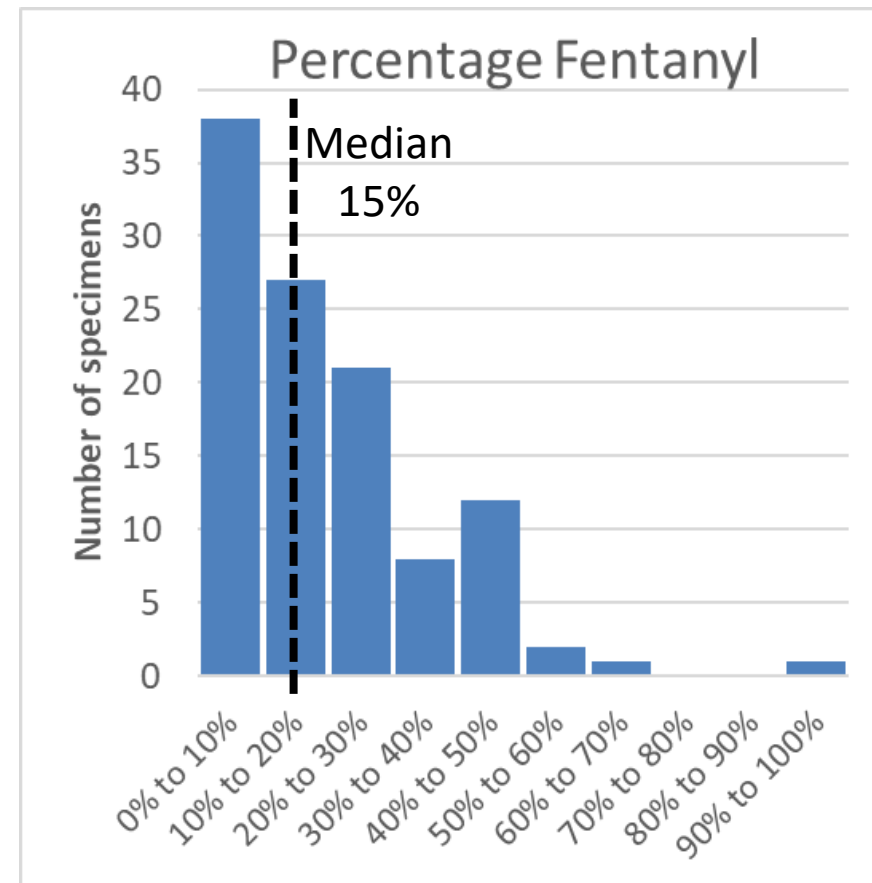
Morphine Range	Specimens N (%)
<2,000 ng/mL <i>Morphine negative by either rule</i>	135 (27%)
2,000-4,000 ng/mL <i>Positive by current rule if MRO obtains clinical evidence of drug abuse. Morphine negative by proposed rule.</i>	79 (16%)
4,000-15,000 ng/mL <i>Positive by current rule if MRO obtains clinical evidence of drug abuse. Morphine positive by proposed rule.</i>	146 (29%)
≥15,000 ng/mL <i>Morphine positive by either rule.</i>	141 (28%)

Assuming no clinical evidence and no legit medical explanations, proposed rule would double morphine positivity.

FENTANYL ANALYTES

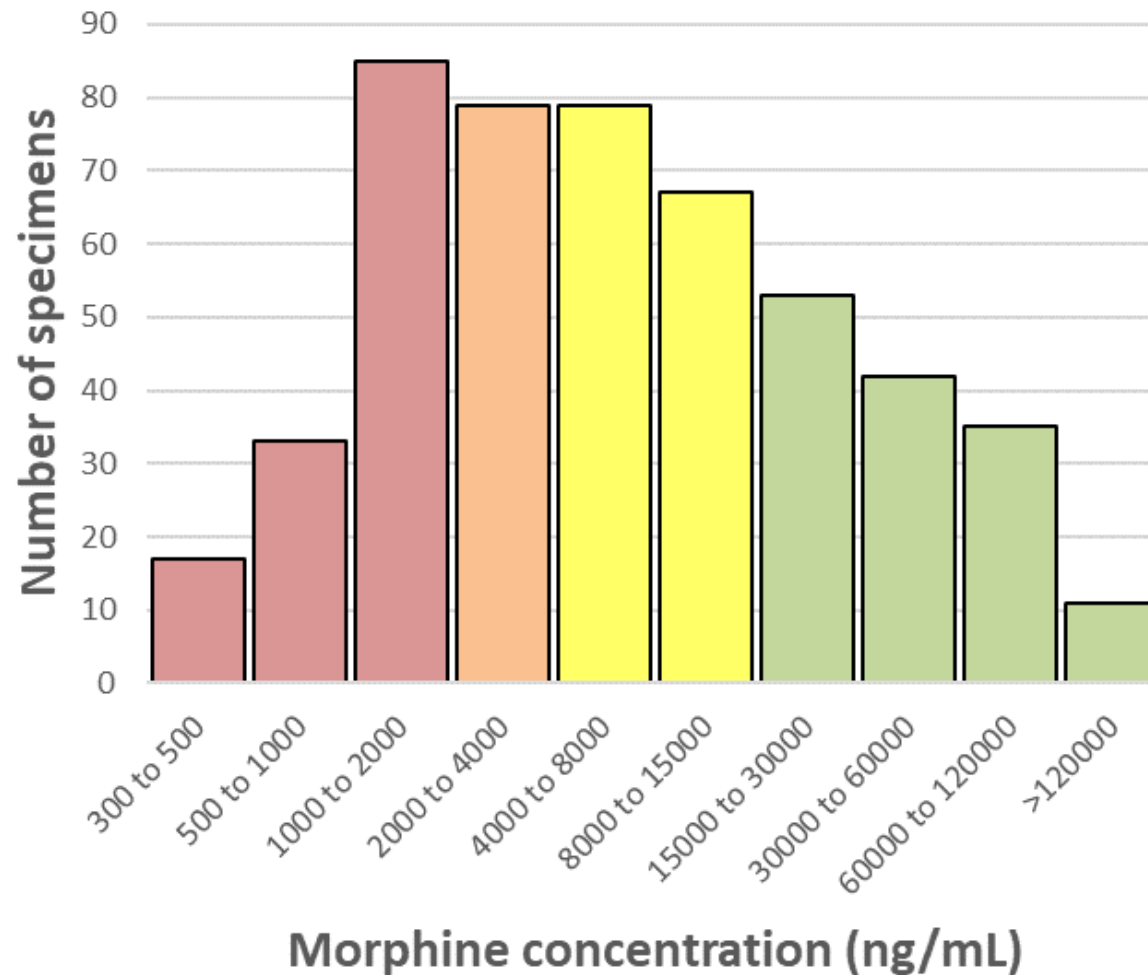
Norfentanyl is a major metabolite

4-ANPP and p-Fluorofentanyl are likely byproducts of manufacturing – higher levels expected in illicit fentanyl



Analyte conc. [ng/mL]	n (% pos)	10%	Q1	Median	Q3	90%	Max
Fentanyl	102 (93%)	1.1	4.8	160	940	2,300	7,000
Norfentanyl	110 (100%)	4.7	33	1,500	4,400	15,000	35,000
4-ANPP	67 (61%)	<1	<1	9.1	50	150	1,600
p-Fluorofentanyl	39 (35%)	<1	<1	<1	6.3	56	610

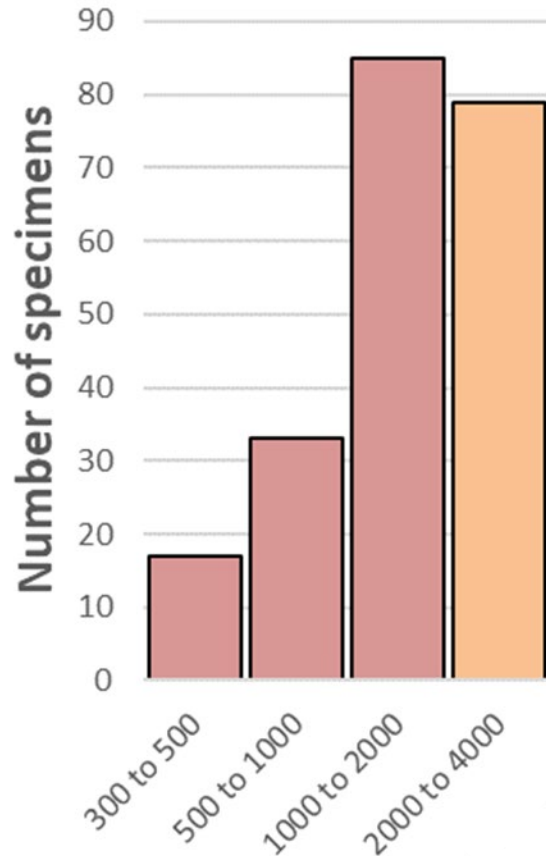
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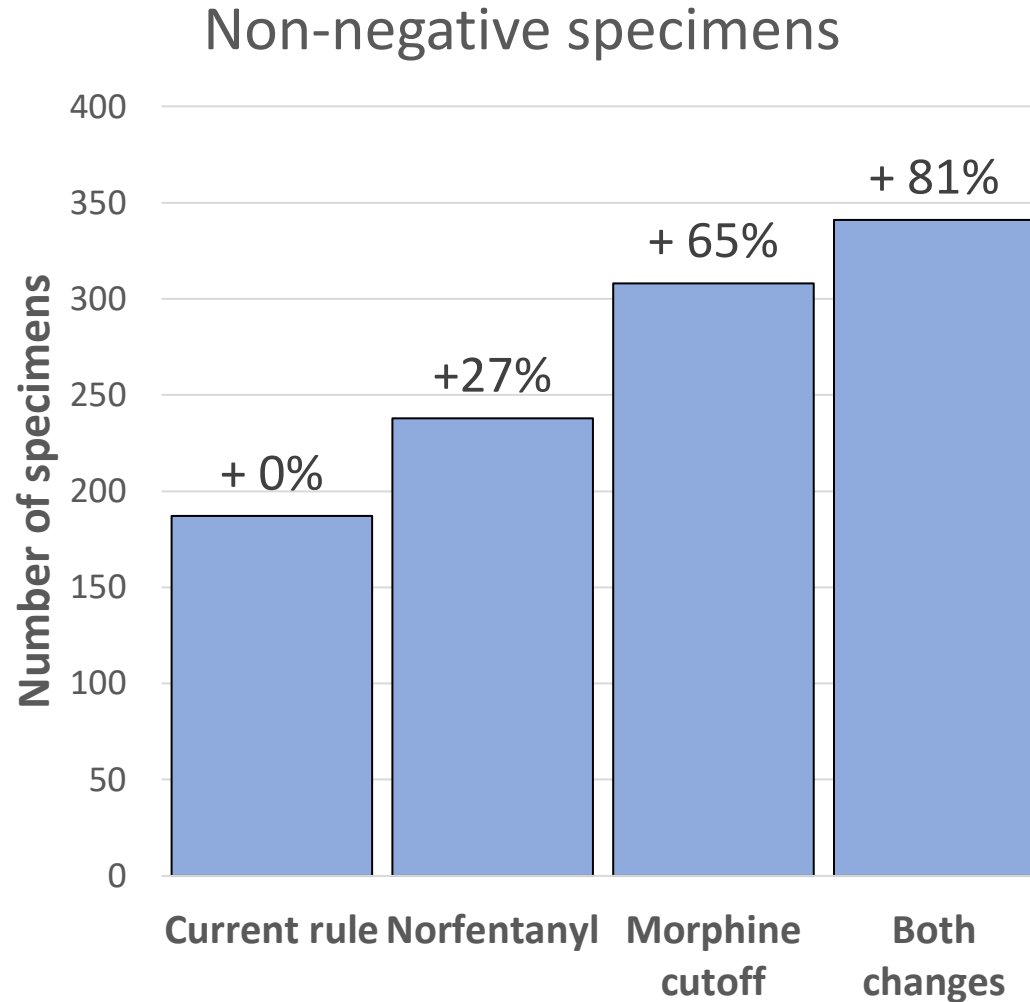
“HEROIN” USE



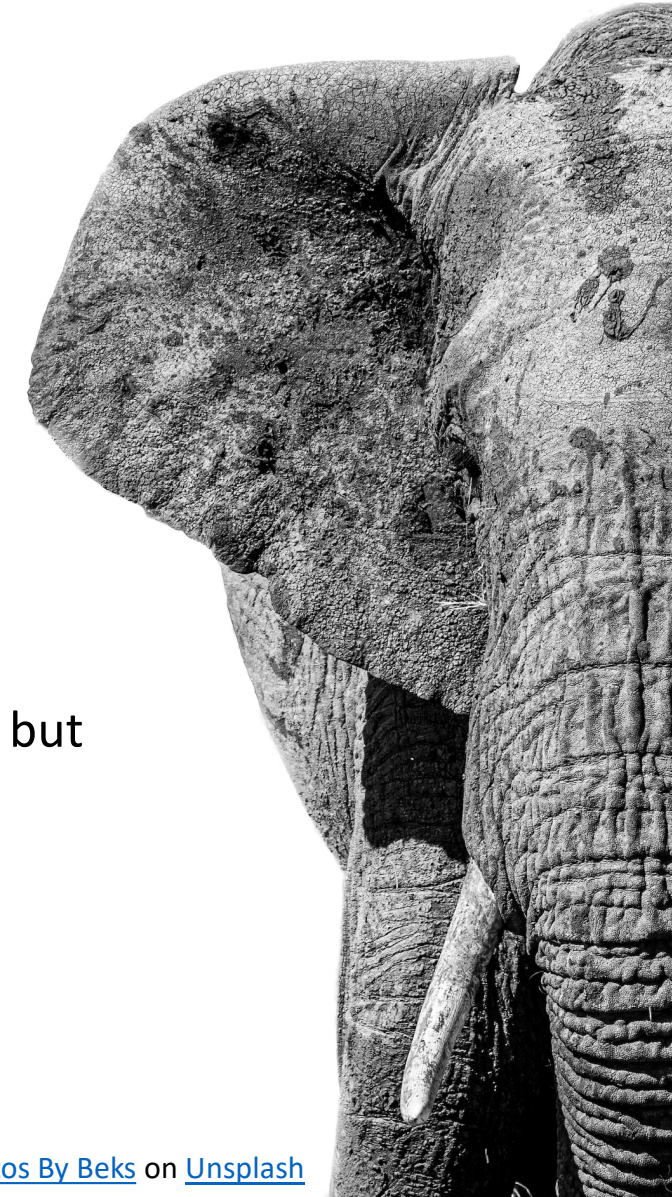
Rule	Specimens N (%)
ALL <4000 ng/mL MOR	214 (100%)
6-AM ONLY (10 ng/mL)	7 (3%)
NORFENTANYL ONLY (1 ng/mL)	33 (15%)
BOTH	14 (7%)
AT LEAST ONE	54 (25%)
<i>6-AM Total</i>	<i>21 (10%)</i>
<i>Norfentanyl Total</i>	<i>47 (22%)</i>

Fentanyl more prevalent than 6-acetylmorphine in morphine positive specimens.

EFFECTS OF DECISION RULES



Specimens with norfentanyl but without morphine are not included. Likely significant number.



DISTRIBUTION OF SPECIMENS

Morphine [ng/mL]	300 – 4,000	4,000 – 15,000	>15,000
Norfentanyl only	33	18	7
Both	14	18	20
6-AM only	7	7	12
Neither Fentanyl Nor 6-AM	160	103	102

Visualization of fentanyl/6-AM prevalence dependent on morphine concentration

Fentanyl prevalence seems independent of concentration

6-AM prevalence increases with morphine concentration.

FENTANYL ANALOGS

- p-Fluorofentanyl use identified in two specimens
 - Concentration > fentanyl
 - In 37 specimens likely byproduct of fentanyl production
- Possible reasons include:
 - Rarely used by donors
 - Limited cross-reactivity in immunoassay
 - Scope limitations (11 analogs)
 - Nitazene drugs not included

Scope of testing		
Methoxyacetyl fentanyl	Acryl fentanyl	Alfentanil
Furanyl fentanyl	Cyclopropylfentanyl	3-Methyl fentanyl
4-Fluoro-isobutyryl fentanyl	4-Fluoro-butyryl fentanyl	Sufentanil
p-Fluorofentanyl	o-Fluorofentanyl	

PULSE TESTING FOR CANNABINOIDS

How common is $\Delta 8$ -THC?

Are there positive initial tests due to CBD metabolites?

Are other THC analogs of interest present?

THE CONCERN WITH $\Delta 8$ -THC

Impairing

- Similar effects as $\Delta 9$ -THC
- Somewhat lower potency

Perceived as legal

- Manufactured using CBD from hemp
- Readily available online and in stores

Prevalent

- Reports of frequent sales and use
- Used to avoid a positive drug test?

Cross-reactivity

- >80% cross-reactivity with Cannabinoid IAs



STUDY DESIGN

1,504 specimens initial test positive for cannabinoids.

- Deidentified
- Rescreened with DRI Cannabinoids IA

LC-MS/MS assay quantifying 15 cannabinoids.

- Δ 8-THCA
- Δ 9-THCA
- Δ 10-THCA
- CBD and metabolites



IMMUNOASSAY PERFORMANCE – POSITIVE INITIAL TEST BUT NEGATIVE CONFIRMATION

Reason	n	% of total
All initial test positive with negative confirmation (Both $\Delta 8$ -THCA and $\Delta 9$ -THCA < 15 ng/mL)	16	100%
Confirmation >50% of cutoff ($\Delta 8$ -THCA and/or $\Delta 9$ -THCA >7.5 ng/mL)	10	63%
Other (See below)	6	27%

Results of other specimens with positive initial test and negative confirmation (ng/mL)					
Initial test ^a	$\Delta 9$ -THCA	$\Delta 8$ -THCA	$\Delta 9$ -THC	7-OH-CBD	CBDA
54	3.4	4.3	<1	370	<1
55	<1	<1	140	<1	35
78	<1	<1	770	<1	<1
73	1.3 ^b	1.8	<1	<1	<1
74	1.1	2.3	<1	3.8	<1
79	<1	1.4	<1	1.4	<1

^a, arbitrary unit (cutoff 50); ^b, LC-MS/MS Interference reported

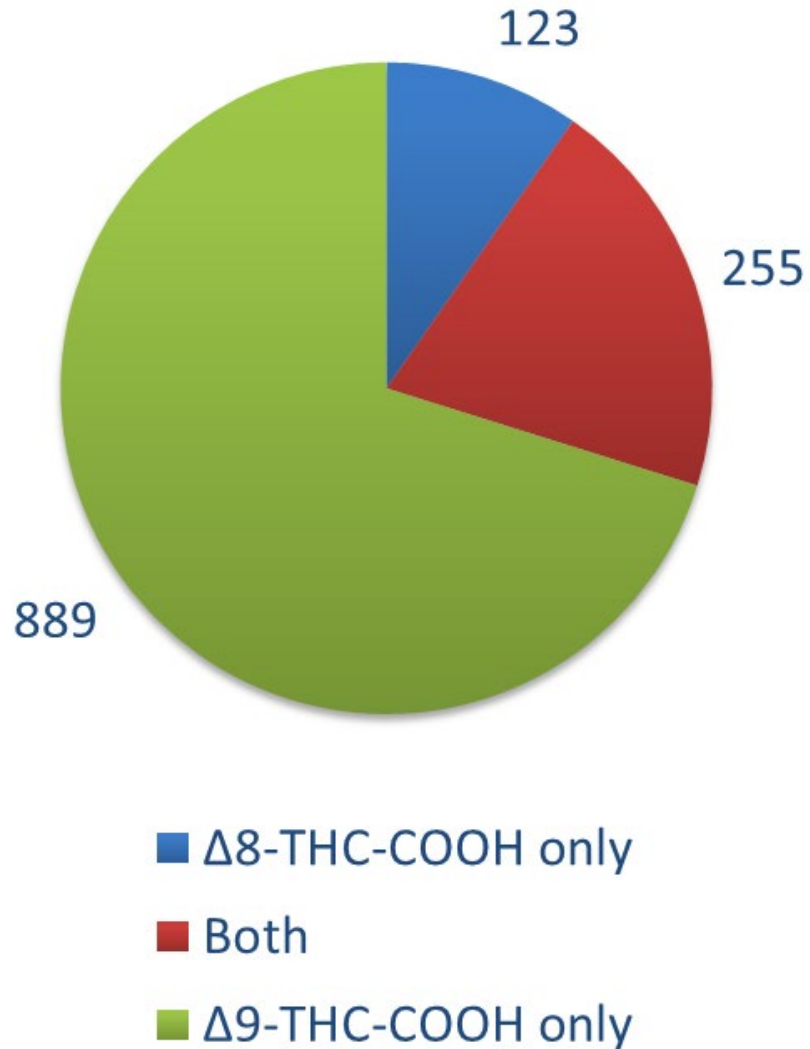
IMMUNOASSAY PERFORMANCE – NEGATIVE INITIAL TEST.

Reason	n	% of negative
All initial test negative (<50)	220	100%
Negative confirmation (Both $\Delta 8$ -THCA and $\Delta 9$ -THCA < 15 ng/mL)	95	43%
Sum of $\Delta 8$ -THCA and $\Delta 9$ -THCA <50 ng/mL ($\Delta 8$ -THCA and/or $\Delta 9$ -THCA ≥ 15 ng/mL)	120	55%
Other (See below)	5	2%

Results of other specimens with negative initial test (ng/mL)					
Initial test ^a	$\Delta 9$ -THCA	11-OH- $\Delta 9$ -THC	$\Delta 9$ -THC	$\Delta 8$ -THCA	$\Delta 8$ -THC
1	60	29	<1	<1	<1
3	80	20	<1	<1	<1
21	76	5.5	<1	<1	<1
-7	1,000	7.9	<1	<1	<1
9	54	8.5	<1	<1	<1

^a, arbitrary unit (cutoff 50)

PREVALENCE OF Δ 8-THCA



- 1,267 specimens positive for Δ 8-THCA and/or Δ 9-THCA
 - 15 ng/mL cutoff
 - Positive initial test
- 11% positive for Δ 8-THCA alone
- An estimated 7,500 specimens annually would be positive for Δ 8-THCA alone in the NLCP program.

THREE POPULATIONS

Cases with both $\Delta 8$ -THCA and $\Delta 9$ -THCA detected (≥ 1 ng/mL)

At least one of them ≥ 15 ng/mL

Three different populations

50% less than 3.7% $\Delta 8$ -THCA

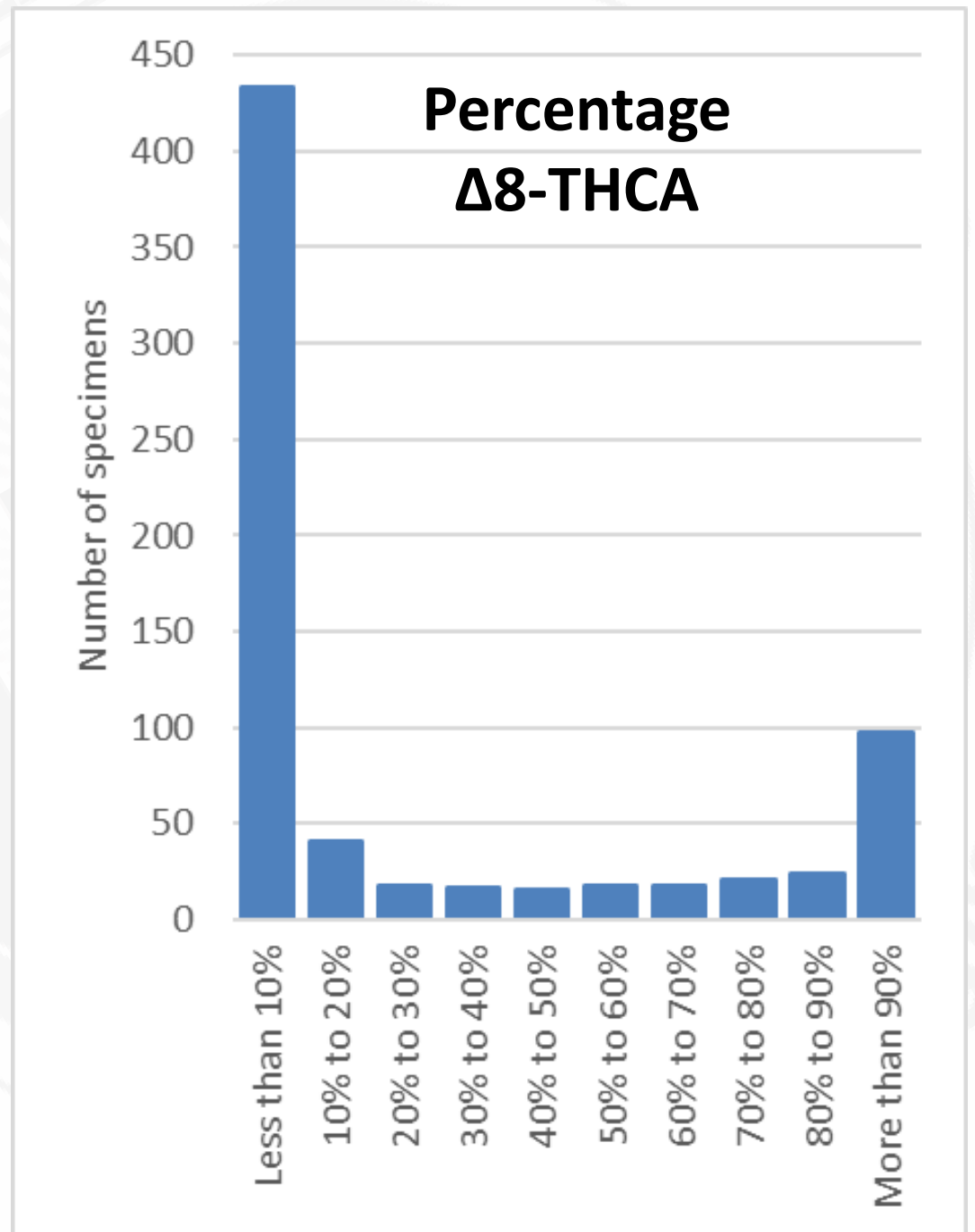
- Residual $\Delta 8$ -THCA from using cannabis?

14% >90% $\Delta 8$ -THCA

- Residual $\Delta 9$ -THCA from using $\Delta 8$ -THC?

25% 10-90% $\Delta 8$ -THCA

- Mixed use of different products?
- Products with higher levels of $\Delta 8$ -THC?



Δ 10-THCA AND CBD

- No specimens positive for Δ 10-THCA identified. Potential reasons include:
 - Limited use in community
 - Limited cross-reactivity in initial test
 - Δ 10-THCA not a major metabolite of Δ 10-THC
- No indications that CBD or metabolites produce positive initial tests.

TAKE-HOME MESSAGES

Opioids

- *Adjusting the morphine decision point to 4,000 ng/mL could increase positivity by 65%.*
- *Fentanyl more common in morphine positive specimens than 6-AM*
- *Urinary concentrations of norfentanyl are higher than those of fentanyl*

Cannabinoids

- *Prevalence of Δ 8-THCA is around 1/3 of Δ 9-THCA prevalence (many contain both)*
- *Including Δ 8-THCA could increase cannabinoid positivity by 11% compared to Δ 9-THCA alone*
- *Positive screening results due to CBD metabolites or other THC analogs are rare*



Thank you

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