Clinical Update:

2025 MID-YEAR UPDATE ONE NOVEL PSYCHOACTIVE SUBSTANCES (NPS) TRENDS

New or Novel Psychoactive Substances (NPS) are a diverse group of synthetic substances created to mimic the effects of prescription or illicit drugs that are often used non-medically.[1] There are various classes of NPS including designer opioids, designer benzodiazepines, synthetic cannabinoids, synthetic stimulants, hallucinogens/dissociatives, and others. NPS may change frequently as legislation to control specific chemical structures or classes of NPS is introduced. Once an NPS has been deemed a controlled substance, often new or modified non-regulated NPS appear. This remains a challenge for regulatory and enforcement agencies, monitoring institutions, clinical and toxicology laboratories, as well as healthcare providers. The goal of this clinical update is to review the prevalence of NPS detected at Aegis and trends in detection from Q1 to Q2 of 2025. The latest update to Aegis NPS testing was in June of 2025.

Aegis offers NPS testing by class in both urine and oral fluid. Test offerings include designer opioids, designer benzodiazepines, synthetic cannabinoids, synthetic stimulants, hallucinogens/dissociatives, and NPS-Other. Shown in **Figure 1** are 2025 NPS order rates by class, for Q1 and Q2. Of the total number of samples with any NPS class ordered, designer opioids class was the most frequently ordered at approximately 95% followed closely by designer benzodiazepines at approximately 90%. The NPS-Other class was the next most frequently ordered class at approximately 76% of samples with any NPS class ordered. Order rates for synthetic cannabinoids and synthetic stimulants were similar, ranging from 61 to 63%. The hallucinogens/dissociatives class was the least frequently ordered class at a rate of roughly 40% of samples with any NPS ordered. Order rates remained similar between Q1 and Q2 for all classes. When evaluating NPS data, it is important to consider that order rates may impact NPS detection and observed prevalence both within a class and between classes. In order to lessen this impact, the data in this clinical update are presented by drug/metabolite as proportion of NPS detected in a given class per quarter. Trends were then evaluated by looking at percent change in proportion from Q1 to Q2.

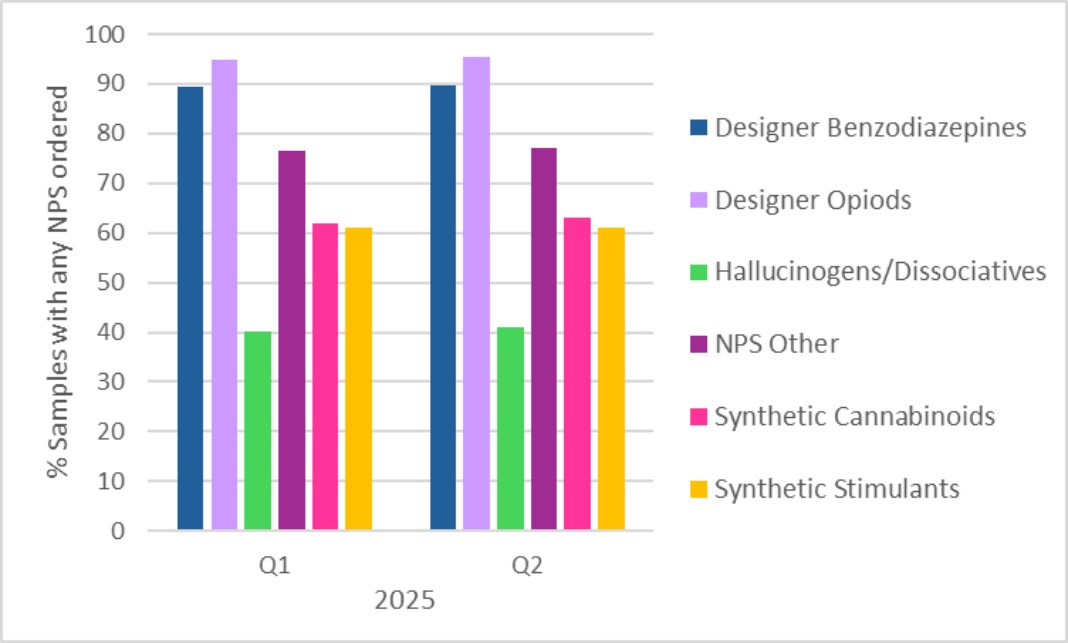

Figure 1. 2025 NPS order rate by class as % of samples with any NPS class ordered in Q1 and Q2

NPS-Other

The NPS-Other category includes substances that do not easily fit within other designated NPS classifications. Not all compounds in this class are specifically NPS, some are veterinary medications or other substances that have been identified as adulterants in the illicit drug supply. For example, xylazine is an alpha-2 adrenergic receptor agonist approved for veterinary use as a sedative with analgesic and muscle relaxant properties. However, it is not approved for use in humans and may cause unique withdrawal episodes and severe necrotic skin ulcers. The U.S. Food and Drug Administration (FDA) previously released an alert regarding risks to patients exposed to xylazine in the illicit drug supply.[2] **Figure 2** shows the proportion of each compound detected in the NPS-Other class by quarter. In **Figure 3**, the percent change in proportion from Q1 to Q2 is shown along with the total number of detections (in parenthesis) in the first half of 2025. This provides information regarding prevalence within a class for the first half of 2025 as well as the change in proportion of each compound from Q1 to Q2.

In both Q1 and Q2 of 2025, xylazine and its metabolite 4-hydroxyxylazine made up the largest proportion of compounds detected in the NPS-Other class. This is not surprising as in 2023 xylazine became the most prevalent NPS detected at Aegis irrespective of NPS class and has remained so through 2024 and the first half of 2025. In Q1, xylazine and its metabolite represented approximately 70% of compounds detected in the NPS-Other class. However this proportion decreased in Q2 mostly due to the change in proportion of metabolite which was -40% (see also **Figure 3**).

Medetomidine and its metabolite 3-hydroxy medetomidine were the next most prevalent compounds in the NPS-Other class. Like xylazine, medetomidine is an alpha-2 adrenergic receptor agonist and has been detected as an adulterant in the illicit drug supply.[3] Recently medetomidine has been reported to be rapidly proliferating across

the United States.[4] From Q1 to Q2 the proportion of medetomidine and its metabolite icreased by 34 and 29% respectively.

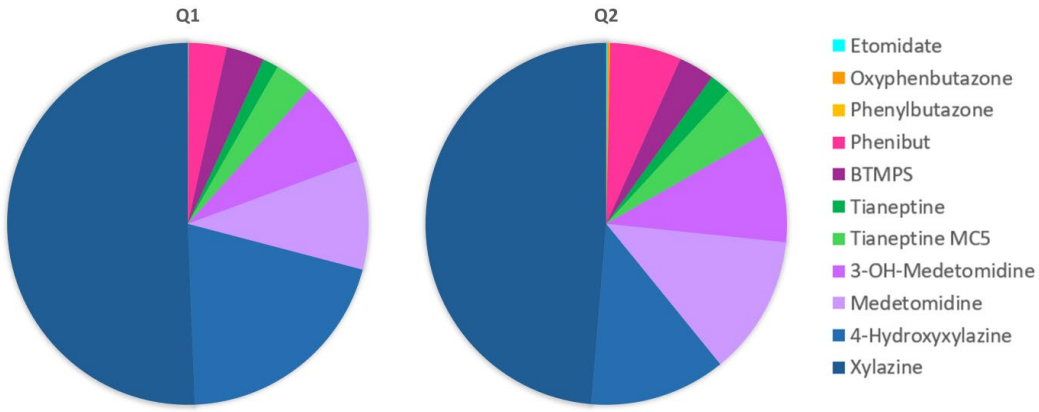

Figure 2. Proportion of NPS - Other compounds detected in Q1 and Q2 of 2025.

The prevalence of tianeptine metabolite MC5, phenibut and emerging adulterant BTMPS in Q1 was nearly identical. In Q2, the proportion of tianeptine and its metabolite increased 36 and 44% respectively from Q1. Tianeptine, also called “gas station heroin”, is structurally classified as an atypical tricyclic antidepressant but at high doses it has mu opioid receptor activity. Thus, misuse can result in opioid-like highs, and users can develop tolerance and dependence. The FDA reported tianeptine products have been linked to serious adverse events including overdose and death.[5,6] Phenibut is a synthetic form of gamma aminobutyric acid (GABA) that acts similarly to benzodiazepines and has been sold as a dietary supplement in the United States. The proportion of phenibut in Q2 increased 88% from Q1 resulting in phenibut having a higher prevalence (505) for the first half of 2025 than tianeptine (465 specimens). BTMPS and was added to Aegis NPS-Other testing in December of 2024. It is an industrial chemical that has been used in the manufacture of plastics and is a potent Ca^{2+} channel blocker.[7] BTMPS rapidly appeared in the illicit drug supply in summer of 2024 and has already been identified as a public health concern.[8,9] The proportion of BTMPS in Q2 decreased by 6% from Q1.

Phenylbutazone and its metabolite oxyphenbutazone were added to Aegis NPS-Other testing in December of 2024. Phenylbutazone is a nonsteroidal anti-inflammatory drug that was withdrawn from the market due to severe adverse effects but has been identified as an adulterant in the illicit drug suppy.[10] Although the percent change in proportion of oxyphenbutazone between Q1 and Q2 is substantial, it should be interpreted with caution as its proportion in Q1 is too small to even be visualized and the prevalence in 2025 is low. Etomidate is the newest addition to Aegis NPS-Other testing (June of 2025). It is a sedative hypnotic drug used in critical care and emergency medicine but has been detected in the illicit drug supply.[11,12] Three etomidate positives were detected in June.

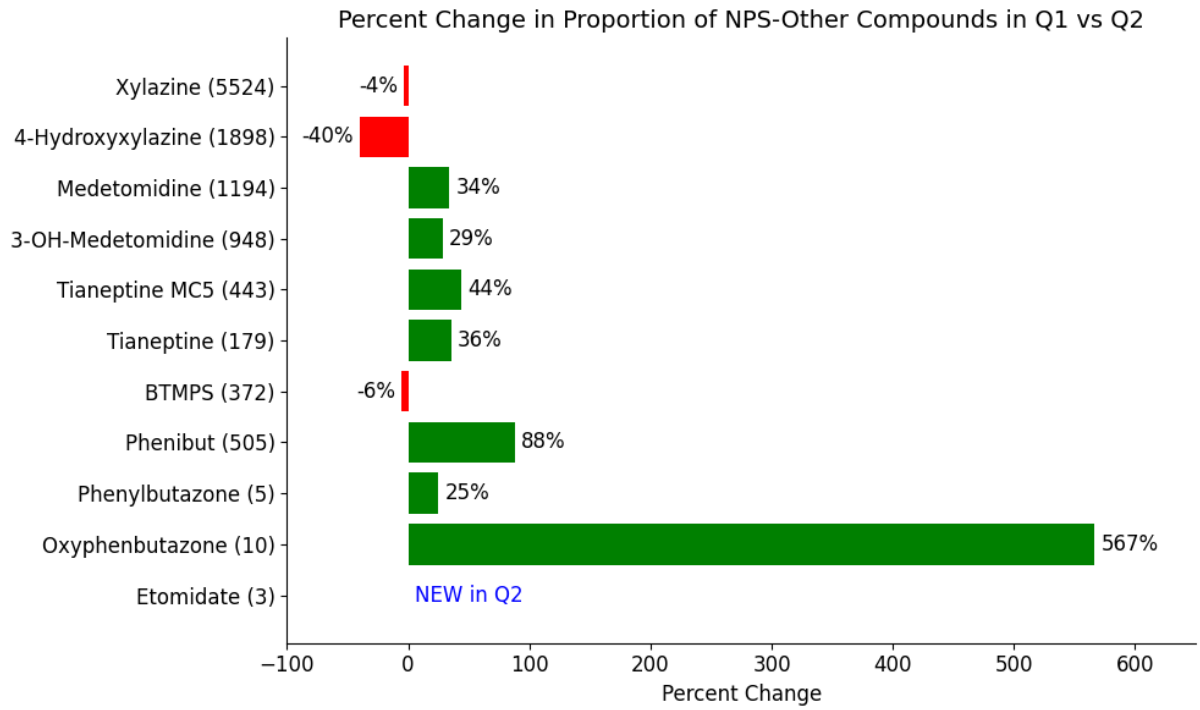

Figure 3. Percent change in proportion of NPS-Other Compounds from Q1 to Q2. Total number of positives in the first half of 2025 is shown in parenthesis.

Designer Opioids

Designer opioids include various subclasses of compounds such as fentanyl analogs (or "fentalogs"), "nitazene analogs," and others. **Figure 4** shows the proportion of designer opioids detected in Q1 and Q2 of 2025. Designer Opioids with less than 5 detections in the first half of 2025 were excluded. Fluoro Fentanyl and related compounds despropionyl fluorofentanyl and fluoro norfentanyl together represent approximately 59% of the proportion of designer opioids detected in Q1. Fluoro fentanyl has three positional isomers (meta-, ortho- and para-) that are not distinguished in Aegis' designer opioids test. The para-fluorofentanyl isomer specifically has been associated with overdose deaths.[13,14] For multiple years, fluoro fentanyl was the most frequently detected NPS at Aegis among all NPS classes. However, in 2023 it was overtaken by xylazine as the most prevalent NPS detected at Aegis irrespective of NPS class. Since then, it has remained the second most prevalent NPS detected at Aegis irrespective of NPS class. In **Figure 5**, the percent change in proportion of designer opioids from Q1 to Q2 is shown along with the total number of detections (in parenthesis) in the first half of 2025. The proportion of fluoro fentanyl and related compounds in Q2 is similar to Q1 but with an approximate decrease of 13% in metabolite fluoro norfentanyl.

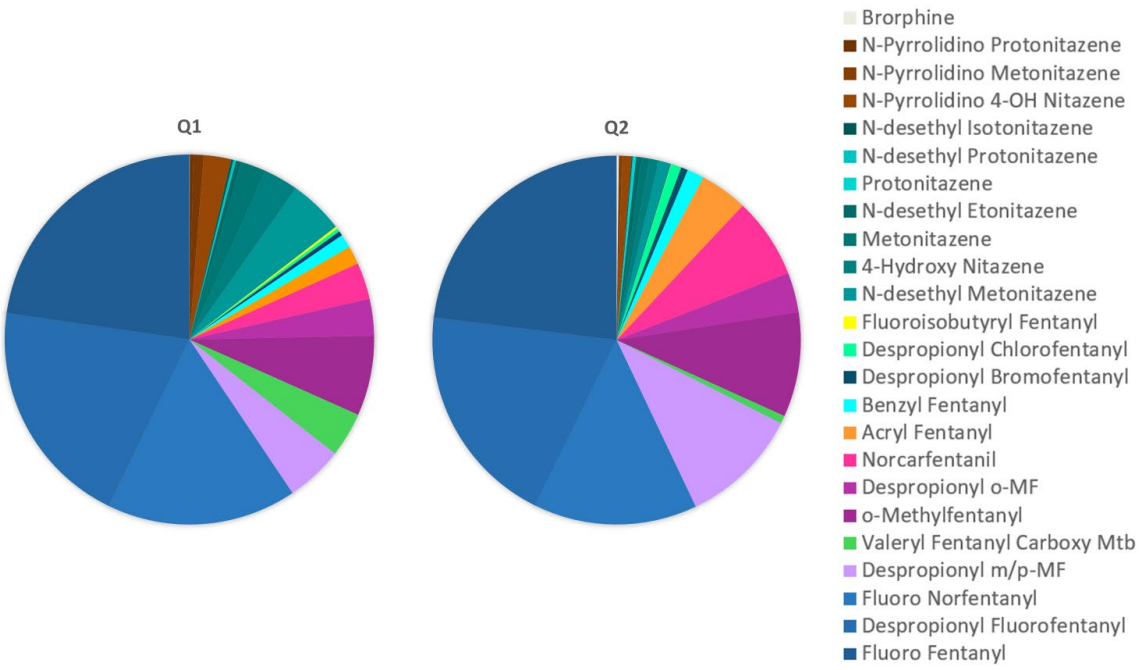

Figure 4. Proportion of Designer Opioids detected in Q1 and Q2 of 2025. Designer Opioids with less than 5 detections in the first half of 2025 were excluded from the graphs.

Looking at 2025 Q1 data, the second largest proportion of designer opioids was o-methylfentanyl and the third largest proportion was despropionyl m/p-methylfentanyl. Methylfentanyl has 3 positional isomers (ortho-, meta- and para-) and was added to Aegis' designer opioid testing in December of 2024. In our testing, the ortho- isomer is distinguished from the meta- and para- isomers, which are not distinguished from one another. The same month testing was implemented, CFSRE released a public alert noting that ortho-methylfentanyl, the newest synthetic opioid identified in fatal drug overdoses, was proliferating across North America.[15] Our December o-methylfentanyl positivity was approximately 90% of valeryl fentanyl carboxy metabolite which was the most prevalent fentanyl analog other than fluoro fentanyl and its related compounds. However, at the time nitazene analogs N-desethyl metonitazene and 4-hydroxy nitazene were more prevalent than valeryl fentanyl carboxy metabolite. In Q1 of 2025 the proportion of N-desethyl metonitazene was similar to despropionyl m/p-Methylfentanyl. However, the percent change in proportion from Q1 to Q2 was opposite with despropionyl m/p-Methylfentanyl increasing 109% and N-desethyl metonitazene decreasing 77% (see Figure 5).

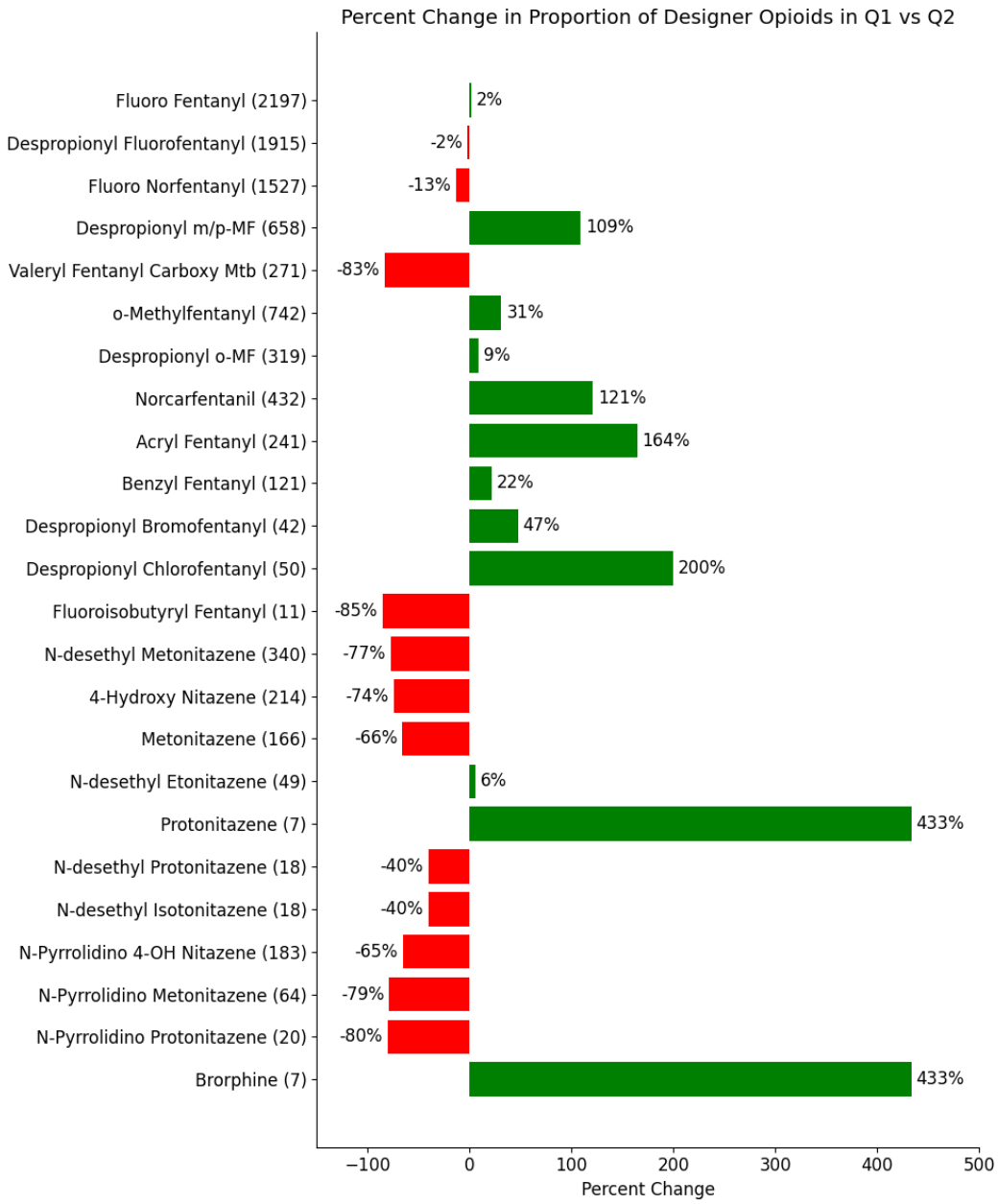

Figure 5. Percent change in proportion of Designer Opioids from Q1 to Q2. Total number of positives in the first half of 2025 is shown in parenthesis.

Looking at **Figure 4**, some of the larger, more noticeable differences in proportion between Q1 and Q2 include increases in despropionyl m/p-Methylfentanyl, norcarfentanil, and acryl fentanyl and decreases in valeryl fentanyl carboxy metabolite, and nitazene and N-pyrrolidino nitazene analogs. The percent change in proportions of norcarfentanil and acryl fentanyl from Q1 to Q2 increased by 121 and 164% respectively (**Figure 5**). However, valeryl fentanyl carboxy metabolite and nitazene and N-pyrrolidino nitazene analogs saw significant decreases in proportion of designer opioids detected (see **Figure 5**).

Percent changes in proportion of despropionyl chlorofentanyl, protonitazene and brorphine seem quite large in Figure 5 especially for protonitazene and brorphine yet those changes are less noticeable in Figure 4. This is because the total number of positives for these designer opioids in 2025 is quite small.

Designer Benzodiazepines

The proportion of designer benzodiazepines detected in Q1 and Q2 of 2025 is shown in **Figure 6**. Designer Benzodiazepines with less than 5 detections in the first half of 2025 were excluded, except for bromazepam as it is included along with its two metabolites with greater positivity. Bromazolam and its metabolite alpha-hydroxybromazolam were approximately 72% of all designer benzodiazepines detected in Q1 of 2025. In 2023, bromazolam became the most prevalent designer benzodiazepine detected at Aegis, surpassing clonazolam which is detected mainly via its metabolite 8-aminoclonazolam. Since then, it has remained the most prevalent designer benzodiazepine (based on annual positivity) detected at Aegis. In July of 2023 the DEA temporarily placed clonazolam, etizolam, flualprazolam, flubromazolam and diclazepam in Schedule I of the Controlled Substances Act (CSA) to limit access to these substances.[16] However, bromazolam has remained unscheduled.

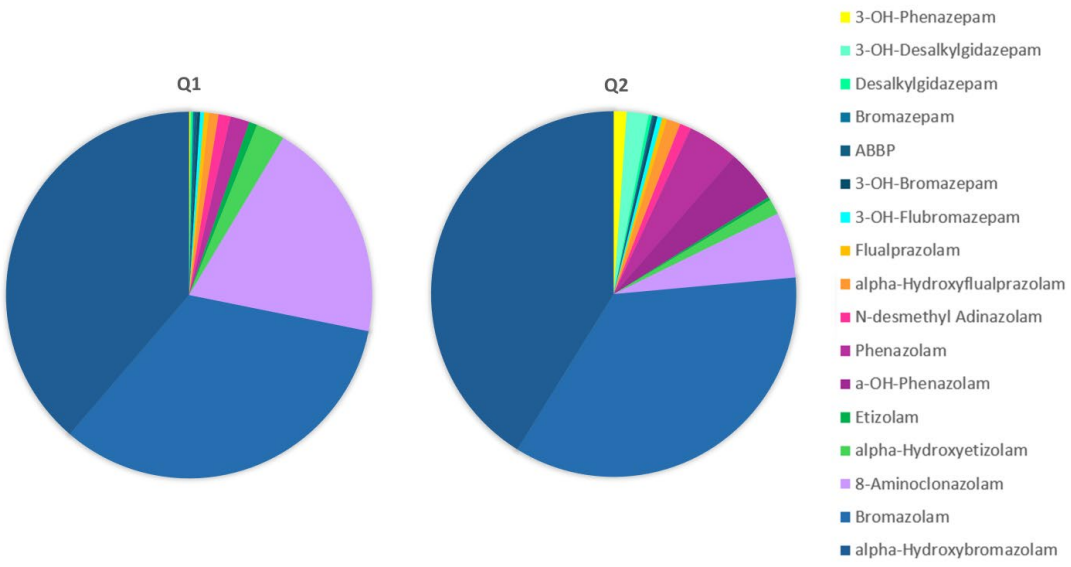

Figure 6. Proportion of Designer Benzodiazepines detected in Q1 and Q2 of 2025. Designer Benzodiazepines with less than 5 detections in the first half of 2025 were excluded.

The second most prevalent designer benzodiazepine in Q1 was 8-aminoclonazolam with nearly 20% of detections. Etizolam and its metabolite alpha-hydroxy etizolam were a distant third most prevalent at ~3% of detections in Q1. Looking at **Figure 6**, noticeable differences in proportion between Q1 and Q2 include increases in bromazolam and its metabolite, phenazolam, desalkylgidazepam, and 3-hydroxy-phenazepam as well as decreases in 8-aminoclonazolam and etizolam and its metabolite. The percent change in proportion of designer benzodiazepines from Q1 to Q2 is shown in **Figure 7** along with the total number of detections in the first half

of 2025 (shown in parenthesis). The largest percent change in proportion of detections from Q1 to Q2 was for 3-hydroxyphenazepam. It is important to consider the number of detections in the first half of 2025. For 3-hydroxyphenazepam, the percent change in proportion is substantial, but the number of detections is quite low. In contrast, phenazolam had a large percent change in proportion of detections from Q1 to Q2 but is the third most prevalent designer benzodiazepine in the first half of 2025.

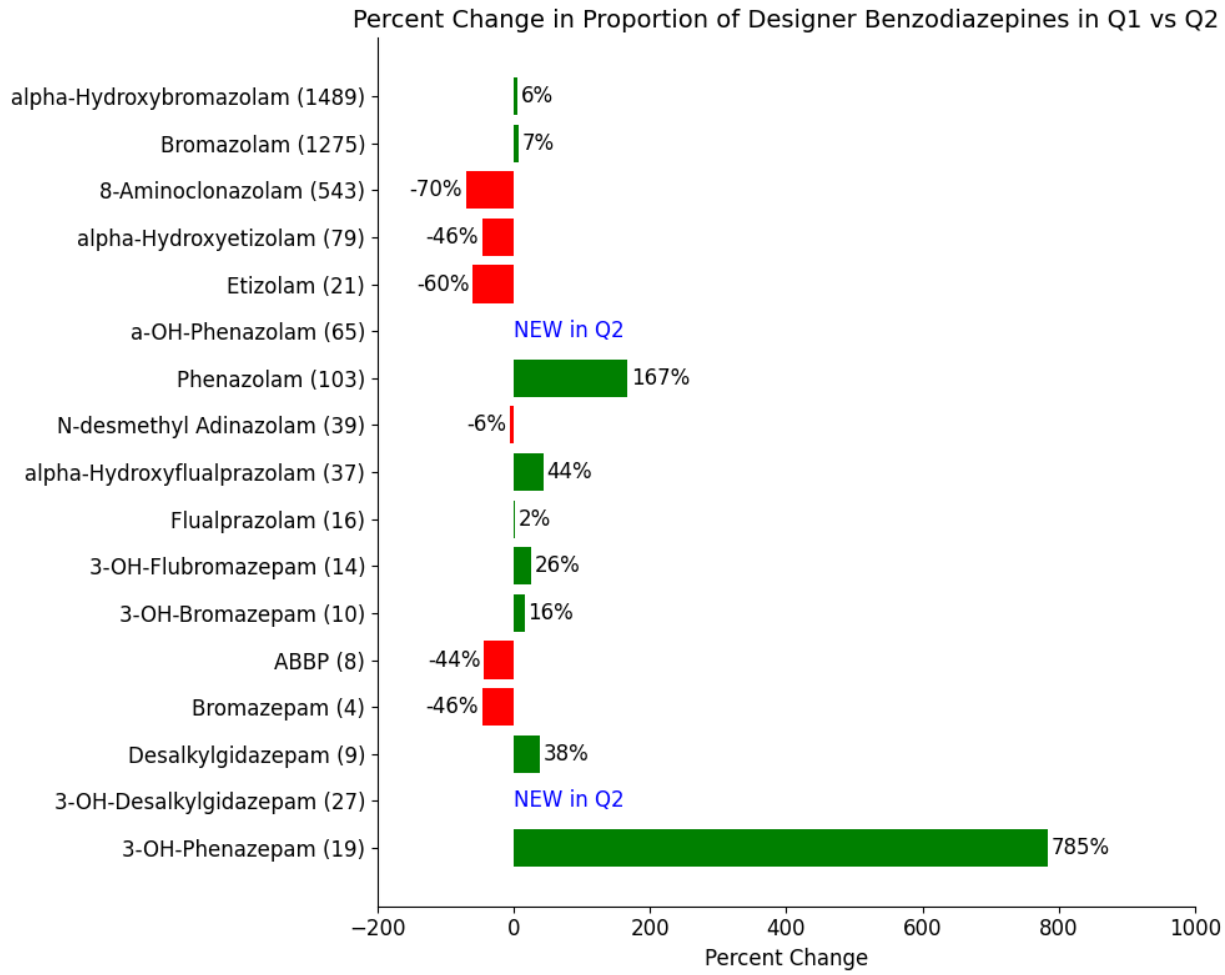

Figure 7. Percent change in proportion of Designer Benzodiazepines from Q1 to Q2. Total number of positives for the first half of 2025 is shown in parenthesis.

In June of 2025, Aegis added metabolites of desalkylgidazepam and phenazolam to designer benzodiazepine testing. In one month, the number of detections of metabolite 3-hydroxy-desalkylgidazepam tripled the number of desalkylgidazepam detections for the first half of 2025.

All 3-hydroxydesalkylgidazepam detections were metabolite only. Thus, it appears the addition of this metabolite will greatly improve the ability to detect desalkylgidazepam use. For metabolite alpha-hydroxyphenazolam, there were 65 detections in June. Of these, 45 (69%) were metabolite only resulting in a total of 148 positive specimens for the first half of 2025. This means that 30% of the positive specimens in the first half of 2025 were identified due to the addition of alpha-hydroxyphenazolam.

Synthetic Cannabinoids

The proportion of synthetic cannabinoids detected in Q1 and Q2 of 2025 is shown in **Figure 8**. MDMB-4en-PINACA, detected mainly via its butanoic acid (BA) metabolite, has been the most predominant synthetic cannabinoid detected at Aegis since 2022. In December of 2023, the Federal Register temporarily placed it in schedule I of the CSA.[17] In April of 2024, MDMB-INACA and its BA metabolite were added to Synthetic Cannabinoid testing. MDMB-INACA is a synthetic cannabinoid precursor that can be used to make several different synthetic cannabinoids including MDMB-4en PINACA.[18] MDMB-INACA, detected mostly as BA metabolite, was often detected with MDMB-4en PINACA and was the second most prevalent synthetic cannabinoid detected in 2024. In the first quarter of 2025, MDMB-4en PINACA and MDMB-INACA were each almost 1/3 of the synthetic cannabinoid detections. 5F-MDMB-PINACA, largely via detection of its M7 metabolite, represented ~20% of the positive results in Q1.

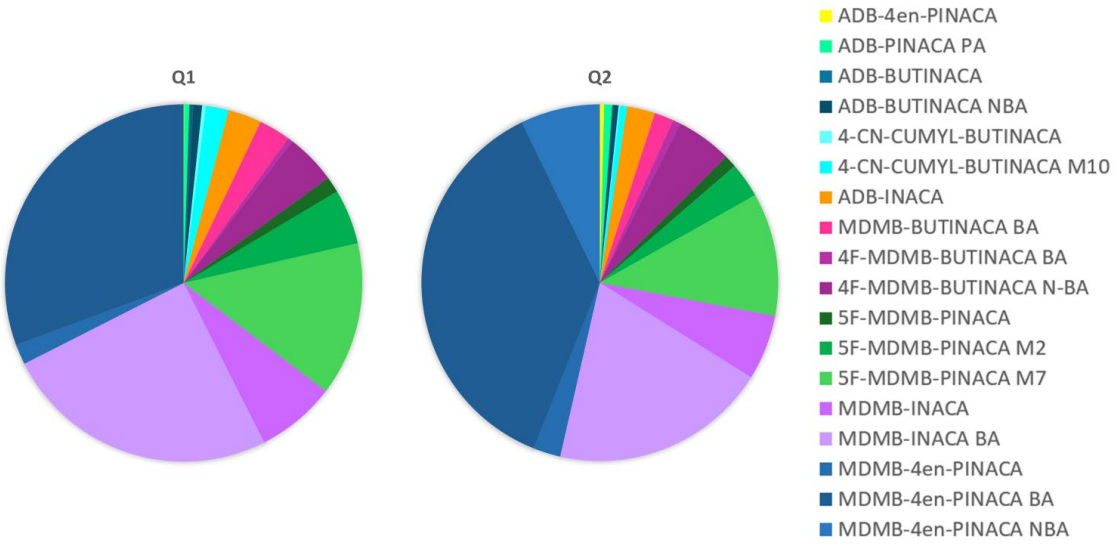

Figure 8. Proportion of Synthetic Cannabinoids detected in Q1 and Q2 of 2025. Synthetic Cannabinoids with less than 5 detections in the first half of 2025 were excluded.

Looking at **Figure 8**, some of the more noticeable changes in proportion between Q1 and Q2 are increases in MDMB-4en-PINACA and decreases in MDMB-INACA and 5F-MDMB-PINACA. In **Figure 9**, the percent change in proportion of synthetic cannabinoids from Q1 to Q2 is shown along with the total number of detections in the first half of 2025 (in parenthesis). In addition to increases in MDMB-4en-PINACA and BA metabolite, increases in 4F-MDMB-BUTINACA metabolites, ADB-PINACA PA and ADB-4en-PINACA were also observed. Although the percent change in proportion of ADB-4en-PINACA is substantial, the number of detections in 2025 is very low and thus should be interpreted with caution. In addition to observed decreases in MDMB-INACA and 5F-MDMB-PINACA, larger percent decreases were observed for ADB-BUTINACA, 4-CN-CUMYL-BUTINACA and MDMB-BUTINACA.

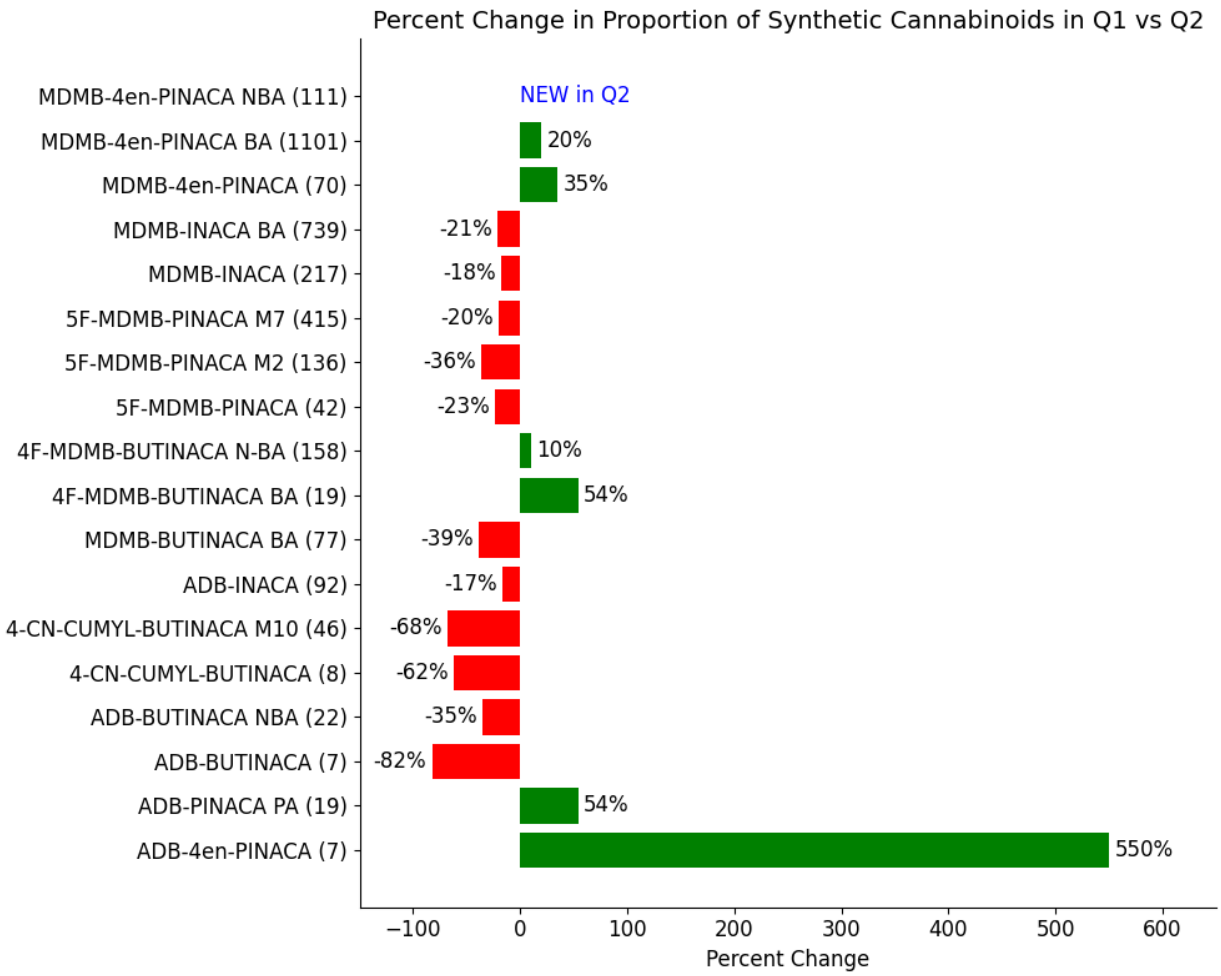

Figure 9. Percent change in proportion of Synthetic Cannabinoids from Q1 to Q2. Total number of positives for the first half of 2025 is shown in parenthesis.

In June of 2025, MDMB-4en-PINACA-NBA, a metabolite of MDMB-4en-PINACA, was added to Synthetic Cannbinoid testing. There were 214 positive specimens in June, 46% were positive for both BA and NBA metabolites, 41% had only BA metabolite, 6% were positive only for the NBA metabolite, another 6% were positive for parent drug and BA metabolite, and 1% were positive for parent drug only.

Synthetic Stimulants

The proportion of synthetic stimulants detected at Aegis in Q1 and Q2 of 2025 is shown in **Figure 10**. *N,N*-dimethylpentylone and its metabolite pentylone have been the most predominant synthetic stimulants detected at Aegis since 2022. Although they remained the most prevalent synthetic stimulants detected, their positivity declined significantly throughout 2024 with December positivity of *N,N*-dimethylpentylone and pentylone being approximately 15% and 7% respectively of their January 2024 positivity. Eutylone has been the second most prevalent synthetic stimulant detected at Aegis since it was overtaken by pentylone in 2022. Interestingly for the first half of 2025, *N,N*-dimethylpentylone and its metabolite pentylone are for the first time in years *not* the most

prevalent synthetic stimulants detected at Aegis. N-isopropyl butylone, a novel substituted cathinone, was first identified by CFSRE in August of 2024 and was added to Synthetic Stimulant testing at Aegis in December of 2024.[19] In Q1 of 2025, N-isopropyl butylone was approximately 27% of synthetic stimulant detections and rivaled *N,N*-dimethylpentylone which had the highest detection at approximately 30%. *N,N*-dimethylpentylone and pentylone together made up approximately 50% of synthetic stimulant detections in Q1. Eutylone was the next most prevalent at approximately 10% followed by N-cyclohexyl methylone at approximately 5% and butylone at 2.6%.

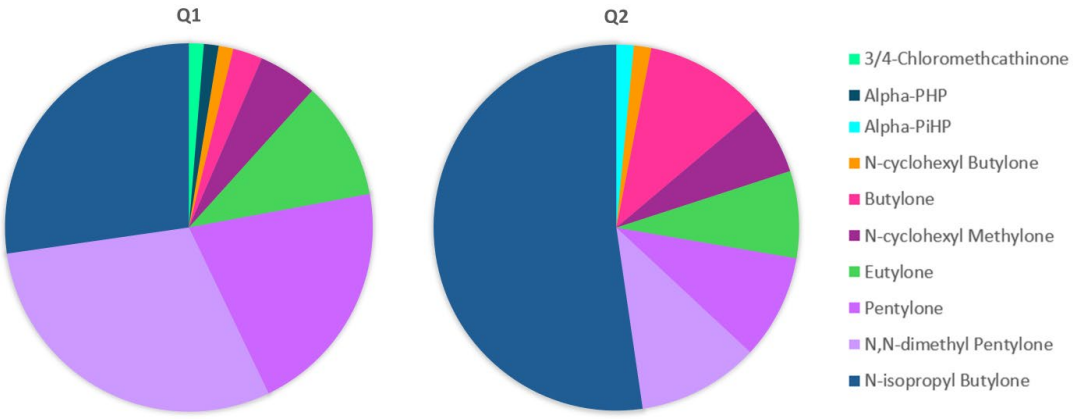

Figure 10. Proportion of Synthetic Stimulants detected in Q1 and Q2 of 2025.

Notable changes from Q1 to Q2 include the proprtion of N-isopropyl butylone almost doubling, whereas *N,N*-dimethylpentylone and pentylone are seemingly halved, eutylone is decreased and the proportion of butyone is significantly increased. In **Figure 11**, the percent change in proportion of synthetic stimulants from Q1 to Q2 is shown along with the total number of detections in the first half of 2025 (in parenthesis).

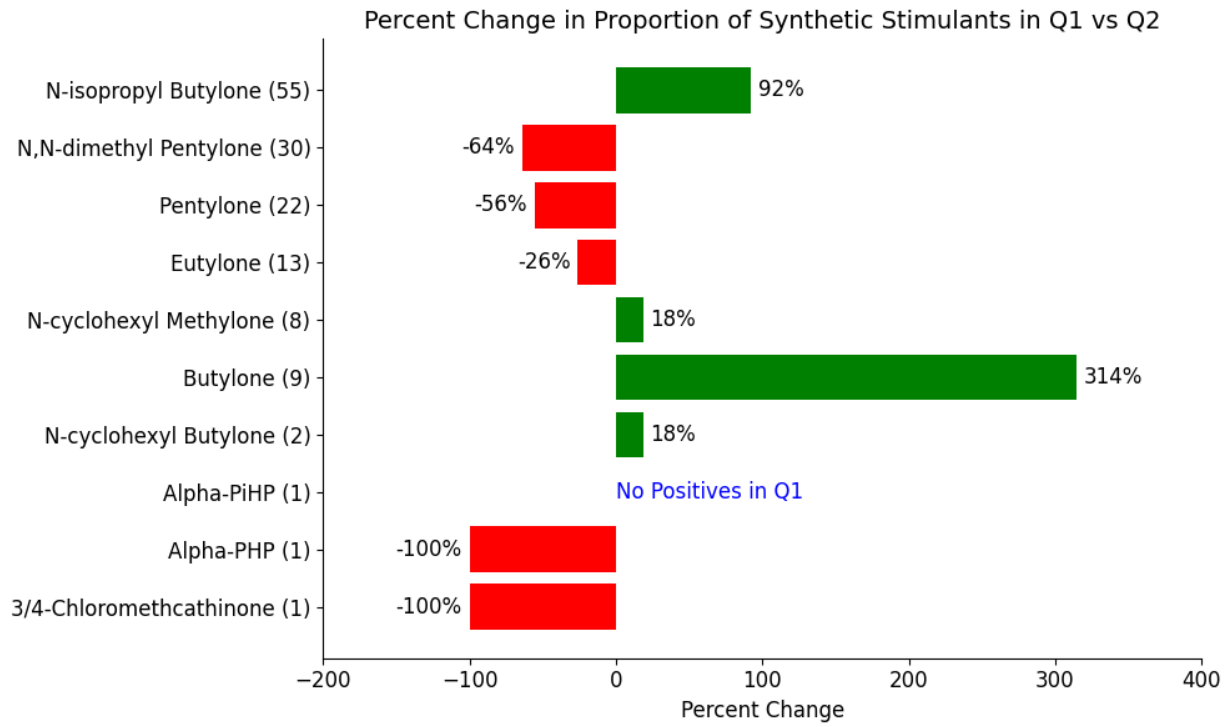

Figure 11. Percent change in proportion of Synthetic Stimulants from Q1 to Q2. Total number of positives for the first half of 2025 is shown in parenthesis.

The proportion of *N,N*-dimethylpentylone and pentylone detections decreased by 64 and 56% respectively from Q1 to Q2 of 2025. Eutylone decreased by 26%. The proportion of N-isopropyl butylone increased by 92% and went from being approximately 27% of the total number of synthetic stimulant positives in Q1 to being 52% in Q2. The largest percent change increase for synthetic stimulants was for butylone, which went from being 2.6% of the total number of synthetic stimulant positives in Q1 to nearly 11% in Q2. Interestingly all of the butylone positives in the first half of 2025 were also positive for N-isopropyl butylone. One third of the butylone positives were copositive with N-isopropyl butylone and eutylone. Of the 55 specimens positive for N-isopropyl butylone in the first half of 2025, 78% were positive for N-isopropyl butylone only. One N-isopropyl butylone positive was copositive with pentylone, another N-isopropyl butylone positive was copositive with N-cyclohexyl Methylone and one N-isopropyl butylone positive sample was copositive with *N,N*-dimethylpentylone, pentylone, N-cyclohexylbutylone, and N-cyclohexyl Methylone. Other synthetic stimulants had very low detections in 2025.

Hallucinogen/Dissociatives

The proportion of hallucinogens/dissociatives detected at Aegis in Q1 and Q2 of 2025 is shown in **Figure 12**. 2F-Deschloroketamine and its metabolite 2F-deschloronorketamine first appeared in April of 2022. 2F-deschloronorketamine became the most prevalent hallucinogen/dissociative compound detected in 2022 and it remained so throughout both 2023 and 2024. In Q1, 2F-deschloronorketamine detections were approximately 58% of the total hallucinogens/dissociatives detected. The next most prevalent was 2F-2-oxo-PCE at approximately 34%. 2F-2-oxo-PCE is a positional isomer of fluorexetamine and is structurally similar to ketamine. It is not currently a federally scheduled drug. However, some states have deemed it a controlled substance. 2F-2-oxo-PCE

was added to Aegis' NPS testing in September of 2023. In May of 2024, CFSRE released a public alert warning that 2F-2-oxo-PCE has been detected in recreational drug markets across North America.[20]

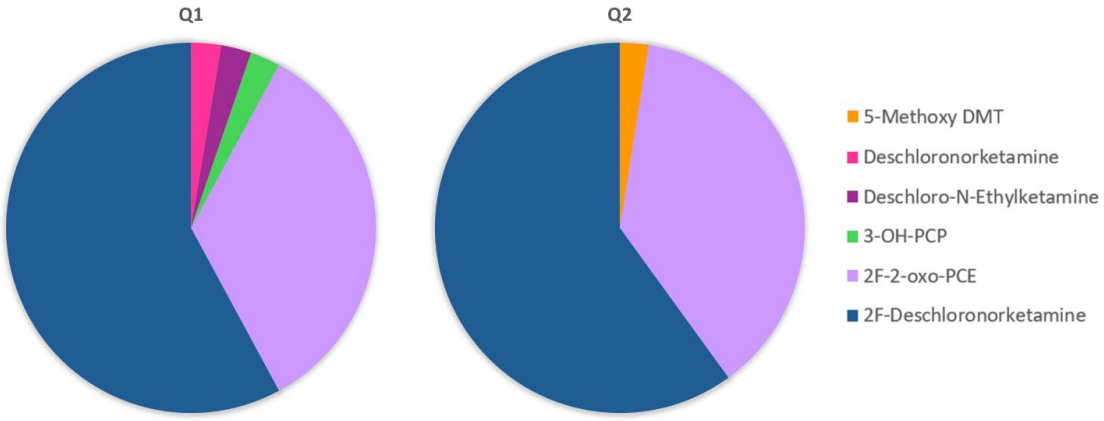

Figure 12. Proportion of Hallucinogens/Dissociatives detected in Q1 and Q2 of 2025.

In **Figure 13**, the percent change in proportion of hallucinogens/dissociatives from Q1 to Q2 is shown along with the total number of detections in the first half of 2025 (in parenthesis). 2F-deschloronorketamine and 2F-2-oxo-PCE made up the vast majority of hallucinogens/dissociatives detected in the first half of 2025. The percent change in proportion from Q1 to Q2 for each of these compounds was minor with both showing a slight increase in proportion from Q1 to Q2 which is likely due to single detections of some hallucinogens/dissociatives in Q1 and not Q2. 5-Methoxy DMT, is a tryptamine derivative that was added to Hallucinogens/Dissociatives testing in December of 2024. However, the first positive was detected in Q2.

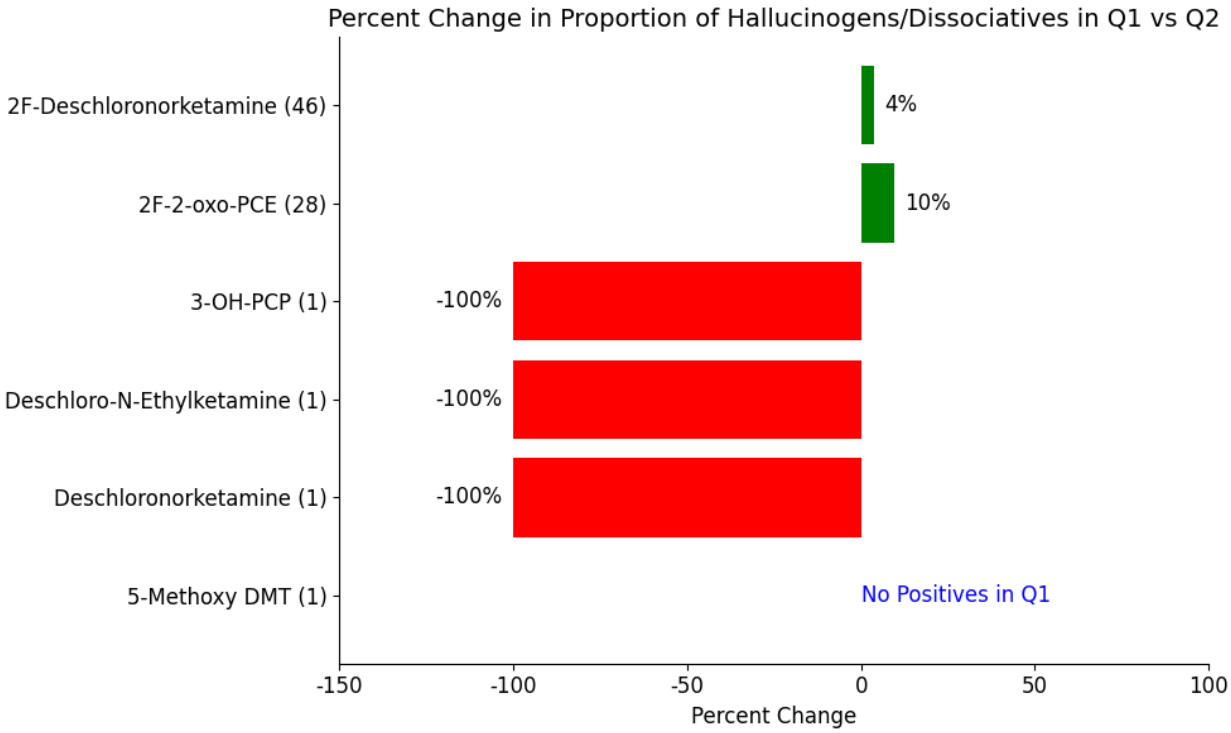

Figure 13. Percent change in proportion of Hallucinogens/Dissociatives from Q1 to Q2. Total number of positives for the first half of 2025 is shown in parenthesis.

ALL NPS

The top NPS detected at Aegis in the first half of 2025, irrespective of NPS class, are shown in **Table 1**. The top three NPS in the first half of 2025 were the same as the top three detected in 2024. There were four NPS appearing in the top NPS detected in the first half of 2025 that were not in the top NPS detected in 2024 including designer opioids o-Methylfentanyl and m/p-Methylfentanyl (detected as despropionyl metabolite), synthetic cannabinoid 5F-MDMB-PINACA, and emerging adulterant in the illicit drug supply, BTMPS. NPS that dropped from the top NPS detected in 2024 and are not present in the top NPS detected in the first half of 2025 include designer opioids 4-hydroxynitazene, N-Pyrrolidino 4-hydroxynitazene, and valeryl fentanyl carboxy metabolite, and synthetic stimulant *N,N*-dimethylpentylone/pentylone. Designer Opioids and NPS-Other were the most represented NPS classes in the top NPS detected. However, designer benzodiazepines and synthetic cannabinoids were represented by third and forth most prevalent NPS detected respectively. Differences in order rates may impact this data as position in the table is based on number of detections.

Table 1. Top NPS Detected at Aegis in Q1 and Q2 of 2025	NPS Classification
Xylazine/4-hydroxyxylazine	NPS-Other
Fluoro Fentanyl (FF)/Despropionyl FF/Fluoro Norfentanyl	Designer Opioids
Bromazolam/alpha-hydroxybromazolam	Designer Benzodiazepines
MDMB-4en-PINACA/ MDMB-4en-PINACA-BA/NBA metabolites	Synthetic Cannabinoids
Medetomidine/3-OH-Medetomidine	NPS-Other
o-Methylfentanyl/Despropionyl o-Methylfentanyl	Designer Opioids
MDMB-INACA/MDMB-INACA BA	Synthetic Cannabinoids
Despropionyl m/p-Methylfentanyl	Designer Opioids
8-Aminoclonazolam	Designer Benzodiazepines
Phenibut	NPS-Other
Tianeptine/Tianeptine MC5	NPS-Other
Norcarfentanil	Designer Opioids
5F-MDMB-PINACA/5F-MDMB-PINACA M2/M7 metabolites	Synthetic Cannabinoids
BTMPS	NPS-Other
Metonitazene/N-desethyl Metonitazene	Designer Opioids

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

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