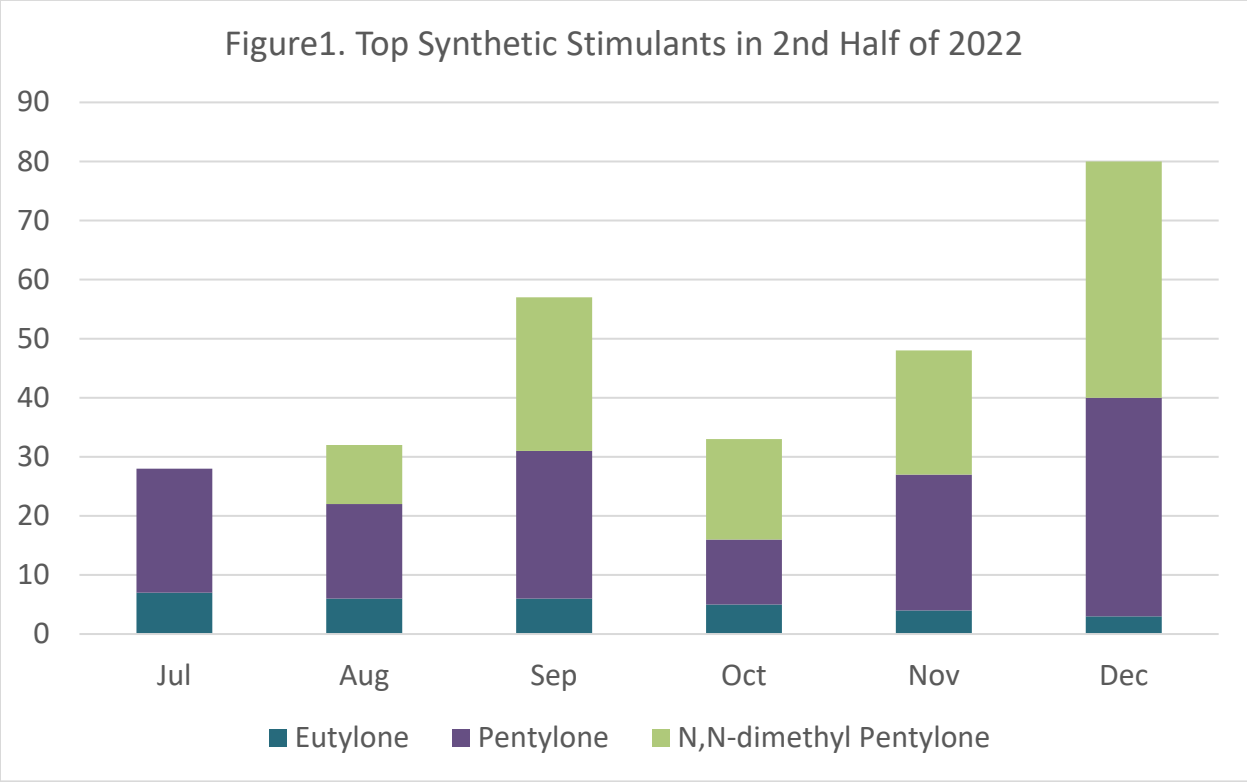
Clinical Update: March 2023

NOVEL PSYCHOACTIVE SUBSTANCES: NEWLY IDENTIFIED THREATS DETECTED IN THE SECOND HALF OF 2022

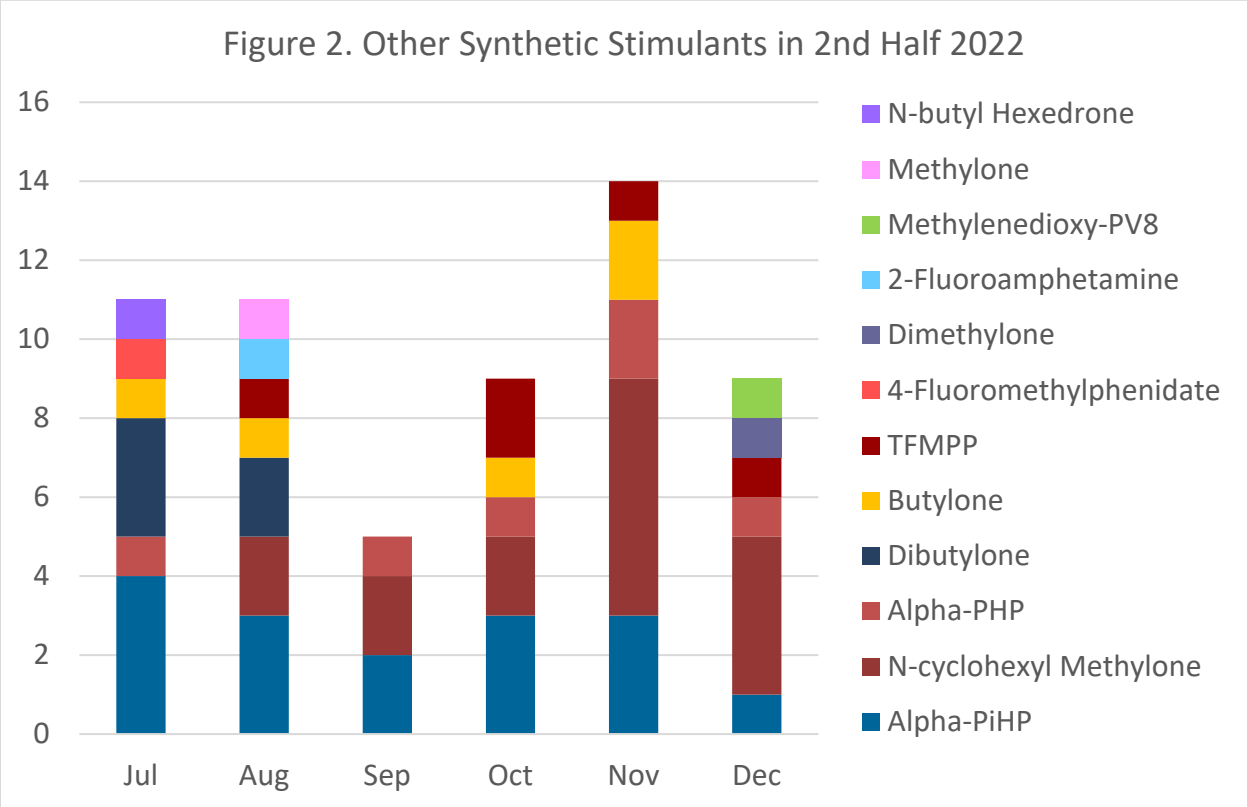
Novel Psychoactive Substances (NPS) are a diverse group of synthetic substances created to mimic the effects of scheduled or illicit drugs. There are various classes of NPS including designer opioids, designer benzodiazepines, synthetic cannabinoids, synthetic stimulants, hallucinogens/dissociatives, 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. The focus of this clinical update is to evaluate changes observed in the prevalence of NPS detected at Aegis in the second half of 2022.

Synthetic Stimulants

Synthetic stimulants tested at Aegis include analogs of amphetamine and methylphenidate as well as cathinones, which have been erroneously sold as "bath salts". The prevalence of the top synthetic stimulants is shown in Figure 1. Eutylone, a synthetic cathinone, was the predominant synthetic stimulant detected through the fourth quarter of 2021. However, as of January 2022, prevalence of eutylone began to decline. Eutylone was added to Schedule I of the Controlled Substances Act as a positional isomer of pentylone, which was placed under Schedule I in 2017 when it was the 5th most frequently reported synthetic cathinone.[1] In the first half of 2022, eutylone detection declined and pentylone increased to become the most prevalent synthetic stimulant detected in the first half of 2022. Since pentylone is a controlled substance, the increase in detection was suspected to be due to it being a metabolite of the novel synthetic stimulant N,N-dimethylpentylone,[2] which was added to Aegis Synthetic Stimulant testing in August of 2022. In the second half of 2022, N,N-dimethylpentylone and its metabolite pentylone were the most predominant synthetic stimulants detected followed by eutylone.

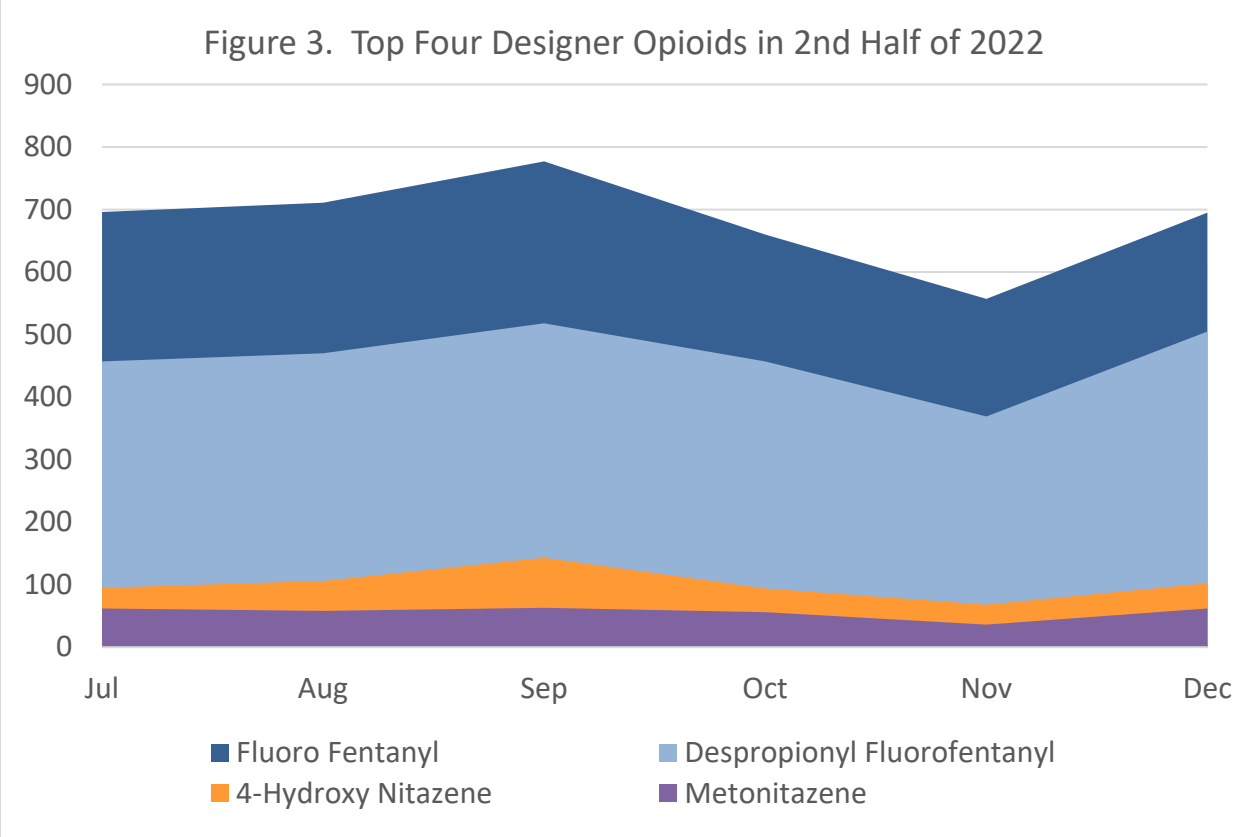


Other synthetic stimulants detected in the second half of 2022 are shown in Figure 2. Detection of alpha-Pyrrolidinoisohexanophenone (α-PiHP) occurred in all months except January and is the third most detected synthetic stimulant overall in 2022. N-cyclohexyl Methylone was newly detected in August of 2022 and was detected in all remaining months of the year at such a frequency as to become the fourth most prevalent synthetic stimulant of 2022 followed by alpha-Pyrrolidinohexiophenone (alpha-PHP) and then butylone and dibutylone. Alpha-PHP was detected throughout the second half of 2022 with the exception of August. Butylone prevalence in 2022 was somewhat sporadic being detected in January, April, July and August and October and November. Dibutylone, another positional isomer of pentylone, was first detected at Aegis in January of 2022, then did not make an appearance again until May and June. Its detection continued into July and August but then it was not detected again for the remainder of 2022. 3-Trifluoromethylphenylpiperazine (TFMPP) was only detected in a single month in the first half of 2022 but, during the second half of 2022, it was detected in four of the six months. 2-Fluoroamphetamine was first detected at Aegis in August of 2021. In 2022, it was detected only in August, nearly a year after it was last detected in October of 2021. In the first half of 2022 there were a number of synthetic stimulants that were newly detected, including N-ethylhexedrone and N-ethylheptedrone, which were each only detected in a single month. Fluorinated amphetamine and methylphenidate analogs, 3/4-fluoroamphetamine and 4-fluoromethylphenidate were also newly detected in the first half of 2022. However, with the exception of 4-fluoromethylphenidate, which was detected in July, none of these compounds newly detected in the first half of 2022 were detected in the second half of 2022. Five synthetic stimulants were newly detected at Aegis in the second half of 2022 including N,N-dimethylpentylone, N-cyclohexyl Methylone, N-butyl Hexedrone, Methylenedioxy-PV8, and dimethylone. Of these, only N,N-dimethylpentylone and N-cyclohexyl Methylone were detected in more than a single month.



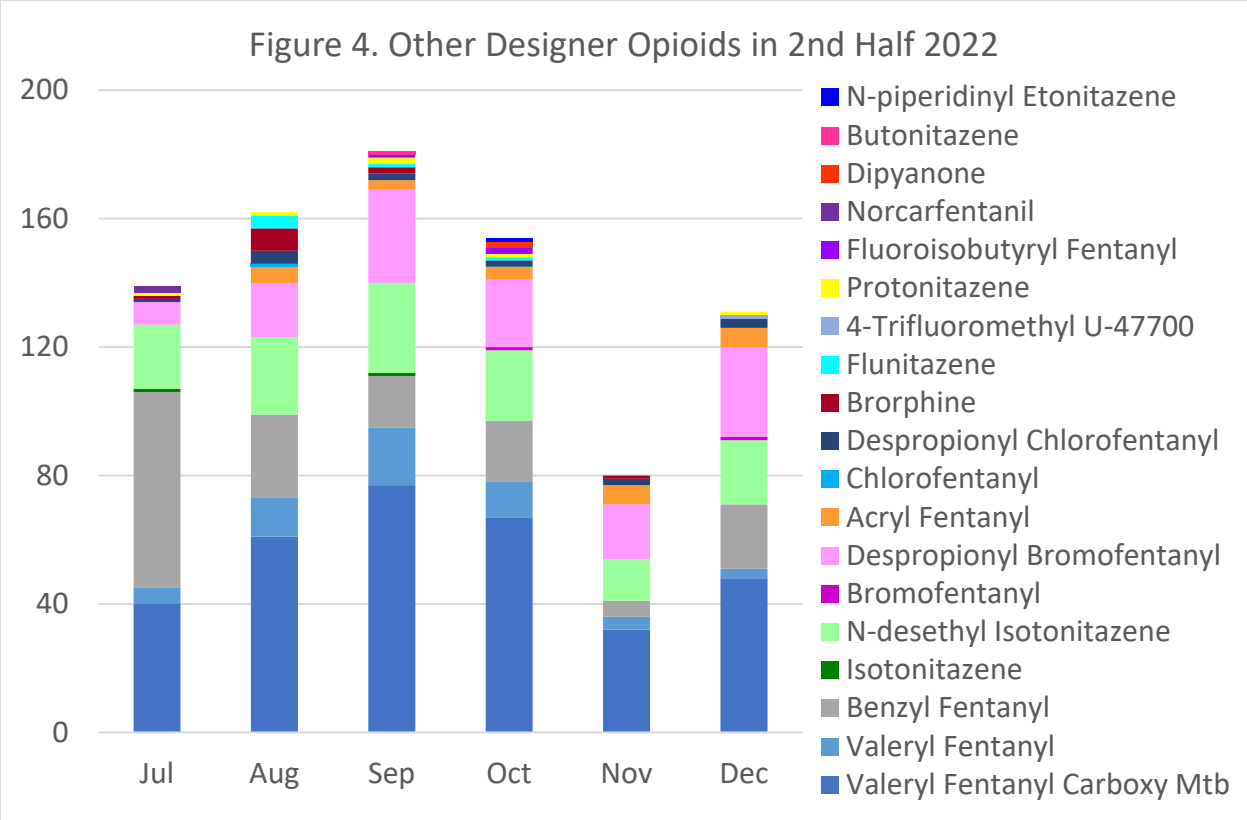
Designer Opioids

Designer opioids include various classes of compounds such as fentanyl analogs, also called "fentalogs," along with "nitazene analogs," "utopioids," and others. The prevalence of the top four designer opioids of the second half of 2022 are shown in Figure 3. The most prevalent designer opioid, fluoro fentanyl, is often detected with despropionyl fluoro fentanyl which may be either a metabolite of fluoro fentanyl or a process impurity. These two designer opioids remain the most frequently detected NPS among all NPS classes tested. In the first half of 2022 there was a rise in detection of "nitazene" compounds, which continued into the second half of 2022, with 4-hydroxy nitazene becoming the third most prevalent designer opioid detected followed closely by metonitazene. 4-hydroxy nitazene and N-desethyl isotonitazene are known metabolites of isotonitazene however, 4-hydroxy nitazene is predominantly detected alone or in combination with metonitazene. It has also been detected with other parent nitazene analogs, so it may eventually be found as a shared metabolite. Metonitazene detections increased throughout 2022, resulting in it becoming the fourth most prevalent designer opioid detected in 2022. Metonitazene was first identified in 2020 and has since been identified as a public health concern as it has been increasingly identified in forensic death investigation casework.[3]



The prevalence of other designer opioids detected in the second half of 2022 is shown in Figure 4. Detection of valeryl fentanyl and its carboxy metabolite increased in 2022 to peak in September. Although its detection decreased somewhat in mid to late Q4 of 2022, it ended as the fifth most prevalent designer opioid of 2022. Benzyl fentanyl detection increased by more than 70% from January to its peak detection in July but due to the rise in nitazene compounds and increase in valeryl fentanyl, it dropped to 6th most prevalent designer opioid detected in 2022. The prevalence of despropionyl bromofentanyl also saw significant increases in 2022 rising more than 9-fold

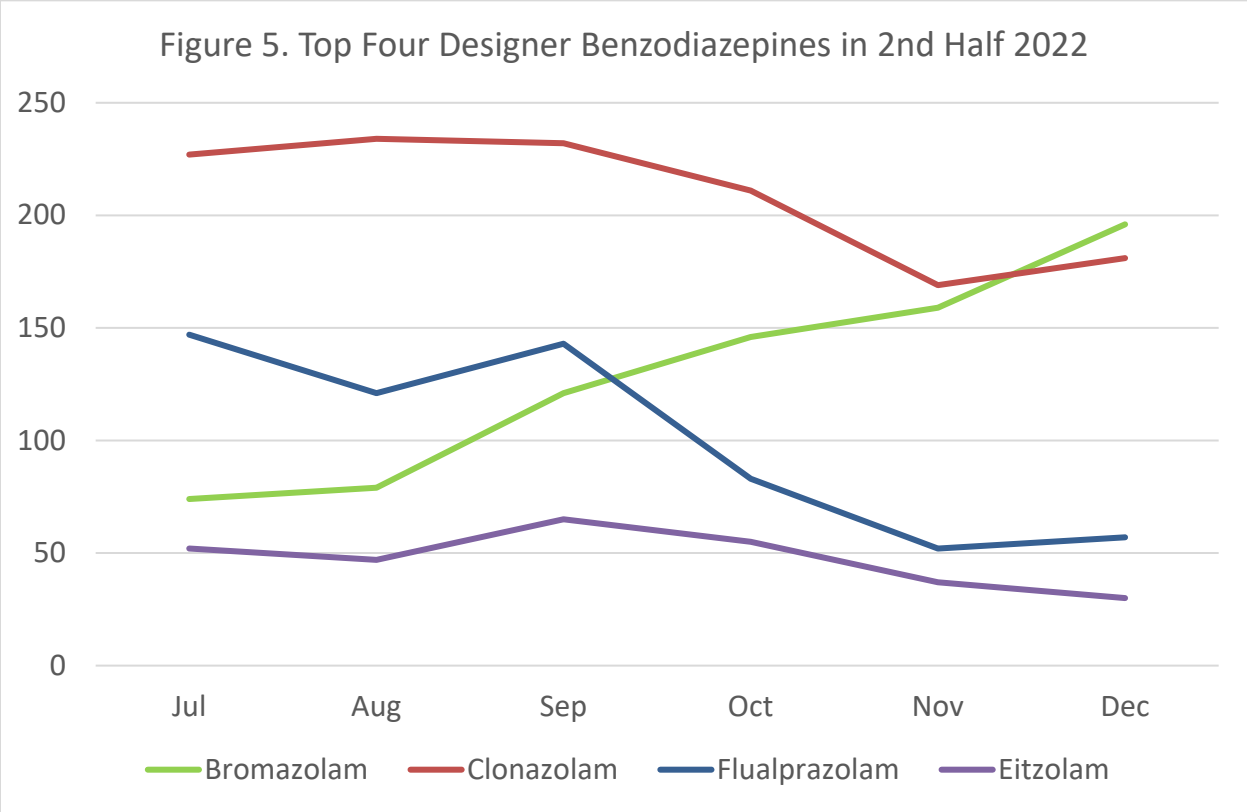
from January to December. Four designer opioids were newly detected in the first half of 2022. These include the utopioid U-47700 and cyclopropyl fentanyl which made an appearance in May and June respectively, protonitazene which appeared in March, April, and June, and despropionyl chlorofentanyl which has been sporadically detected, with the most occurrences in June. Of these, only protonitazene and despropionyl chlorofentanyl were detected in the second half of 2022, each being detected throughout with protonitazene being detected in all months except November. There were five new designer opioids detected in the second half of 2022, 4-Trifluoromethyl U-47700, dipyanone, N-piperidinyl Etonitazene, butonitazene and flunitazene. Of these only flunitazene was detected in more than one month, being detected in a three consecutive month period from August through October.



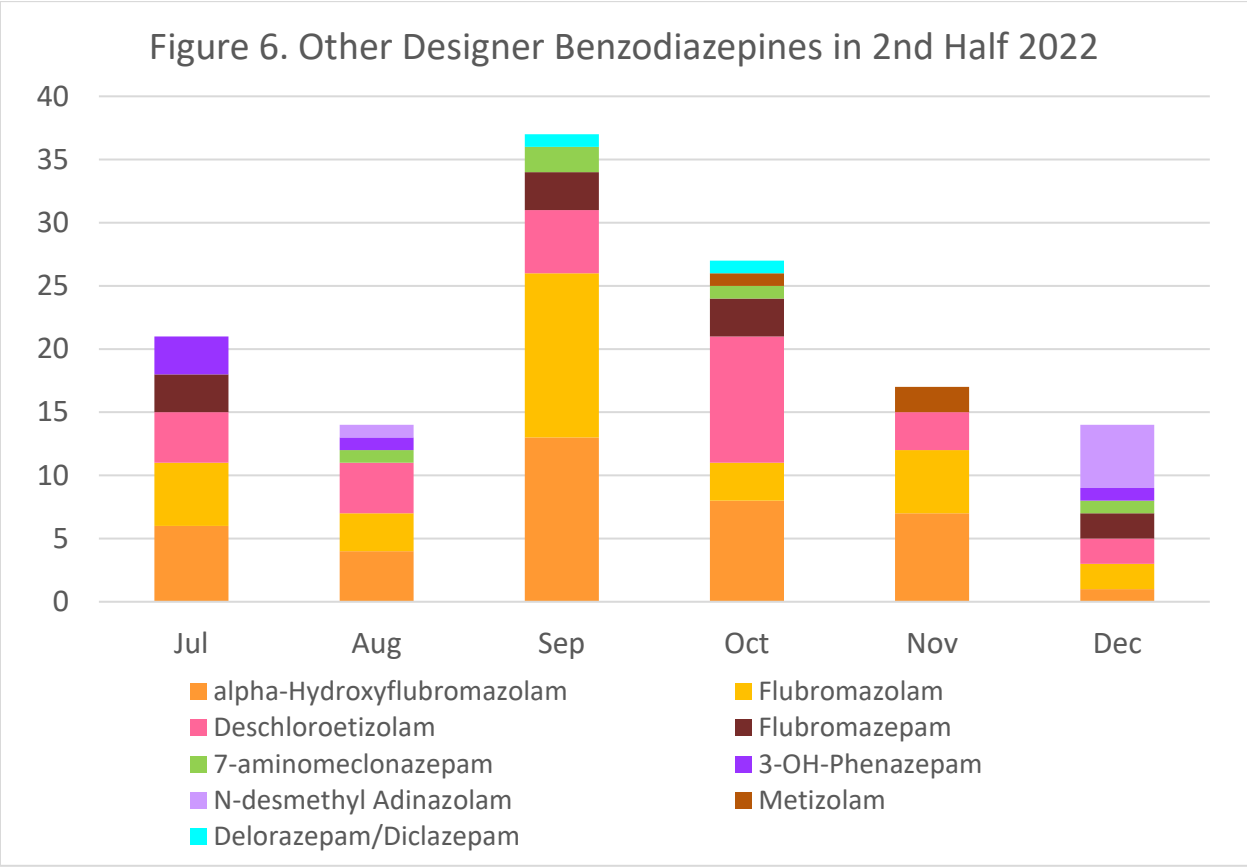
Designer Benzodiazepines

The prevalence of the top four designer benzodiazepines detected in the second half of 2022 is shown in Figure 5. In the first half of 2022, clonazolam was the most prevalent designer benzodiazepine detected followed by flualprazolam. Based on the number of detections, clonazolam remains the most prevalent designer benzodiazepine detected in 2022, although its positivity in the fourth quarter of 2022 is decreasing, with the number of bromazolam positives exceeding those of clonazolam in December. In January of 2022, flualprazolam and bromazolam had the same number of positive results but from January to May of 2022 bromazolam doubled whereas flualprazolam increased by more than 6-fold. However, this trend did not continue into the second half of 2022. There is an overall decreasing positivity for three of the top four designer benzodiazepines, the exception being bromazolam which has continued to increase, more than doubling from July to December. Interestingly, as of December of 2022 the DEA has temporarily placed clonazolam, etizolam, flualprazolam, flubromazolam and diclazepam in Schedule I of the Controlled Substances Act to attempt to limit access to these substances.

Bromazolam was not included in this list of scheduled designer benzodiazepines, so demand for it may increase if it becomes sought after as a replacement. As of January of 2023, bromazolam has continued to increase.

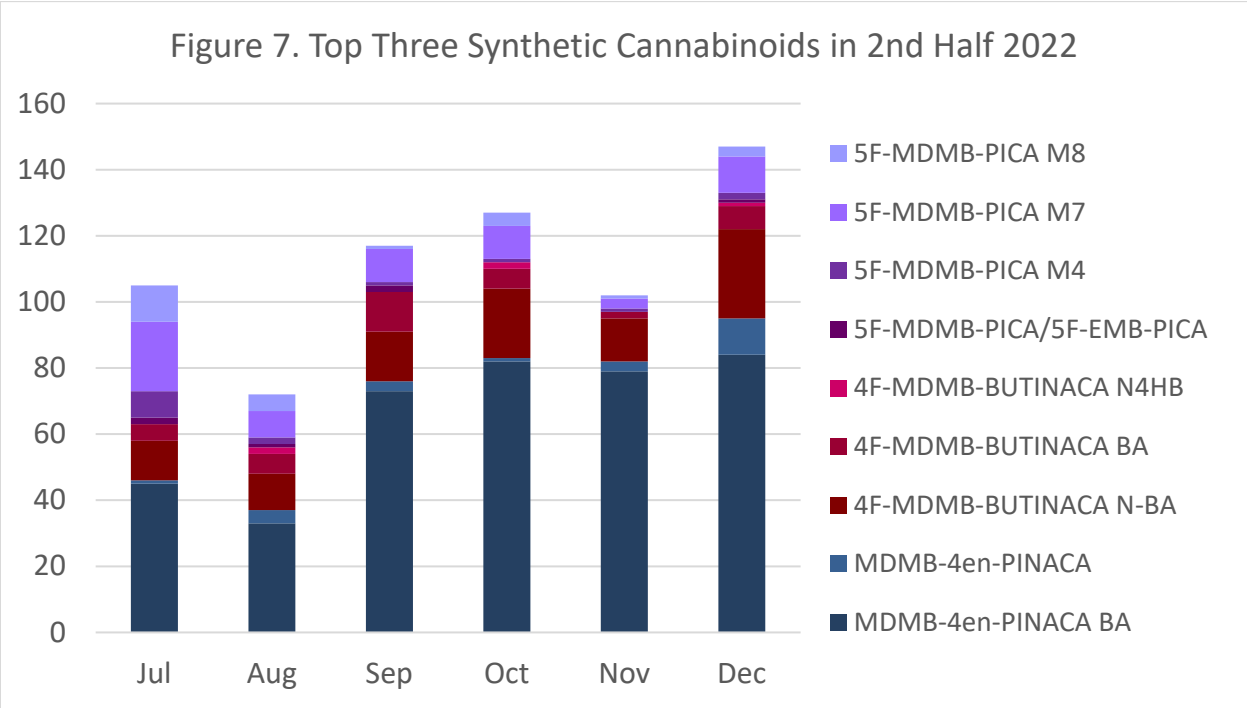


The prevalence of other designer benzodiazepines detected in the second half of 2022 is shown in Figure 6. After the top four, flubromazolam and its metabolite alpha-hydroxyflubromazolam were the next most prevalent designer benzodiazepines detected, with detection throughout 2022, its lowest prevalence being in December. Flubromazepam, which was detected every month of the first half of 2022, was detected less and more sporadically in the second half. Detection of diclazepam and/or its metabolite delorazepam occurred over a consecutive three-month period from February through April and then again in September and October. 3-OH-Phenazepam was sporadically detected in April, June through August, and again in December. Deschloroetizolam was newly detected in February of 2022 with detection in all subsequent months of 2022, increasing to peak in October. Adinazolam was also newly detected in 2022, appearing only in March. In the second half of 2022, it's metabolite N-desmethyl adinazolam was detected in August but predominantly in December. Metizolam and the meclonazepam metabolite 7-aminomeclonazepam were the only designer benzodiazepines newly detected in the second half of 2022. Metizolam was detected only in October and November whereas 7-aminomeclonazepam was detected August through December, with the exception of November.

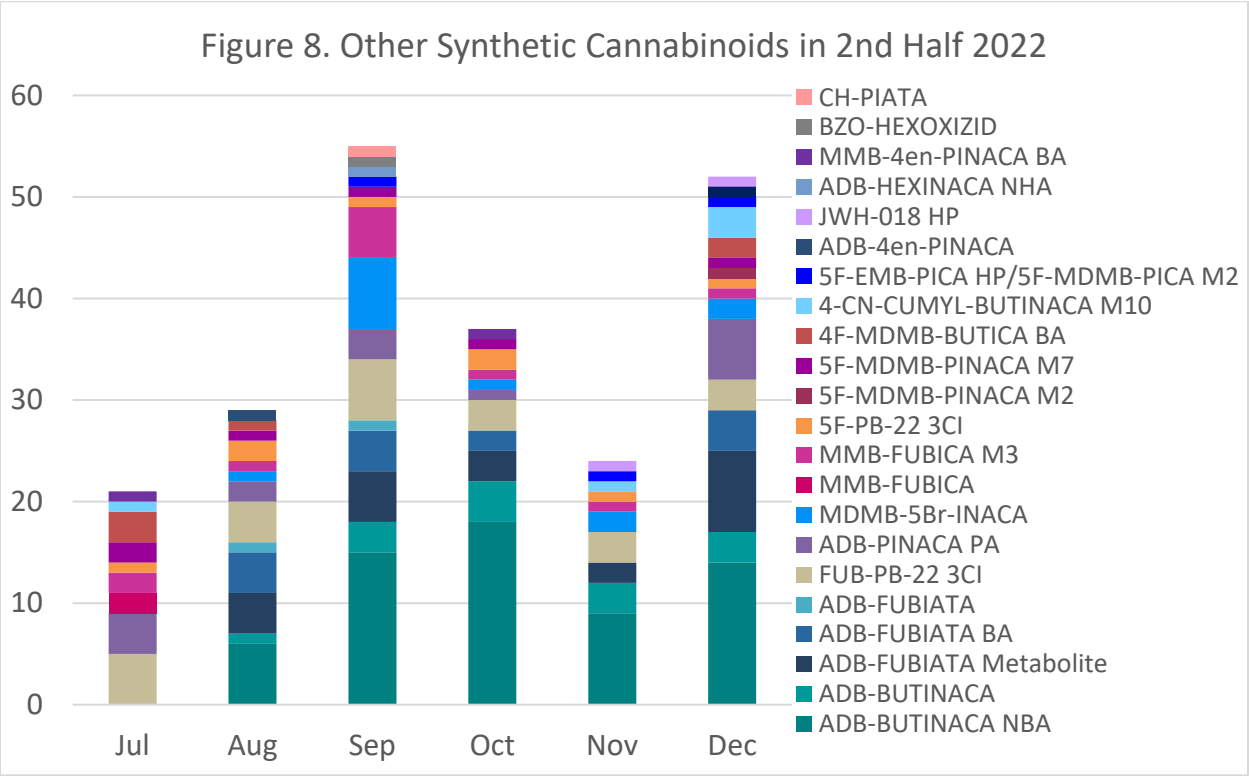


Synthetic Cannabinoids

The top synthetic cannabinoid compounds detected in the first half of 2022 were MDMB-4en-PINACA and its butanoic acid metabolite, 5F-MDMB/EMB-PICA and metabolites, and metabolites of 4F-MDMB-BUTINACA. The top three most prevalent synthetic cannabinoids detected in the second half of 2022 are shown in Figure 7. MDMB-4en-PINACA butanoic acid detection increased by approximately 86% during the second half of 2022 and it remained the most prevalent synthetic cannabinoid detected at Aegis in 2022. 5F-MDMB-PICA M7 was the most frequently detected metabolite of 5F-MDMB/EMB-PICA and its detection increased to peak in May with an overall decreasing trend through the remainder of the year. 4F-MDMB-BUTINACA N-BA detection was steady in the first half of 2022 but saw an overall increasing trend in the second half of 2022. These top three along with FUB-PB-22 3Cl were the only synthetic cannabinoids that were detected in every month of 2022.



The prevalence of other synthetic cannabinoids detected in 2022 is shown in Figure 8. What is first noticeable is the large number of compounds detected, many of which were detected for the first time. These include ADB-BUTINACA and metabolite, ADB-FUBIATA and metabolites, ADB-4en-PINACA, ADB-HEXINACA metabolite, MDMB-5Br-INACA, 5F-EMB-PICA HP/5F-MDMB-PICA M2, BZO-HEXOXIZID, CH-PIATA and JWH-018 HP. Many of these were added to synthetic cannabinoid testing at Aegis in August of 2022. Of the newly added compounds, ADB-BUTINACA and metabolite together were the most frequently detected and quickly became the fourth most prevalent synthetic cannabinoid in 2022 rivaling the prevalence of FUB-PB-22 3Cl which was detected for the entirety of 2022. ADB-FUBIATA and metabolites were also newly added compounds that became some of more prevalent synthetic cannabinoids detected in 2022. In addition to ADB-BUTINACA and ADB-FUBIATA metabolites, MDMB-5Br-INACA was the only other newly added synthetic cannabinoid that was detected for the remainder of 2022. Other newly added compounds including ADB-4en-PINACA, ADB-HEXINACA metabolite, BZO-HEXOXIZID, CH-PIATA and JWH-018 HP were only detected in one to two months of 2022.

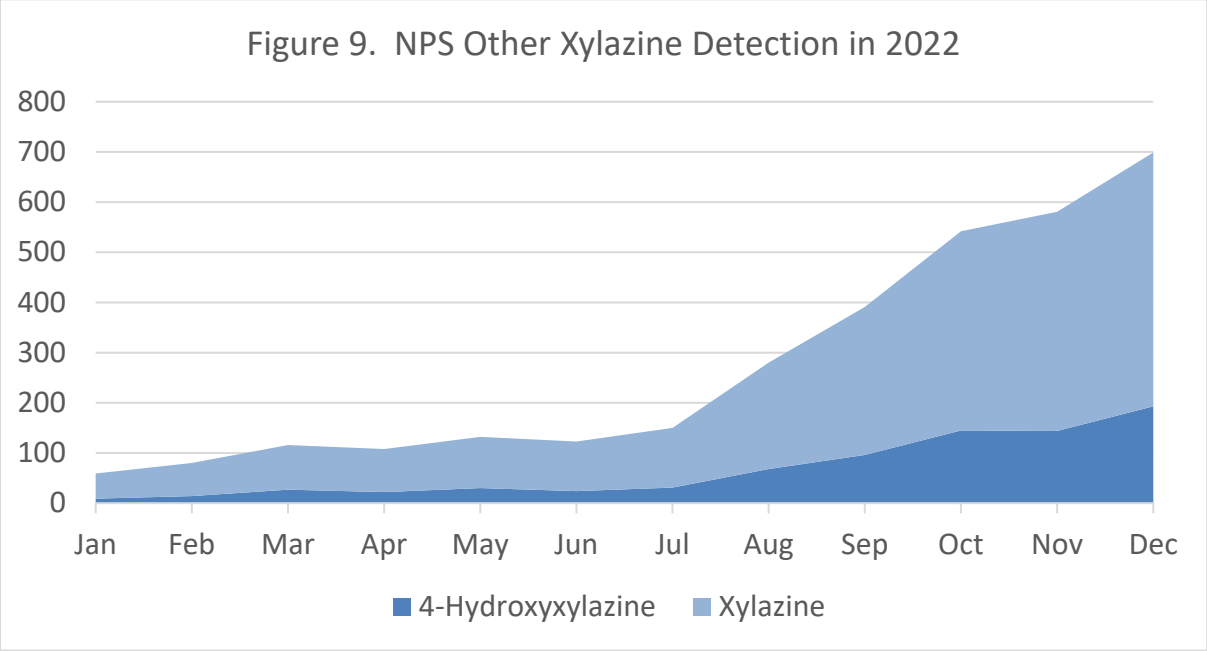


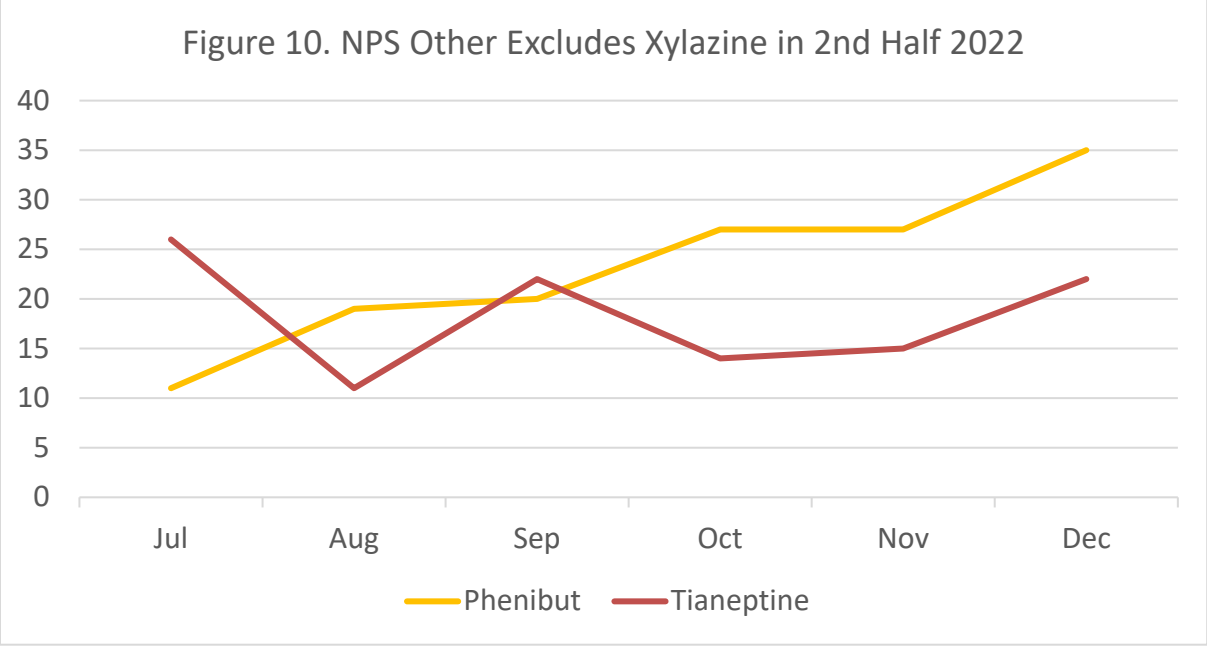
Hallucinogens/Dissociatives

Four compounds of the hallucinogen/dissociative NPS class were newly detected in the first half of 2022. These included 2F-Deschloroketamine and its metabolite 2F-deschloronorketamine, 3F-PCP and Deschloro-N-Ethylketamine. 2F-Deschloroketamine and its metabolite 2F-deschloronorketamine first appeared in April and metabolite was detected throughout the remainder of 2022 becoming the most prevalent hallucinogen/dissociative compound detected in 2022. 3F-PCP was first reported in March and was detected through June and then again in September and October. It ranks as the third most prevalent compound in the Hallucinogen/Dissociative class detected in 2022. Deschloro-N-Ethylketamine was only detected in May of 2022. In the second half of 2022, hydroxetamine and the PCP analog, 3-hydroxy PCP, were the only newly detected compounds in the Hallucinogen/Dissociative class. Hydroxetamine was detected only in August of 2022 whereas 3-hydroxy PCP was detected September through November, yet was the second most prevalent hallucinogen/dissociative detected in 2022. Interestingly, deschloroketamine and its metabolite deschloronorketamine, which have not been detected since October of 2021, were detected in November and December of 2022.

NPS-Other

Xylazine continues to be the predominant NPS detected in the NPS-Other category. The prevalence of xylazine and its metabolite 4-hydroxy xylazine are shown in Figure 9. Xylazine detection approximately doubled in the first half of 2022 but increased by more than 4-fold in the second half of 2022. Prevalence of additional compounds in the NPS Other category are shown in Fig 10. Phenibut detection increased by approximately 3-fold in the second half of 2022 whereas tianeptine, although consistently detected since March, fluctuated with its highest detection being in July.





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