



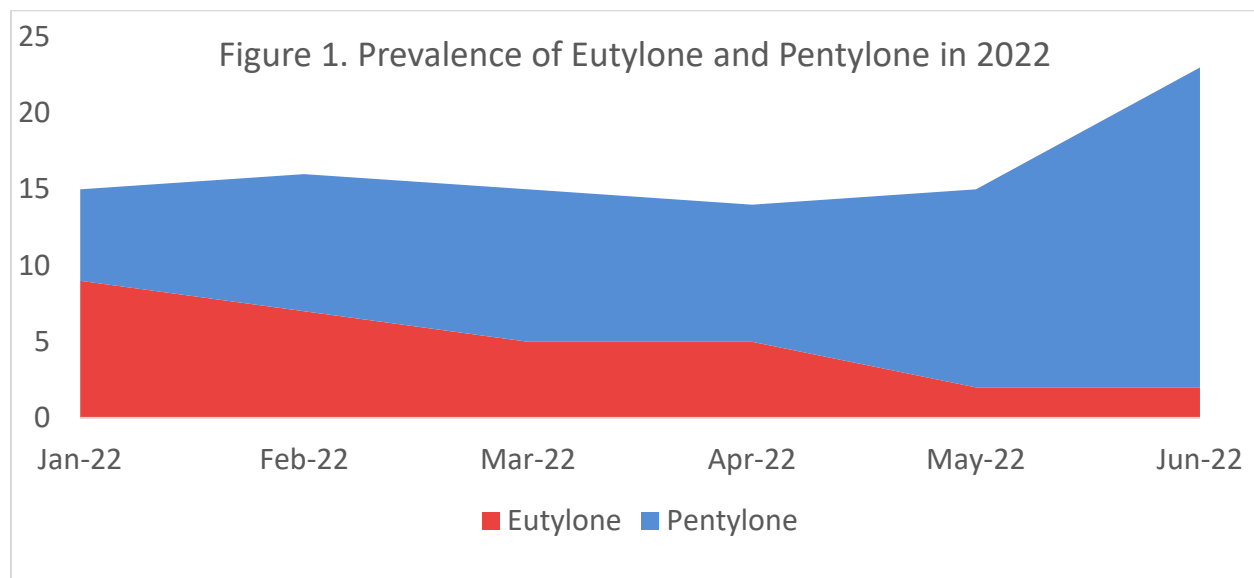
Clinical Update: July 2022

NOVEL PSYCHOACTIVE SUBSTANCES (NPS): WHAT'S NEW IN 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 benzodiazepines, designer opioids, 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 first half of 2022.

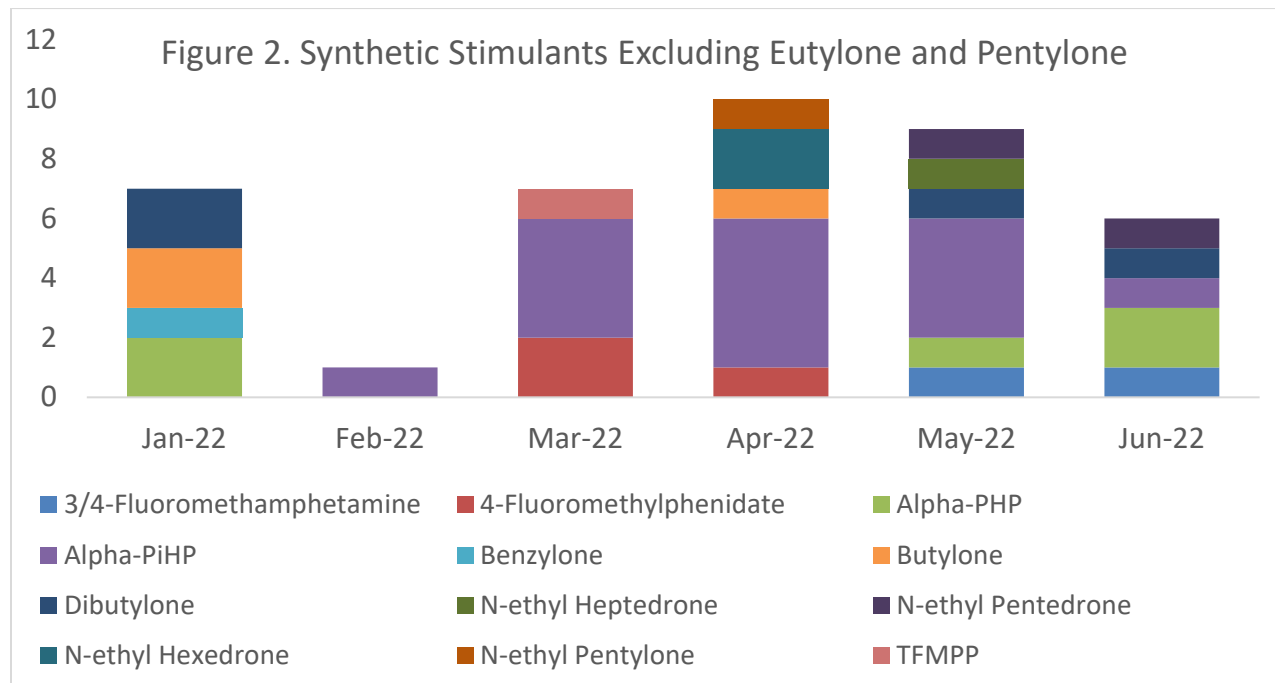
SYNTHETIC STIMULANTS

Synthetic stimulants tested at Aegis include analogs of amphetamine and methylphenidate as well as cathinones which have been erroneously sold as “bath salts”. Eutylone, a synthetic cathinone, has been the predominant synthetic stimulant detected through the fourth quarter of 2021. However, as of January 2022, prevalence of eutylone has been declining. Eutylone was added to Schedule I of the Controlled Substances Act as a positional isomer of pentylone, which was placed under Schedule I control in 2017 when it was the 5th most frequently reported synthetic cathinone.¹ Interestingly, as shown in Figure 1, prevalence of eutylone has decreased in 2022 as prevalence of pentylone has increased. Pentylone was first detected at Aegis in the third quarter of 2021, and has since replaced eutylone as the most prevalent synthetic stimulant detected in 2022. The increase in pentylone detection may be explained by recent data that suggests pentylone may be a major metabolite of the novel synthetic stimulant *N,N*-dimethylpentylone.²





Other synthetic stimulants detected in 2022 are shown in Figure 2. Butylone, which reached peak detection in July of 2021, was the third most prevalent synthetic stimulant detected in the fourth quarter of 2021. However, in 2022 prevalence of butylone decreased, only being detected in January and April. The third most detected synthetic stimulant in 2022, behind pentylone and eutylone, is alpha-Pyrrolidinoisohexanophenone (α -PiHP). Although detection of α -PiHP is not new in 2022, 65% of α -PiHP positive results occurred in 2022. Dibutylone, another positional isomer of pentylone, was in 2017 the second most commonly reported synthetic cathinone in the United States.¹ Dibutylone was first detected at Aegis in January of 2022, then did not make an appearance again until May and June. Two other stimulants of the synthetic cathinone class, N-ethylhexedrone and N-ethylheptedrone, were detected for the first time in 2022 but were each only detected in a single month. Also, newly detected synthetic stimulants in 2022 include fluorinated amphetamine and methylphenidate analogs, 3/4-fluoroamphetamine and 4-fluoromethylphenidate. 3/4-fluoroamphetamine is a metabolite of 3/4-fluoromethamphetamine which was first detected by itself in the fourth quarter of 2021. All of the 3/4-fluoroamphetamine positives detected in 2022 also had 3/4-fluoromethamphetamine present and thus are represented in Figure 2 as 3/4-fluoromethamphetamine.

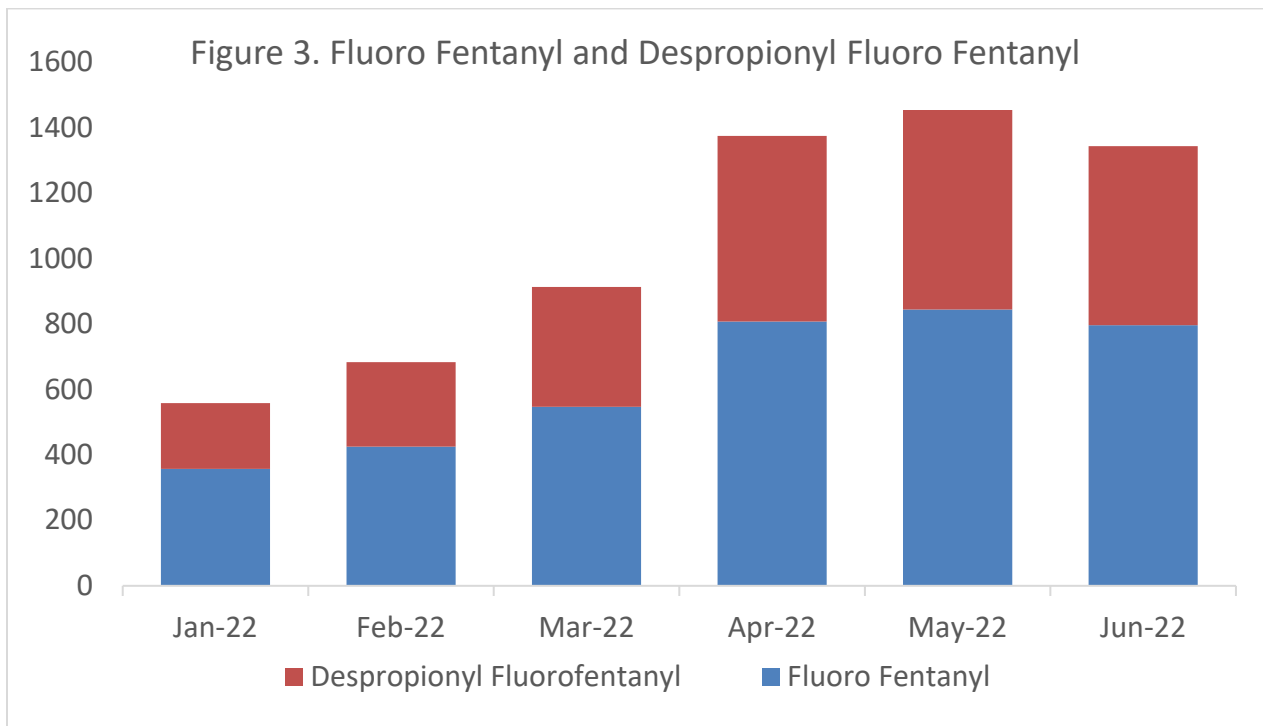


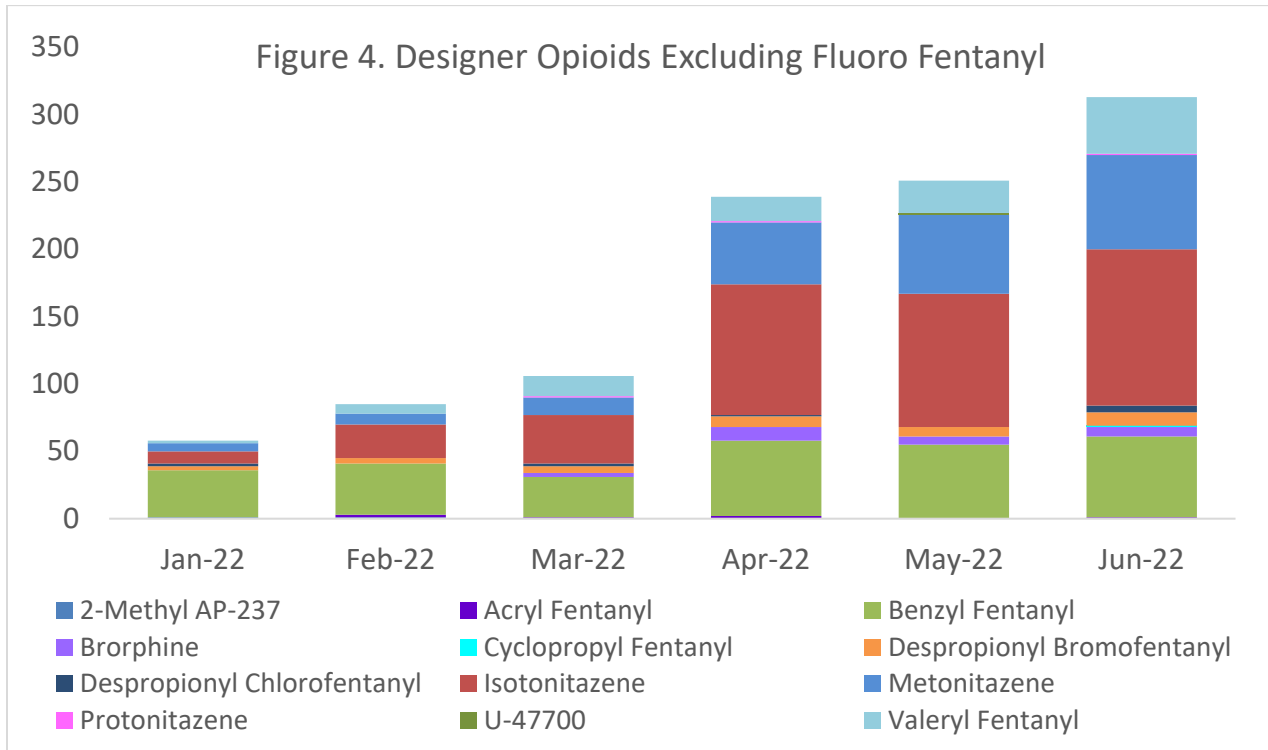
DESIGNER OPIOIDS

Designer opioids include various classes of compounds including fentanyl analogs, “nitazenes,” and “utopioids,” among others. The fentanyl analog Fluoro Fentanyl is often detected with despropionyl fluoro fentanyl which may be either a metabolite of fluoro fentanyl or an impurity. As of June of 2022, these two designer opioids remain the most frequently detected NPS among all NPS classes tested. The frequency of detection of these fentanyl analogs has increased in 2022 reaching a peak in May (see Figure 3). The prevalence of designer opioids detected in 2022, other than fluoro fentanyl and despropionyl fluoro fentanyl, is shown in Figure 4. Benzyl fentanyl was the third most frequently detected designer opioid in the fourth quarter of 2021 but dropped to fourth most prevalent in the first



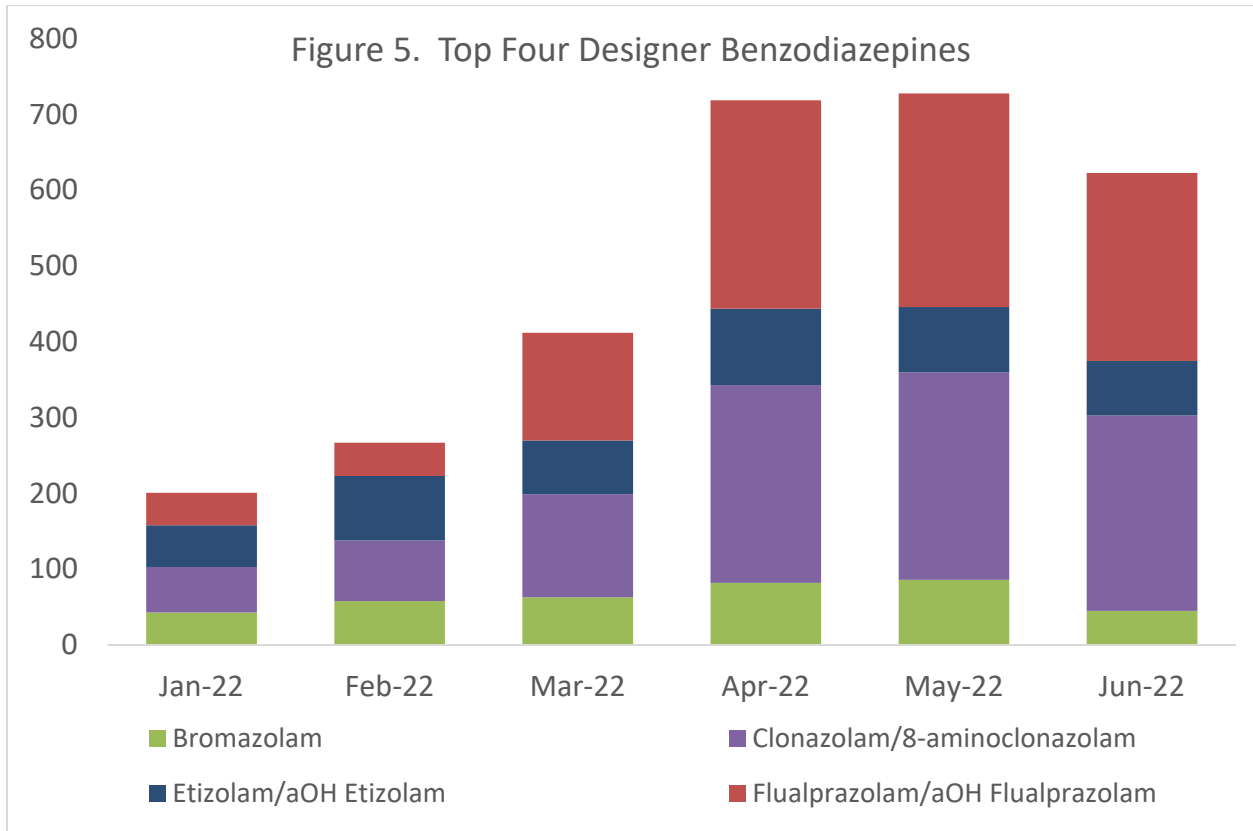
half of 2022, despite its detection being steady throughout 2022 and increasing approximately 67% from the average of the first quarter to the second. This is primarily due to the rise in the prevalence of nitazene compounds, specifically isotonitazene, which surpassed benzyl fentanyl to become the third most frequently detected designer opioid in the first half of 2022. Detection of isotonitazene and metabolites 4-hydroxy nitazene and N-desethyl isotonitazene, increased in 2022 reaching peak detection of greater than 7-fold its average detection in 2021. Another nitazene compound on the rise in 2022 is metonitazene, which 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 Detection of valeryl fentanyl and its carboxy metabolite increased throughout 2022 with the highest detection in June. Four designer opioids were newly detected in 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.



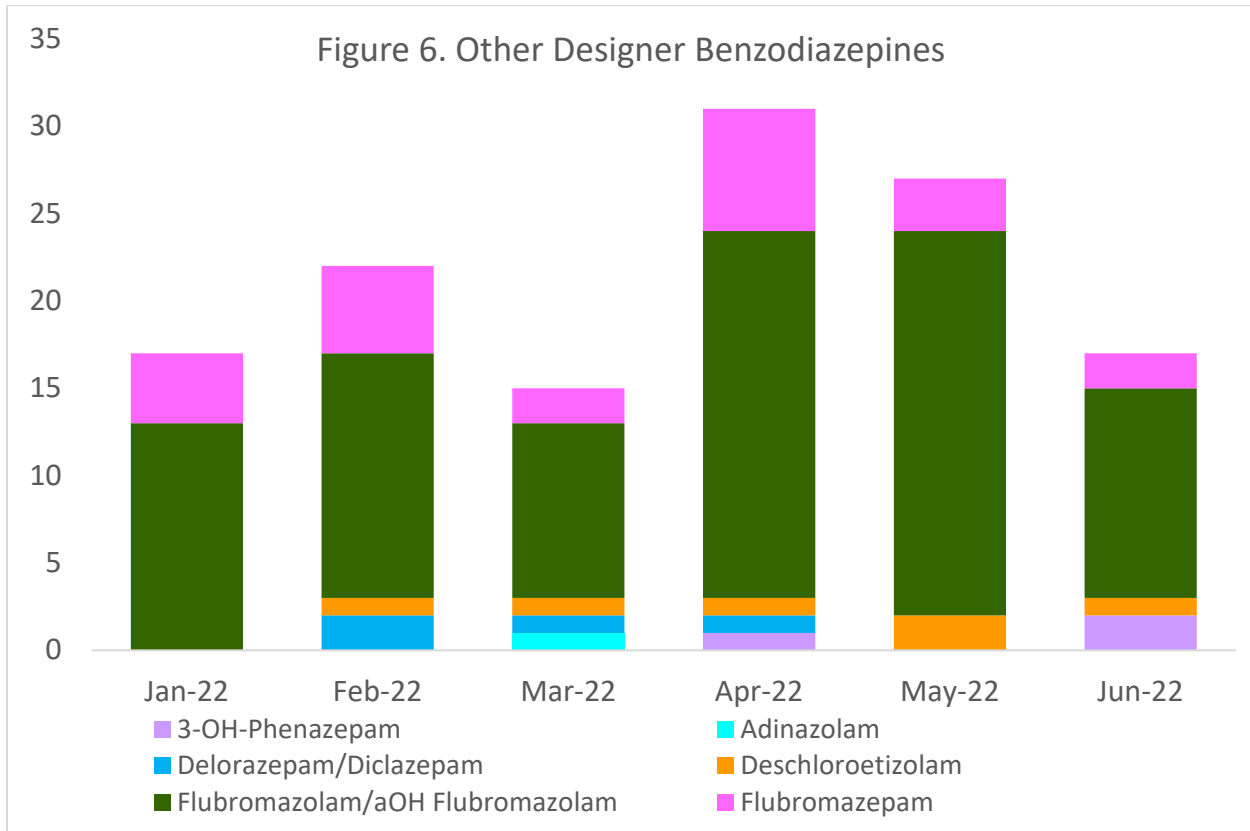


DESIGNER BENZODIAZEPINES

The prevalence of the top four designer benzodiazepines detected in 2022 is shown in Figure 5. Clonazolam and etizolam were the most prevalent designer benzodiazepines detected in 2021. In 2022, the prevalence of etizolam fluctuated whereas clonazolam increased to peak in May. The prevalence of flualprazolam increased more than 6-fold in 2022 rivaling detection of clonazolam. Bromazolam detection was steady in 2021, increasing slightly through November and then increasing by approximately 5-fold to peak in May of 2022.

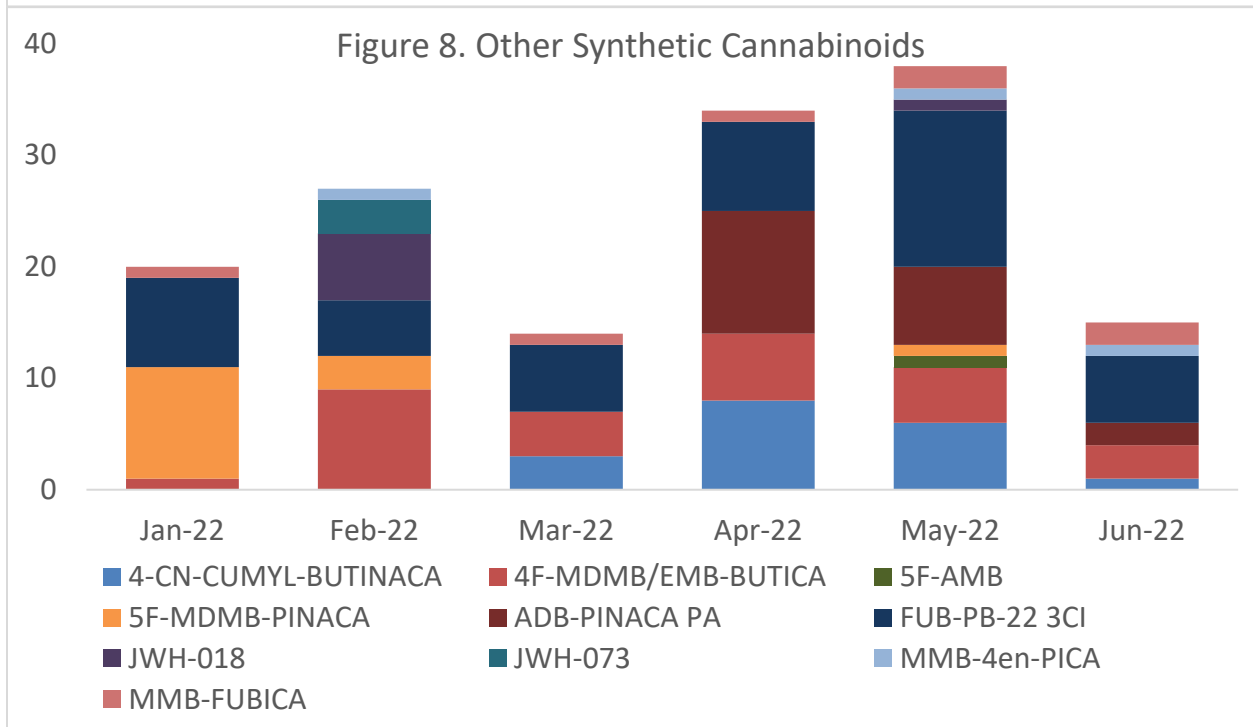
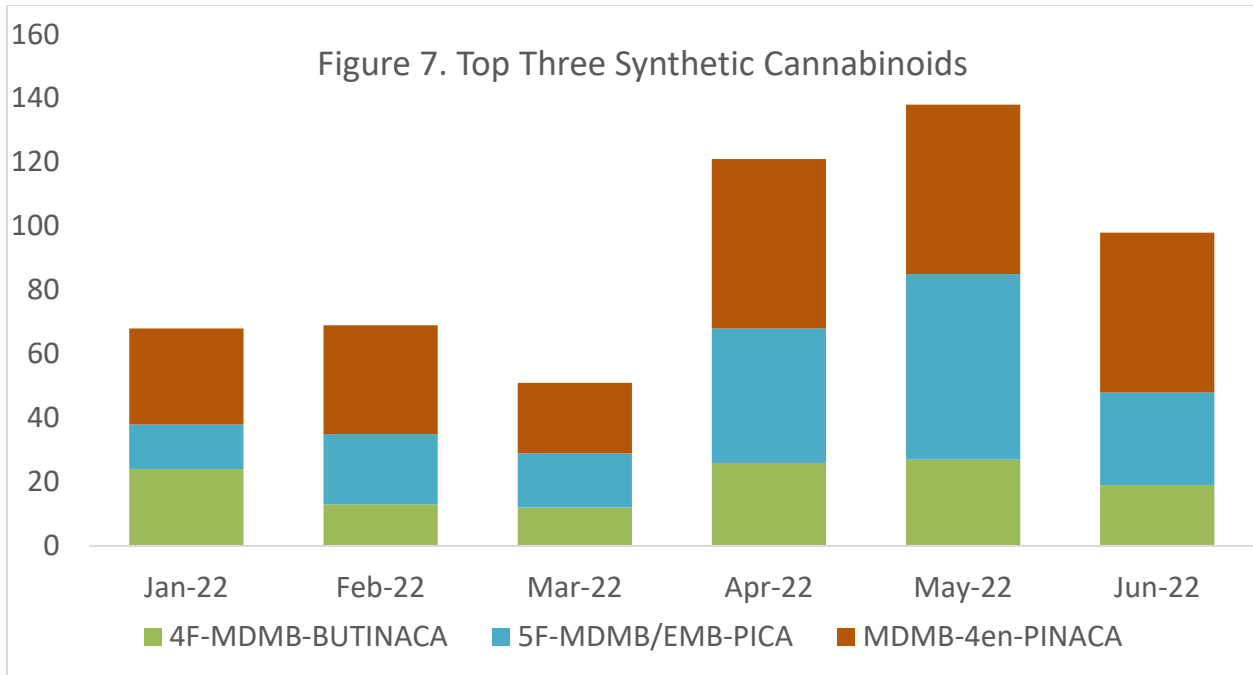


The prevalence of other designer benzodiazepines detected in 2022 is shown in Figure 6. Flubromazolam and flubromazepam were the next most prevalent designer benzodiazepines detected, both being detected throughout 2022. Detection of diclazepam and/or its metabolite delorazepam occurred over a consecutive three-month period from February through April 2022. 3-OH-Phenazepam was sporadically detected in April and June. Adinazolam and deschloroetizolam were newly detected in 2022 with adinazolam appearing only in March and deschloroetizolam being detected in every month except January.



SYNTHETIC CANNABINOIDS

The top synthetic cannabinoid compounds detected in the fourth quarter of 2021 were FUB-PB-22-3CI, MDMB-4-en-PINACA, and metabolites of 5F-MDMB/EMB-PICA. The top three most prevalent synthetic cannabinoids in the first half of 2022 are shown in Figure 7. MDMB-4en-PINACA was the most prevalent synthetic cannabinoid in 2022, with detection increasing by more than 80% from the first quarter of 2022 to the second. Similarly, detection of 5F-MDMB/EMB-PICA and its metabolites also increased from quarter one to quarter two; however, a larger increase of approximately 143% was observed. Monthly prevalence of MDMB-4-en-PINACA was greater than that of 5F-MDMB/EMB-PICA and its metabolites except for May, when 5F-MDMB/EMB-PICA was most prevalent. Metabolites of 4F-MDMB-BUTINACA were third most prevalent, with detection fluctuating somewhat throughout 2022. The prevalence of other synthetic cannabinoids detected in 2022 is shown in Figure 8. Detection of FUB-PB-22-3CI, which was the most prevalent synthetic cannabinoid detected in the fourth quarter of 2021, decreased from its peak in November of 2021, dropping to the fourth most prevalent synthetic cannabinoid behind metabolites of 4F-MDMB-BUTINACA. The prevalence of FUB-PB-22-3CI in 2022 was consistent except in May, when detection approximately doubled that of other months. 4F-MDMB/EMB-BUTICA is the only other synthetic cannabinoid that was detected in every month of 2022. MMB-FUBICA was detected in all months except February, and 4-CN-CUMYL-BUTINACA was detected March through June. 5F-MDMB-PINACA and MMB-4en-PICA were sporadically detected in 2022. JWH-018 and JWH-073 were some of the first synthetic cannabinoids marketed as “spice” and were declared schedule I controlled substances in 2012. Interestingly, the metabolites JWH-018 NPA and JWH-073 NBA were detected in 2022, indicating these synthetic cannabinoids are still available despite being controlled substances.



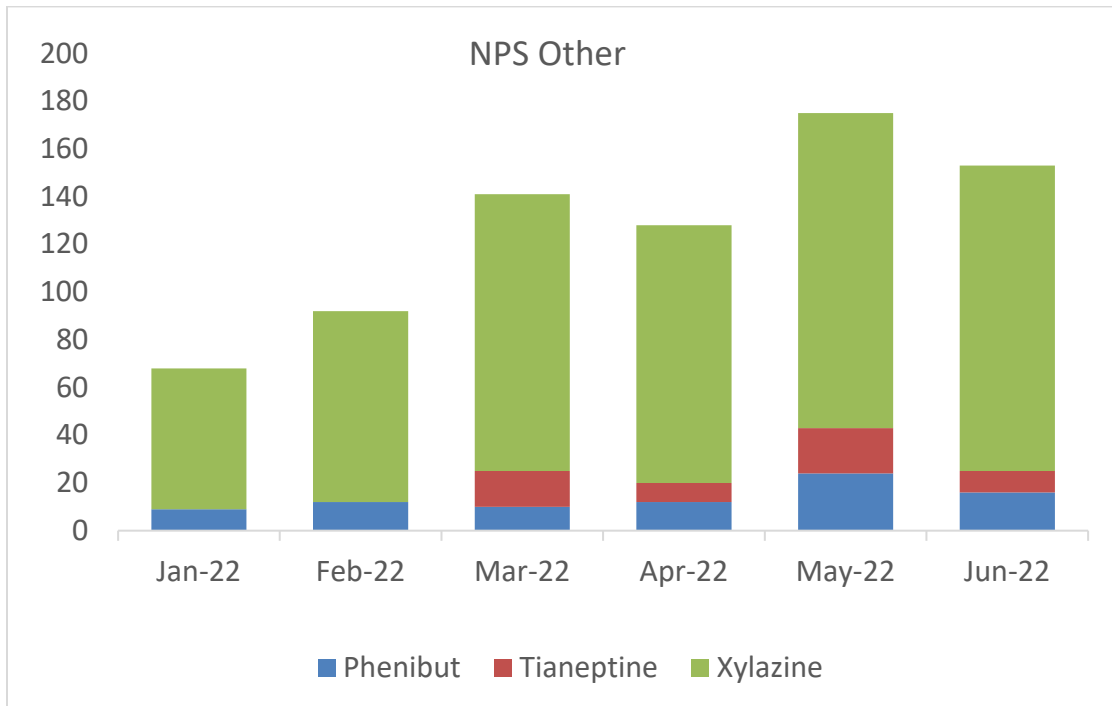
HALLUCINOGENS/DISSOCIATIVES

Four compounds of the hallucinogen/dissociative NPS class are newly detected in 2022. 3F-PCP was first reported in March and has been detected through June. 2F-Deschloroketamine and its metabolite 2F-deschloronorketamine first appeared in April and have been detected through June. Deschloro-N-Ethylketamine was detected in May 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 increased in the first half of 2022 reaching peak in May. Phenibut detection was steady for the first part of 2022 until May, when detection more than doubled that of prior months. Tianeptine was sporadically detected in 2021 but, since March of 2022, it has been detected consecutively from March through June.



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.

References:

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- https://www.npsdiscovery.org/wp-content/uploads/2021/12/NN-Dimethylpentylone_121721_CFSRE-Toxicology_Report.pdf
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