Clinical Update: April 2024

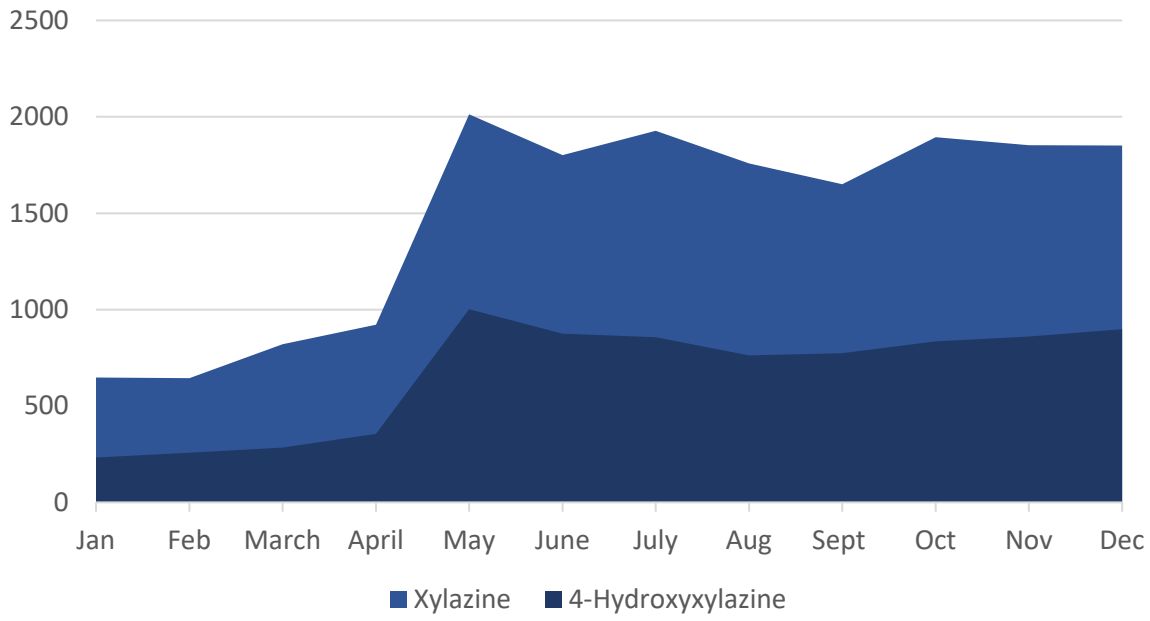
NOVEL PSYCHOACTIVE SUBSTANCE TRENDS IN 2023

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 focus of this clinical update is to evaluate changes observed in the prevalence of NPS detected at Aegis in 2023.

NPS-Other

The NPS-Other category includes substances that do not easily fit within a designated NPS classification. This group currently consists of xylazine, tianeptine (also known as gas station heroin), phenibut, and medetomidine which was added to NPS testing in September of 2023. Arguably the most interesting story of NPS in 2023 is xylazine. Xylazine continues to be the predominant NPS detected in the NPS-Other category, but in 2023 it became the most prevalent NPS detected at Aegis irrespective of NPS classification. The prevalence of xylazine and its metabolite 4-hydroxy xylazine in 2023 are shown in Figure 1. In the first half of 2022, xylazine detection approximately doubled but increased by more than 4-fold in the second half of 2022. In 2023, prevalence of xylazine and its metabolite continued to increase with an approximate 45% increase in detection from January to April. However, a sharp increase in detection of xylazine and its metabolite was observed from April to May, in which maximum detection occurred. For the remainder of 2023, detection stayed high but fluctuated somewhat and the year ended with detection at about 91% of the maximum observed.

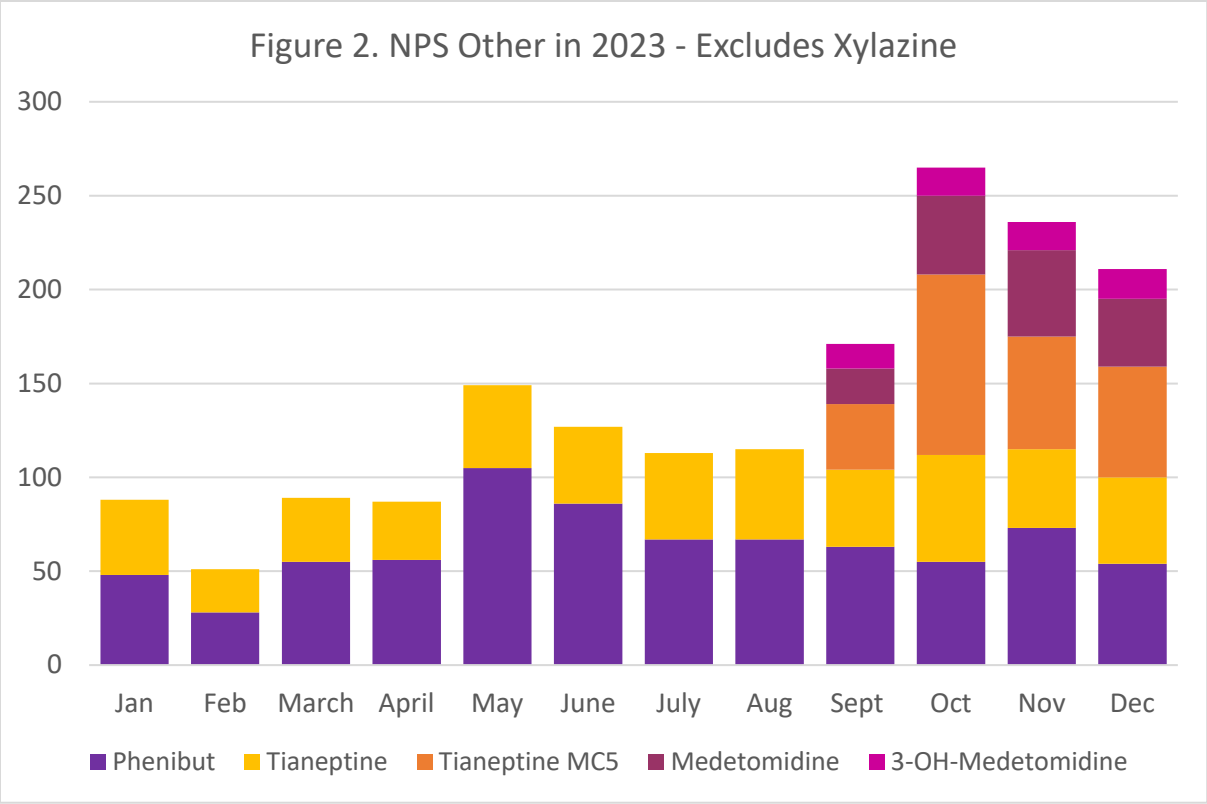
Figure 1. Xylazine in 2023



Prevalence of additional compounds in the NPS-Other category in 2023 are shown in Figure 2. Phenibut detection increased by approximately 3-fold in the second half of 2022, and in 2023, with the exception of February, it continued a slight increase from January through April. In May, detection increased nearly 88% to peak then slowly decreased throughout the remainder of the year, other than a slight bump in November, to levels seen in March and April.

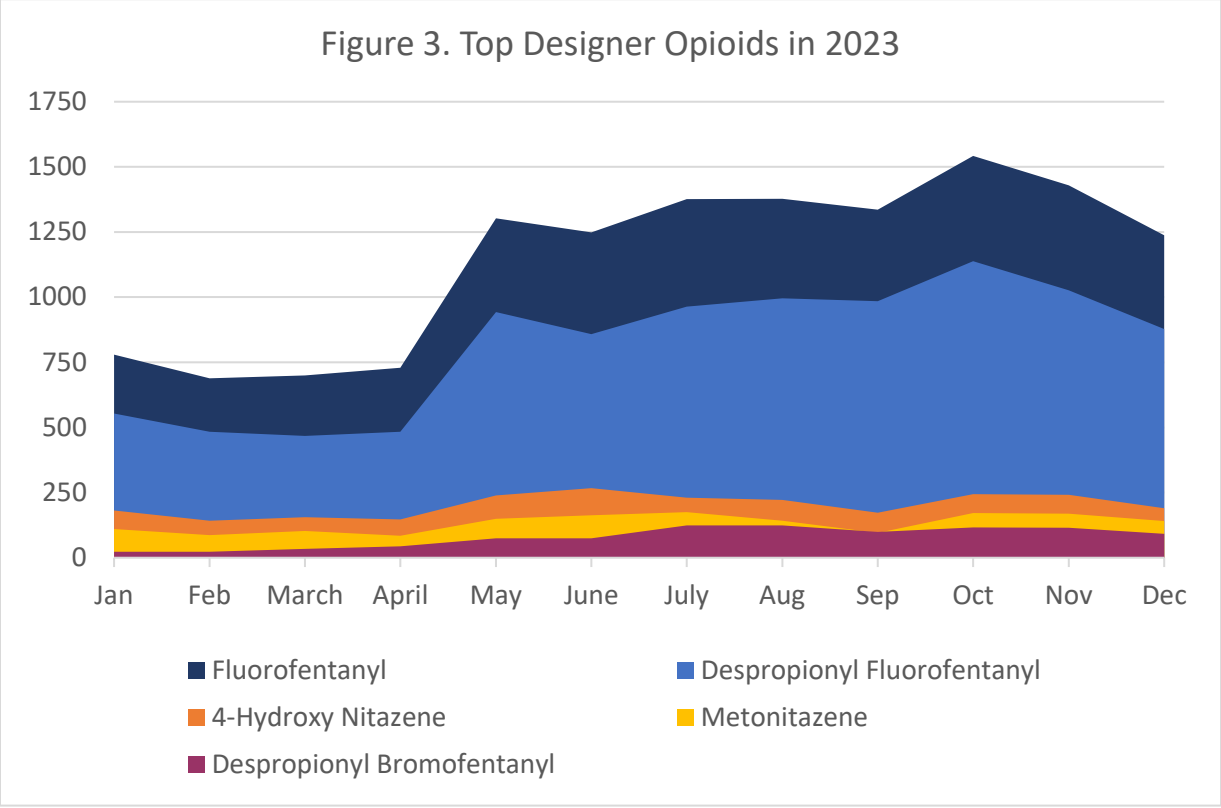
Tianeptine detection averaged 30% more in the second half of 2023 compared to that in the first half. In September of 2023, tianeptine metabolite MC5 was added to NPS testing. Its detection increased by approximately 174% from September to October to reach its highest for the year. For the remainder of the year, detection decreased to approximately 62% of the maximum. Interestingly, in approximately 33% of tianeptine positive samples both tianeptine and tianeptine MC5 were detected, whereas 38% were positive only for tianeptine and 29% were positive only for tianeptine MC5. This indicates the importance of including the metabolite in NPS testing for tianeptine.

Medetomidine and its metabolite 3-hydroxymedetomidine were also added to NPS testing in September. Medetomidine has been approved for medical use by the FDA and is available in both veterinary and human pharmaceutical formulations. However, like xylazine, medetomidine has been detected as an adulterant in the illicit drug supply.[2] Remarkably, of samples positive for medetomidine in 2023, nearly 98% were also positive for xylazine.



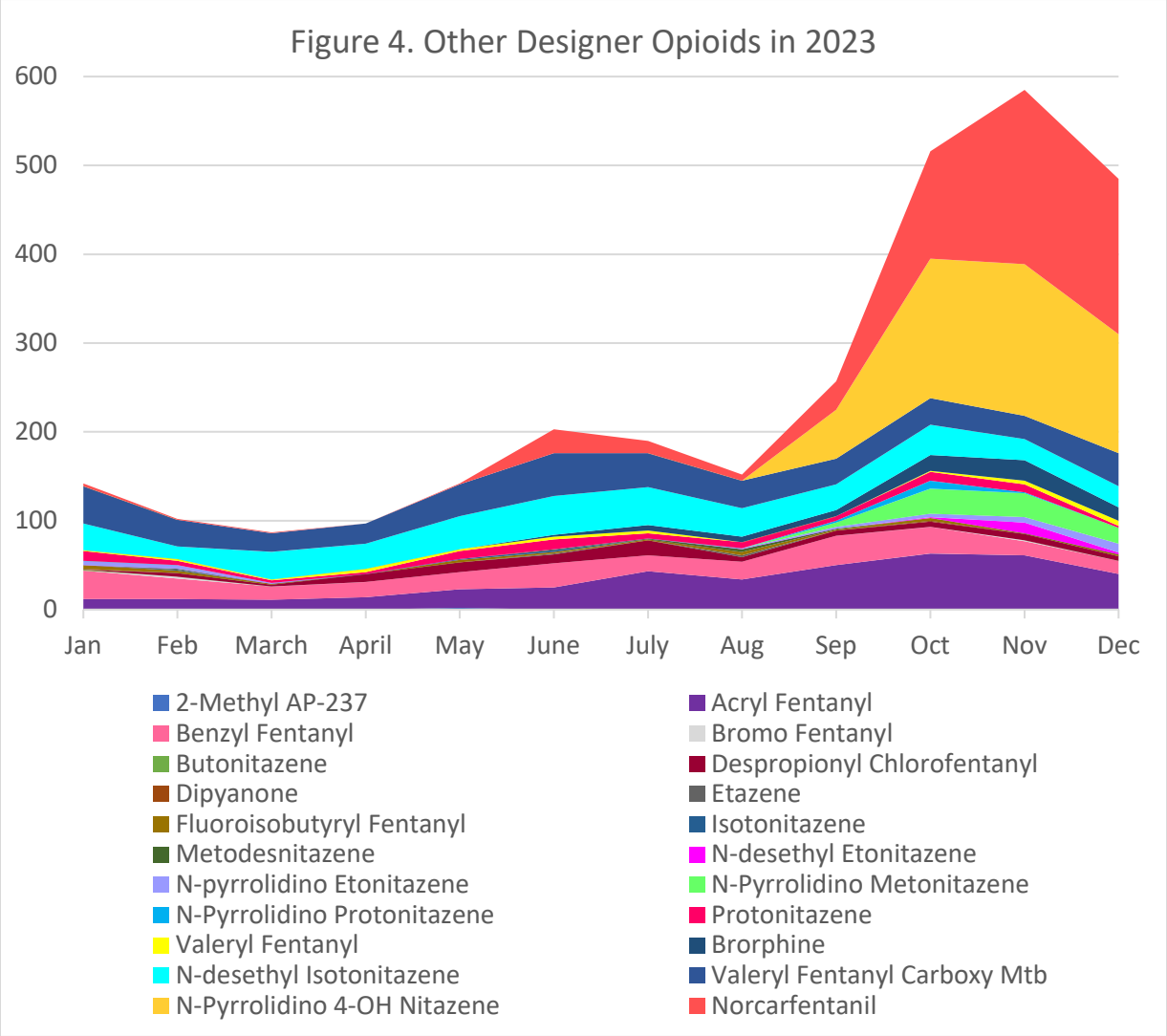
Designer Opioids

Designer opioids include various classes of compounds such as fentanyl analogs or "fentalogs," along with "nitazene analogs," and others. The prevalence of the top designer opioids detected in 2023 is shown in Figure 3. The most prevalent designer opioid, fluorofentanyl, is often detected with despropionyl fluorofentanyl which may be either a metabolite of fluorofentanyl or a process impurity. Fluorofentanyl has been the most frequently detected NPS among all NPS classes tested for at least two years. However, by April of 2023 xylazine overtook it as the most prevalent NPS detected at Aegis irrespective of NPS class, and this continued through the remainder of the year with fluorofentanyl being the second most frequently detected NPS. Fluorofentanyl detection in 2023 decreased slightly from January to April, then increased sharply in May and remained at high levels throughout the rest of 2023, peaking in October but then decreasing through December to approximately 95% of the May detection level. Despropionyl fluorofentanyl detection followed that of fluorofentanyl but at approximately 70% of its detection level. Fluorofentanyl has three positional isomers (meta-, ortho- and para-) that are not distinguished in Aegis' designer opioids test. In April of 2023, meta-fluorofentanyl was temporarily placed in schedule I of the Controlled Substances Act (CSA).[3] This was the last of these isomers to be scheduled as ortho- isomer was added to schedule I in October of 20194 and para-fluorofentanyl was added to schedule I in 1986 through the passing of the Controlled Substances Analogue Act (The Federal Analogue Act, P.L. 99-570). Despite this, para-fluorofentanyl reemerged in the illicit drug supply in 2020 and has been associated with overdose deaths.[5,6]



In 2019, there were class-wide bans on fentanyl-related substances in both the United States and China that impacted the availability of this type of designer opioid.[7] In 2022, a rise in detection of "nitazene" compounds ocurred, with 4-hydroxy nitazene becoming the third most prevalent designer opioid marker detected at Aegis followed closely by metonitazene. This trend continued in 2023 with 4-hydroxy nitazene and metonitazine again being the third and fourth most prevalent designer opioid analytes detected respectively. 4-hydroxy nitazene has been identified as a universal metabolite of nitazene analogs containing a 5-nitro group, N,N-diethylamine and an

associated phenyl ether.[8] This includes isotonitazene, metonitazene, etonitazene, protonitazene and butonitazene, all of which have been temporarily placed in schedule I of the CSA as of April of 2022.[9,10] In Aegis testing, 4-hydroxy nitazene has predominantly been detected alone or in combination with metonitazene but it has also been detected with other parent nitazene analogs. The fifth most prevalent designer opioid in 2023 was despropionyl bromofentanyl which saw increases in 2022 that continued in 2023 with detection increasing by approximately 5-fold from January to July, decreasing somewhat from August to December but still 4-fold greater than in January (see Figure 3). The prevalence of other designer opioids detected in 2023 is shown in Figure 4.

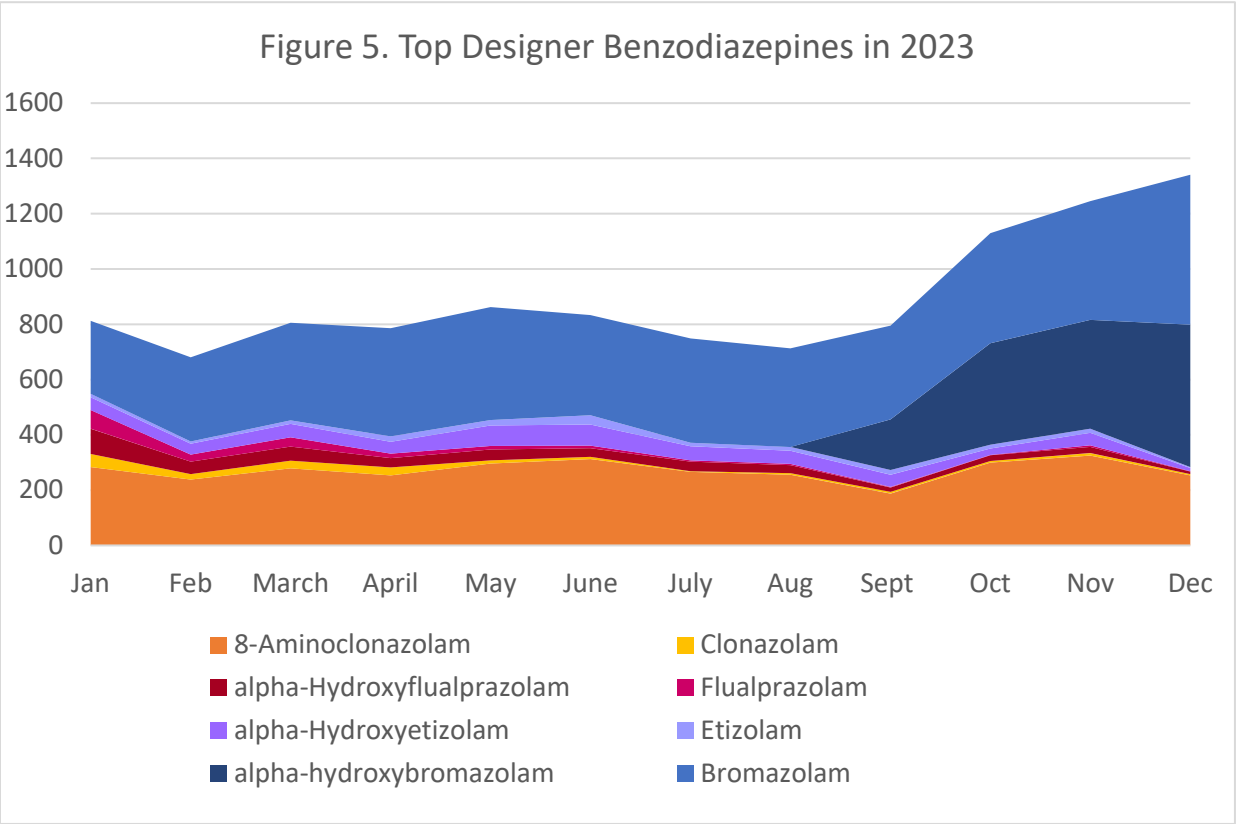


Detection of norcarfentanil is one of the more interesting results in designer opioid detection in 2023. Norcarfentanil is a shared metabolite of carfentanil and remifentanil and until recently had very minor detection in prior years. For example, in 2022 it was detected very minimally and in the month of July only. In 2023, norcarfentanil was detected in every month other than April. Detection was minimal in the first part of the year but increased significantly in the fourth quarter, such that it reached sixth most prevalent designer opioid in 2023. Valeryl fentanyl carboxy metabolite, N-desethyl isotonitazene, benzyl fentanyl and acryl fentanyl were all detected in every month of 2023. Detection of valeryl fentanyl carboxy metabolite increased from 2022 to 2023 yet it dropped in prevalence from fifth most prevalent designer opioid in 2022 to eighth most prevalent in 2023.

Detection of acryl fentanyl also increased in 2023 compared to 2022 with detection in the second half of 2023 approximately 3-fold greater than that of the first half. Benzyl fentanyl detection fluctuated a bit throughout the year but was fairly steady as the average detection in the first half of the year was identical to that of the second half. A number of nitazene analog analytes were added to Aegis' designer opioid testing in September of 2023 including N-Pyrrolidino 4-OH Nitazene, N-desethyl Etonitazene, N-Pyrrolidino Metonitazene, and N-Pyrrolidino Protonitazene and all were newly detected in the second half of 2023. N-Pyrrolidino 4-OH Nitazene was detected so frequently that it became the seventh most prevalent designer opioid detected in 2023. It is likely that as 4-hydroxy nitazene is a universal metabolite for nitazene compounds with certain structural characteristics that N-Pyrrolidino 4-OH Nitazene will be a universal metabolite for the Pyrrolidino form of those same nitazenes.

Designer Benzodiazepines

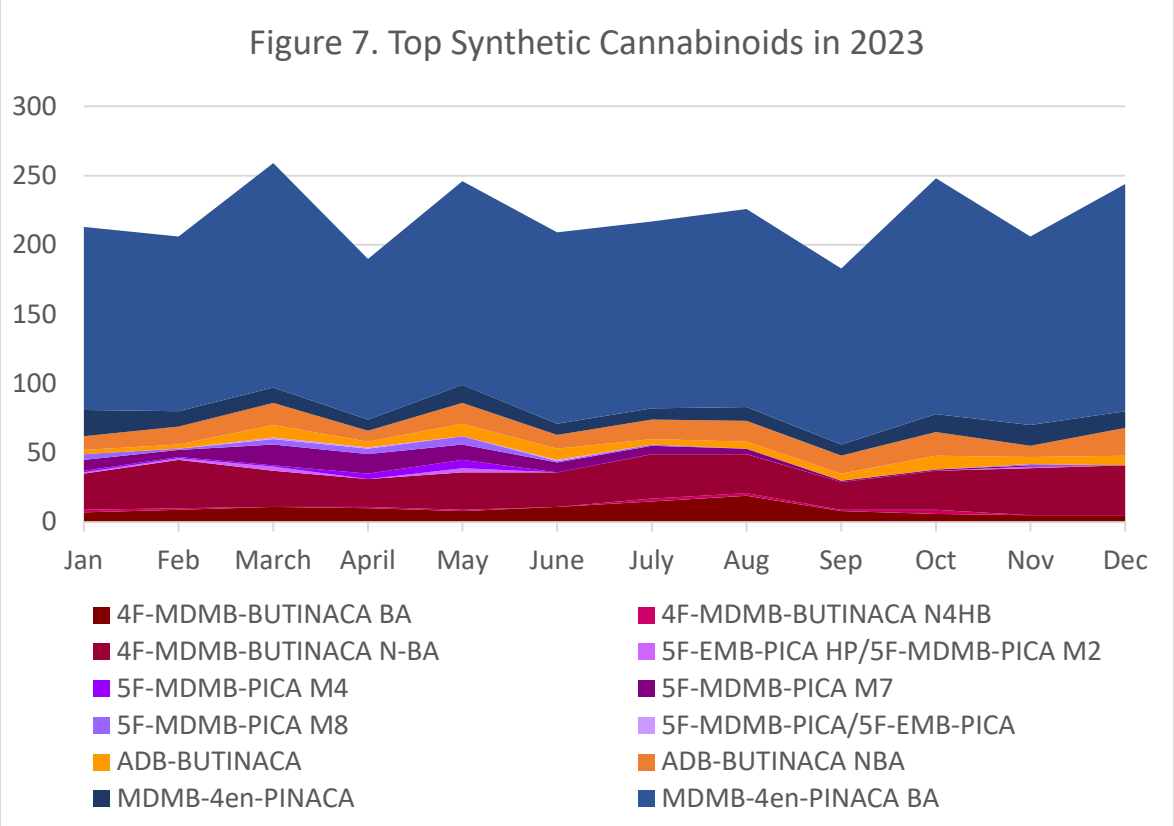
The prevalence of the top designer benzodiazepines detected in 2023 is shown in Figure 5. These compounds were also the top designer benzodiazepines detected in 2022 with clonazolam and metabolite being the most prevalent, followed by flualprazolam and metabolite. However, from September of 2022 through the end of the year there was an overall decrease in detection of three of the four top designer benzodiazepines. The exception being bromazolam which continued to increase, and more than doubled from July to December of 2022. Interestingly, as of December of 2022, the DEA temporarily placed clonazolam, etizolam, flualprazolam, flubromazolam and diclazepam in Schedule I of the CSA to attempt to limit access to these substances. However, bromazolam was not included in this list of scheduled designer benzodiazepines. Bromazolam detection continued to increase through May of 2023, decreased somewhat through September but then increased for the remainder of the year. Bromazolam was the most prevalent designer benzodiazepine detected in 2023 surpassing clonazolam which dropped to the second most prevalent. The bromazolam metabolite alpha-hydroxybromazolam was added to Aegis' testing in September of 2023 and in the fourth quarter of 2023 its detection was second only to bromazolam. Unlike detection of clonazolam and its metabolite 8-aminoclonazolam, which remained fairly steady throughout 2023, detection of flualprazolam and its metabolite alpha-hydroxyflualprazolam significantly decreased throughout the year causing it to drop to fourth most prevalent designer benzodiazepines in 2023. Detection of etizolam and its metabolite alpha-hydroxyetizolam fluctuated somewhat with significant increases in May and June and significant decreases in October and December. Overall, a decreasing trend in detection of etizolam and metabolite was observed with December levels of alpha-hydroxyetizolam being approximately 26% of that observed in January.



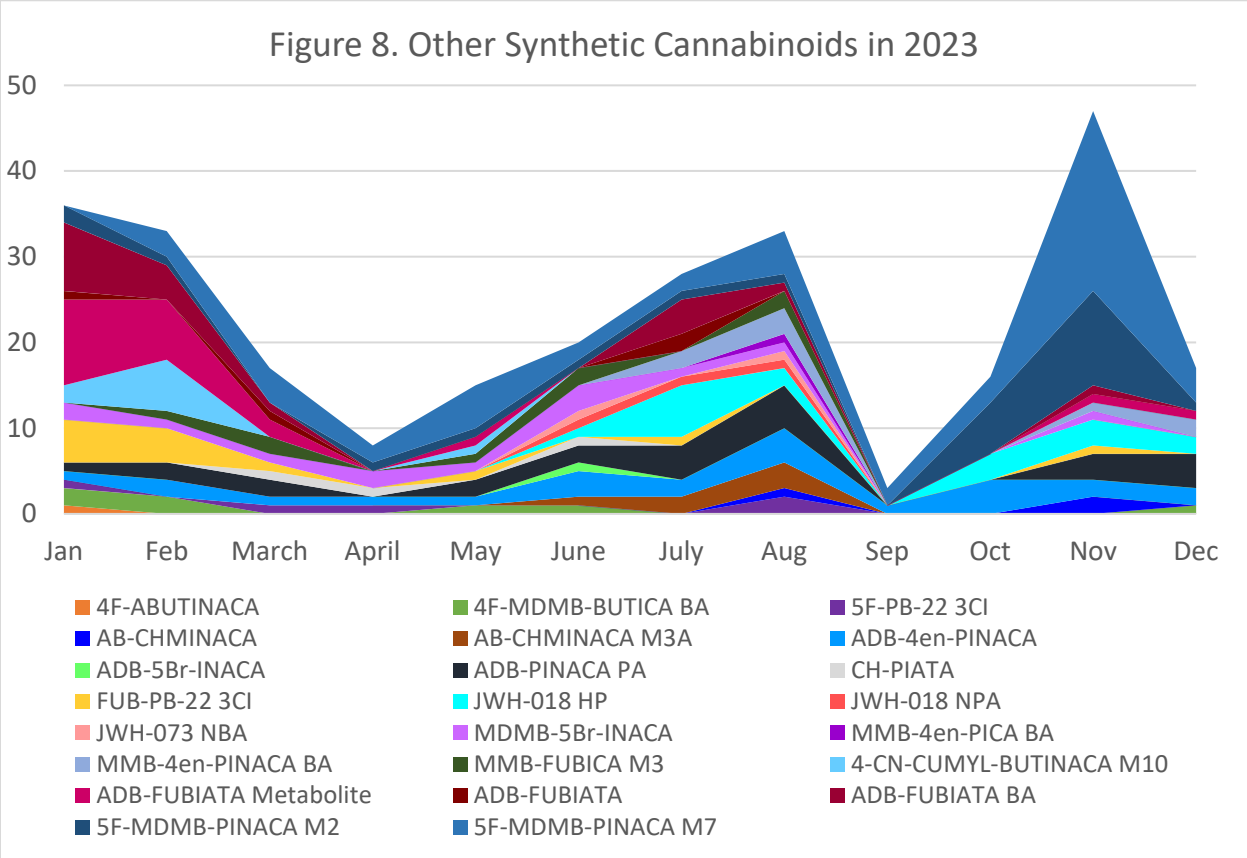
The prevalence of other designer benzodiazepines detected in 2023 is shown in Figure 6. Flubromazolam and its metabolite alpha-hydroxyflubromazolam were the fifth most prevalent designer benzodiazepines detected in 2022, with detection occurring throughout the year. However, in 2023, other than in January, detection was very minor, occurred only in seven months of the year and not at all in the fourth quarter. This is consistent with the scheduling of flubromazolam in December of 2022. Conversely flubromazepam is not currently a controlled substance under the CSA. Flubromazepam detection in the second half of 2022 was minor and sporadic. Yet in 2023, it became the fifth most prevalent designer benzodiazepine being detected in all months but July. In September of 2023 its metabolite 3-hydroxyflubromazepam was added to Aegis' testing. Its detection in the fourth quarter of 2023 alone exceeded that of flubromazepam detection for the entire year thus demonstrating its utility in detection of flubromazepam use. Adinazolam, deschloroetizolam and metizolam were newly detected in 2022. Adinazolam metabolite, N-desmethyl adinazolam, was detected in August and December of 2022 whereas in 2023, it was detected in nine months out of the year with the highest detection in Q1 and Q4 making it the next most prevalent designer benzodiazepine in 2023. Deschloroetizolam was first detected in February of 2022 with detection in all subsequent months of the year. In 2023, although detection occurred in nine months of the year, the prevalence of deschloroetizolam in 2023 was half of that detected in just the second half of 2022. Metizolam was only detected in October and November of 2022. Its detection in 2023 was highest in January and occurred in eight months out of the year.

Synthetic Cannabinoids

Synthetic cannabinoids and synthetic stimulants were among the first classes of NPS available in the United States with synthetic cannabinoids appearing first and in greater abundance than synthetic stimulants. However, reports of detection of these two classes of NPS have been declining in recent years, likely due to legislation that targets specific chemical structures and entire classes of substances. In 2021, China issued a class-wide ban of a specific structural class of synthetic cannabinoids. The prevalence of the top synthetic cannabinoids detected in 2023 are shown in Figure 7. MDMB-4en-PINACA and its butanoic acid metabolite were the most predominant synthetic cannabinoid detected at Aegis in 2022 and its predominance continued through 2023. Detection of the metabolite MDMB-4en-PINACA BA fluctuated throughout 2023 but overall increased approximately 24% from January to December. In April of 2023, The Federal Register issued a notice of intent to temporarily place MDMB-4en-PINACA in schedule I of the CSA.[11] However, this has not yet seemed to impact its detection. 4F-MDMB-BUTINACA metabolites were the second most prevalent synthetic cannabinoid detected at Aegis in 2023. 4F-MDMB-BUTINACA N-BA is the most frequently detected metabolite of 4F-MDMB-BUTINACA. Its detection fluctuated throughout 2023 yet overall was increased as December values were approximately 44% greater than January values. In the first half of 2023, detection of ADB-BUTINACA and its metabolite surpassed that of 5F-MDMB/EMB-PICA and metabolites to become third most prevalent synthetic cannabinoid detected at Aegis. ADB-BUTINACA and metabolite have been detected every month since they were included in the Aegis synthetic cannabinoid testing method in August of 2022. Detection of the metabolite ADB-BUTINACA NBA varied throughout the year but overall was increased as December detection was double that of January. In 2023, 5F-MDMB/EMB-PICA and metabolites dropped to fourth most prevalent synthetic cannabinoid detected at Aegis. 5F-MDMB-PICA M7 has been the most frequently detected metabolite of 5F-MDMB/EMB-PICA and its detection was highest in the first half of the year with very minimal detection in the second half of the year.



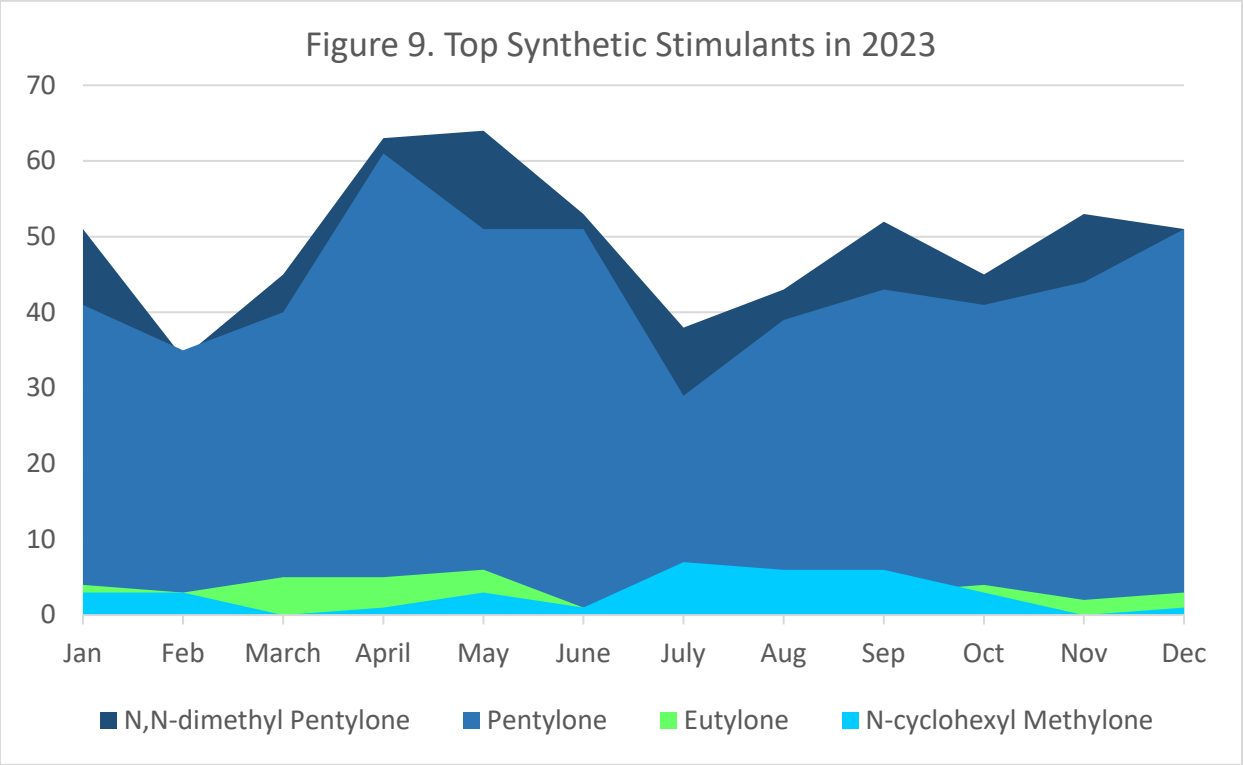
The prevalence of other synthetic cannabinoids detected in 2023 is shown in Figure 8. The next most prevalent synthetic cannabinoid analytes detected in 2023 were metabolites of 5F-MDMB-PINACA. Detection of 5F-MDMB-PINACA M2 and 5F-MDMB-PINACA M7, fluctuated somewhat but was fairly consistent through the first three quarters of 2023. In the fourth quarter, mostly in November, detection increased significantly but by December had returned to prior levels. ADB-FUBIATA and metabolites were newly added to Aegis' testing in August of 2022 and became some of the more prevalent synthetic cannabinoid analytes detected in 2022. In 2023, detection of ADB-FUBIATA and metabolites was highest in the first quarter but decreased the remainder of the year with some months not having any detected. ADB-4en-PINACA and ADB-PINACA PA had a similar prevalence in 2023, yet ADB-4en-PINACA was detected in every month of 2023 and ADB-PINACA PA was detected in 9 months.



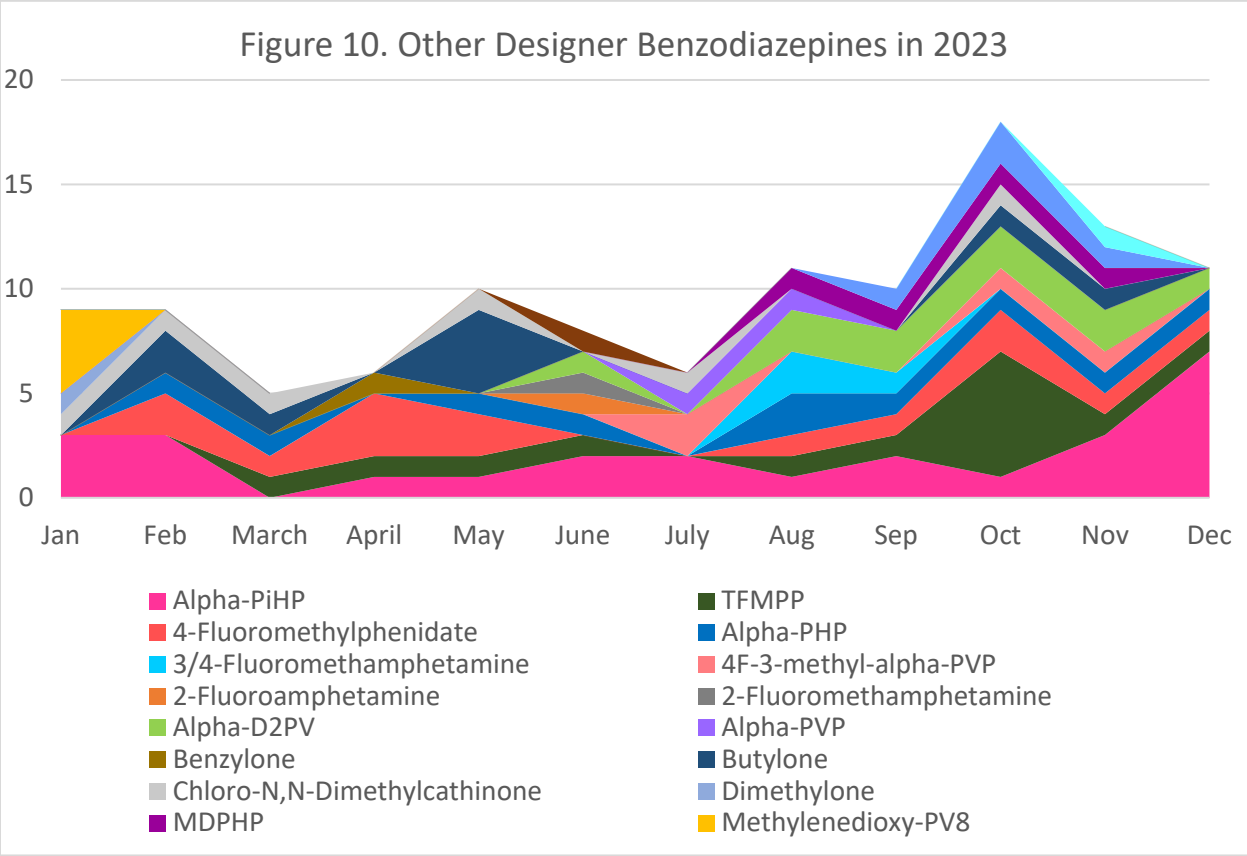
Synthetic Stimulants

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 9. Eutylone, a synthetic cathinone, was the predominant synthetic stimulant detected through the fourth quarter of 2021. However, the prevalence of eutylone began to decline in 2022. As eutylone detection declined, detection of pentylone increased to become the most prevalent synthetic stimulant detected in 2022. Pentylone was added to Schedule I of the CSA in 2017.[12] 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,[13] 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. This trend

continued in 2023. In August of 2022, N-cyclohexyl Methylone was newly detected and its detection for the remainder of the year was at such a frequency that it became the fourth most prevalent synthetic stimulant of 2022. N-cyclohexyl Methylone was detected throughout 2023 with the exception of March and November. In July through September, its detection exceeded that of eutylone. However, its overall prevalence for the year was less than that of eutylone.

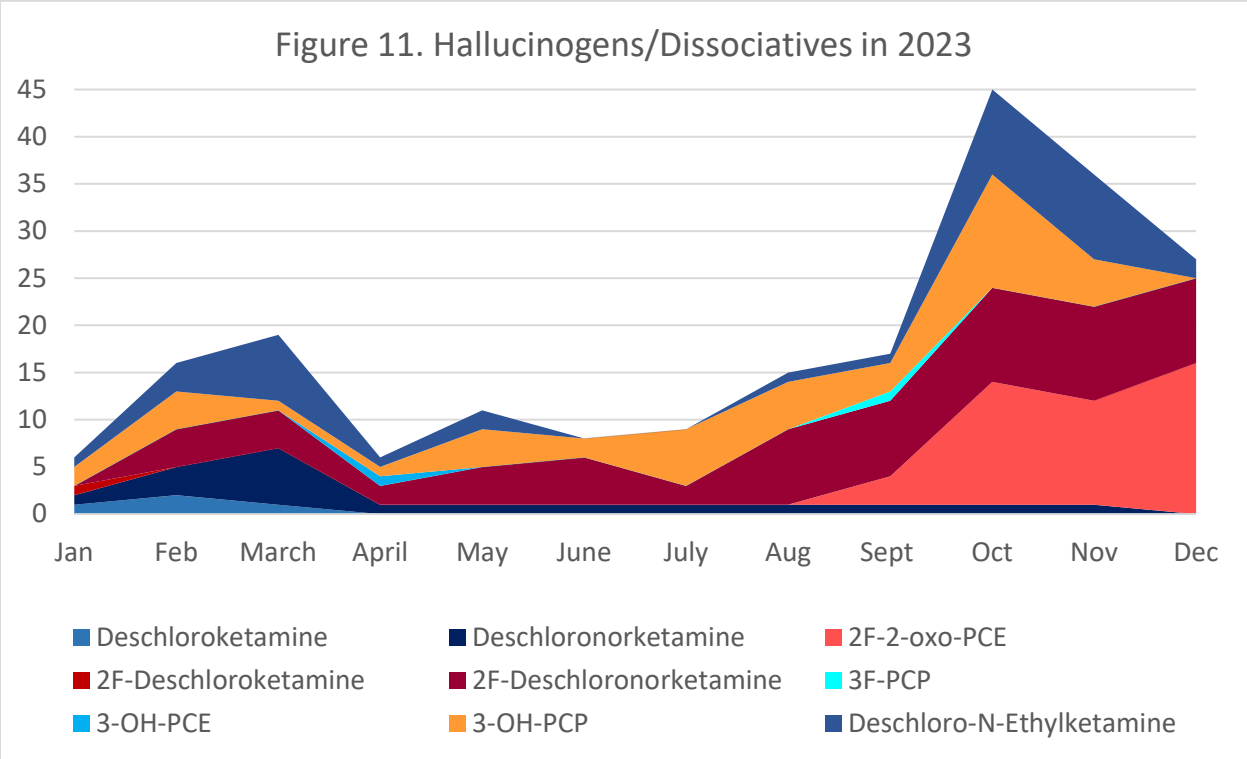


Other synthetic stimulants detected in 2023 are shown in Figure 10. Alpha-Pyrrolidinoisohexanophenone (α-PiHP) was overall the third most detected synthetic stimulant in 2022. However, although it was detected throughout 2023 with the exception of March, its prevalence in 2023 dropped to fourth most detected synthetic stimulant behind N-cyclohexyl Methylone. The next most prevalent synthetic stimulants in 2023 were 3-Trifluoromethylphenylpiperazine (TFMPP) and 4-fluoromethylphenidate. TFMPP was detected in only five months of 2022. Whereas in 2023, it was detected in 9 months. 4-fluoromethylphenidate was newly detected in the first half of 2022, and in the second half of 2022 it was only detected in July. Like TFMPP, it was detected in 9 months of 2023. Its detection was slightly more in the first half of the year compared to the second half. The next most prevalent synthetic stimulants in 2023 were alpha-Pyrrolidinohexiophenone (alpha-PHP), Alpha-D2PV, and butylone. Each of these had somewhat different detection in 2023 with butylone being detected more in the first half of the year, Alpha-D2PV being detected more in the second half of the year, and alpha-PHP being detected more throughout the year.



Hallucinogen/Dissociatives

The prevalence of hallucinogens/dissociatives in 2023 are shown in Figure 11. 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. In 2023, it remained the most predominant hallucinogen/dissociative compound, being detected in all months except January and with greater detection in the second half of the year compared to the first. The second most prevalent hallucinogen/dissociative in 2023 was the PCP analog, 3-hydroxy PCP which was newly detected in the second half of 2022. In 2023, it was detected in all months except December with greater detection in the second half of the year. 2F-2-oxo-PCE was added to Aegis' NPS testing in September of 2023 and was so frequently detected in the fourth quarter that it nearly reached the prevalence of 3-hydroxy PCP becoming the third most prevalent hallucinogen/dissociative compound detected in 2023. Deschloro-N-Ethylketamine was newly detected in 2022 but only in May. In 2023, it was detected in all months except June and July and detection was greatest in the first and last quarters of the year.



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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