

SYNTHETIC CANNABINOIDS

Novel Psychoactive Substances (NPS) are a diverse group of synthetic substances created to mimic the effects of prescription or illicit drugs that are often abused.¹ There are various classes of NPS including synthetic cannabinoids, synthetic stimulants, designer opioids, designer benzodiazepines, 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, 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.

Synthetic cannabinoids and synthetic stimulants were among the first classes of NPS available in the United States. However, reports of detection of these two classes of NPS have been declining in recent years (Figure 1). This is likely due to legislation that targets specific chemical structures and entire classes of substances. In 2021, China, often a source of synthetic drugs, issued a class-wide ban of synthetic cannabinoid receptor agonists.

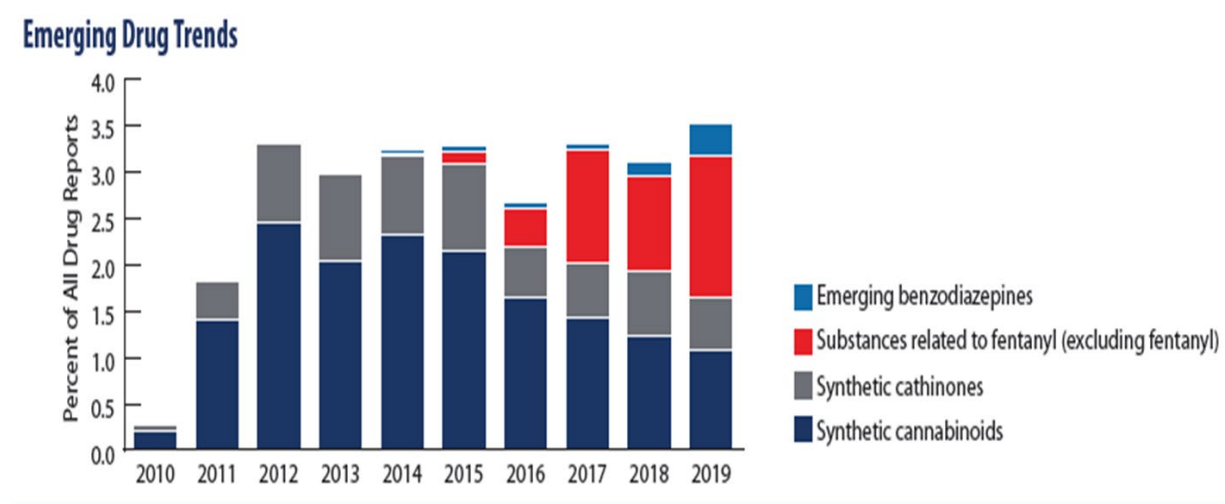


Figure 1. National Forensic Laboratory Information System (NFLIS)-Drug

Synthetic Cannabinoids

Synthetic cannabinoids are compounds designed to selectively bind to cannabinoid receptors. Many synthetic cannabinoid receptor agonists were developed as potential therapeutic agents. However, some of these compounds have been synthesized for illicit use to mimic the effects of tetrahydrocannabinol (THC), the main psychoactive component of *Cannabis sativa*. However, unlike THC, synthetic cannabinoids are often full agonists at cannabinoid receptors with high binding affinity and thus can be more potent than THC.

Synthetic cannabinoids are sprayed on or mixed with plant material and sold as herbal incense products often labeled “not for human consumption”. Generically, synthetic cannabinoids are known as “K2” or “Spice” but are sold among numerous other names and are available in convenience stores, smoke/tobacco shops, and online. Synthetic cannabinoids may be smoked as dried plant material or brewed as a tea. They may also be available in liquid forms that can be vaporized using electronic cigarettes.



Adverse effects associated with synthetic cannabinoid use include cardiovascular effects (primarily tachycardia but including myocardial infarction among others), anxiety, agitation, altered mental status, confusion, paranoia, hallucinations, psychosis, nausea, vomiting, kidney injury, tremors, seizures, respiratory depression, and death.

Drug Enforcement Agency (DEA) National Drug Threat Assessment Reports and NFLIS-Drug Reports have shown a decreasing number of synthetic cannabinoid reports over the past several years (Figure 2).

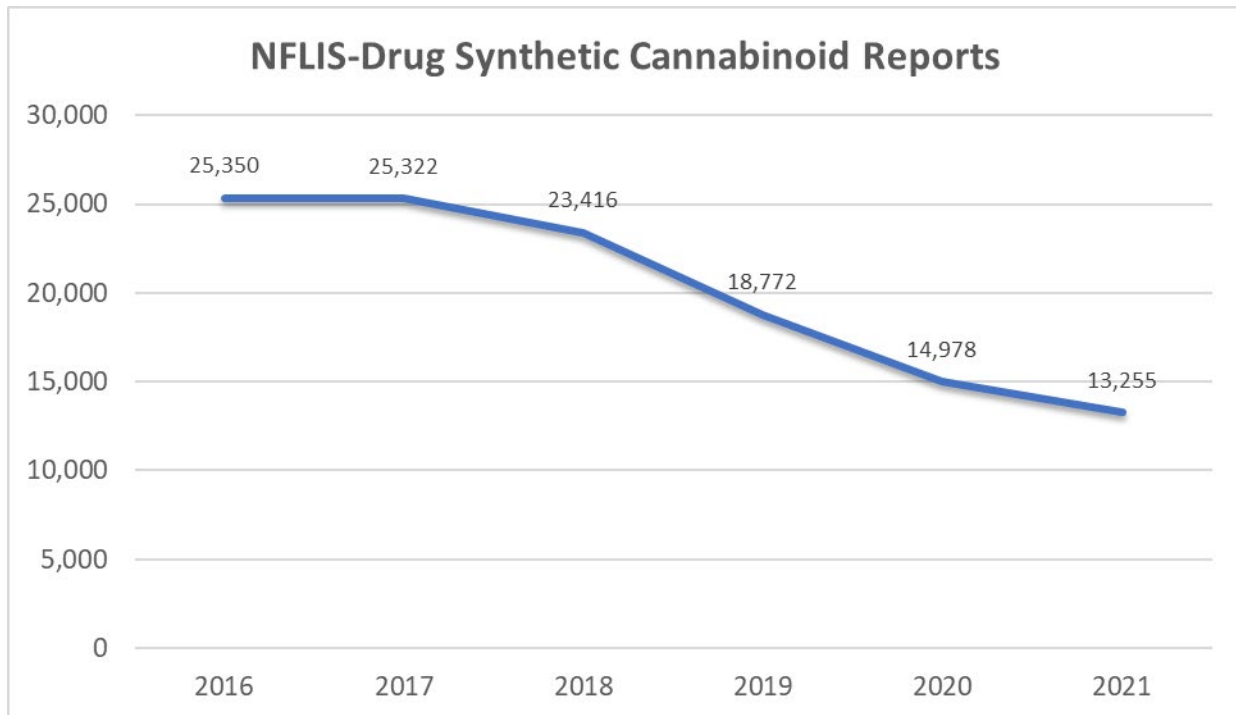


Figure 2. NFLIS-Drug Synthetic Cannabinoid Reports.^{1,2,3,4,5}

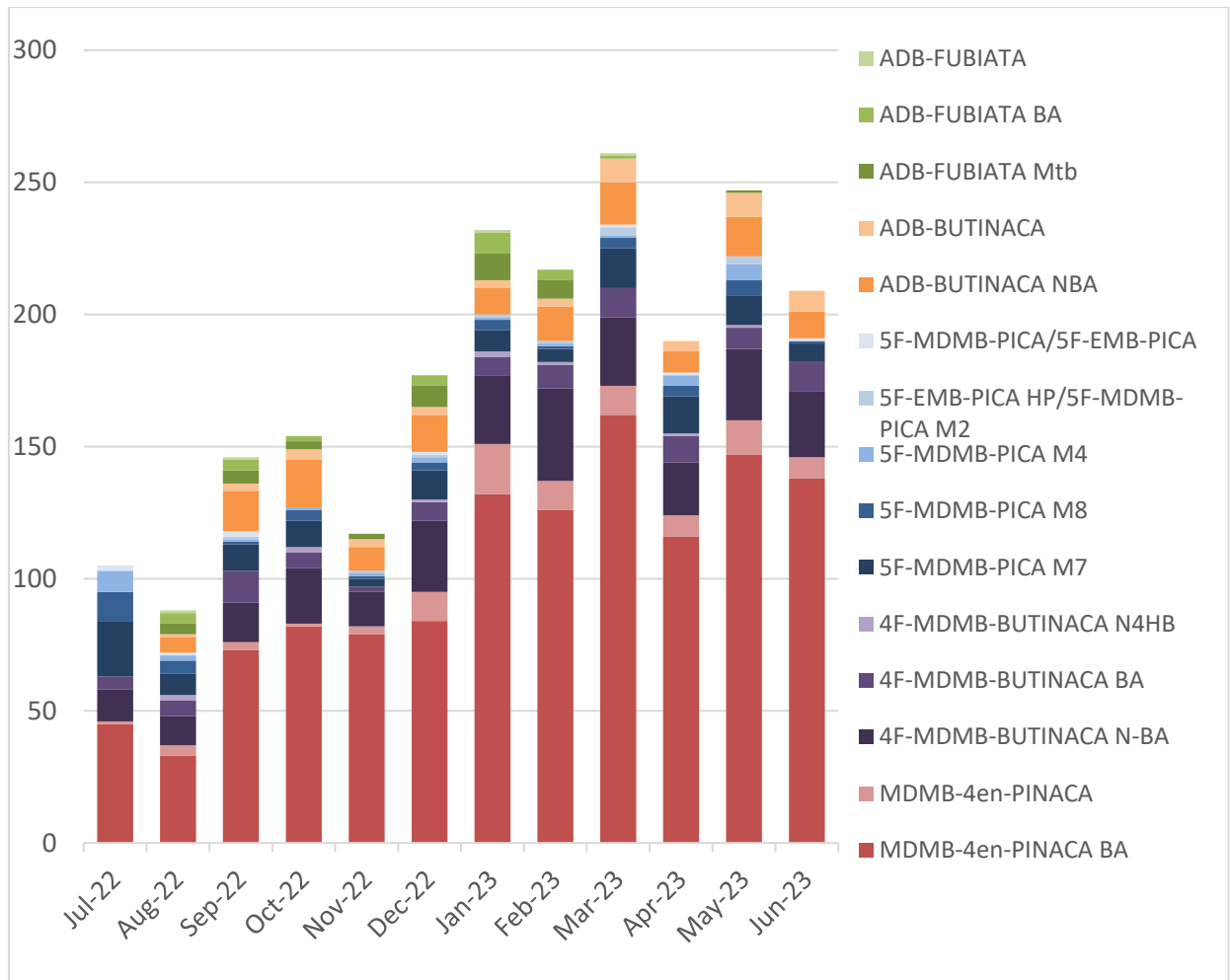


Figure 3. Top 5 Synthetic Cannabinoids detected at Aegis from July, 2022 – June, 2023

The top synthetic cannabinoid compounds detected at Aegis in 2022 were MDMB-4en-PINACA and its butanoic acid metabolite, 5F-MDMB/EMB-PICA and metabolites, and metabolites of 4F-MDMB-BUTINACA. Figure 3 shows the Top 5 Synthetic Cannabinoids detected at Aegis from July, 2022 through June, 2023. During this period, there was an overall increasing trend in MDMB-4en-PINACA detection (Figure 4), and it remains the most predominant synthetic cannabinoid detected at Aegis throughout 2022 and the first half of 2023. According to the 2022 Midyear NFLIS-Drug report, there were a total of 2,298 reports of synthetic cannabinoids between January and June of 2022. MDMB-4en-PINACA was the most prevalent at 31.4% of reports followed by ADB-BUTINACA at 22.7%.⁶ In April of 2023, The Federal Register issued a notice of intent to temporarily place MDMB-4en-PINACA in schedule I of the Controlled Substances Act (CSA).⁷

4F-MDMB-BUTINACA was the second most prevalent synthetic cannabinoid detected at Aegis in the first half of 2023. Detection of metabolite 4F-MDMB-BUTINACA N-BA was steady in the first half of 2022 but saw an overall increasing trend in the second half of 2022 and generally remained steady throughout the first half of 2023 (Figure 5). According to NFLIS-Drug data, 4F-MDMB-BUTINACA was the fourth most prevalent synthetic cannabinoid in the United States in 2021.⁵ However, in the NFLIS-Drug 2022 Midyear report it was not even in the top 10.⁶ Interestingly, 4F-MDMB-BUTINACA (aka 4F-MDMB-BINACA) has been included in schedule I of CSA since 2017 as an isomer of 5F-AMB, but it was not specifically listed in until June of 2021.⁸

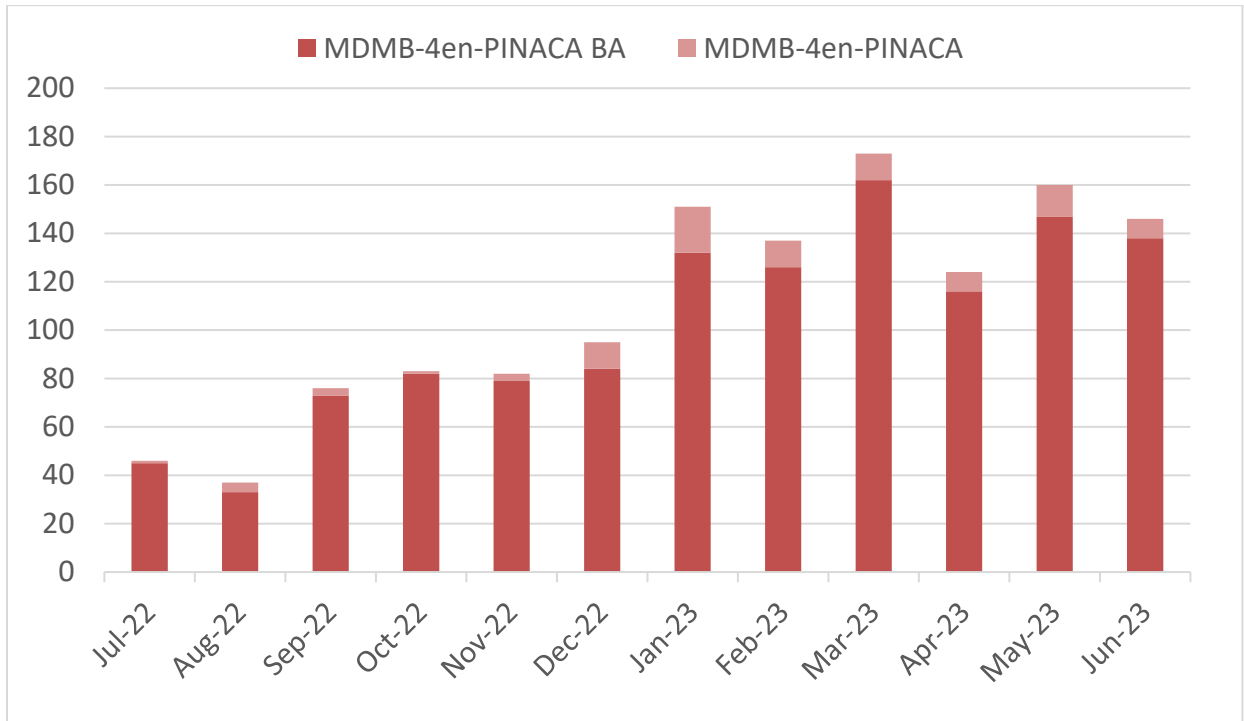


Figure 4. MDMB-4en-PINACA and metabolite detection at Aegis from July, 2022 – June, 2023

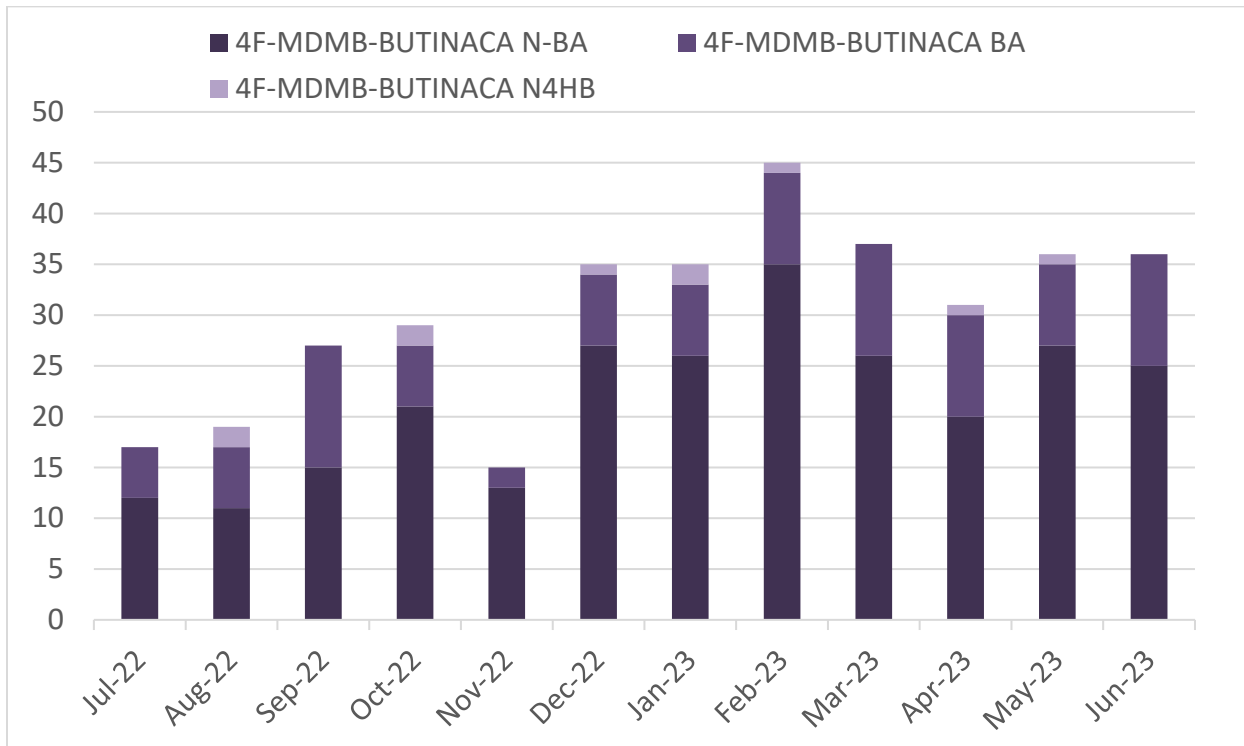


Figure 5. 4F-MDMB-BUTINACA and metabolite detection at Aegis from July, 2022 – June, 2023



5F-MDMB-PICA was the most common synthetic cannabinoid detected in the United States in 2019.² It was placed in schedule I of the CSA in April 2019.² In 2020, 5F-MDMB-PICA dropped to second most prevalent with MDMB-4en-PINACA replacing it as most identified synthetic cannabinoid.⁴ In 2021, according to NFLIS-Drug data, there were a total of 13,255 synthetic cannabinoid reports with ADB-BUTINACA being the most prevalent at 36% of reports, followed by MDMB-4en-PINACA which accounted for 29%, and 5F-MDMB-PICA coming in a distant third at 5%.⁵ Although 5F-MDMB-PICA is a controlled substance and national reports are decreasing, it still remained in the top five synthetic cannabinoids detected nationally in the first half of 2022.⁶ 5F-MDMB/EMB-PICA and metabolites were the third most prevalent synthetic cannabinoid detected at Aegis in the second half of 2022. Its detection dropped significantly from July 2022 but saw a slight uptick March through May of 2023 (Figure 6). 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.

As previously mentioned ADB-BUTINACA was the most prevalent synthetic cannabinoid detected nationally in 2021.⁵ In the first half of 2022, ADB-BUTINACA dropped below MDMB-4en-PINACA to become the second most prevalent synthetic cannabinoid accounting for 22.7% of synthetic cannabinoid reports.⁶ ADB-BUTINACA and metabolite are among a number of compounds that 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 detected at Aegis in 2022. ADB-BUTINACA and metabolite have been detected every month since they were included in the Aegis synthetic cannabinoid testing method, but their detection has been somewhat variable (Figure 7).

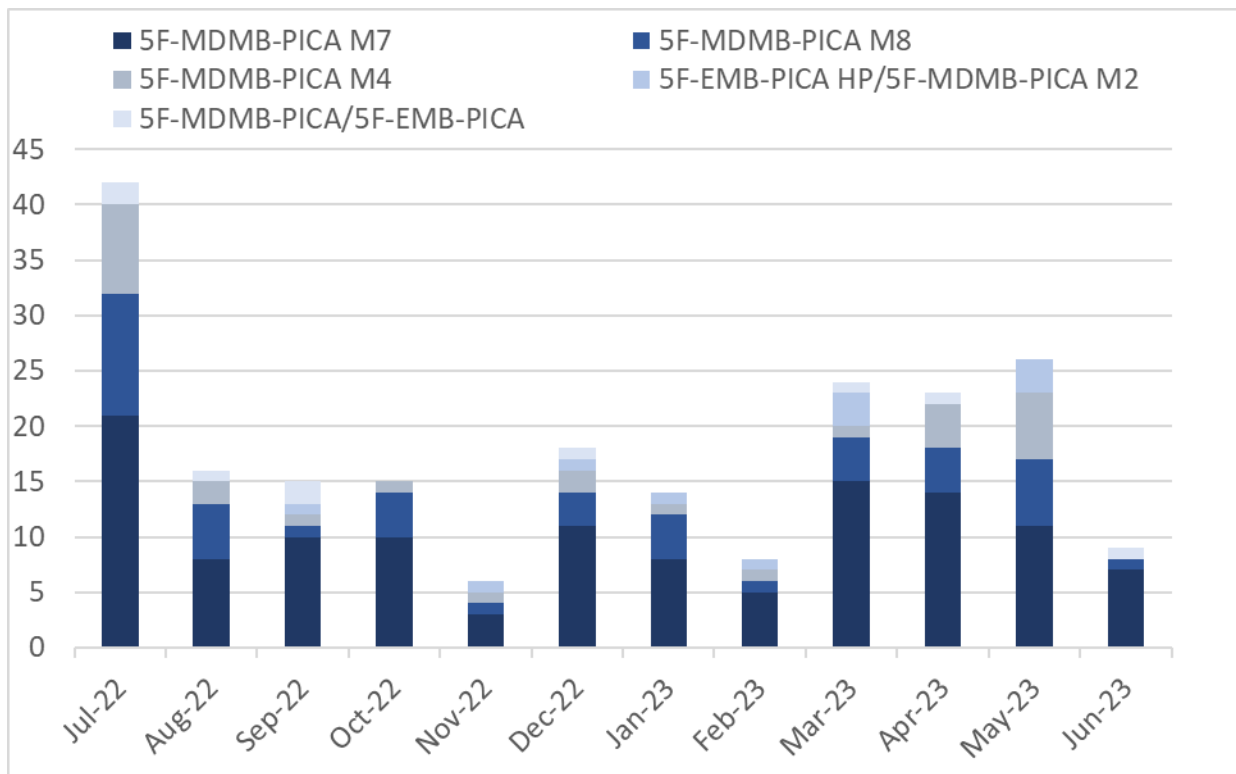


Figure 6. 5F-MDMB/EMB-PICA and metabolite detection at Aegis from July, 2022 – June, 2023

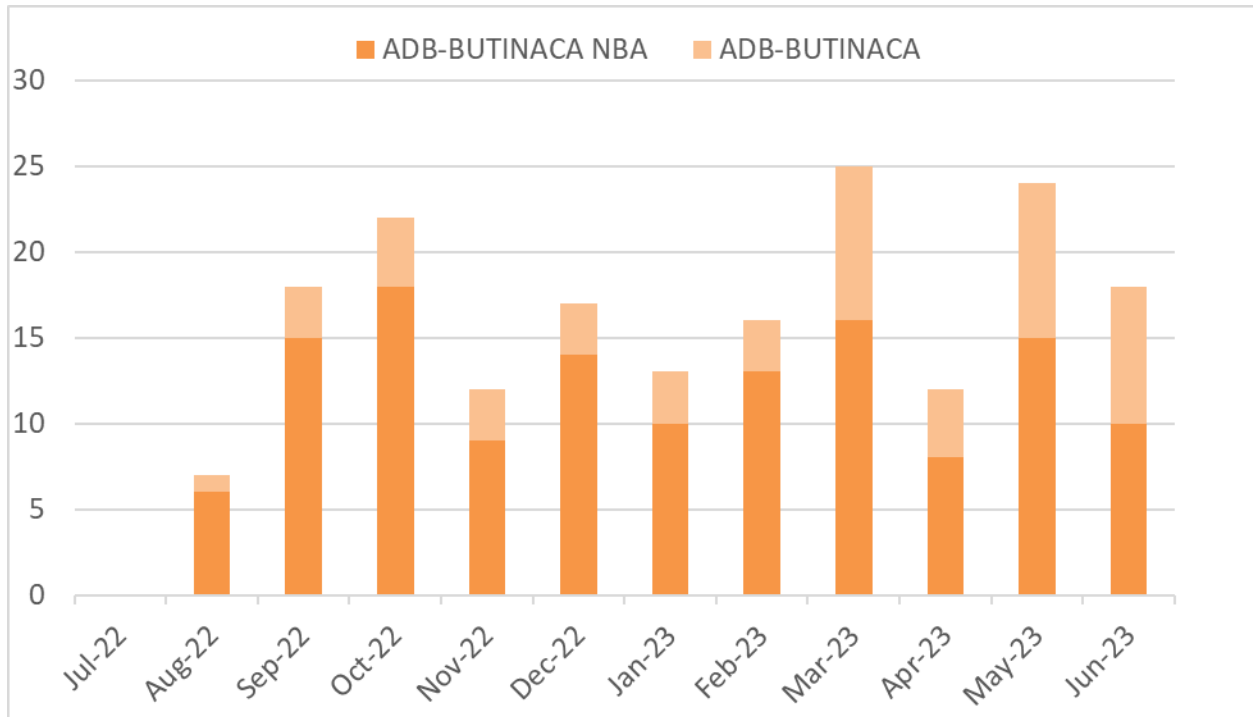


Figure 7. ADB-BUTINACA and metabolite detection at Aegis from July, 2022 – June, 2023

ADB-FUBIATA and metabolites were also newly added compounds to synthetic cannabinoid testing at Aegis in August of 2022. They became some of the more prevalent synthetic cannabinoids detected at Aegis in 2022 even being fifth most prevalent synthetic cannabinoid detected at Aegis in the first half of 2023. However, their detection was highly variable (Figure 8). Nationally, ADB-FUBIATA detection moved from fourteenth most prevalent in 2021 to third most prevalent in the first half of 2022.^{6,7} This move may be related to the 2021 China ban on synthetic cannabinoids as ADB-FUBIATA has new core and linker structures that are aimed to circumvent the ban.⁹

The prevalence of other synthetic cannabinoids detected in the first half of 2023 is shown in Figure 9. MDMB-5Br-INACA was the only other newly added synthetic cannabinoid that was detected for the remainder of 2022 following its introduction in August and its detection continued throughout the first half of 2023. Other notable synthetic cannabinoids detected at Aegis include metabolites of 5F-MDMB-PINACA (also known as 5F-ADB) which was the number one detected synthetic cannabinoid in 2018 accounting for 46% of synthetic cannabinoid reports.¹⁰ It's abuse has been associated with over 40 fatalities and it was temporarily placed in Schedule I of the CSA in April of 2017.^{11,12} It's prevalence has been dropping nationally^{5,6} but 5F-MDMB-PINACA metabolites are the sixth most prevalent synthetic cannabinoid detected at Aegis in the first half of 2023.

Overall, what is noticeable is the large number of compounds detected. Interestingly, many have been scheduled as controlled substances for a number of years. New compounds are to be anticipated as manufacturers of synthetic cannabinoids work to circumvent new legislation.

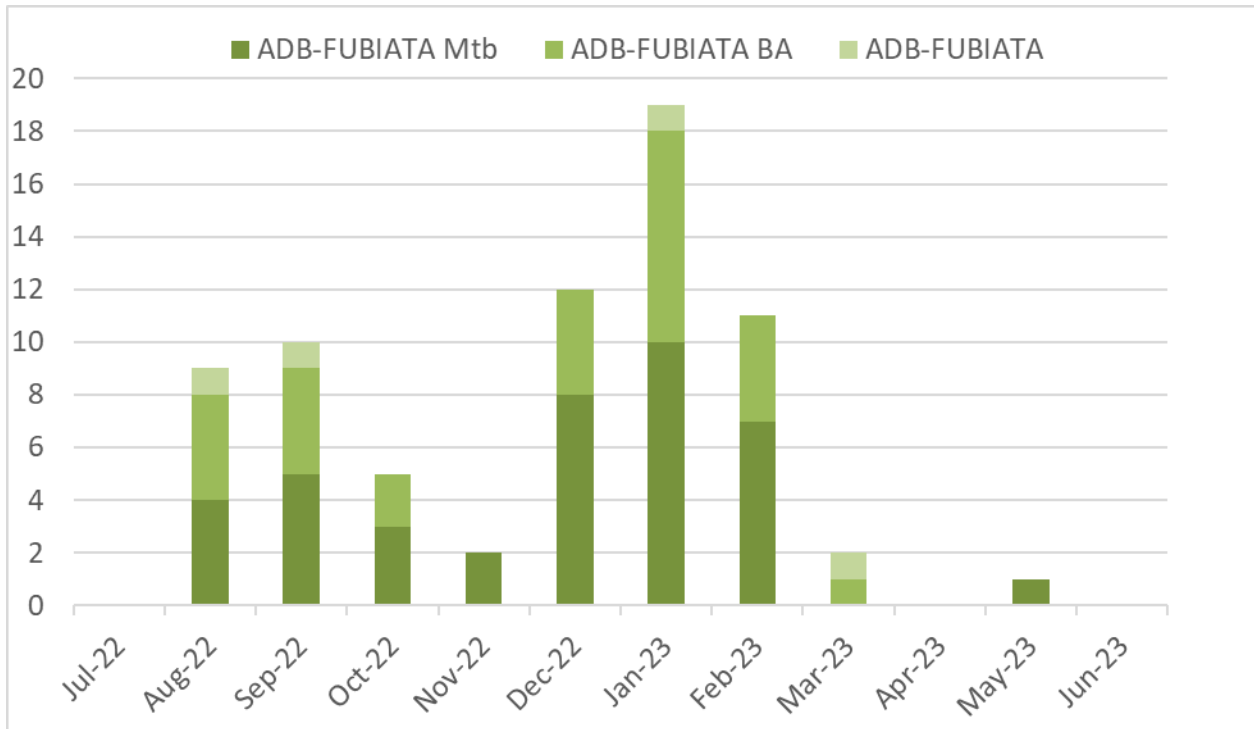


Figure 8. ADB-FUBIATA and metabolites detection at Aegis from July, 2022 – June, 2023

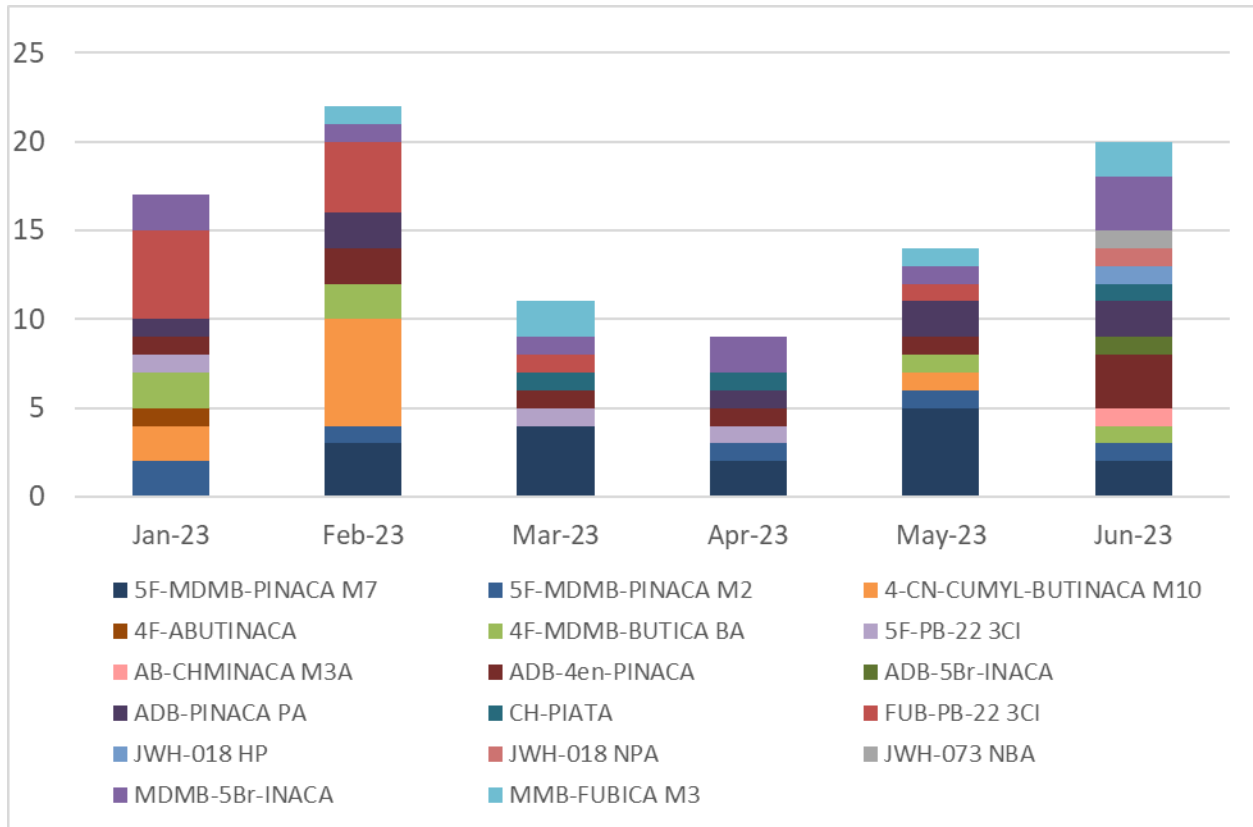


Figure 9. Other Synthetic Cannabinoids detected at Aegis in 1st Half of 2023

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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