



Toxic Adulterant Alert

Substance abuse treatment providers, clinicians, outreach workers, and public health agencies should be aware of the following information. Para-Fluorofentanyl (pFF) has been reported as an adulterant in the illicit drug supply in recent years, particularly with the rise in illicit fentanyl. pFF is a fentanyl analogue, and is considered a narcotic analgesic. In laboratory studies, pFF is approximately *three times less potent* compared to fentanyl, however, concentrations in drug deaths suggest that deaths can occur with concentrations similar to those involving fentanyl. pFF is believed to be added to fentanyl to increase total drug volume for distribution, to dilute the drug being cut and to enhance the pharmacological effect. Its increase in prevalence may also be a result of transition by illicit manufacturers to more readily available precursors. Its adverse effects include sedation, respiratory depression, coma, and potentially death. In a study at Fredric Rieders Family Foundation (FRFF) supported by the Colombo Plan on the presence of toxic adulterants in heroin/fentanyl, methamphetamine and cocaine seized drugs cases in the United States (n=2,027), pFF was found in approximately 3% percent of the total exhibits and almost always found together with fentanyl (93% of the time). CNS stimulants, methamphetamine and/or cocaine were identified in 19 of the 60 cases, generally in addition to other opioids and adulterants. Of the 60 cases positive for pFF, there were four cases where fentanyl was not detected. One case was pFF only, one was pFF and tramadol, one was pFF and a fentanyl synthesis precursor, and the last case contained pFF and the novel opioid, **N-Pyrrolidino Etonitazene** (etonitazepyne).

Background: pFF briefly infiltrated the drug market in the 1980's and later re-emerged in 2016 during a period of fentanyl analogue proliferation. Following core-structure scheduling for fentanyl-related substances in 2018, fentanyl analogue positivity, including pFF, dropped dramatically. pFF started to re-appear again in seized drug materials and toxicology samples in Q4 2020, largely in conjunction with illicit fentanyl. This potential shift may be related to the availability of para-fluoro 4-AP as a legal precursor subsequent to DEA scheduling of 4-AP, which was a commonly used precursor/intermediate for the manufacturing of illicit fentanyl. Drug checking efforts have also reported fentanyl and pFF together in seized materials.

Death Investigations involving pFF: Data shared from **NMS Labs** from toxicology cases reported between 2016 and 2023 pFF was identified in 8,510 blood samples. In sorting the data by collection date, there is a dramatic increase in positivity over the last nine years. There were 4 reports of pFF from 2016, but by Q4 of 2020 alone, there were 269 cases. By 2021 and 2022, there were 2,803 and 2,346 reports of pFF, respectively. In 2023, there were 3,019 reported blood cases. Quantitative blood concentrations of pFF (n=8,508) ranged from 0.05 ng/mL (lowest detectable amount) to over 1,000 ng/mL, with average and median concentrations being 12±40 ng/mL and 4.1 ng/mL, respectively. A histogram of blood concentrations is shown in Figure 1 and geographical heat maps are shown in Figures 2 and 3 for two different time periods.

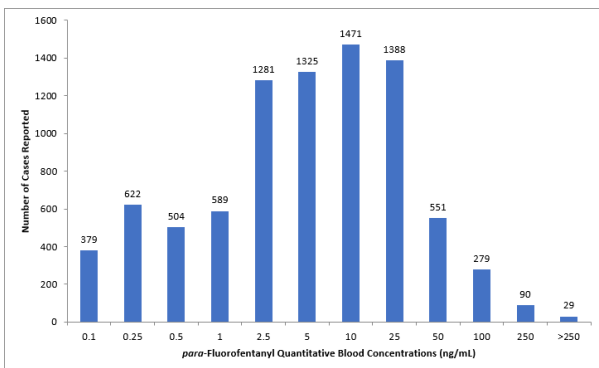


Figure 1: Histogram of pFF blood concentrations reported

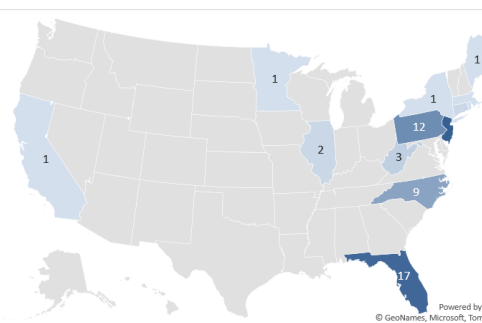


Figure 2: States reporting blood pFF 2016-2019

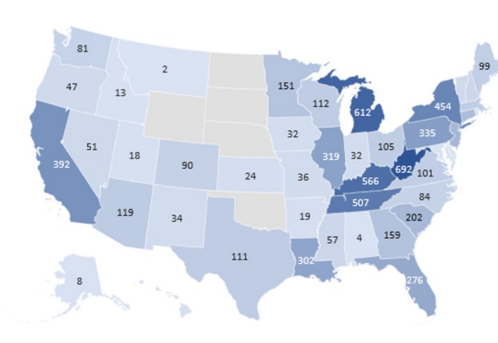


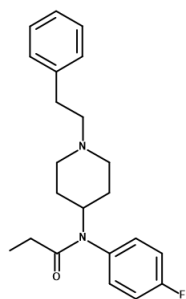
Figure 3: States reporting blood pFF 2020-2023

Susceptibility to the lethal effects of pFF will depend on tolerance, drug interactions, but pFF would be considered contributory to any case in which fentanyl is present, and can be a cause of death in its own right in susceptible individuals in the absence of other drugs.

para-Fluorofentanyl

Recommendations for Clinicians

- Be mindful that hospital drug testing methods may not detect fentanyl, its analogues, or other new opioids.
- Be attentive to signs and symptoms associated with opioid use (e.g. sedation, respiratory depression), even with negative toxicology results.
- Naloxone should be administered to reverse critical respiratory depression.
- Counsel about the dangers of synthetic opioid products and other drugs.



Frequent Indicators of Opioid Toxicity

- Unresponsiveness
- Unconsciousness
- Shallow or arrested breathing
- Sedation
- Miosis (pinpoint pupils)
- Cold or clammy skin
- Cyanosis
- Constipation
- Muscle rigidity

Recommendations for MEs & Coroners

- Conduct directed testing for **para-fluorofentanyl** in suspected opioid-related fatalities.

Recommendations for Forensic and Clinical Laboratories

- Include **para-fluorofentanyl** in the routine scope of testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including **para-fluorofentanyl** (>0.05ng/mL).
- Monitor laboratory analysis of seized drug samples taken from suspected drug overdose investigations.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners and coroners.



Health Impacts:

para-Fluorofentanyl (pFF) has been identified as an adulterant in the illicit opioid supply chain, and exposure may occur intravenously when these drugs are injected. In cases in which pFF and fentanyl were both included in the scope of testing, fentanyl and/or its metabolite norfentanyl were reported in 86% of pFF positive blood samples (n=6,700). In those cases, fentanyl blood concentrations ranged from 0.14-5,100 ng/mL. Both pFF and fentanyl blood concentrations vary widely, however, 77% of cases reported higher concentrations of fentanyl compared to pFF. In a case of a decedent found unresponsive with a white powder, pFF was reported at 51 ng/mL, while the fentanyl blood concentration was 0.24 ng/mL. There is also potential that pFF may be mixed with illicit simulants such as cocaine; fentanyl and cocaine have been reported together in seized drug material and pFF can readily be used in substitution. In one suspected polydrug overdose after purchasing “bad” crack cocaine, pFF was reported at 36 ng/mL in a gray top tube of cardiac blood; the only other toxicological findings were ethanol at 19 mg/dL and benzoylecgonine (the inactive metabolite of cocaine), at 3,700 ng/mL. Positivity for pFF has ranged from 2.5-3.4% in 2023 from reviewing comprehensive testing of postmortem samples. Across the US, testing toxicology samples for the presence of pFF is one avenue to distinguish illicit fentanyl use from pharmaceutical fentanyl use, as pFF is not found in pharmaceutical preparations of fentanyl.

Consumption of larger doses of pFF may result in more severe symptoms including sedation, coma, and respiratory depression, which may progress to death. Health providers should maintain airways in patients with suspected pFF toxicity, and naloxone administration and supporting breathing should still be considered the best practice for treating pFF overdoses.

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Acknowledgements: This report was prepared by Donna M. Papsun M.S., D-ABFT-FT, Amanda L.A. Mohr, M.S., Thom Browne, and Barry K. Logan, Ph.D. Funding for this document was received by the Fredric Rieders Family Foundation from the Colombo Plan via U.S. Department of State/INL under 2019-RG-061 and 2017-RG-61, and other Colombo Plan funding sources.

The opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of State. More information on pFF is available by contacting mandi.mohr@cfsre.org.