



## **Opium's Pathway to Fentanyl**

### **CRL's Fentanyl Results in Urine and Oral Fluids**

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#### **Introduction**

Narcotic abuse has been a problem for centuries all over the world. Opium became a problem in East Asia during the 7th century and Europe in the 1800's. The ability to manage the opium problem back then was ineffective and we see a similar ineffectiveness in the U.S. today.

#### **Opium Background**

Opium has been referred to as "poppy tears" since it is derived from the dried latex in the seed capsule of the opium poppy *Papaver somniferum*. The seeds date back to 5000 BC with records going back to 2100 BC.

Poppy opium extract was already used for pain relief by the 1st century; however, opium was not introduced into China for medical use until the 7th century. By the 15th century, the Chinese elites adopted opium as a recreational drug. England began using opium in the 1800's for treatment of cholera and dysentery to replace arsenic and mercury. Even in the U.S., opium tinctures for control of intestinal spasms and diarrhea were available without a prescription until 1970.

Countries near the Mediterranean Sea were the initial locations for poppy crops used for opium trade to China in exchange for spice, tea, and other products. Major trading of opium was advanced by the British East India Company which was chartered by Queen Elizabeth I in 1600 as a private business. At its peak, the British East India Company employed an army of 200,000 soldiers plus war ships to protect and expand their trading to the Far East. In 1874 it was dissolved following nearly 300 years of existence.



## **Opium Wars**

The British East India Company controlled the illicit opium trade to China until the mid-1800's with estimates of up to 30% of the Chinese population addicted to opium. The Qing Dynasty tried to control addiction by banning opium four times between 1829-1831 without success. The issues came to head in 1839 when the Chinese government destroyed 1,400 tons of opium. The East India Company responded with 20,000 troops and harbor blockades to defeat China. The First Opium War ended in 1842 with the Treaty of Nanking which gave Hong Kong island along with \$21million as payment for the opium financial losses to the British East India Company. The Second Opium War (1856-1860) occurred over the legalization of opium, opening ports, travel, and trade by Britain and France. Hong Kong was finally returned to China in 1997 after 155 years as conditions of the treaties.

But the British were not the only ones who benefited from the opium trade. The United States sourced their opium largely from Turkey for trade with China as well. Millions were made in the opium trade by businessmen in the Northeast. By 1818, the U.S. was responsible for a third of the opium trade to China. These efforts were justified as "fair, honorable and legitimate trade".

## **Beginning of Widespread Opium Use in the U.S.**

Although opium was available in the U.S., its widespread use did not begin until the Civil War. Opium pills, laudanum (mixture of opium and alcohol), and morphine injections were administered for battle wounds and diarrhea. The Union Army reported to have administered 10 million opium pills with 2.8 million ounces of opium powders and tinctures. Countless veterans became addicted which continued after leaving the army. Addiction was termed "opium slavery" and "morphine mania" and by 1888 Boston reported that 15% of all prescriptions were opiates. Also, during the Civil War, the syringe was invented to administer opium which certainly helped in pain relief but likely increased addiction.

Narcotics in the U.S. were easily available in the late 1800's to 1914. During this time, heroin was briefly sold through Sears & Roebuck catalog for \$1.50 and included two vials of heroin, a syringe, two needles and a heroin kit carrying case. This ended with the Harrison Narcotic Act of 1914 with heroin and cocaine as the first two controlled drugs. But "control" was limited to registering with the government and paying a small tax.



## **Heroin vs. Fentanyl Creation**

Heroin is created from opium and was first synthesized in 1874 and promoted by Bayer Company in 1898 as the safer alternative to morphine for pain management and cough suppression. Heroin creation even predates aspirin. Aspirin was also marketed by Bayer, but not available until 1899. To make heroin, the harvested opium latex is dissolved in water, filtered and precipitated with acid to obtain morphine. Morphine is then refluxed with acetic anhydride to create heroin. The process to grow poppies and harvest takes months.

Fentanyl is much easier to create as it can be completed in your garage. The primary starter or "backbone" for the fentanyl molecule is from 4-ANPP and is predominately sourced from a chemical supply business or chemists in China and Southeast Asia. Simple refluxing/mixing of 4-ANPP with propionyl chloride creates fentanyl. One kilogram of 4-ANPP (\$800) can make 500,000 pills with a street value of \$1 million. Creating your own pills is extremely easy by mixing of the fentanyl powder with compressible sugars and using a \$400 pill press purchased online.

## **Public Availability**

Fentanyl is an amazing drug for severe pain relief, but it is also very addictive. The illicit distribution of fentanyl throughout the U.S. as a single drug or mixed with other drugs accounts for at least 70,000 deaths each year. In 2023, the number of these unintentional deaths fell between those attributed to diabetes and kidney disease.

Initially fentanyl was mixed with other narcotics, such as heroin, to create a more potent and addicting narcotic. More than 30 fentanyl derivatives were originally created and distributed as novel compounds which were not under Drug Enforcement Administration (DEA) control. Once the DEA placed all derivatives into Schedule I status, their availability rapidly dropped as the regulatory punishment became the same for distribution of designer or medical fentanyl.

Around the year 2000, the first wave of narcotic abuse in the U.S. started due to opioid prescription overdoses and "fake" pain clinics. The second wave began in 2010 when the DEA countered with a reduction in opioid (oxycodone and hydrocodone) manufacturing, which resulted in a spike in heroin use. The third wave began in 2013 as heroin became in shorter supply and fentanyl became the substitute. But in the current or fourth phase, fentanyl is being mixed with stimulants, such as cocaine and methamphetamine. The combination deaths of fentanyl plus stimulants are nearly identical to fentanyl overdose alone.

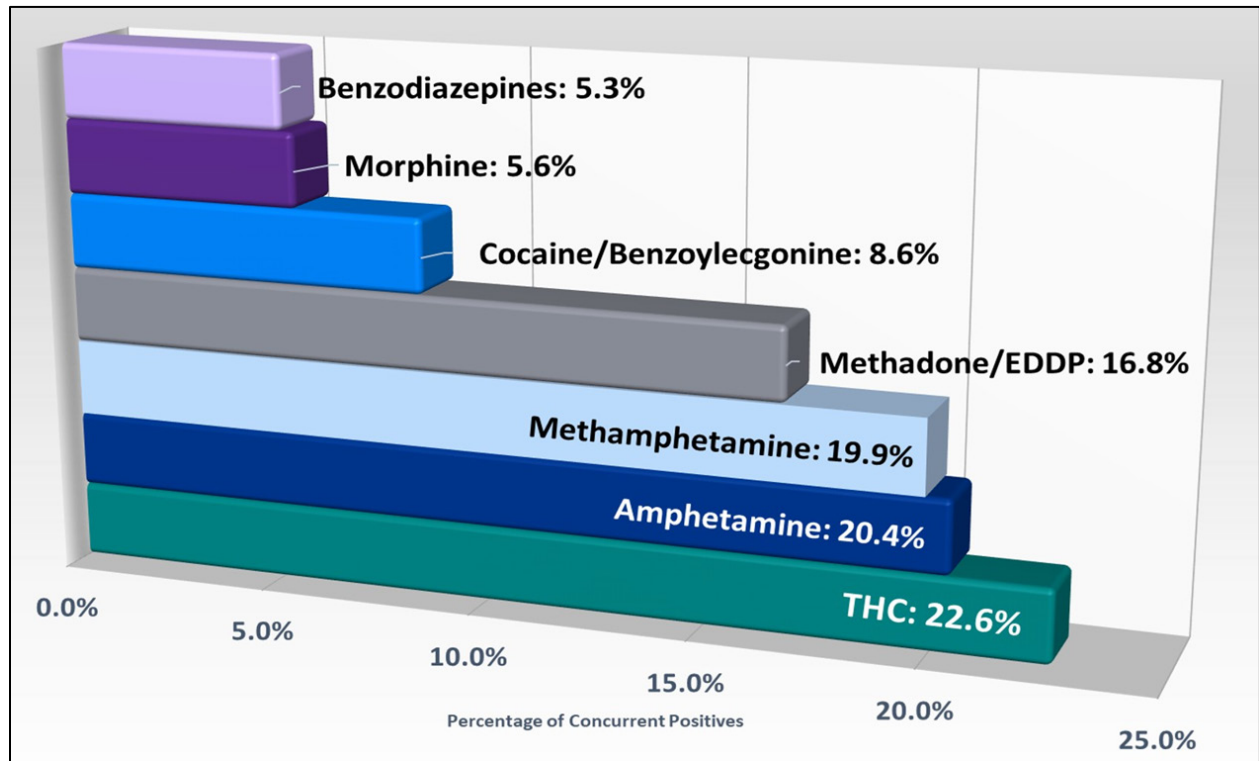


### CRL Fentanyl Testing Results

CRL has been testing for fentanyl in urine and oral fluids for years. Urine levels have been exceptionally high, indicating the drug is routinely ingested and easily detected. The urine median value for fentanyl is 12.6 ng/mL with a high value of more than 36,000 ng/mL. The fentanyl metabolite, norfentanyl, is approximately 4-fold higher than fentanyl.

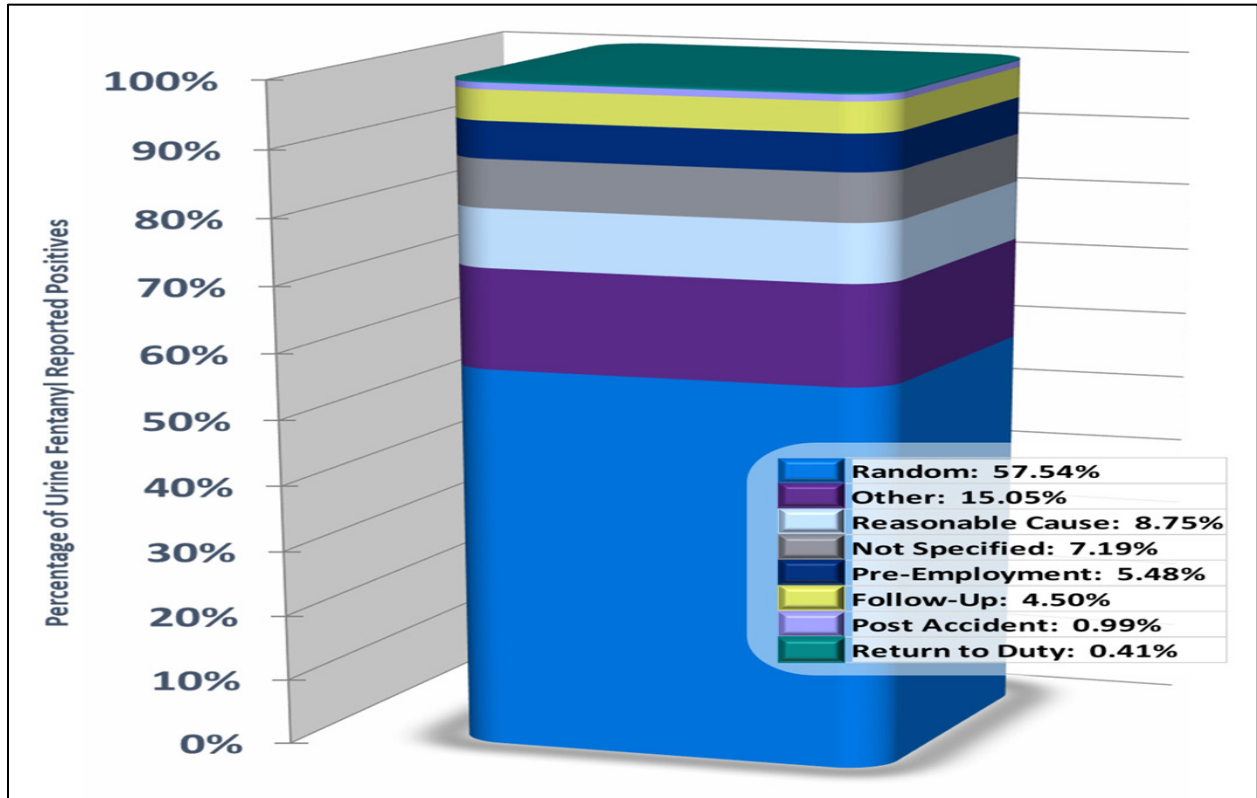
In oral fluids the levels of fentanyl are reversed with fentanyl levels 5-fold higher than norfentanyl, which also allows for easy detection with a median value of 19.7 ng/mL.

In both urine and oral fluids, the belief that fentanyl is mixed predominantly with other opioids is incorrect based on CRL's retrospective analysis of workplace drug testing results. Only 10% of positive fentanyl samples contain an opioid indicating that other drugs are present. The most common drugs found in a positive fentanyl sample are marijuana, followed by amphetamines, methadone, and cocaine.



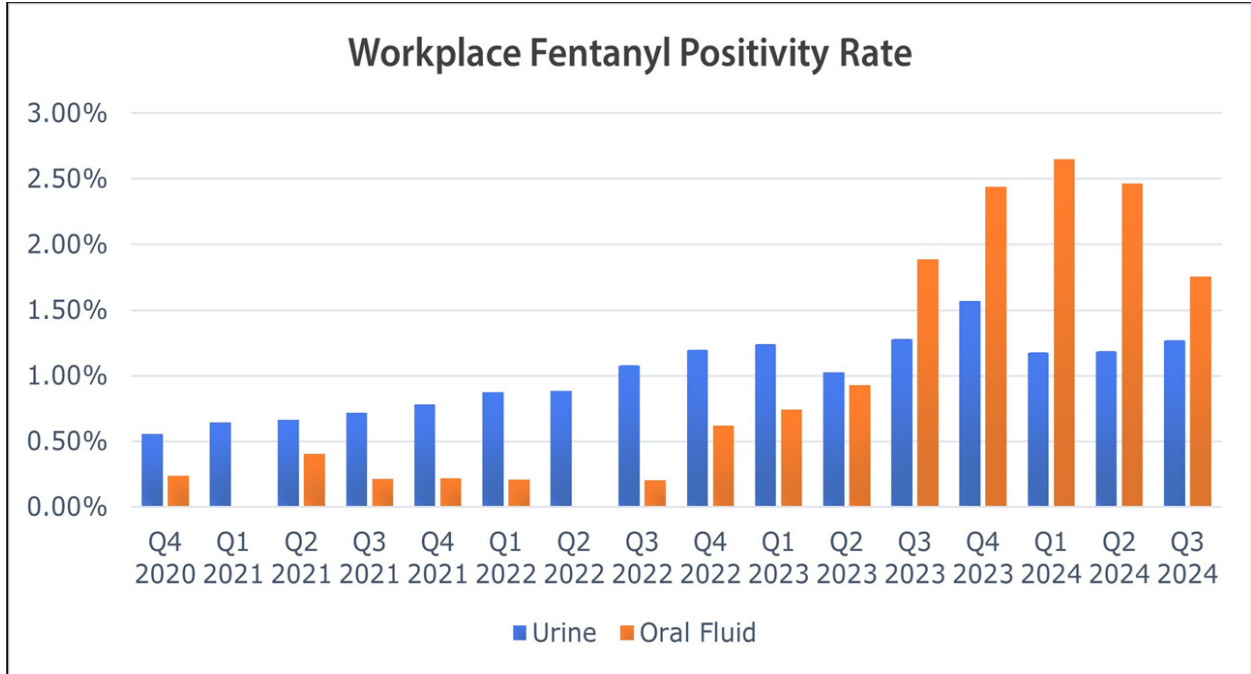


The "reasons for test" breakout also provides unexpected findings. The primary reason for drug testing is a pre-employment test. However, 57.5% of all fentanyl positives occur in the random category while pre-employment was only 5.48%. These percentages are nearly the same in oral fluids.



The proposed rationale for the higher rate in random testing is likely the unexpected addition of fentanyl to the company drug testing policy. Pre-employment is likely diminished due to either using a synthetic urine or simply discontinuing all drug use for a few days prior to the test.

The overall positive percentage of samples tested for fentanyl in urine and oral fluids are dramatic with positive rates in oral fluids substantially higher than urine. In early January 2024, the fentanyl positive rate in oral fluids was greater than 2.5% while urine positivity rate runs between 1-1.5%. This again is likely related to the witnessed oral fluid collection and eliminating synthetic urine substitution.



### Summary

The history of the opium trade with China has several similarities to the U.S. war on drugs. In the U.S., drug smuggling is dominated by the Mexican cartels. In the 1700-1800's China had illegal smuggling from Great Britain and the U.S. Due to opium abuse, the Chinese rulers attempted to ban narcotics, just as the U.S. did in the 1980s. China attempted to regulate opium and tax the sale to improve the government financial position. The U.S. is currently trying to regulate and tax marijuana to support schools and roads.

China went through more than a century of drug abuse due to the smuggling of opium into their country by western countries. It now appears the reverse is happening. The basic chemicals for the manufacture of fentanyl are coming from China. Once the popularity of fentanyl is over, the next generation of drugs are already on their shelf and starting to appear in the U.S. Nitazines are 50-fold more potent than fentanyl. Looking for this group of designers will be extremely difficult as fatalities from an even smaller dose are happening.

Fentanyl testing in urine and oral fluids is more important now than ever, as the detection rates are high and continue to increase. The significant impact to safety on the road and workplace cannot be diminished and should be considered part of a drug deterrence program.



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