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Designing Traceable Opioid Material§ Kits to Improve Laboratory Testing During the U.S. Opioid Overdose Crisis

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Abstract

In 2017, the U.S. Department of Health and Human Services and the White House declared a public health emergency to address the opioid crisis (Hargan, 2017). On average, 192 Americans died from drug overdoses each day in 2017; 130 (67%) of those died specifically because of opioids (Scholl et al., 2019). Since 2013, there have been significant increases in overdose deaths involving synthetic opioids – particularly those involving illicitly-manufactured fentanyl. The U.S. Drug Enforcement Administration (DEA) estimates that 75% of all opioid identifications are illicit fentanyls (DEA, 2018b). Laboratories are routinely asked to confirm which fentanyl or other opioids are involved in an overdose or encountered by first responders. It is critical to identify and classify the types of drugs involved in an overdose, how often they are involved, and how that involvement may change over time. Health care providers, public health professionals, and law enforcement officers need to know which opioids are in use to treat, monitor, and investigate fatal and non-fatal overdoses. By knowing which drugs are present, appropriate prevention and response activities can be implemented.

Laboratory testing is available for clinically used and widely recognized opioids. However, there has been a rapid expansion in new illicit opioids, particularly fentanyl analogs that may not be addressed by current laboratory capabilities. In order to test for these new opioids, laboratories require reference standards for the large number of possible fentanyls. To address this need, the Centers for Disease Control and Prevention (CDC) developed the Traceable Opioid Material§ Kits product line, which provides over 150 opioid reference standards, including over 100 fentanyl analogs. These kits were designed to dramatically increase laboratory capability to confirm which

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opioids are on the streets and causing deaths. The kits are free to U.S based laboratories in the public, private, clinical, law enforcement, research, and public health domains.

Keywords

Opioid; Fentanyl; Traceable Opioid Material§ Kits; TOM Kits§; Opioid CRM Kit; FAS Kit; Fentanyl Analog Screening Kit; Opioid Certified Reference Material Kit; Fentanyl Analogs; Opioid Overdose Crisis

Background

Despite morphine's discovery 200 years ago (Schmitz, 1985), chemical variants of opioid compounds are still produced. New opioids are formulated pharmaceutically for the alleviation of pain for a wide variety of clinical indications - from surgical operations to chronic pain disorders. These opioids go through rigorous testing and human trials to ensure that regulatory agencies have the information they need before approving drug formulations for pharmaceutical use (Van Norman, 2016). However, many of the more powerful opioids are synthesized illegally without any testing of the potential dangers associated with their abuse (DEA, 2018c). This illegal market of non-pharmaceutical opioids continues to supply an array of synthetic opioids and negatively affect U.S. forensic cases and fatal overdoses involving opioids. For instance, Figure 1 illustrates data reported by the National Forensics Laboratory Information System (NFLIS) on forensic cases (or drugs seized in law enforcement operations) for opioids from 2010-2017 (NFLIS, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017). The figure compares an overall number of cases reported for opioids, specifically heroin, oxycodone, and fentanyl analogs. The overall number of forensic cases rose from 2010 to 2015, but the period between 2015 and 2017 remained relatively static. During this period, there was a decrease in heroin and oxycodone cases, a stark contrast to the rapid rise in fentanyl analog cases. In fact, fentanyl analog forensic cases increased from 945 cases in 2013 to 71,341 cases in 2017 (7,500% increase). Even with the NFLIS annual case representation increasing from 91% in 2013 to 98% in 2017, this is still considered a notable rise in detections.

Unfortunately, this increase in fentanyl and fentanyl analog forensic cases foreshadowed the deadly consequences highlighted in Figure 2. A comparison of the same compounds analyzed in the Figure 1 are shown in terms of opioid deaths (Hedegaard et al., 2018a; Hedegaard et al., 2018b; Warner et al., 2016). While oxycodone prescription deaths remained relatively static since 2010, illegal heroin and fentanyl analog fatal cases continued to rise. In fact, fatalities involving fentanyl analogs increased from 4,223 deaths in 2014 to 18,335 cases in 2016 (an increase of 434%).

Although more data is becoming available on the growing impact of illicit opioids, one of the primary gaps that remains is an understanding of which opioid variants are contributing to the crisis. In 2015, members of the scientific community called for more specificity in opioid laboratory analyses (Slavova et al., 2015), and until 2016, national epidemiological data about the specific illicit fentanyl analogs entering the market or causing death was

sparse. Table 1 lists data from NFLIS, DEA, and CDC on specific types of opioid novel psychoactive substances (DEA, 2016; NFLIS, 2018; O'Donnell et al., 2017).

One observation from a detailed reporting of 18 unique compounds was the large number of cases for U-47700, a compound that is neither a fentanyl analog nor a pharmaceutical opioid. Before it was scheduled by the DEA, the U-47700 compound belonged to a class of opioids sold online under the name of "research chemicals", which were intended for use in scientific research but were consumed illicitly instead (Elliott et al., 2016). Furthermore, Supplemental Table 1 provides the names, structures, and selected sources of fentanyl analogs, fentanyl class chemical precursors, fentanyl class metabolites, and opioid "research chemicals" that have been reported through April 5, 2019 in scientific journals, open domestic and international government reports, and open independent laboratory reports. The table lists 66 unique compounds, however, a myriad of more structural analogs are still possible.

The increase in fatalities is not only tied to an increase in illicit sales but also the potency of illicit fentanyl analogs. Fentanyl analogs have potencies ranging from 0.4-30,000 times that of morphine (Brine et al., 1997; Higashikawa and Suzuki, 2008), where a deadly dose of fentanyl (estimated to be 100 times more potent than heroin (Janssen, 1982; van Daele et al., 1976)) is generally only two milligrams (EMCDDA, 2015). Furthermore, new fentanyl analogs may be 10,000 times more potent than heroin, as is the case of carfentanil (Janssen, 1982), making street drugs exponentially more deadly. Therefore, the incorporation of a small quantity of an illicit fentanyl analog into street products is more likely to result in unintended deaths. Most consumers of illicit fentanyl analogs have no knowledge of the type or the amount of substances in their purchases, which makes the chance of overdose much higher than other opioids like heroin (Ciccarone et al., 2017).

The large number of possible fentanyl analogs can also impact how they are reported in news outlets. In 2018, an advertisement for "Fentanyl Pure HCL, Methozymethylfentanyl '30490', molly, pure lofentanil, and MMAF New Product" was reported (DOJ, 2018). This advertisement is an example of how dubious information can obscure laboratory investigations. For instance, Methozymethylfentanyl '30490' and MMAF are not known names for any fentanyl analogs. The names likely refer to 4-Methoxymethylfentanyl (R-30490) (Maguire et al., 1992) and Methoxyacetyl fentanyl (MAF) (EMCDDA, 2018), respectively. Furthermore, lofentanil is a non-pharmaceutical fentanyl analog that has not been heavily studied since the late 1980s (Bilsback et al., 1985). An illegal manufacture of lofentanil would require advanced chemical expertise and is unlikely to be produced outside of a professional laboratory setting and has a particularly high potency (Malaquin et al., 2010). A positive identification of such a compound would be an indication of advanced synthetic abilities of the illegal market. Ultimately, forensic analysis never revealed the presence of lofentanil or a new compound "Methozymethylfentanyl". Successful identification of a drug's presence in incidents like the above is largely dependent on a testing laboratory's access to a reference standard for comparison and confirmation.

However, it is prohibitively expensive for laboratories across the nation to have an inventory of standards at the ready to characterize opioid emergencies. In fact, the vast majority of

analytical testing is outsourced to a small number of private analytical laboratories. With only a few laboratories measuring most of the cases and varying access to reference standard libraries, data reporting can be delayed due to bottlenecking of sample analyses and data interpretation. Therefore, U.S. laboratories need more resources, including relevant reference standards, so reports are timelier and accurately represent the epidemiology of death and distribution of illegal opioids.

Traceable Opioid Material§ Kits

To address this critical gap, the CDC developed a product line of Traceable Opioid Material§ Kits to support the detection of emerging opioids (CDC, 2019b). The kits' contents are based on needs identified, in part, using DEA Emerging Threat Reports. The 2018 mid-year report from DEA identified fentanyl and fentanyl-related compounds as accounting for 75% of the opioids they reported (DEA, 2018b). The kits are comprised of analytical and certified reference materials and do not eliminate the need for recipient laboratories to meet the analytical method requirements of other federal agencies. Kit requests are submitted directly to the respective vendor and are available to academic, public, or private laboratories with a current DEA registration and in compliance with their state and local regulations. The kits are available at no charge, and although laboratories request multiple kits, supplies are limited and requests will be filled based on their availability.

The first product from the Traceable Opioid Material§ Kits launched in February 2019 and was the largest collection of fentanyl analogs ever produced, containing 120 fentanyl analogs. Referred to as the Fentanyl Analog Screening (FAS) Kit (Cayman, 2019), the FAS Kit provides 100% coverage for the compounds listed in Supplemental Table 1. Even if laboratories have differing detection capabilities, the FAS Kit will allow mass spectrometry, ultraviolet spectroscopy, and immunosorbent assays to report critical confirmation data, such as mass confirmation, structure elucidation, and cross reactivity. With the March 2019 addition of an Emergent Panel V1 (FAS-V1), the total number of opioids in the kit increased to 150, including 129 fentanyls, 8 precursors, 6 metabolites and 7 "research chemicals." The FAS Kit, therefore, better prepares laboratories across the U.S. to identify new emerging opioids entering the illegal drug trade.

The eight precursors contained in the FAS Kit and FAS-V1 will support surveillance of illicit syntheses. The major synthetic routes to produce fentanyl analogs are illustrated in Scheme 1. In reaction route A (sometimes referred to as the Janssen method (DEA, 2018c)), a protecting group (PG) is used on the piperidone during the reduction and condensation steps to produce a fentanyl analog, but this route also requires a later deprotection step, an advanced chemical technique (Casy and Huckstep, 1988; Janssen, 1982; Kudzma et al., 1989). In reaction route B (sometimes referred to as the Siegfried method (DEA, 2018c; Mayer et al., 2016)), the same reduction and condensation steps are required, but there is no deprotection of the nitrogen on the piperidone (Valdez et al., 2014). Hence, route B is a simpler method for the illegal production of fentanyl that does not require advanced equipment or staff. The difference in the complexities between routes A and B are supported in the 2018 Annual DEA Emerging Threat Report where 218 cases of NPP and 4-ANPP (route B intermediates) are reported, but only 10 instances of the protected intermediates

benzyl fentanyl and N-methyl norfentanyl (route A intermediates) are reported (DEA, 2018a).

The reagents for the synthetic routes outlined in Scheme 1 can be bought or synthesized in a variety of chemical structures making the span of standards needed for laboratory preparedness difficult to acquire, detect, and maintain. For instance, one fentanyl analog that has not been reported in the literature, but is in the kit, is pivaloyl fentanyl. The difference in synthesis of fentanyl and pivaloyl fentanyl is that instead of the use of propionyl chloride (Scheme 1, **where LG_1 = Cl, [$CH_2CH_3(C=O)Cl$]**), pivaloyl chloride (**$C(CH_3)_3(C=O)Cl$**) is used in the condensation step of the routes described Scheme 1. New, previously undetected fentanyl analogs are no harder to synthesize, and most importantly to illegal drug manufacturers, just as cheap. Propionyl chloride that is used to produce fentanyl can be obtained at $0.10/g (Sigma-Aldrich, 2019b), while the pivaloyl chloride used to synthesize the pivaloyl fentanyl analog is $0.12/g (Sigma-Aldrich, 2019a), which represents a nominal cost increase for manufacture. Not only is pivaloyl fentanyl relatively inexpensive and requires no new synthetic route, but it is also an isomer of a common illegal fentanyl analog, valeryl fentanyl. Thus, the FAS Kit was designed to include a large selection of likely analogs and distinguish between their isomers.

The second product in the Traceable Opioid Material§ Kits launched in April 2019 and included for the first time carbon-13 and nitrogen-15 stable, isotopically-labeled standards for 22 synthetic opioids. This product is referred to as the Opioid Certified Reference Material (CRM) Kit (Cerilliant, 2019) and was designed to include over 80% of the opioids reported in the 2017 DEA 4th Quarter Emerging Threat Report and the 2016 NFLIS Annual Report (Supplemental Table 2). The Opioid CRM Kit well-exceeded initial coverage goals, from 99.0% of the opioid cases reported in the 2017 4th Quarter DEA Emerging Threat Report to 99.7% by the following 2018 3rd Quarter Report. The design of the Opioid CRM Kit provides the fluidity needed to respond as new trends emerge, partially due to the aforementioned variety of possible fentanyl analogs. After the Opioid CRM Kit was designed, a new fentanyl analog and a forensic precursor were reported in the 2018 1st Quarter DEA Emerging Threat Report. The CDC quickly incorporated the compounds and their isotopically-labeled pairs into the Opioid CRM Kit. This rapid addition of an emerging need was a demonstration of how the Traceable Opioid Material§ Kits product line can be modified and thus serve as a model for how standard reference materials can adapt quickly during a public health emergency.

Since the Opioid CRM Kit provides the first collection of carbon-13 and nitrogen-15 isotopically-labeled opioid reference materials, quantitative mass spectrometric data will improve current surveillance efforts. Isotopically-labeled reference standards are important for quantitative and qualitative methods because they can be used as internal standards that account for differences in clinical matrices, which affect the signal observed between samples. Additionally, the internal standards can correct for variability in analyte recovery if they are introduced prior to sample preparation. This new product can be used to monitor the opioid overdose crisis with respect to exposure sample’s opioid concentration or identification.

Laboratories interested in receiving Traceable Opioid Material§ Kits can visit the CDC's Opioids Portal tab for "Opioid Laboratory Testing Materials" (CDC, 2019a) and link to the CDC's Division of Laboratory Sciences' site for more information on the products (CDC, 2019b). The Traceable Opioid Material§ Kits were designed to expand the national laboratory testing capability for human exposure to synthetic opioids like those found in the forensic, drug material seizures, and post-mortem cases. Laboratories are asked to acknowledge the use of the Traceable Opioid Material§ Kits in presentations, publications, reports, and other communications by using the following citation: "Laboratory findings were made possible, in part, by the Centers for Disease Control and Prevention's design and support of Traceable Opioid Material§ Kits. #tomkits"

The work reported here establishes a model for addressing chemical, public health emergencies by first providing testing laboratories with the accredited reference standards they critically need. This action ensures a high confidence in subsequent reports confirming human exposure and evaluating any downstream public health impacts. Like the Traceable Opioid Material§ Kits product line, future models designed to support the detection of emerging threats should be able to adapt quickly to new needs and prioritize the reference standards required to cover at least 80% of the cases being reported initially. Further, quarterly threat reports should be reviewed to ensure a sustainable product line that is dynamic in the face of an ever-changing crisis. It is this paradigm that has made the Traceable Opioid Material§ Kits a successful strategy in supporting the laboratory surveillance of the U.S. opioid overdose crisis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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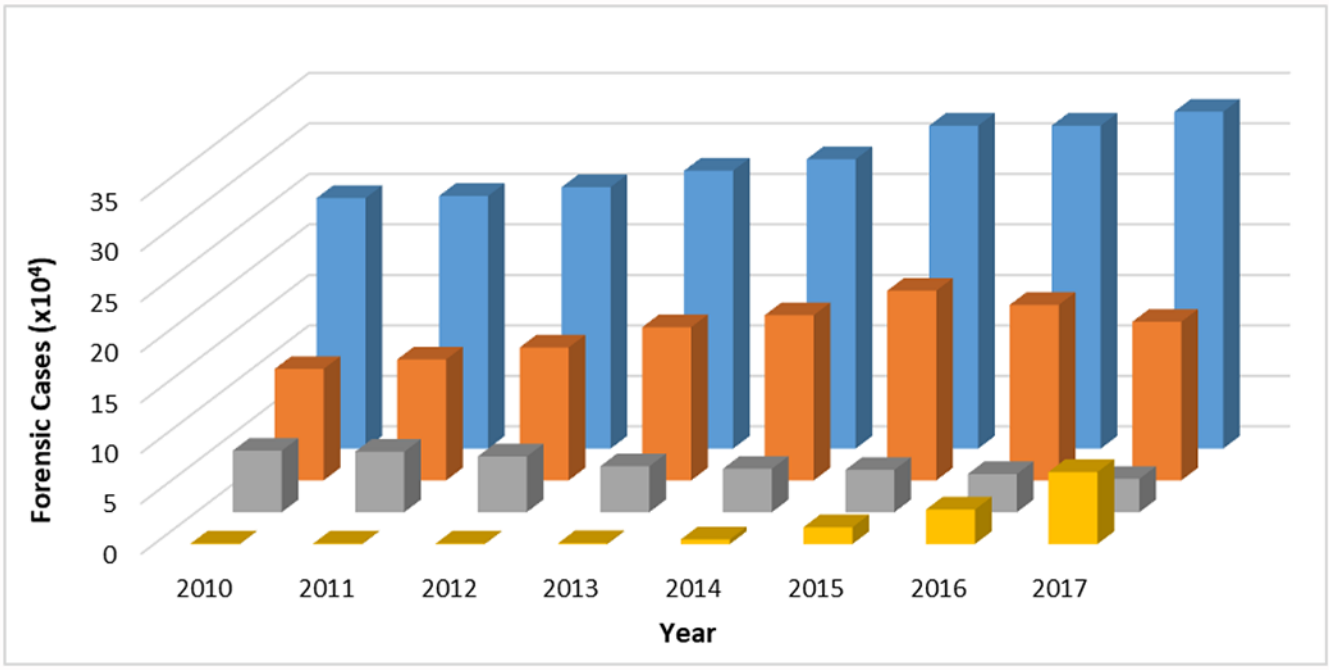


Figure 1: NFLIS forensic analysis cases of all opioids.

Forensic cases are plotted for fentanyl analogs* (***Yellow***), oxycodone (***Gray***), heroin (***Orange***), and all opioids** (***Blue***) from the National Forensic Laboratory Information System (NFLIS) from 2010 to 2017. Overall opioid forensic cases have increased from 2010 to 2017. With both heroin and oxycodone (historically, the two most prevalently abused opioids) decreasing between 2015 and 2017, fentanyl analogs are significantly impacting the increase in illegal opioids on the street.

*NFLIS reports contain a category called “Other Narcotic Analgesics”, which may encompass more fentanyl analogs, but are not added to these figures.

**Seizure reports may result in multiple reporting of different fentanyls with mixed drug cases. Illegal fentanyls often contain other opioids, so while a fentanyl may be found, other analogs may be reported in the same sample.

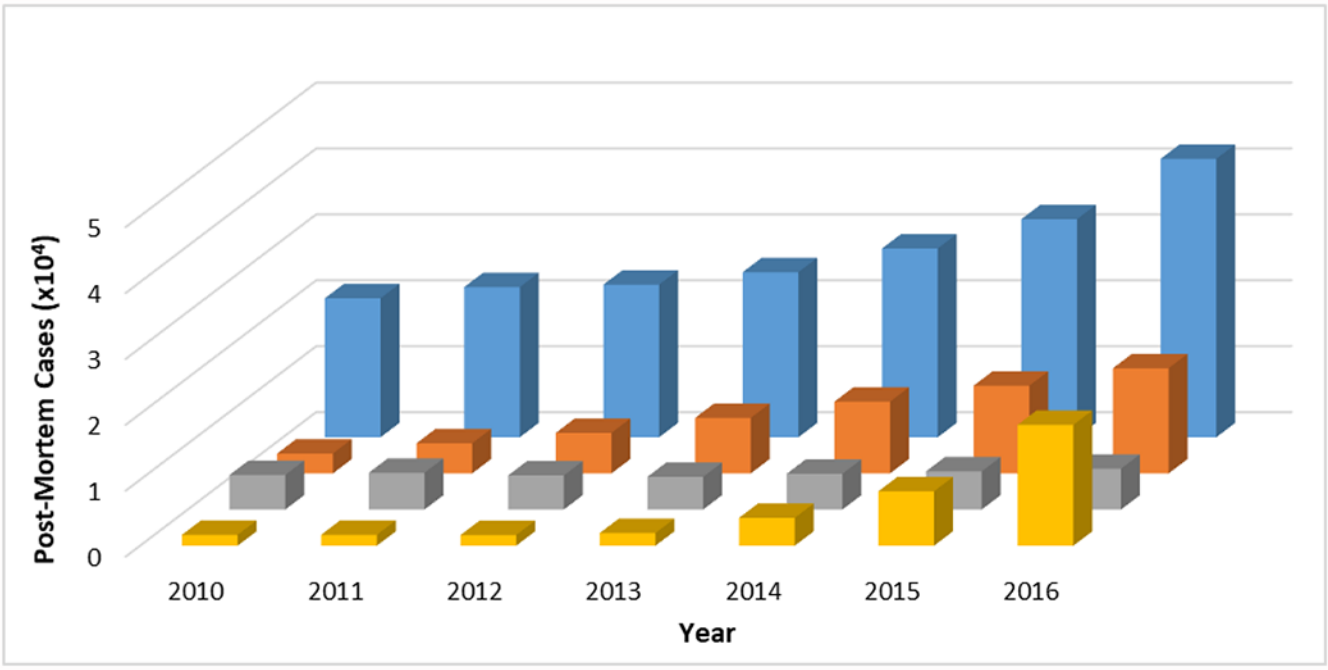
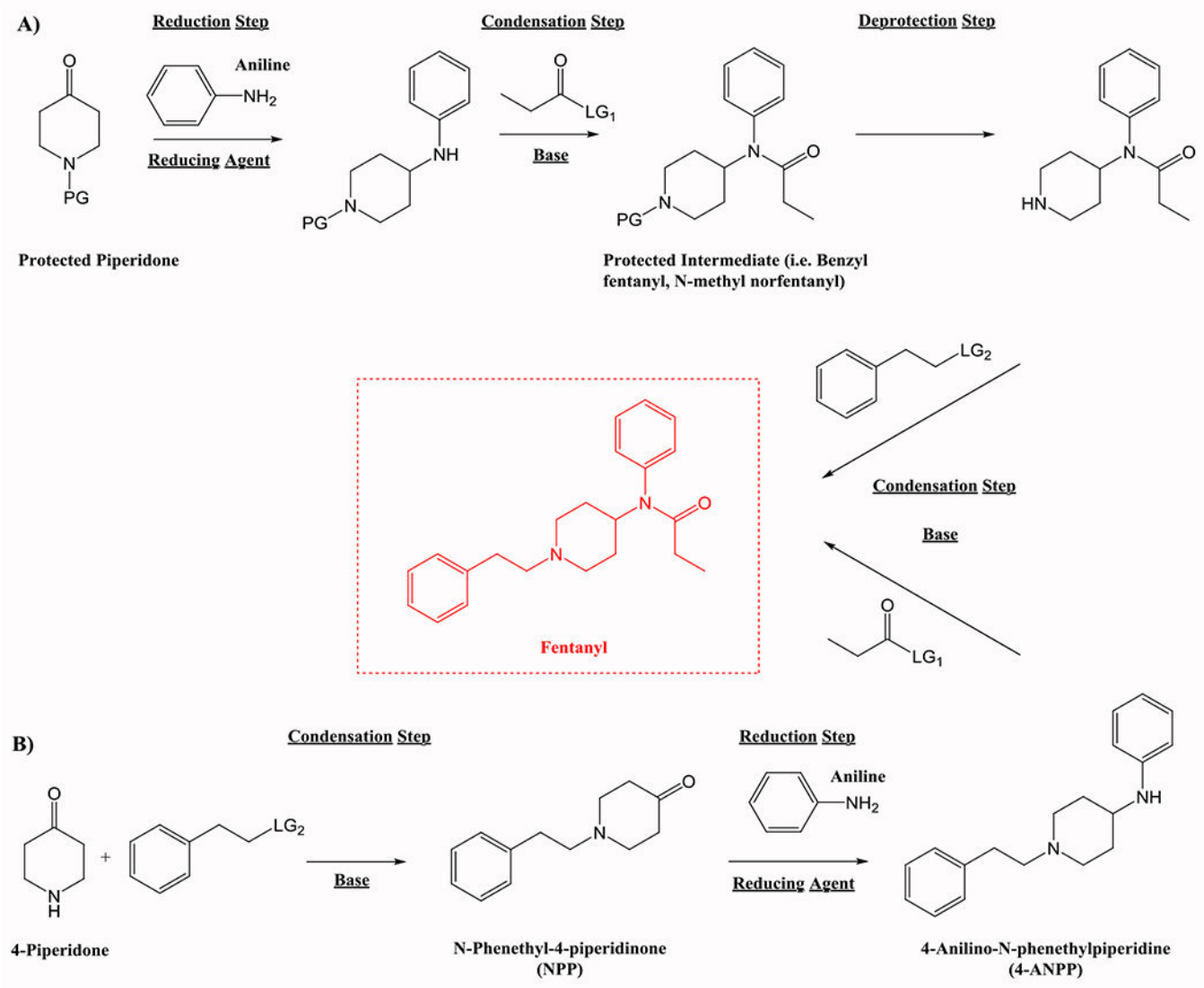


Figure 2: Drug Overdose Deaths involving Opioids.

Fatal cases are plotted for fentanyl analogs* (***Yellow***), oxycodone (***Gray***), heroin (***Orange***), and all opioids** (***Blue***) from the Centers of Disease Control and Prevention's (CDC) National Vital Statistics System between 2010 and 2016. Overall opioid fatalities increased steadily from 2010 to 2013, but increased by 434% between 2014 and 2016.

* Caution should be used when comparing numbers across years. The reporting of at least one specific drug or drug class in the literal text, as identified using ICD–10 multiple cause-of-death codes T36–T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016

**Death reports may result in multiple reporting of different fentanyls with mixed drug cases. Illegal fentanyls often contain other opioids, so while a fentanyl may be found, other analogs may be reported in the same sample.



Scheme 1: Generalized synthesis of illicit fentanyl.

A) Protected piperidone synthesis route. **B**) Unprotected piperidone synthesis route. The bases, reducing agents, leaving groups (LG_1, LG_2) and protecting groups (PG) can vary to include several organic reagents.

Table 1:

Comparison of fentanyl analog, fentanyl precursor, fentanyl metabolite and “research chemical” diversity in 2016 from forensic (NFLIS, 2018), material seizure (DEA, 2016), and post-mortem cases* (O’Donnell et al., 2017).

2016 Illicit Opioid Cases from NFLIS, DEA, and CDC			
Illicit Opioid	**NFLIS – Forensic**	**DEA – Material Seizure**	**CDC –- SUDORS fatal data***
Fentanyl	34,199	877	2,903
Furanyl fentanyl	2,273	142	182
Acetyl fentanyl	1,669	112	147
Carfentanil	1,251	17	389
U-47700	533	50	40
3-methyl fentanyl	427	2	present (out of 74) **
Fluoro iso/butyryl fentanyl	230	23	present (out of 74) **
Butyryl fentanyl	93	13	present (out of 74) **
Valeryl fentanyl	52	10	--
Acryl fentanyl	26	13	present (out of 74) **
4-Fluoro fentanyl	5	--	present (out of 74) **
4-ANPP	8	32	present ***
2-Fluoro fentanyl	3	4	--
Benzyl fentanyl	--	13	--
Tetrahydrofuranyl fentanyl	--	4	--
4-Fluorobutyryl fentanyl	--	3	--
Alpha-methyl fentanyl	1	--	--
Acetyl norfentanyl	--	1	--
Total	**40,237**	**1,316**	**3,735**

* CDC data collected from July – December 2016 by 10 State Unintentional Drug Overdose Reporting System (SUDORS) participants using death certificates and medical examiner and coroner reports including toxicological results.

** Study contains an “Others” section with 74 non-specific cases represented (out of 74), but specifically includes 3-methyl fentanyl, acryl fentanyl, butyryl fentanyl, 4-fluoro fentanyl, 4-fluoro butyryl fentanyl, and 4-fluoro isobutyryl fentanyl as being present. Since there are no number of cases assigned to the specific compounds included, they are listed as “present (out of 74)”.

*** Study found cases of 4-ANPP, but since it does not contribute to overdose toxicity, it is not included in the case mortality numbers.