

**Supplemental Information for Nine Fentanyl and Fentanyl Analogue Precursors:
4-Anilinopiperidine, 4-Anilino-1-boc-piperidine, Norfentanyl, Acetyl Norfentanyl, Butyryl
Norfentanyl, Cyclopropyl Norfentanyl, Furanyl Norfentanyl, Isobutyryl Norfentanyl, and
Valeryl Norfentanyl**

The United States is currently experiencing an epidemic of overdose deaths involving synthetic opioids including illicitly manufactured fentanyl and fentanyl analogues. We recognize that the United States is not the only country negatively impacted by an increase in illicitly manufactured fentanyl and fentanyl analogues. To address this global problem, the United States requests the initiation of steps to add fentanyl precursor chemicals to the international chemical tables under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 (1988 Convention). Specifically, the U.S. proposes taking measures to control:

1. *N*-phenylpiperidin-4-amine (4-anilinopiperidine; *N*-phenyl-4-piperidinamine; 4-AP)
2. *tert*-butyl 4-(phenylamino)piperidine-1-carboxylate (also known as 4-anilino-1-boc-piperidine; 1-boc-4-anilinopiperidine; *t*-boc-4-anilinopiperidine; *t*-boc-4-AP; 1-boc-4-AP; boc-4-AP)
3. *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl)

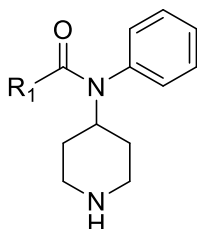
In addition, information on the following related fentanyl analogue precursor chemicals, which are all amides of 4-AP listed above, is also provided in this document:

4. *N*-phenyl-*N*-(piperidin-4-yl)acetamide (acetyl norfentanyl)
5. *N*-phenyl-*N*-(piperidin-4-yl)butyramide (butyryl norfentanyl)
6. *N*-phenyl-*N*-(piperidin-4-yl)cyclopropanecarboxamide (cyclopropyl norfentanyl)
7. *N*-phenyl-*N*-(piperidin-4-yl)furan-2-carboxamide (furanyl norfentanyl)
8. *N*-phenyl-*N*-(piperidin-4-yl)isobutyramide (isobutyryl norfentanyl)
9. *N*-phenyl-*N*-(piperidin-4-yl)pentanamide (valeryl norfentanyl)

Since the addition of *N*-phenethyl-4-piperidone (NPP) and 4-anilino-*N*-phenethylpiperidine (ANPP) to the international chemical tables under the 1988 Convention, the chemicals listed above have emerged as precursor chemicals used for illicitly-produced fentanyl and many fentanyl analogues. These precursor chemicals are controlled under the United States Controlled Substances Act (CSA) by specific listing or by definition. Under the CSA, norfentanyl is controlled under Schedule II as an immediate precursor to fentanyl. 4-AP is specifically listed as a List I chemical under the CSA, which includes amides, carbamates, and salts of 4-AP. The chemical structure of boc-4-AP defines it as a carbamate of 4-AP, and the chemical structures of acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl define them as amides of 4-AP. Therefore, these chemicals are controlled as List I chemicals under the CSA.

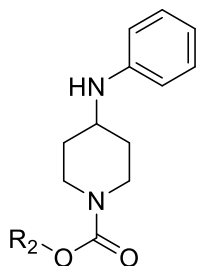
As can be seen from a review of the chemical structures of the precursor chemicals listed above, all of these precursor chemicals would meet the definitions provided in the United States' control of 4-AP (see Figures 1 and Figure 2). If not for the Drug Enforcement Administration's (DEA) placement of norfentanyl in Schedule II of the CSA, it would be defined as an amide of

4-AP. In addition, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl are all amides of 4-AP. Importantly, these examples are listed in the International Narcotics Control Board's (INCB) document "Fentanyl-Related Substances with No Known Legitimate Uses," and each are precursor chemicals used in the synthesis of fentanyl analogues.



$R_1 = \text{CH}_3$	acetyl norfentanyl
$R_1 = \text{CH}_2\text{CH}_3$	norfentanyl
$R_1 = \text{CH}_2\text{CH}_2\text{CH}_3$	butyryl norfentanyl
$R_1 = \text{cyclopropyl}$	cyclopropyl norfentanyl
$R_1 = \text{furan-2-yl}$	furanyl norfentanyl
$R_1 = \text{CH}(\text{CH}_3)_2$	isobutyryl norfentanyl
$R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	valeryl norfentanyl

Figure 1. Examples of Amides of 4-AP



$R_2 = \text{tert-butyl}$ boc-4-AP

Figure 2. Example of a Carbamate of 4-AP

Background

In the United States, fentanyl is a schedule II controlled substance with high abuse potential which may lead to severe psychological or physical dependence. Fentanyl and its analogues are the most potent opioids available for human and veterinary use. Fentanyl produces opioid effects that are indistinguishable from morphine or heroin, but fentanyl is approximately 50 times as potent as heroin and has a shorter duration of action.

The legitimate medical use of fentanyl is for anesthesia and analgesia, but fentanyl's euphoric effects are highly sought after in illicit drug market by people who use opioids. Fentanyl can serve as a direct pharmacological substitute for heroin in opioid-dependent individuals. However, fentanyl is a very dangerous substitute for heroin because the amount that produces a euphoric effect also induces respiratory depression. Furthermore, due to fentanyl's

greater potency, illicit drug dealers have trouble adjusting (i.e. “cutting”) pure fentanyl into non-lethal dosage concentrations. People who use heroin or other illicit opioids similarly have difficulty determining how much to take to get a euphoric effect and sometimes mistakenly take a lethal quantity of the fentanyl. Further, due to the proliferation of various fentanyl analogues with different potency into the illicit drug market in the U.S., individuals who use drugs often do not know the potency or exact contents of the illicit opioid they are using, introducing unpredictability in the drug market and heightening overdose risk. Unfortunately, only a slight excess of fentanyl can be, and is often, lethal because the resulting level of respiratory depression is sufficient to cause the individual to stop breathing.

Historical U.S. Control Actions Relating to Fentanyl Deaths and Illicit Production

In 2005 and 2006, DEA saw a sharp increase in the seizures of illicit fentanyl. The distribution of illicit fentanyl or illicit fentanyl combined with heroin or with cocaine (i.e., a “speedball”) resulted in an outbreak with hundreds of confirmed and suspected fentanyl-related overdose deaths in the United States.

To address this emergency health situation, DEA controlled the precursor to fentanyl, *N*-phenethyl-4-piperidone (NPP), as a List I chemical in rulemakings published April 23, 2007 (72 FR 20039) and finalized July 25, 2008 (73 FR 43355). As DEA discussed extensively in those rulemakings, at least 972 confirmed fentanyl-related deaths and 162 suspected fentanyl-related deaths were initially reported to the DEA. Following control of the precursor NPP in 2007, the number of fentanyl-related deaths significantly decreased and continued at lower levels. In a separate action, DEA controlled the “immediate precursor” to fentanyl, ANPP, as a Schedule II controlled substance by a rulemaking published on August 30, 2010 (75 FR 37296).

Beginning in 2012, the United States observed an increase of fentanyl reports from law enforcement and public health officials. By 2017, 39 percent of all drug overdose deaths in the United States (27,299 of 70,237 deaths) involved fentanyl, including fentanyl metabolites, precursors, and analogues, for an age-adjusted rate of 8.7 per 100,000, more than any other drug, including heroin, cocaine and methamphetamine.¹ DEA Diversion reporting and analysis of seized material suggested that fentanyl was largely being derived from illicit manufacturing and was not being diverted from legitimate channels. In 2016, the United States requested that the INCB initiate steps to list NPP and ANPP to the international chemical tables under the 1988 Convention, since both precursor chemicals are used in the illicit manufacture of fentanyl. Subsequently, both NPP and ANPP were added to the chemical tables under the 1988 Convention at the 2017 Commission on Narcotic Drugs (CND).

As Member States began to comply with the addition of NPP and ANPP to the chemical tables under the 1988 Convention, illicit fentanyl manufacturers sought out strategies to evade new regulations. Clandestine fentanyl manufactures explored and employed other synthetic routes to fentanyl; one of these was previously described in the patent literature.² In addition,

¹ Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M. Regional differences in the drugs most frequently involved in drug overdose deaths: United States, 2017. National Vital Statistics Reports; vol 68 no 12. Hyattsville, MD: National Center for Health Statistics. 2019.

² Gupta P.K., et al, WO 2009/116084, September 24, 2009.

illicit fentanyl manufacturers began to utilize protecting groups on precursor chemicals in attempt to evade detection, enhance yields in the synthetic process, or both.

In response to the ongoing health crisis involving illicitly manufactured fentanyl and fentanyl analogues and due to the shift to new precursor chemicals used in the illicit manufacture of fentanyl, DEA controlled *N*-phenylpiperidin-4-amine (4-anilinopiperidine; *N*-phenyl-4-piperidinamine; 4-AP), including its amides, its carbamates, and its salts, and *N*-(1-benzylpiperidin-4-yl)-*N*-phenylpropionamide (benzylfentanyl), including its salts, as List I chemicals by finalization of a rulemaking on May 15, 2020 (85 FR 20822). DEA also controlled *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl) as a schedule II immediate precursor to fentanyl on May 18, 2020 (85 FR 21320). As DEA discussed in those rulemakings, the U.S. has experienced a re-emergence of illicitly manufactured fentanyl and fentanyl analogues since 2012.

Synthesis of Fentanyl

Legitimate pharmaceutical firms utilize two primary synthetic routes for the production of fentanyl. In 1965, Janssen Pharmaceutical patented the original synthetic procedure for fentanyl. Benzylfentanyl and norfentanyl serve as the key precursor chemicals in this synthetic route (see Figure 3). The Janssen method was previously thought to be beyond the skills of most clandestine laboratory operators, due to the debenzoylation of benzylfentanyl to norfentanyl. Since norfentanyl is the product of this difficult step, norfentanyl is an attractive precursor chemical to illicit fentanyl manufacturers.

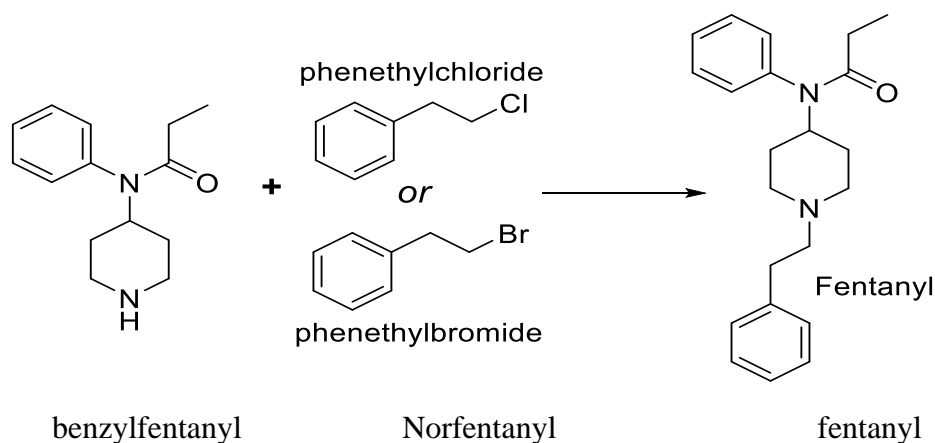


Figure 3. Janssen Synthetic Route From Benzylfentanyl

In the early 1980s, an alternate route for fentanyl synthesis was published in the scientific literature using NPP as the starting material.³ The NPP synthesis route is described on the Internet and is referred to as the “Siegfried method.” The chemical intermediary ANPP is produced during the synthesis and is the immediate precursor used in the illicit manufacture of fentanyl in the last stage of the “Siegfried method” (see Figure 4). This synthesis route attracted

³ S.H. Zee, W.K. Wang, A New Process for the Synthesis of Fentanyl, *Journal of the Chinese Chemical Society*, 147-149 (1980). A. Jonczyk, J. Jawdosiuk, M. Makosza, *Poszukiwanie Nowej Metody Syntezy Srodka Analgetycznego "Fentanyl," Przemysl Chemiczny*, 131-134 (1978).

the attention of clandestine fentanyl manufactures due to the lack of international controls on NPP and ANPP.

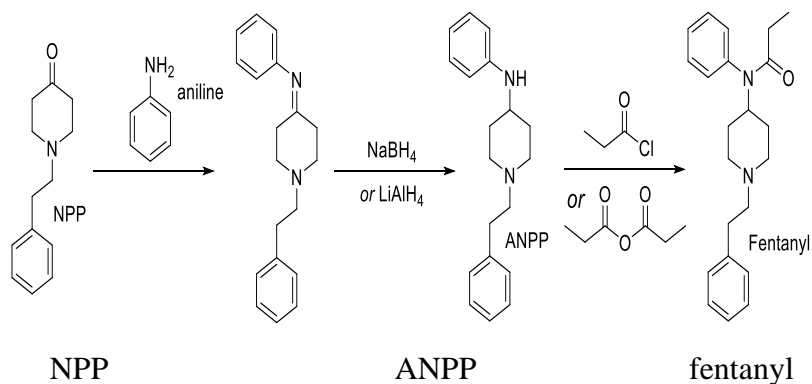


Figure 4. Siegfried Synthetic Route

The U.S. is once again experiencing increased deaths and reported abuse of fentanyl and its analogues. Law enforcement encounters of new fentanyl precursor chemicals, forensic identification of specific reaction byproducts, and detailed forensic analysis of illicitly manufactured fentanyl samples demonstrate that illicit fentanyl manufacturers have developed new synthetic strategies to evade regulations placed on NPP and ANPP. The synthetic modifications from the Janssen and Siegfried synthetic routes and law enforcement encounters are discussed in later sections.

Role of 4-AP, boc-4-AP, and Norfentanyls in the Synthesis of Fentanyl

The precursor chemical 4-AP is a starting point in the synthesis of fentanyl and many fentanyl analogues via the “Gupta method”⁴ in illicit drug laboratories (see Figure 5). DEA has controlled the precursor 4-AP as a List I chemical under the regulatory control provisions of the U.S. CSA. In addition, DEA controlled amides and carbamates of 4-AP in the same control action. This strategy allowed the United States to control additional precursor chemicals utilizing protecting groups, as well as precursors in the norfentanyl series (see Figure 5).

⁴ Gupta P.K., et. al, WO 2009/116084, September 24, 2009.

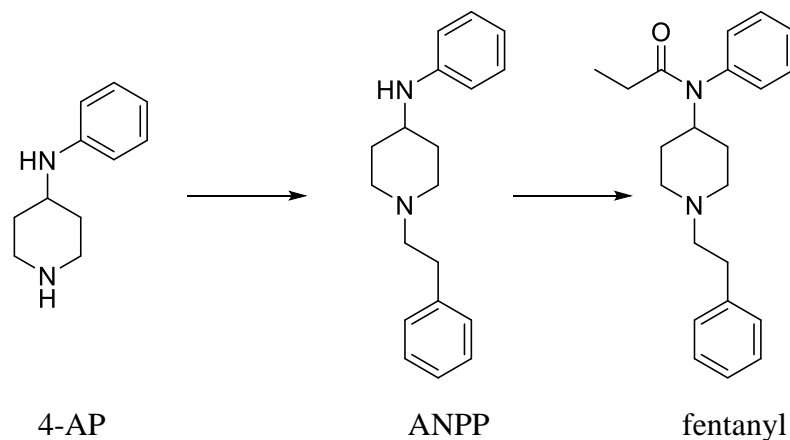


Figure 5. Gupta Synthetic Route

The use of 4-AP to synthesize fentanyl was originally reported in the patent literature.⁵ Since that time, other reports have discussed this synthetic route in the scientific literature or modified versions of this synthetic route.⁶ In this synthetic route, 4-AP serves as a replacement precursor for NPP, albeit through a different synthetic route, to synthesize ANPP. This synthetic step is accomplished by alkylating 4-AP with a phenethyl halide at the 1-position of the piperidine ring to produce ANPP.

The resulting ANPP is then converted to fentanyl or a fentanyl analogue by acylation of the anilino-nitrogen atom with propionic anhydride, propionyl chloride, or the corresponding acid chloride or anhydride. Based on laboratory analysis of seized drug evidence, bis-alkylation can occur. Both secondary amines are available to alkylation: the piperidine nitrogen as well as the anilino-nitrogen atom (see Figure 6). Phenethyl ANPP has been identified and reported in forensic analysis, supporting the use of 4-AP as a precursor chemical in the illicit manufacture of fentanyl and fentanyl analogues.

⁵ *Id.*

⁶ M.M. Vandeputte, *et al.* Phenethyl-4-ANPP: A Marginally Active Byproduct Suggesting a Switch in Illicit Fentanyl Synthesis Routes, *Journal of Analytical Toxicology* (2021). DOI: 10.1093/jat/bkab032. N. Gilbert, R.E. Mewis, O.B. Sutcliffe. Fast & Fluorinated – Development and Validation of a Rapid Benchtop NMR Approach and Other Routine Screening Methods for the Detection and Quantification of Synthesized Fluorofentanyl Derivatives, *Forensic Chemistry* (2021). DOI: 10.1016/j.forc.2021.100321. S. Vikingsson, *et al.* LC-QTOF-MS Identification of Major Urinary Cyclopropylfentanyl Metabolites Using Synthesized Standards, *Journal of Analytical Toxicology* (2019). DOI: 10.1093/jat/bkz057.

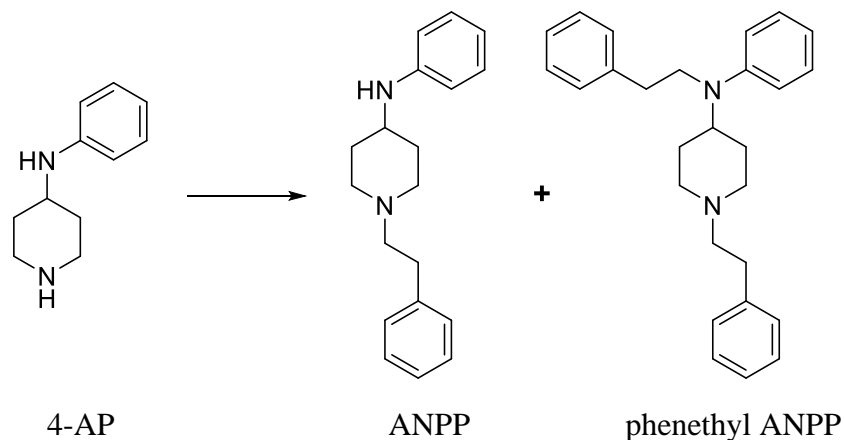


Figure 6. Alkylation of 4-AP

Alternatively, boc-4-AP utilizes a protecting group on the piperidine nitrogen atom. This precursor chemical may have been introduced to illicit fentanyl manufactures in an effort to evade detection by law enforcement or to aid in the regioselectivity of *N*-acylation. As discussed above, both secondary amines of 4-AP are available for alkylation with a phenethyl halide (see Figure 6). In fact, dialkylation has been observed in fentanyl seizures by the identification of *N*,1-diphenethyl-*N*-phenylpiperidin-4-amine (phenethyl ANPP). In addition, the identification of phenethyl ANPP was recently reported in the scientific literature.⁷

Upon protection of the piperidine nitrogen atom, acylation with propionyl chloride or propionic anhydride (or another acid chloride in the synthesis of certain fentanyl analogues) yields *tert*-butyl 4-(*N*-phenylpropionamido)piperidine-1-carboxylate (boc-norfentanyl). Subsequent deprotection provides norfentanyl, which is a schedule II immediate precursor to fentanyl under the United States CSA. Norfentanyl is then subjected to the alkylation reaction described above to provide fentanyl (see Figure 7). This synthetic strategy was employed in the synthesis of several fentanyl analogues as reported in the scientific literature.⁸

The synthetic strategy of utilizing protecting groups appears to have been employed by clandestine fentanyl manufacturers in recent years. The introduction of boc-4-AP as a precursor chemical use in the illicit manufacture of fentanyl serves multiple purposes:

1. Intended to “mask” the precursor 4-AP in an attempt to avoid law enforcement detection;
2. Provide regiospecific *N*-acylation of the aniline nitrogen atom, which upon deprotection, regiospecific *N*-alkylation can be achieved.

⁷ M.M. Vandeputte, *et al.* Phenethyl-4-ANPP: A Marginally Active Byproduct Suggesting a Switch in Illicit Fentanyl Synthesis Routes, *Journal of Analytical Toxicology* (2021). DOI: 10.1093/jat/bkab032.

⁸ N. Gilbert, R.E. Mewis, O.B. Sutcliffe. Fast & Fluorinated – Development and Validation of a Rapid Benchtop NMR Approach and Other Routine Screening Methods for the Detection and Quantification of Synthesized Fluorofentanyl Derivatives, *Forensic Chemistry* (2021). DOI: 10.1016/j.forc.2021.100321. S. Vikingsson, *et al.* LC-QTOF-MS Identification of Major Urinary Cyclopropylfentanyl Metabolites Using Synthesized Standards, *Journal of Analytical Toxicology* (2019). DOI: 10.1093/jat/bkz057.

From a synthesis perspective, *N*-acylation of the aniline nitrogen atom of boc-4-AP with the desired acid chloride (propionyl chloride, acetyl chloride, etc.) or anhydride provides regioselectivity. That is to say, the amide is formed at the anilino-nitrogen atom without acylation at the piperidine nitrogen atom. The desired norfentanyl series intermediate is then provided by boc-deprotection. Similar to the Janssen route described above, the norfentanyl series precursor is then alkylated with a phenethyl halide (or equivalent) to provide fentanyl or fentanyl analogues.

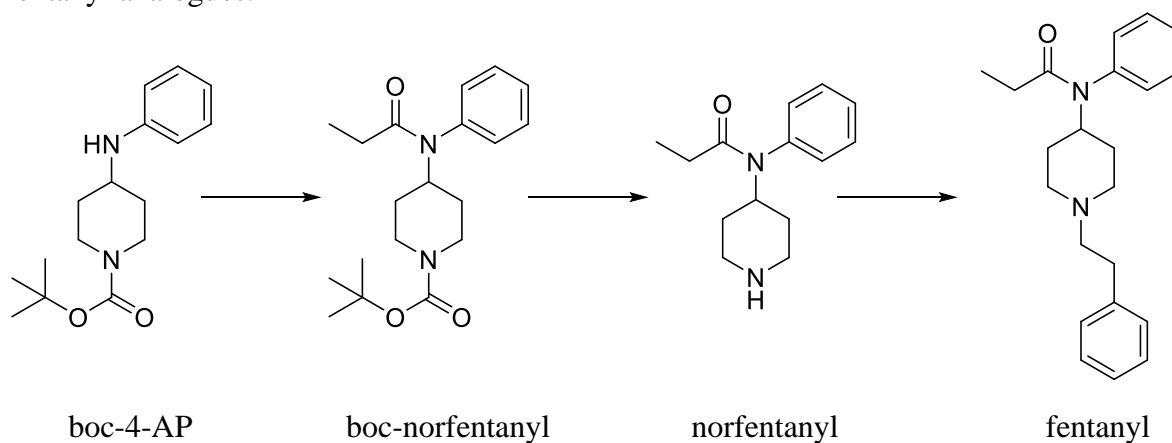


Figure 7. Utility of Protecting Groups in the Manufacture of Fentanyl: Modified Janssen Synthetic Route

Alternatively, boc-4-AP can be deprotected to provide 4-AP. 4-AP can then be used in the synthesis of fentanyl, as described in the “Gupta Method” (see Figure 8). Information gathered during law enforcement investigations shows that this route was considered in the illicit manufacture of fentanyl. The forensic identification of phenethyl ANPP also supports that clandestine fentanyl manufacturers can be deprotecting boc-4-AP prior to alkylation.

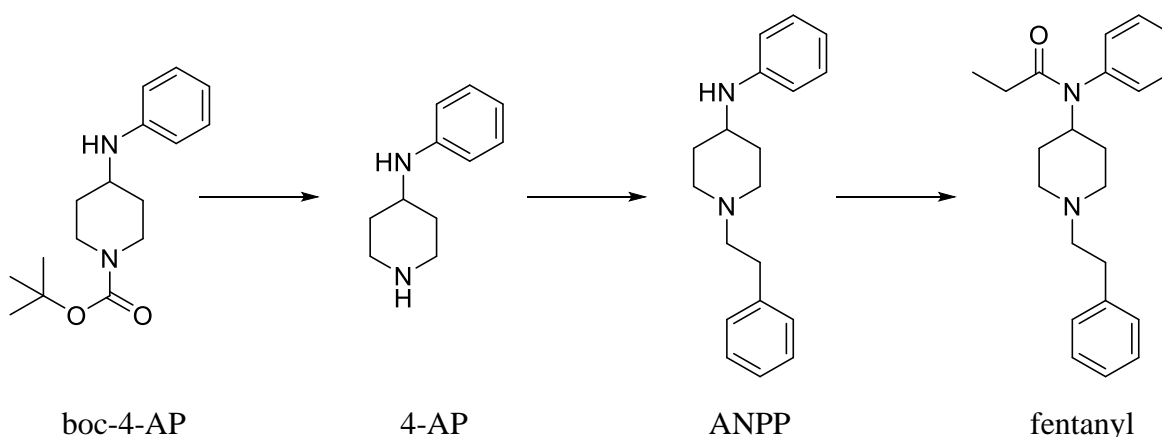


Figure 8. Utility of Protecting Groups in the Manufacture of Fentanyl: Modified Gupta Synthetic Route

Norfentanyl is a well-known precursor to fentanyl, as described in the original synthesis by Janssen.⁹ Similarly, related precursor chemicals, such as acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl, can be used as replacements to norfentanyl to synthesize the corresponding fentanyl analogue (see Figure 9). As discussed previously, these precursors have been reported by the INCB in the Project OPIOIDS “Fentanyl-related Substances with No Known Legitimate Uses” document. Therefore, it is reasonable to believe that these precursors can be utilized in the synthesis of fentanyl and their corresponding analogues.

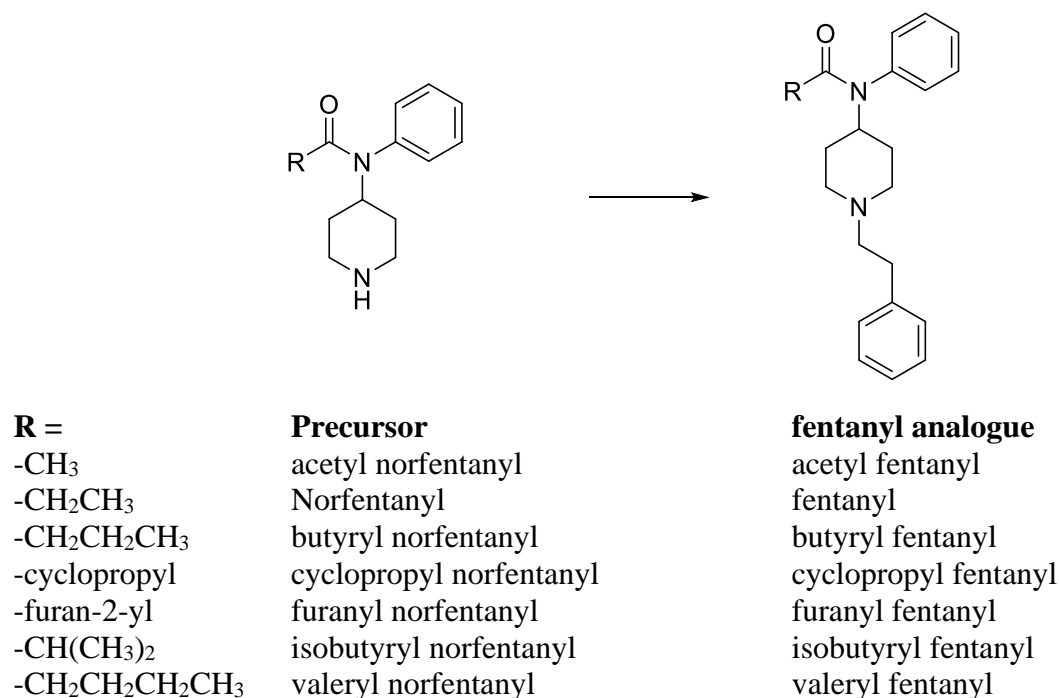


Figure 9. Norfentanyls Used in the Synthesis of Fentanyl and Select Fentanyl Analogues

DEA believes control of 4-AP, boc-4-AP, norfentanyl, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl are necessary to prevent unscrupulous chemists from synthesizing these precursors as unregulated material, and selling them through the Internet and other channels to individuals who may wish to acquire precursors for fentanyl or fentanyl analogue synthesis. DEA believes this action is also advisable in order to deter the theft of these chemicals from legitimate pharmaceutical firms where they are generated in the course of fentanyl production.

Forensic Analysis of Seized Fentanyl and Fentanyl Analogue Samples

The Fentanyl Profiling Program (FPP) profiles illicit fentanyl and fentanyl-related compounds with the goal of identifying the synthetic route utilized to synthesize the final

⁹ W.F.M. Van Bever, C.J.E. Niemegeers, K.H.L. Schellekens & P.A.J. Janssen, N-4-Substituted 1-(2-Arylethyl)-4-piperidiny-N-phenylpropanamides, a Novel Series of Extremely Potent Analgesics with Unusually High Safety Margin, *Arzneimittelforschung*, 1548-1551 (1976).

product. 4-AP is a critical precursor employed in the Gupta route of fentanyl production.¹⁰ Based on current research at DEA's Special Testing and Research Laboratory, the Gupta route was identified as the synthetic route utilized in 454 samples (66%, N=689) seized in CY 2020 and analyzed by the FPP. One additional sample seized in CY 2020 was identified as having mixed routes, one of which was the Gupta route. This route was identified as the synthetic route utilized in 12 samples (80%, N=15) seized in CY 2021 and analyzed by the FPP.

Norfentanyl is a chemical intermediate formed in the Janssen and boc-4-AP methods for fentanyl production. It also can be found in Gupta-type samples as an unintended consequence during fentanyl production. Norfentanyl was identified in 18 samples (3%, N=689) that were seized in CY 2020 and analyzed by the FPP. Two samples (13%, N=15) that were seized in CY 2021 and analyzed by the FPP were also found to contain norfentanyl. In addition to the Gupta route samples referenced in the above paragraph, samples found to be synthesized using the Janssen method would also have norfentanyl as a chemical intermediate. The Janssen method (or possibly the boc-4-AP method) was identified as the synthetic route utilized in 67 samples (10%, N=689) that were seized in CY 2020 and analyzed by the FPP. This possible classification was identified as the synthetic route utilized in two samples (13%, N=15) that were seized in CY 2021 and analyzed by the FPP.

Licit Uses

DEA has evaluated and determined that the precursor chemicals 4-AP, boc-4-AP, norfentanyl, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl are available through a number of chemical suppliers. Suppliers and legitimate uses of 4-AP, boc-4-AP, norfentanyl, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl are provided in in Appendix A: Chemical Information.

While legitimate pharmaceutical firms treat their synthetic routes as proprietary, most of the larger DEA-registered pharmaceutical manufacturers in the U.S. appear to be using NPP and/or ANPP as their preferred route for legitimate fentanyl production. DEA is not aware of legitimate fentanyl manufactures in the U.S. using 4-AP or boc-4-AP as precursor chemicals in their processes. Although it is possible that U.S. manufacturers may use norfentanyl in their synthetic route to fentanyl, the Aggregate Production Quota (APQ, see description below) does not support a substantial quantity of fentanyl being produced from norfentanyl for legitimate purposes. The 2021 APQ for norfentanyl was only 25 grams. In addition, DEA solicited comment from industry during the rulemaking process to control 4-AP, boc-4-AP, and norfentanyl under the CSA. Legitimate industry did not comment during that time as to their use of these precursor chemicals in fentanyl or any other manufacturing processes.

In the United States norfentanyl is a Schedule II controlled substance (as an immediate precursor) and 4-AP, boc-4-AP, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl are List I chemicals. There are specific regulatory requirements for handling these precursor chemicals under the CSA and

¹⁰ Gupta P.K., et. al, WO 2009/116084, September 24, 2009. Gupta P.K., et. al, US Patent #20110021781A1, January 27, 2011.

its implementing regulations. DEA-registered manufacturers and importers of norfentanyl are required to be registered with DEA, manufacturing quotas and procurement quotas authorization is required, material must be securely maintained in a vault/safe, import and export permits must be issued, and DEA forms and reports are required for distribution and sale. 4-AP, boc-4-AP, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl regulatory requirements include registration, recordkeeping and import/export reporting, and a provision for the reporting of suspicious transactions.

The United States also regulates the manufacture of norfentanyl and fentanyl through the issuance of quotas and import permits. The Aggregate Production Quota (APQ) is the total amount of a controlled substance that can be manufactured in a calendar year to provide for the estimated medical, scientific, research, and industrial needs of the United States, for lawful export requirements, and for the establishment and maintenance of reserve stocks. The 2021 APQ for the United States for norfentanyl is 25 grams and for fentanyl is 731.45 kilograms. The legal and regulatory requirements for Schedule II controlled substances and Listed Chemicals in the U.S. are based on those of the UN drug control treaties.

Published Reports of Deaths Involving Fentanyl and Fentanyl Analogues

According to the U.S. Centers for Disease Control and Prevention (CDC), in 2019 the United States identified 36,359 overdose deaths involving synthetic opioids other than methadone. This category is primarily comprised of overdose deaths involving fentanyl and its analogues. This represents a more than 1,000 percent increase in deaths involving this category since 2013. Provisional CDC data indicates that there were 56,865 overdose deaths involving synthetic opioids other than methadone in 2020 and that the number of fentanyl-involved deaths is continuing to rise, as shown in Table 1.

Table 1: Number of Overdose Deaths Involving Synthetic Narcotics Other Than Methadone

Year	2012	2013	2014	2015	2016	2017	2018	2019	2020*
Overdose Deaths	2,628	3,105	5,544	9,580	19,413	28,466	31,335	36,359	56,865

2020*: count is provisional.¹¹

Illicit Fentanyl and Fentanyl Analogue's Negative Impact on Global Public Health

Over the past decade, illicit fentanyl use and related harms have emerged as a critical public health threat in countries around the world. Illicit fentanyl use has caused particularly high numbers of overdose fatalities in North American and some European countries. A dearth

¹¹ Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2019, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at <http://wonder.cdc.gov/mcd-icd10.html> on May 5, 2021. Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021. Accessed at <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> on July 14, 2021.

of reliable data, however, prevents a reliable estimate of illicit fentanyl’s full impact. Many countries do not have the capacity to conduct toxicology screening tests for fentanyl or to distinguish it from other synthetic opioids.

The United Nations Office on Drugs and Crimes (UNODC), Global Synthetic Drugs Assessment 2020, mentioned some fentanyl fatalities covered by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), although the data are somewhat dated. The report states that,

“Synthetic opioids have been associated with severe adverse health events, including fatalities. In the 30 European countries covered by the EMCDDA, the fentanyl analogue cyclopropylfentanyl was involved in 78 deaths, carfentanil in 61 and acrylfentanyl in 47, in 2017 and 2018. For instance, in England and Wales a total of 74 fentanyl-related deaths and 31 deaths relating to fentanyl analogues were recorded in 2018. Several countries reported a decline in deaths relating to fentanyl or fentanyl analogues including Germany (from 157 deaths in 2017 to 59 in 2018), Estonia (from 86 in 2017 to 12 in 2018) and Sweden (from 131 in 2017 to 30 in 2018).”

Law Enforcement Encounters with Illicit Fentanyl and Select Fentanyl Analogues in the United States

According to the National Forensic Laboratory Information System (NFLIS-Drug), a DEA system that collects data from Federal, State, and local forensic laboratories, laboratory submissions containing fentanyl increased dramatically from 2011-2020, and this increase has continued into 2021 (see Table 2). The DEA believes the primary source of fentanyl encountered on the illicit market is synthesized clandestinely by international sources. The U.S. also observed an increase of fentanyl and fentanyl analogues during this time period. Reports to NFLIS-Drug of selected fentanyl analogues are included below, specifically those that can be synthesized from acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl.

Table 2. Number of Fentanyl and Select Fentanyl Analogue Reports to NFLIS-Drug by Year

Substance	2012	2013	2014	2015	2016	2017	2018	2019	2020*	2021*	Total
Fentanyl	693	1,049	5,538	15,458	37,157	61,641	89,790	106,905	112,034	30,813	461,078
Acetyl fentanyl		9	63	2,069	1,950	1,767	7,838	13,581	4,349	821	32,447
Butyryl fentanyl			7	211	194	704	230	124	36	1	1,507
Cyclopropyl fentanyl					1	1,565	1,017	65	17		2,665
Furanyl fentanyl				5	2,980	5,503	804	250	40	8	9,590
Isobutyryl fentanyl						5	19	21			45
Valeryl fentanyl				1	76	6	514	2,213	516	25	3,351

* Reports are still pending for Q4 of 2020 and all of 2021.¹²

¹² DEA, NFLIS-Drug, Data Query System, Base Drug List, accessed at <https://www.nflis.deadiversion.usdoj.gov/> on July 19, 2021.

DEA is concerned that the international availability and lack of control of 4-AP, boc-4-AP, norfentanyl, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl is directly contributing to the recent increase of illicitly produced fentanyl and fentanyl analogues, even with the U.S. control of these precursor chemicals under the CSA. While many synthetic routes are possible to manufacture fentanyl, these precursor chemicals appear to have replaced NPP and ANPP as key precursors in synthetic routes primarily used by clandestine operations, as indicated by law enforcement encounters of these precursor chemicals and in the impurity profiles obtained from law enforcement seizures. Therefore, DEA believes that controlling 4-AP, boc-4-AP, norfentanyl, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl is necessary to prevent the illicit production of fentanyl.

Law Enforcement Encounters in the United States

Currently, there is little evidence of clandestine fentanyl synthesis in the U.S. The U.S. appears to be a transit country, as fentanyl precursor chemicals are imported to the U.S. from Eastern Asia, with final destinations in Mexico. Law enforcement encounters of fentanyl precursor chemicals typically occur at ports of entry while in transit to another destination country. A summary of law enforcement encounters of fentanyl precursor chemicals is provided in Appendix B: Table of Law Enforcement Encounters.

Summation/Desired Outcome of International Listing

The United States strongly believes the illicit manufacture of fentanyl and its analogues is a global problem with far-reaching negative effects on global public health and safety. The fundamental role that 4-AP, boc-4-AP, and norfentanyl, along with related chemicals acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl play in the ever-increasing rise of illicit fentanyl and fentanyl analogue manufacturing, use, and accelerating overdose deaths demands immediate and deliberate action on the part of the international community.

The international listing of these precursor chemicals is a necessary step in stemming the tide of the manufacture and use of illicit fentanyl and its analogues. However, this action in and of itself should be viewed as part of a larger international effort to reduce the availability and use of illicit fentanyl, as well as a tangible means to help address the increasing number of overdose deaths involving fentanyl and its analogues. A complex problem such as this requires a comprehensive response including those taken to prevent the diversion of fentanyl from its legal medical purposes, evidence-based prevention programs to reduce the number of new initiates to illicit opioid use, treatment and recovery programs to assist those with opioid use disorders in their path to long-term recovery, and actions to address the overall reduction of the global availability and use of all illicit opioids such as heroin and morphine. Member states have repeatedly shown their dedication to this comprehensive and balanced approach to reducing the availability and use of illicit opioids, and the international listing of these precursor chemicals will directly support those efforts.

The United States fundamentally believes, based upon its own experience, that this action will directly and positively impact this problem on a global scale. 4-AP, boc-4-AP, norfentanyl, acetyl norfentanyl, butyryl norfentanyl, cyclopropyl norfentanyl, furanyl norfentanyl, isobutyryl norfentanyl, and valeryl norfentanyl are currently regulated within the United States. According to both Federal and state law enforcement officials, the number of illicit fentanyl manufacturing labs is extremely low in the United States. It is highly likely that the United States' strict control on these chemicals, along with those chemicals defined in the domestic control action, has prevented the widespread growth of clandestine fentanyl and fentanyl analogue labs within the country. The United States believes that greater international controls on precursor chemicals offer the international community the very best opportunity to prevent the establishment of illicit fentanyl manufacturing labs in other countries as well.

The availability and use of illicit fentanyl and its analogues, as well as the overdose deaths involving fentanyl and fentanyl analogues, is a problem shared by many countries around the world. The United States requests the assistance and cooperation of the international community in stemming the tide of this international problem by increasing controls on the chemicals used to manufacture these dangerous drugs as part of a comprehensive global effort to address this complex national security, law enforcement, and public health crisis.

Appendix A: Chemical Information

4-Anilinopiperidine

Other Names: 4-AP; *N*-phenyl-4-piperidinamine; 4-(phenylamino)piperidine; *N*-(piperidine-4-yl)aniline; *N*-phenylpiperidin-4-amine; NSC 80678

Molecular Formulas: C₁₁H₁₆N₂

Molecular Weight: 176.26

CAS Number: 23056-29-3 (HCl salt: 1193388-65-6; diHCl salt: 99918-43-1; HBr salt: 24775-80-2; 2 x HBr salt: 24998-99-0; tosylate salt: 918535-64-5)

Melting Point:

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) including its amides, its carbamates, and its salts.

- Manufacturers-base
 - 42 suppliers
 - 24 in stock, 3 custom synthesis, 15 didn't list
 - Most offer milligram to gram quantities, with a few offering 1 kg or bulk
 - United States (28), United Kingdom (3), Germany (1), China (8), Lithuania (1), France (1), Canada (1), Hong Kong (2), Austria (3), Latvia (1), Slovakia (1), Ukraine (1)
- Manufactures – HCl salt
 - 16 suppliers
 - 3 in stock, 1 custom synthesis, 2 limited quantities; 10 didn't list
 - Most offer milligram to gram quantities, 3 offer 1 kg, 4 offer generic "bulk"
 - China (6), United States (6), Austria (2), Hong Kong (2), United Kingdom (2), Canada (1), Germany (1), Latvia (1), Slovakia (1)
- Manufactures – diHCl salt
 - 27 suppliers
 - 12 in stock, 3 custom synthesis, 2 limited quantities; 10 didn't list
 - Most offer milligram to gram quantities, 4 offer 1 kg, 10 offer generic "bulk"
 - United States (16), China (7), Austria (2), Hong Kong (2), United Kingdom (2), Germany (1), Latvia (1), Slovakia (1), Switzerland (1)
- Manufactures – HBr salt
 - 3 suppliers
 - 3 didn't list
 - Most didn't list amounts; 1 offer 1 kg
 - China (1), Hong Kong (2)
- Manufactures – 2 x HBr salt
 - 3 suppliers

- 3 didn't list
- Most didn't list amounts; 1 offer 1 kg
- China (1), Hong Kong (2)
- Manufactures – tosylate salt
 - 3 suppliers
 - 3 didn't list
 - Most didn't list amounts; 1 offer 1 kg
 - China (1), Hong Kong (2)

1-boc-4-anilinopiperidine

Other Names: 4-anilino-1-boc-piperidine; 4-ANBocP; *N*-boc-4-AP; 1-boc-4-AP; boc-4-AP; 1-boc-4-(phenylamino)piperidine; *tert*-butyl 4-(phenylamino)piperidine-1-carboxylate; *tert*-butyl 4-anilinopiperidine-1-carboxylate; 4-(phenylamino)-1-piperidinecarboxylic acid 1,1-dimethylethyl ester; 1,1-dimethylethyl 4-(phenylamino)-1-piperidinecarboxylate

Molecular Formulas: C₁₆H₂₄N₂O₂

Molecular Weight: 276.37

CAS Number: 125541-22-2 (HCl salt: 1197227-86-3)

Melting Point: 139-141 °C

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) as a carbamate of 4-anilinopiperidine

- Manufacturers - base
 - 78 suppliers
 - 44 maintain stock, 10 synthesis on demand, 4 limited quantities/intermittent availability, 20 didn't say
 - Most companies offer gram or milligram quantities, a few offer 1 kg; two companies offered up to 100 kg (ASW Med Chem and BOC Sciences in U.S.); several offered generic "bulk"
 - United States (52), China (17), United Kingdom (10), Canada (3), France (3), Germany (3), Hong Kong (3), Japan (3), Republic of Korea (3), Austria (2), Latvia (2), Israel (1), Slovakia (1), Taiwan (1), Ukraine (1)
- Manufacturers – HCl salt
 - 9 suppliers
 - 2 maintain stock, 1 synthesis on demand, 6 didn't say
 - Most companies offer gram or milligram quantities, 3 offer 1 kg; one offered generic "bulk"
 - China (3), United States (3), Hong Kong (2), Austria (1), France (1)

Norfentanyl

Other Names: *N*-phenyl-*N*-4-piperidinylpropanamide; 4-(*N*-propionanilido)piperidine; *N*-piperidine-4-yl-*N*-phenylpropionamide; *N*-phenyl-4-yl-*N*-piperidinylpropionamide; NSC 89293; 4-(*N*-propionylaniline)piperidine; *N*-4-piperidyl-propionanilide

Molecular Formulas: C₁₄H₂₀N₂O

Molecular Weight: 232.32

CAS Number: 1609-66-1 (HCl salt: 22352-81-4; hydrate: 1628111-00-1; oxalate salt: 1211527-24-0)

Melting Point: 83-85 °C

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (Schedule II substance)

- **Manufacturers - base**
 - 46 suppliers
 - 26 maintain stock, 6 synthesis on demand, 2 limited quantities/intermittent availability, 12 didn't say
 - Most companies offer gram or milligram quantities, 9 offer at least 1 kg; three companies offered up to 100 kg (ASW Med Chem in U.S. two listings and HE Chemical Product in China.); HE Chemical Product in China offered 1 metric ton (1000 kg); several offered generic "bulk"
 - United States (24), China (7), United Kingdom (7), Hong Kong (3), Norway (3), Austria (2), Canada (1), France (1), Germany (1), Japan (1), Slovakia (1), Ukraine (1)
- **Manufacturers – HCl salt**
 - 5 suppliers
 - 2 maintain stock, 3 didn't say
 - Most companies offer gram or milligram quantities or don't say
 - United States (2), Norway (2), Hong Kong (1)
- **Manufacturers - hydrate**
 - 4 suppliers
 - 2 maintain stock, 2 didn't say
 - Most companies offer gram or milligram quantities or don't say
 - United States (3), France (1)
- **Manufacturers – oxalate salt**
 - 4 suppliers
 - 2 maintain stock, 2 didn't say
 - Most companies offer gram or milligram quantities or don't say
 - United States (3), France (1)

Acetyl Norfentanyl

Other Names: *N*-phenyl-*N*-4-piperidinylacetamide; *N*-4-piperidyl-acetanilide; *N*-phenyl-*N*-(piperidine-4-yl)acetamide; 4-(*N*-phenylacetamido); *N*-(4-piperidinyl)phenylacetamide; NSC 74308

Molecular Formulas: C₁₃H₁₈N₂O

Molecular Weight: 218.29

CAS Number: 1607-68-7 (HCl salt: 22352-82-5; oxalate salt: 2320863-97-4)

Melting Point: 129-130 °C

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of butyryl fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) as an amide of 4-anilinopiperidine

- Manufacturers - base
 - 9 suppliers
 - 3 synthesis on demand, 6 didn't say
 - Most companies offer gram quantities, 1 offer at least 50 kg; one offered generic "bulk"
 - United States (6), China (2), Hong Kong (1) (Austria is also listed with 2 but is correlated to a company in the US)
- Manufacturers – HCl salt
 - 10 suppliers
 - 2 maintain stock, 1 limited quantities/intermittent availability, 7 didn't say
 - Most companies offer gram or milligram quantities, 2 offer at least 1 kg; one company offered up to 100 kg (ASW Med Chem in U.S.), one offered generic "bulk"
 - United States (4), China (3), Canada (1), Hong Kong (1), Norway (1) (Austria is also listed with 2 but is correlated to a company in the US)
- Manufacturers – oxalate salt
 - 3 suppliers
 - 1 maintain stock, 2 didn't say
 - Didn't say quantity
 - United States (1), France (1) (Austria is also listed with 1 but is correlated to a company in the US)

Butyryl Norfentanyl

Other Names: *N*-phenyl-*N*-4-piperidinylbutanamide; *N*-4-piperidyl-butyranyl; *N*-phenyl-*N*-(piperidine-4-yl)butanamide

Molecular Formulas: C₁₅H₂₂N₂O

Molecular Weight: 246.35

CAS Number: 1432-03-7

Melting Point:

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of butyryl fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) as an amide of 4-anilinopiperidine

- Manufacturers - base
 - 1 supplier
 - didn't say
 - Offers up to 50 kg; can ship within 2 weeks
 - China (1)
- Manufacturers – salts
 - Salt is not listed on Scifinder; however HCl salt sold by Cayman Chemical (United States)

Furanyl Norfentanyl

Other Names: *N*-phenyl-*N*-4-piperidinyl-2-furancarboxamide

Molecular Formulas: C₁₆H₁₈N₂O₂

Molecular Weight: 270.33

CAS Number: 1047187-49-4

Melting Point:

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of furanyl fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) as an amide of 4-anilinopiperidine

- Manufacturers - base
 - 0 suppliers
- Manufacturers – HCl salt (no CAS)
 - Salt is not listed on Scifinder; however HCl salt sold by Cayman Chemical (United States)

Cyclopropyl Norfentanyl

Other Names: *N*-phenyl-*N*-4-piperidinyl-cyclopropanecarboxamide; *N*-4-piperidyl-cyclopropanecarboxanilide

Molecular Formulas: C₁₅H₂₀N₂O

Molecular Weight: 244.33

CAS Number: 802543-92-6 (HCl salt: 1432-04-8)

Melting Point:

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of cyclopropyl fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) as an amide of 4-anilinopiperidine

- Manufacturers - base
 - 0 suppliers
- Manufacturers – HCl salt
 - 7 suppliers
 - 5 maintain stock, 1 synthesis on demand, 1 didn't say
 - Most companies offer milligram quantities, one offered generic "bulk"
 - United States (5), Norway (2) (Austria is also listed with 1 but is correlated to a company in the US)

Isobutyryl Norfentanyl

Other Names: 2-methyl-N-phenyl-N-4-piperidinyl-propanamide

Molecular Formulas: C₁₅H₂₂N₂O

Molecular Weight: 244.33

CAS Number: 1046436-53-6

Melting Point:

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of isobutyryl fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) as an amide of 4-anilinopiperidine

- Manufacturers - base
 - 8 suppliers
 - 5 maintain stock, 1 synthesis on demand, 2 didn't say
 - Most companies offer milligram or gram quantities, one offered generic "bulk"
 - United States (6), China (2) (Austria is also listed with 1 but is correlated to a company in the US)

Valeryl Norfentanyl

Other Names: N-phenyl-N-4-piperidinyl-pentanamide

Molecular Formulas: C₁₆H₂₄N₂O

Molecular Weight: 244.33

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Annex I - Supplemental Information

CAS Number: 702627-19-8 (HCl salt: 22352-83-6)

Melting Point:

Description:

Illicit Use: Precursor in clandestine laboratory manufacture of valeryl fentanyl.

Where Controlled or Regulated: U.S. Controlled Substances Act (List I chemical) as an amide of 4-anilinopiperidine

- Manufacturers - base
 - 0 suppliers
- Manufacturers – HCl salt
 - 0 suppliers

APPENDIX B: Table of Law Enforcement Encounters

Domestic Seizures from 2019 to 2021:

May 28, 2020 – Los Angeles, California

10.438 kg of 4-anilinopiperidine (4-AP) from a flight that originated from China with a fuel stop at the Los Angeles International Airport and continuing its flight to Guadalajara, Mexico.

August 19, 2020 – Anchorage, Alaska

27 kg of 4-Anilinopiperidine (4-AP) from a flight originating from Jiangsu, China en route to Mexico.

September 17, 2020 - Anchorage, Alaska

52.35 kilograms of 4-anilino-1-boc-piperidine (boc-4-AP) from an air shipment.

September 25, 2020 – Anchorage, Alaska

90.72 kg of 4-anilinopiperidine (4-AP) from an air shipment at the Anchorage International Airport.

November 04, 2020 – Anchorage, Alaska

21.75 kg of 4-anilino-1-boc-piperidine (boc-4-AP) from an air shipment.

January 28-29, 2021 – Memphis, Tennessee

11.7 kg of 4-anilino-1-boc-piperidine (boc-4-AP) in two air shipments.

February 9, 2021 – Memphis, Tennessee

5.15 kg of 4-anilino-1 boc-Piperidine (boc-4-AP) in a FedEx shipment.

May 6 – 12, 2021 – Cincinnati, Ohio

220 kg of *N*-(*tert*-butoxycarbonyl)-4-piperidine (boc-4-AP), in two air separate shipments that originated in China, through Cincinnati, Ohio, transiting Laredo, TX, and ultimately destined to Guadalajara, Mexico.

Foreign Seizures from 2019 to 2021:

August 22, 2019 – Michoacán, Mexico

Mexican Customs seized 274 kg of 4-anilinopiperidine (4-AP) at Lazaro Cardenas, Michoacán.

September 28, 2019 – Mexico City, Mexico

Mexican authorities seized 29.16 kg of 4-anilinopiperidine (4-AP) at the Mexico City Airport.

April 3, 2020 – Mexico City, Mexico

Mexican authorities seized 45.8 kg of 4-anilinopiperidine (4-AP) at the Mexico City Airport.

May 22, 2020 – Ensenada, Mexico

Mexican authorities seized 69.17 kg of 4-anilinopiperidine (4-AP) at Ensenada, Baja California.

August 10, 2020 - Mexico City, Mexico

Mexican authorities inspected a shipment, which departed from Dubai UAE, transiting through Zaragoza, Spain, before arriving in Mexico City, Mexico. Tests stated that the powder contained *N*-phenylpiperidin-4-amine (4-AP), with a total weight of 224 kg.

November 30, 2020 – Guadalajara, Mexico

Mexican officials seized approximately 55 kg of *N*-phenylpiperidin-4-amine dihydrochloride (4-AP) at the Guadalajara International Airport.