Precursor Chemicals Trends:
U.S. Perspectives

Liqun L. Wong
Unit Chief
Drug & Chemical Evaluation Section
Diversion Control Division
United States Drug Enforcement Administration
Opioid Health Crisis

Total Number of Overdose Deaths, 1999 - 2018

- Psychostimulants with abuse potential
- Benzodiazepines
- Methadone
- Synthetic Opioids
- Natural and Semisynthetic Opioids
- Cocaine
- Heroin

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Total Number of Deaths

No provisional data for benzodiazepine drug class

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2018 Provisional data (12-Month Period Ending on December 2018)
Number of NPS Encounters in U.S.

Total Number of NPS Drug Reports by Drug Category and Year

- Synthetic Cannabinoids
- Synthetic Cathinones
- Synthetic Opioids

Source: National Forensic Laboratory Information System (NFLIS), DEA, Queried as of June 12, 2019. *NFLIS reporting still pending.
Number of NPS in U.S.

Number of Drugs by Category  2009 - 2018*

- Synthetic Cannabinoids
- Synthetic Cathinones
- Synthetic Opioids

* NFLIS reporting still pending.

Source: National Forensic Laboratory Information System (NFLIS), DOE/DC/DEA, Queried as of June 12, 2019
April 2005 - March 2007: Spike in fentanyl seizures
Over 1013 documented non-pharmaceutical (NPF) overdose deaths
Primary synthetic route identified as Siegfried method

- $N$-phenethyl-4-piperidone (NPP) added as a List 1 chemical in 2007
- 4-anilino-$N$-phenethyl-4-piperidine (ANPP) added as a Schedule II immediate precursor in 2010

Clandestine Pill Press Operation
**Fentanyl Synthesis - Siegfried Route**

**Synthesis of the ANPP**

The reaction mixture from (a) is filtered from the Molecular Sieves which are rinsed with 2*2ml THF, the filtrate and washings are poured into a 50 ml flask, whereupon 20 ml dry Methanol is added, and the mix is stirred.

About 1-1.5 gr of Sodium Borohydride is very slowly added to the mixture at room temperature, and the mix is stirred for about 2 h. The conversion into ANPP is checked with any method and if not completely reduced, add slowly another 0.5gr NaBH₄ and stir for one more hour.

When the conversion into ANPP is complete (more than 95%).
Synthetic Opioids in Counterfeit Tablets

[Images of counterfeit tablets]
Control of Precursor Chemicals

Internationally controlled (CND, 2017)

NPP

4-ANPP

Fentanyl
Variety of Delivery Methods

cyclopropyl fentanyl spray

decesed tested positive for acetyl fentanyl

carfentanil on blotter paper

aerosolized acetyl
Synthetic Route Determined for Fentanyl Seized in CY 2018

- Janssen: 96% (N=172)
- Siegfried: 4% (N=7)
Analysis of Fentanyl Synthesis

Janssen

NPP → ANPP

Diversion Control Division
Fentanyl Synthesis - Other Methods

4-anilinopiperidine (4-AP)

4-piperidone

United States Patent
Gupta et al.

METHOD FOR THE PREPARATION OF FENTANYL

NPP
ANPP
fentanyl
Fentanyl Synthesis – New Precursors

- New method utilizes a substance called 4-AP instead of NPP
- INCB reported 32 notifications (late 2018 - early 2019) representing **30 kg of 4-AP**
- Origins: China, Hong Kong, Netherlands, Singapore, India
- Destination: Mexico

30 kg of 4-AP can produce 57 kg of fentanyl!

falsely declared as “foodstuffs or consumables”, “gifts”, “unspecified goods”, “glass bottles” and “protein”
Fentanyl Precursor - Packaging

Picture 9 (© PGR Mexico)
Country of origin: Singapore
Goods declared: gift

Picture 10 (© PGR Mexico)
Country of origin: Netherlands
Goods declared: glass bottles

Picture 12 (© PGR Mexico)
Country of origin: China
Goods declared: n/a

Picture 14 (© PGR Mexico)
Country of origin: China
Goods declared: protein
“discreet package: the packing suits you best would be chosen to cross customs safely. or if you have your own ideal way, it could be also taken into consideration.”

“safety guarantee (we do this business long time, we know how to disguise let the product through customs)”

“our company promise to deliver clients' package to his hands safely, or we'll cover the total loss and reship in time”
Precursor Chemical Names

N-Phenyl-4-piperidinamine is also known under the following common synonyms (list not exhaustive):

- N-Phenylpiperidin-4-amine
- 4-Anilinopiperidine
- 4-AP
- Despropionyl norfentanyl
- Piperidine, 4-anilino-
- 4-Piperidinamine, N-phenyl-

CAS registry number: 23056-29-3

From a January 2019 International Alert

<table>
<thead>
<tr>
<th>Salt form</th>
<th>CAS number</th>
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<tbody>
<tr>
<td>Base</td>
<td>23056-29-3</td>
</tr>
<tr>
<td>Hydrochloride (1:1)</td>
<td>1193388-65-6</td>
</tr>
<tr>
<td>Hydrobromide (1:1)</td>
<td>24775-80-2</td>
</tr>
<tr>
<td>Hydrobromide (1:2)</td>
<td>24998-99-0</td>
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<tr>
<td>4-methylbenzenesulfonate (1:?</td>
<td>918535-64-5</td>
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## Precursor Chemical – CAS Numbers

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Internet Sales - Precursor Chemicals

N-PHENYLPIPERIDIN-4-AMINE DIHYDROCHLORIDE

CAS 99918-43-1 (daisy@crovellbio.com) Factory supply 99% 4-Anilinopiperidine powder, CAS: 99918-43-1 Fentanyl Intermediates 4-Anilinopiperidine (hydrochloride) China supplier, hot selling N-Phenylpiperidin-4-Amine Dihydrochloride in stock Email: daisy@crovellbio.com Factory

Hebei Guanlang Biotechnology Co., Ltd

email: daisy@crovellbio.com
whatsapp +86 19930503252
Heibe Guanlang Biotechnology (Crovellbio)

- All products have a connection to drug trade
  - Designer precursors
  - Cutting agents
  - Non-controlled solvents
- Product offerings evolve re: chemical controls
- Pervasive online presence
- Marking materials reference a "Mexico Branch"
- Only one of many of examples
Designer Precursor Chemicals

CAS number: 125541-22-2

tert-butyl 4-(phenylamino)piperidine-1-carboxylate

N-Phenyl-4-piperidinamine is also known under the following common synonyms (list not exhaustive):
- N-Phenylpiperidin-4-amine
- 4-Anilinopiperidine
- 4-AP
- Despropionyl norfentanyl
- Piperidine, 4-anilino-
- 4-Piperidinamine, N-phenyl-
- CAS registry number: 23056-29-3
Masked Precursor
Methamphetamine Designer Precursor Chemicals

MAPA
methyl 3-oxo-2-phenylbutanoate
methyl alpha-acetylphenylacetate
CAS 16648-44-5
“designer” precursor: A close chemical relative of a controlled precursor that is purpose-made to circumvent controls and usually does not have any recognized legitimate use.

- Established in 2013, in response to the proliferation of “designer” precursors
- The list currently contains 53 individual substances
- Expanded the list in a generic manner
- ISSL and definitions cover:
  - esters and other simple derivatives
  - Stable chemical intermediates,
  - Purpose-made chemical intermediates
  - Masked derivatives of controlled precursors
  - others
Contact Information

Liqun L. Wong
DPE@usdoj.gov
+1-202-307-7183

U.S. Drug Enforcement Administration
www.deadiversion.usdoj.gov