



# Economic and Social Council

Distr.: General  
4 January 2024

Original: English

## Commission on Narcotic Drugs

Sixty-seventh session

Vienna, 14–22 March 2024

Item 5 (a) of the provisional agenda\*

**Implementation of the international drug control treaties: changes in the scope of control of substances**

### **Changes in the scope of control of substances under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988: 4-piperidone and 1-boc-4-piperidone**

Note by the Secretariat

#### *Summary*

The present document contains information and recommendations for consideration by the Commission on Narcotic Drugs pursuant to the international drug control treaties.

The Commission will have before it, for review, the information transmitted by the International Narcotics Control Board pursuant to article 12, paragraph 4, of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 with regard to the assessments of 4-piperidone and 1-boc-4-piperidone and, for consideration, the recommendation of the Board that 4-piperidone and 1-boc-4-piperidone be included in Table I of the 1988 Convention.

\* E/CN.7/2024/1.



## I. Introduction

1. The United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, in its article 12, paragraph 2, provides as follows:

If a Party or the Board has information which in its opinion may require the inclusion of a substance in Table I or Table II, it shall notify the Secretary-General and furnish him with the information in support of that notification. The procedure described in paragraphs 2 to 7 of this article shall also apply when a Party or the Board has information justifying the deletion of a substance from Table I or Table II, or the transfer of a substance from one Table to the other.

2. On 5 July 2023, the Government of the United States of America submitted a notification to the Secretary-General pursuant to article 12, paragraph 2, of the 1988 Convention, requesting the initiation of steps to evaluate two fentanyl precursors, namely 4-piperidone and 1-boc-4-piperidone, for possible inclusion in Table I of that Convention. The letter to the Secretary-General is contained in annex II to the present document.

3. In accordance with the provisions of article 12, paragraph 3, of the 1988 Convention, the notification and relevant information submitted by the Government of the United States to the Secretary-General in support of its recommendations were transmitted by a note verbale dated 3 August 2023 to all parties to the 1988 Convention. Also in that note, two questionnaires, one on 4-piperidone and one on 1-boc-4-piperidone, were sent to Governments, requesting them to submit their comments regarding the notification and any supplementary information that might assist the International Narcotics Control Board (INCB) in establishing an assessment by 29 September 2023. A reminder was circulated to Governments on 27 September 2023.

4. In response to that note, as at 10 November 2023, 60 Governments and the European Commission had responded to the questionnaire on 4-piperidone and 61 Governments and the European Commission had responded to the questionnaire on 1-boc-4-piperidone (listed in the appendix to annex I). Three additional responses<sup>1</sup> were received after that date, as at 4 January 2024.

## II. Notification from the International Narcotics Control Board concerning scheduling under the 1988 Convention

5. On 23 November 2023, in accordance with article 12, paragraph 4, of the 1988 Convention, the President of INCB notified the Chair of the Commission on Narcotic Drugs that the Board had completed its assessments of 4-piperidone and 1-boc-4-piperidone for possible inclusion in the tables of the 1988 Convention.

6. The Board recommends that 4-piperidone and 1-boc-4-piperidone be included in Table I of the 1988 Convention.

7. The notification from the President of INCB and the assessments, findings and recommendations of the Board in respect of both substances are contained in annex I to the present document, for consideration by the Commission at its sixty-seventh session.

## III. Action to be taken by the Commission on Narcotic Drugs

8. In accordance with article 12, paragraph 5, of the 1988 Convention, the Commission, taking into account the comments submitted by the parties and the comments and recommendations of the Board, whose assessment shall be

---

<sup>1</sup> From Iraq, Italy and the Republic of Korea.

determinative as to scientific matters, and also taking into due consideration any other relevant factors, may decide by a two-thirds majority of its members to place a substance in Table I or Table II of the Convention.

9. From a practical point of view, this means that, for a decision to be adopted, an affirmative vote of at least 36 members of the Commission is required.

10. The Commission should therefore decide:

(a) Whether it wishes to place 4-piperidone in Table I of the 1988 Convention or, if not, what other action, if any, might be required;

(b) Whether it wishes to place 1-boc-4-piperidone in Table I of the 1988 Convention or, if not, what other action, if any, might be required.

## Annex I

### **Notification dated 23 November 2023 from the President of the International Narcotics Control Board to the Chair of the Commission on Narcotic Drugs at its sixty-seventh session concerning the scheduling of 4-piperidone and 1-boc-4-piperidone under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988**

1. The President of the International Narcotics Control Board presents his compliments to the Chair of the Commission on Narcotic Drugs and has the honour to inform him that the Board, in conformity with article 12, paragraphs 4 and 5, of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, has completed its assessment of 4-piperidone and 1-boc-4-piperidone for possible inclusion in the tables of the 1988 Convention.
2. The Board finds that 4-piperidone and 1-boc-4-piperidone are frequently used and very suitable precursors for the illicit manufacture of fentanyl and a number of fentanyl analogues, and that the volume and extent of the illicit manufacture of fentanyl and fentanyl analogues pose serious public health or social problems so as to warrant international action. The Board therefore recommends that 4-piperidone and 1-boc-4-piperidone be included in Table I of the 1988 Convention.
3. The assessments, findings and recommendations of the Board in respect of the substances are attached hereto and have been prepared for submission to the Commission at its sixty-seventh session. Information about the substances has also been published since 2020, in the case of 4-piperidone, and 2021, in the case of 1-boc-4-piperidone, in the reports<sup>1</sup> of the Board on the implementation of article 12 of the 1988 Convention, pursuant to paragraph 13 of that article.

---

<sup>1</sup> *Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances: Report of the International Narcotics Control Board for 2020 on the Implementation of Article 12 of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988* (E/INCB/2020/4), and the corresponding reports for subsequent years. The 2023 report on precursors will be launched on 5 March 2024.

## Appendix

### Assessments of 4-piperidone and 1-boc-4-piperidone pursuant to article 12, paragraph 4, for inclusion in the tables of the 1988 Convention

#### A. Background

1. On 5 July 2023, the Government of the United States of America notified the Secretary-General of its proposal to add two precursors of fentanyl and fentanyl-related substances, namely 4-piperidone and 1-boc-4-piperidone, to the tables of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

2. In accordance with the provisions of article 12, paragraph 3, of the 1988 Convention, the Secretary-General transmitted the information contained in that notification to all parties and to other countries, along with two questionnaires (NAR/CL.10/2023), requesting their comments concerning the notification and all supplementary information that might assist the Board in carrying out its assessments. The questionnaires were sent to Governments on 3 August 2023 with the request to submit any comments on the proposal by 29 September 2023. A reminder was circulated to Governments on 27 September 2023.

#### B. Assessments

3. Article 12, paragraph 4, of the 1988 Convention stipulates the factors which the Board is to consider when assessing a substance for possible control:

If the Board, taking into account the extent, importance and diversity of the licit use of the substance, and the possibility and ease of using alternate substances both for licit purposes and for the illicit manufacture of narcotic drugs or psychotropic substances, finds:

(a) That the substance is frequently used in the illicit manufacture of a narcotic drug or psychotropic substance;

(b) That the volume and extent of the illicit manufacture of a narcotic drug or psychotropic substance creates serious public health or social problems, so as to warrant international action,

it shall communicate to the Commission an assessment of the substance, including the likely effect of adding the substance to either Table I or Table II on both licit use and illicit manufacture, together with recommendations of monitoring measures, if any, that would be appropriate in the light of its assessment.

4. In making its assessments, in accordance with article 12, paragraph 4, of the 1988 Convention, the Board had at its disposal the information contained in the notification of the Government of the United States of America to the Secretary-General, as well as the comments and supplementary information received from Governments pursuant to article 12, paragraph 3. As at 10 November 2023, 60 Governments and the European Commission had responded to the questionnaire on 4-piperidone and 61 Governments and the European Commission had responded to the questionnaire on 1-boc-4-piperidone, both of which had been sent out by the Secretary-General on 3 August 2023.<sup>2</sup> All Governments either stated direct support

<sup>2</sup> Australia, Austria, Azerbaijan, Belarus, Belgium, Bhutan, Bolivia (Plurinational State of), Brazil, Brunei Darussalam, Bulgaria, Canada, Côte d'Ivoire, Cyprus, Czechia, Denmark, Dominican Republic, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Ghana, Greece, Guatemala, Holy See, Hungary, Ireland, Japan, Jordan, Latvia, Lithuania, Luxembourg, Malaysia, Malta, Mexico, Montenegro, Morocco, Myanmar, Netherlands (Kingdom of the), Panama, Poland, Portugal, Republic of Moldova (reply for 1-boc-4-piperidone only), Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovenia, Spain, Sweden, Syrian Arab

for or registered no objection to the proposals to schedule 4-piperidone and 1-boc-4-piperidone. The European Commission conveyed the non-objection to both proposals of three additional States members of the European Union, which did not submit individual responses to the questionnaires.

5. In conducting the assessments, the Board has taken the following factors into consideration:

(a) 4-Piperidone (chemical name: piperidin-4-one) and 1-boc-4-piperidone (chemical name: *tert*-butyl 4-oxopiperidine-1-carboxylate) are very suitable precursors for the illicit manufacture of fentanyl and a number of fentanyl analogues, several of which are included in Schedule I of the 1961 Convention; some are also included in Schedule IV of that Convention;

(b) 4-Piperidone and 1-boc-4-piperidone are alternative chemicals for other fentanyl precursors under international control;

(c) Specifically:

(i) 4-Piperidone is an early-stage precursor involved in most synthetic routes to fentanyl and some fentanyl analogues. It can be used to make NPP (*N*-phenethyl-4-piperidone), ANPP (4-anilino-*N*-phenethylpiperidine), 4-AP (*N*-phenyl-4-piperidinamine) and norfentanyl, all four of which are listed in Table I of the 1988 Convention;

(ii) 1-Boc-4-piperidone is a chemically protected derivative of 4-piperidone and can be used to make 1-boc-4-AP (*tert*-butyl 4-(phenylamino)piperidine-1-carboxylate) and subsequently norfentanyl, both of which are listed in Table I of the 1988 Convention. 1-Boc-4-piperidone may also be converted back into 4-piperidone;

(d) Fentanyl and fentanyl analogues are very potent narcotic drugs, typically 10 to 100 times stronger than heroin. Consequently, small amounts of 4-piperidone and 1-boc-4-piperidone (in the kilogram range) are sufficient to manufacture millions of doses of end products (fentanyls). The high potency of the end products has resulted not only in overdose deaths in users, but also in inadvertent exposure of law enforcement personnel and other personnel along the distribution chain (e.g. employees of courier and postal services);

(e) The number, size and frequency of seizures and other incidents involving 4-piperidone and 1-boc-4-piperidone have to be seen in the context of the potency and potential lethality of the end products.

### C. Findings

6. In view of the above-mentioned factors, the Board finds that:

(a) The volume and extent of public health or social problems caused by illicitly manufactured fentanyl and fentanyl analogues are issues that warrant international action;

(b) 4-Piperidone and 1-boc-4-piperidone are substances which are very suitable for the illicit manufacture of fentanyl and a number of fentanyl analogues. Incidents involving the two substances have been reported in North America and Europe. Given the limited experience with, and capacity related to the identification and forensic analysis of these chemicals, the extent of their trafficking and illicit use may be larger;

(c) There is limited known legitimate manufacture of and trade in 4-piperidone and 1-boc-4-piperidone. The majority of Governments that responded to the questionnaires were unable to identify and quantify legitimate uses of

---

Republic, Tajikistan, Thailand, Turkmenistan, United Arab Emirates, United Kingdom of Great Britain and Northern Ireland, United States of America and Uruguay.

4-piperidone and 1-boc-4-piperidone. With a few exceptions, the majority of reported trade involved very small amounts for research and development purposes;

(d) No Government foresaw difficulties in supporting the scheduling of 4-piperidone and 1-boc-4-piperidone under the 1988 Convention. The availability of the two chemicals for limited research and development purposes is determined by the controls implemented by Governments at the national level. Those controls should be structured in a manner that ensures their availability and distribution for relevant legitimate uses.

#### **D. Recommendations**

7. The Board is of the opinion that the international control of 4-piperidone and 1-boc-4-piperidone is required to limit their availability to traffickers with a view to reducing the quantity of fentanyl and fentanyl analogues illicitly manufactured from these substances and trafficked internationally. Given the versatility of 4-piperidone and 1-boc-4-piperidone as precursors in most synthetic routes to fentanyl, placing them under control of the 1988 Convention may also serve as a preventive measure in the synthesis of existing and potentially new fentanyl analogues in the future. Those controls would have no adverse effect on the availability of 4-piperidone and 1-boc-4-piperidone for any legitimate uses. In view of the above, the Board recommends that both 4-piperidone and 1-boc-4-piperidone be placed under control of the 1988 Convention.

8. Currently, the only difference between Table I and Table II of the 1988 Convention is the possibility for Governments to invoke article 12, paragraph 10 (a), of that Convention to request pre-export notifications for substances in Table I. The inclusion of 4-piperidone and 1-boc-4-piperidone in Table I of the 1988 Convention would therefore provide Governments with the possibility to request pre-export notifications, which would in turn allow the monitoring of manufacture of and trade in the substances.

9. In light of the above, the Board recommends that 4-piperidone and 1-boc-4-piperidone be added to Table I of the 1988 Convention.

## Annex II

### **Letter dated 5 July 2023 from the Secretary of State of the United States of America addressed to the Secretary-General**

The international community has had much success in placing international controls on fentanyl precursors. However, drug traffickers continue to circumvent existing controls by adjusting their chemical synthesis methods to utilize precursor chemicals that are not under international control. This is a global challenge that requires global action across the international community.

We ask that you initiate steps to evaluate the fentanyl precursor chemicals 4-piperidone and 1-boc-4-piperidone for possible inclusion in Table I of the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, in accordance with the procedures described in article 12 of that Convention. Controlling the aforementioned precursor chemicals is a critical step in ensuring traffickers cannot use them as a substitute for other controlled precursor chemicals. This request includes supplemental information describing (1) the extent, importance and diversity of the licit commercial use of these chemicals; and (2) to what extent these chemicals are used in the illicit manufacture of narcotic drugs responsible for serious public health and social harms so as to warrant international action.

The Government of the United States requests your assistance in initiating this chemical control process. Specifically, I ask that you pass this request and its supplemental information to the International Narcotics Control Board for evaluation as soon as possible, with a view toward providing a recommendation in advance of the sixty-seventh session of the Commission on Narcotic Drugs in 2024. Bearing in mind the urgency of the global threats posed by synthetic drugs, my Government is committed to ensuring the Commission considers this request during its sixty-seventh session.

Thank you in advance for your assistance on this important issue. My Government looks forward to its continued collaboration with the United Nations.



## Appendix

### Supplemental information on fentanyl precursors 4-piperidone and 1-boc-4-piperidone

1. The United States continues to experience an epidemic of overdose deaths due to synthetic drugs, in particular overdose deaths involving synthetic opioids, including illicitly manufactured fentanyl and fentanyl analogues. Beginning in 2013, the United States observed an increase of fentanyl reports from law enforcement and public health officials. According to the United States Centers for Disease Control and Prevention (CDC), in 2021 the United States identified 70,601 overdose deaths involving synthetic opioids other than methadone.<sup>1</sup> This category is primarily comprised of overdose deaths involving fentanyl and its analogues. In 2021, 69,943 drug overdose deaths involved fentanyl (including fentanyl analogues, precursors and metabolites) in the United States, for an age-adjusted rate of 21.6 per 100,000 population. This was an increase of 279 per cent since the beginning of the study in 2016 (5.7 per 100,000 standard population).<sup>2</sup> The latest provisional data from 2022 indicate that this trend in synthetic opioid overdose deaths has continued to increase.<sup>3</sup>

2. The United States is not the only country adversely impacted by an increase in illicitly manufactured fentanyl. To help 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. Specifically, the United States proposes taking measures to control:

- (a) 4-piperidone (piperidin-4-one);
- (b) 1-boc-4-piperidone (*tert*-butyl 4-oxopiperidine-1-carboxylate).

3. Since the addition of *N*-phenethyl-4-piperidone (NPP), 4-anilino-*N*-phenethylpiperidine (ANPP), 4-anilinopiperidine (4-AP), *tert*-butyl 4-(phenylamino)piperidine-1-carboxylate (1-boc-4-AP) and *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl) to the international chemical tables under the 1988 Convention, 4-piperidone and 1-boc-4-piperidone have emerged as precursor chemicals used to illicitly manufacture fentanyl and its analogues. These precursor chemicals are controlled under the United States Controlled Substances Act by specific listing or by definition. 4-Piperidone is specifically controlled as a list I chemical under the Act. Acetals, amides, carbamates and salts of 4-piperidone are also defined as list I chemicals under the Act. The chemical structure of 1-boc-4-piperidone defines it as a carbamate of 4-piperidone and is therefore controlled as a list I chemical under the Act.

---

<sup>1</sup> United States, Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, Provisional Mortality on CDC WONDER online database. Data are from the final Multiple Cause of Death Files, 2018–2021, and from provisional data for years 2022–2023, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Available at <https://wonder.cdc.gov/mcd-icd10-provisional.html> (accessed on 17 April 2023).

Merianne Rose Spencer, Arialdi M. Miniño and Margaret Warner, *Drug Overdose Deaths in the United States, 2001–2021*, National Center for Health Statistics Data Brief, No. 457 (Hyattsville, Maryland, United States, National Center for Health Statistics, 2022).

<sup>2</sup> Merianne Rose Spencer and others, “Estimates of drug overdose deaths involving fentanyl, methamphetamine, cocaine, heroin, and oxycodone: United States, 2021”, Vital Statistics Rapid Release Report, No. 27 (Hyattsville, Maryland, United States, National Center for Health Statistics, 2023).

<sup>3</sup> Farida B. Ahmad and others, “Provisional drug overdose death counts”, National Center for Health Statistics. Available at [www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm](http://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm).

## Background

4. In the United States, fentanyl is a schedule II controlled substance under the Controlled Substances Act because it has a high potential for abuse that may lead to severe psychological or physical dependence. Fentanyl and fentanyl 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 more potent than heroin and has a shorter duration of action.

5. In the United States, the Food and Drug Administration has approved the use of fentanyl as an anaesthetic and as an analgesic; unfortunately, illicitly manufactured fentanyl has also been introduced into the illicit drug market. The euphoric effects of fentanyl are sought after by some drug users, whereas others may be subjected to fentanyl unknowingly. The margin of error between the amount of fentanyl that produces a euphoric effect and the amount that induces life-threatening respiratory depression is very small. Due to the high potency of fentanyl, illicit drug traffickers have trouble introducing (i.e. “cutting”) it into other substances in non-lethal dosage concentrations. Similarly, people who use drugs have difficulty determining the presence or concentration of fentanyl in the drug supply.

## Recent fentanyl precursor control actions in the United States

6. Drug Enforcement Administration (DEA) reporting and analysis of seized material suggests that fentanyl on the illicit drug market continues to be primarily sourced from illicit manufacturing and not diverted from legitimate commerce. In 2016, the United States requested that the International Narcotics Control Board (INCB) initiate steps to add 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 Table I under the 1988 Convention at the sixtieth session of the Commission on Narcotic Drugs.

7. 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 these new regulations. Clandestine fentanyl manufacturers explored and employed other synthetic routes to produce fentanyl; one of these was previously described in the patent literature.<sup>4</sup> In addition, illicit fentanyl manufacturers began to utilize protective groups (also called protecting groups or masking groups) on precursor chemicals in an attempt to evade detection and streamline the synthetic process.

8. In response to the ongoing health crisis involving illicitly manufactured fentanyl, and due to the shift to alternative precursor chemicals used in the illicit manufacture of fentanyl, DEA controlled 4-AP, including its amides, its carbamates (including 1-boc-4-AP) and its salts, and *N*-(1-benzylpiperidin-4-yl)-*N*-phenylpropionamide (benzylfentanyl), including its salts, as list I chemicals by finalization of a rule-making on 15 May 2020.<sup>5</sup> DEA also controlled norfentanyl as a schedule II immediate precursor to fentanyl on 18 May 2020.<sup>6</sup> In 2021, the United States requested that INCB initiate steps to add 4-AP, 1-boc-4-AP and norfentanyl to the international chemical tables under the 1988 Convention. Following this request, these three precursor chemicals were added to Table I of the 1988 Convention by vote at the sixty-fifth session of the Commission on Narcotic Drugs, in March 2022.

<sup>4</sup> Pradeep Kumar Gupta and others, World Intellectual Property Organization (WIPO) publication, No. WO 2009/116084 (24 September 2009).

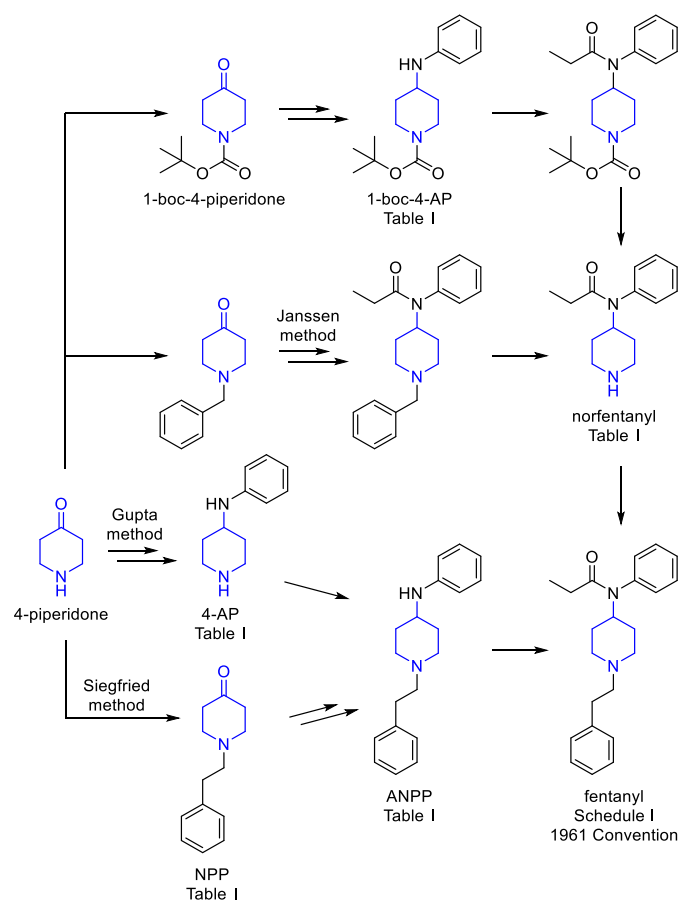
<sup>5</sup> United States, Department of Justice, Drug Enforcement Administration, *Federal Register*, vol. 85, No. 75 (15 April 2020), p. 20822.

<sup>6</sup> *Ibid.*, vol. 85, No. 75 (17 April 2020), p. 21320.

## Synthesis of fentanyl

9. In response to the domestic and international controls discussed above, illicit fentanyl manufacturers began to explore and employ unregulated, early-stage precursor chemicals in their operations. These precursor chemicals include 4-piperidone and 1-boc-4-piperidone, both of which, in response to their increased trafficking, were controlled as list I chemicals in the United States effective 12 May 2023.<sup>7</sup> 4-Piperidone serves as an early-stage precursor chemical involved in most synthetic routes to fentanyl. 4-Piperidone and its carbamate-protected derivative, 1-boc-4-piperidone, can be used to make NPP, ANPP, norfentanyl, 4-AP and 1-boc-4-AP, all of which are Table I chemicals under the 1988 Convention due to their role in the illicit manufacture of fentanyl (see figure).

### Synthetic routes to fentanyl from 4-piperidone and 1-boc-4-piperidone



### Role of 4-piperidone and 1-boc-4-piperidone in the synthesis of fentanyl

#### Janssen method

10. The Janssen<sup>8</sup> method is a synthetic pathway to fentanyl that involves the key precursors benzylfentanyl, a list I chemical in the United States, and norfentanyl, a schedule II immediate precursor in the United States and Table I precursor chemical under the 1988 Convention. Benzylfentanyl is synthesized from *N*-benzyl-4-piperidone, which can be obtained from *N*-benzylation of 4-piperidone with benzyl

<sup>7</sup> United States, Department of Justice, Drug Enforcement Administration, *Federal Register*, vol. 88, No. 70 (12 April 2023), p. 21902.

<sup>8</sup> Willem F.M Van Bever and others, "*N*-4-substituted 1-(2-arylethyl)-4-piperidinyl-*N*-phenylpropanamides: a novel series of extremely potent analgesics with unusually high safety margin", *Arzneimittelforschung*, vol. 26, No. 8 (1976), 1548–1551.

bromide.<sup>9</sup> Effectively, the *N*-benzyl group serves as a protective group on the piperidine nitrogen atom in this synthetic route, which is a similar strategy to using a *tert*-butoxycarbonyl protecting group (i.e. 1-boc-4-piperidone, discussed below). Norfentanyl is obtained from catalytic debenzoylation of benzylfentanyl, which is then alkylated with phenethyl bromide to provide fentanyl.

11. Similarly, 1-boc-4-piperidone, a list I chemical in the United States, is a carbamate-protected version of 4-piperidone; in this case, the piperidine nitrogen atom is protected with a *tert*-butoxycarbonyl group (instead of a benzyl group as in *N*-benzyl-4-piperidone). 1-Boc-4-AP, a list I chemical in the United States and Table I precursor chemical under the 1988 Convention, is produced by reductive amination of 1-boc-4-piperidone and aniline. *N*-Acylation of 1-boc-4-AP with propionyl chloride or propionic anhydride provides 1-boc-norfentanyl, which is easily converted to norfentanyl, a schedule II immediate precursor in the United States and Table I precursor chemical under the 1988 Convention, upon hydrolysis of the carbamate. *N*-Alkylation of norfentanyl with phenethyl bromide provides fentanyl.

12. The exploration and use of protective groups on precursor chemicals used in the illicit manufacture of fentanyl has continued following the placement of 1-boc-4-AP in Table I of the 1988 Convention. As was the case with 1-boc-4-AP, the piperidine nitrogen atom of 4-piperidone is protected as a carbamate to avoid law enforcement detection (“masked precursor”), to prevent undesired reactions (i.e. dimerization) of 4-piperidone, to provide regiospecificity of *N*-acylation of the anilino-nitrogen atom or a combination of these reasons. The protection of the piperidine nitrogen atom as a carbamate offers a synthetic advantage over protection of the piperidine nitrogen atom with a benzyl group. The *tert*-butoxycarbonyl group can be easily hydrolyzed under acidic conditions, whereas the removal of the *N*-benzyl group is completed by catalytic hydrogenation, which requires hydrogen gas (or a method to create hydrogen in situ) and a metal catalyst such as palladium.

#### Siegfried method

13. The Siegfried<sup>10</sup> method involves the important precursor chemicals NPP and ANPP. NPP, a list I chemical in the United States and Table I precursor chemical under the 1988 Convention, is synthesized directly from 4-piperidone by *N*-alkylation of the piperidine nitrogen atom. Reductive amination of NPP and aniline provides ANPP, a schedule II immediate precursor in the United States and Table I precursor

<sup>9</sup> Masayuki Iwakubo and others, “Design and synthesis of rho kinase inhibitors (III)”, *Bioorganic and Medicinal Chemistry*, vol. 15, No. 2 (January 2007), pp. 1022–1033; Tim Goebel and others, “In search of novel agents for therapy of tropical diseases and human immunodeficiency virus”, *Journal of Medicinal Chemistry*, vol. 51, No. 2 (January 2008), pp. 238–250; Thomas M. Bridges and others, “Synthesis and SAR of analogues of the M1 allosteric agonist TBPB. Part 1: exploration of alternative benzyl and privileged structure moieties”, *Bioorganic and Medicinal Chemistry Letters*, vol. 18, No. 20 (October 2008), pp. 5439–5442; Mahmoud M. Abd Rabo Moustafa and Brian L. Pagenkopf, “Synthesis of 5-azaindoles via a cycloaddition reaction between nitriles and donor-acceptor cyclopropanes”, *Organic Letters*, vol. 12, No. 14 (July 2010), pp. 3168–3171; Harichandra D. Tagad and others, “Structure-guided design and synthesis of P<sub>1</sub>' position 1-phenylcycloalkylamine-derived pentapeptidic BACE1 inhibitors”, *Bioorganic and Medicinal Chemistry*, vol. 19, No. 17 (September 2011), pp. 5238–5246; Kishor D. Mane, Rohit B. Kamble and Gurunath Suryavanshi, “Short enantioselective total synthesis of (+)-tofacitinib”, *Tetrahedron Letters*, vol. 67, art. No. 152838 (March 2021); Jung-Ho Son and others, “1-benzylspiro[piperidine-4,1'-pyrido[3,4-*b*]indole] ‘co-potentiators’ for minimal function CFTR mutants”, *European Journal of Medicinal Chemistry*, vol. 209, art. No. 112888 (January 2021); and Nicola Relitti and others, “Novel quinolone-based potent and selective HDAC6 inhibitors: synthesis, molecular modeling studies and biological investigation”, *European Journal of Medicinal Chemistry*, vol. 212, art. No. 112998 (February 2021).

<sup>10</sup> Shengs-Hsu Zee and Wan-Kung Wang, “A new process for the synthesis of fentanyl”, *Journal of the Chinese Chemical Society*, vol. 27, No. 4 (December 1980), pp. 147–149; A. Jonczyk, J. Jawdosiuk and M. Makosza, “Poszukiwanie nowej metody syntezy srodka analgetycznego ‘fentanyl’”, *Przemysl Chemiczny*, (1978), pp. 131–134; and C.A. Carlos A. Valdez, Roald N. Leif and Brian P. Mayer, “An efficient, optimized synthesis of fentanyl and related analogs”, *PLoS One*, vol. 9, No. 9 (September 2014).

chemical under the 1988 Convention, which easily undergoes *N*-acylation with propionyl chloride or propionic anhydride to provide fentanyl.

#### Gupta method

14. The Gupta<sup>11</sup> method involves the important precursors 4-AP, a list I chemical in the United States and Table I precursor chemical under the 1988 Convention, and ANPP, a schedule II immediate precursor in the United States and Table I precursor chemical under the 1988 Convention. Reductive amination of 4-piperidone and aniline provides 4-AP, which is alkylated at the piperidine nitrogen atom with phenethyl bromide to provide ANPP. *N*-Acylation with propionyl chloride or propionic anhydride provides fentanyl.

15. The United States believes control of 4-piperidone and 1-boc-4-piperidone is necessary to prevent unscrupulous actors from synthesizing these precursors as unregulated material and selling them through the Internet and other channels for the illicit manufacture of fentanyl. The United States believes this control measure is also advisable in order to deter the theft of these chemicals from legitimate pharmaceutical firms where they are generated in the course of legitimate fentanyl production.

#### Forensic analysis of seized fentanyl samples

16. The DEA Fentanyl Profiling Program (FPP) profiles seized fentanyl and fentanyl-related compounds with the goal of identifying the synthetic route utilized to manufacture the fentanyl found on the illicit drug market. Current data through FPP suggests the Gupta method is the dominant route used to manufacture fentanyl found on the illicit drug market. As stated above, 4-piperidone and 1-boc-4-piperidone serve as precursors to 4-AP and 1-boc-4-AP, respectively, both of which are list I chemicals in the United States and Table I precursor chemicals under the 1988 Convention due to their utility in the illicit manufacture of fentanyl. Analytical profiling of seized drug exhibits from the first half of calendar year 2022 shows that 66.4 per cent of powders analysed by FPP exhibit a Gupta-type profile. Similarly, 75.2 per cent of tablets seized over the same time period demonstrated a Gupta-type profile.

#### Licit uses

17. DEA has evaluated and determined that the precursor chemicals 4-piperidone and 1-boc-4-piperidone are offered for sale through 40 and 54 domestic chemical suppliers, respectively. Many of these suppliers offer both 4-piperidone and 1-boc-4-piperidone. It is unclear as to how many of these entities maintain stock of these chemicals and how many synthesize these chemicals upon request. However, it is important to note that industry did not provide comments for this information during the rule-making process to control 4-piperidone and 1-boc-4-piperidone, as a carbamate of 4-piperidone, under the Controlled Substances Act.

18. While legitimate pharmaceutical firms treat their synthetic routes as proprietary, most of the larger DEA-registered pharmaceutical manufacturers in the United States appear to be using NPP and/or ANPP as their preferred precursor chemicals for legitimate fentanyl production. DEA is not aware of legitimate fentanyl manufactures in the United States using 4-piperidone or 1-boc-4-piperidone as precursor chemicals in their processes. In addition, DEA solicited comment from industry during the rule-making process to control 4-piperidone and 1-boc-4-piperidone, as a carbamate of 4-piperidone, under the Controlled Substances Act. No entities from the pharmaceutical industry provided comment or information as to their use of these precursor chemicals in fentanyl or any other manufacturing processes during the rule-making process.

19. In the United States, 4-piperidone and 1-boc-4-piperidone are list I chemicals. There are specific regulatory requirements for handling these precursor chemicals under the Controlled Substances Act and its implementing regulations to include

<sup>11</sup> See footnote 7 above.

registration, recordkeeping and import/export reporting, and a provision for the reporting of suspicious transactions. The legal and regulatory requirements for listed chemicals in the United States are consistent with those of the United Nations drug control treaties.

### Published reports of deaths involving fentanyl

20. According to CDC, in 2021 the United States identified 70,601 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 2,500 per cent increase in deaths involving this category since 2013. Provisional CDC data indicate that there were 75,217 overdose deaths involving synthetic opioids other than methadone in the 12-month period ending in December 2022 (1 January 2022 to 31 December 2022), as shown in table 1.

Table 1

#### Number of overdose deaths involving synthetic opioids other than methadone<sup>12</sup>

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022*
Overdose deaths	3 105	5 544	9 580	19 413	28 466	31 335	36 359	56 516	70 601	75 217

\* The 2022 count is the provisional predicted value for the 12-month period ending in December 2022 (1 January 2022 to 31 December 2022).<sup>13</sup>

### Negative impact of illicit fentanyl and fentanyl analogues on global public health

21. In a report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA),<sup>14</sup> it was noted that in 2016 and 2017 there were 659 deaths involving fentanyl and 383 deaths involving fentanyl analogues. Thirteen countries reported cases, with most cases reported in Estonia, Germany, Sweden, the United Kingdom and Finland.

22. In its *Global Synthetic Drugs Assessment 2020*, the United Nations Office on Drugs and Crime further elaborated on some fentanyl fatalities covered by 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 fentanyl in the United States

23. According to the National Forensic Laboratory Information System, a DEA system that collects data from federal, state and local forensic laboratories, laboratory submissions containing fentanyl increased dramatically from 2013 to 2021, and this increase continued into 2022 (see table 2). DEA believes the primary source of

<sup>12</sup> See footnote 4 above.

United States, Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality 1999–2020 on CDC WONDER online database, released in 2021. Data are from the Multiple Cause of Death Files, 1999–2020, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Available at <https://wonder.cdc.gov/mcd-icd10.html> (accessed on 11 May 2022).

<sup>13</sup> See footnote 6 above. Accessed on 17 May 2023.

<sup>14</sup> European Monitoring Centre for Drugs and Drug Addiction, *Drug-related Deaths and Mortality in Europe: Update from the EMCDDA Expert Network* (Luxembourg, Publications Office of the European Union, 2021).

fentanyl encountered on the illicit market is synthesized clandestinely by international sources.

Table 2

**Number of fentanyl reports to the National Forensic Laboratory Information System by year**

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022*
Fentanyl	1 042	5 553	15 461	37 154	61 638	89 953	108 087	125 796	163 037	147 261

\* Reports are still pending for 2022.<sup>15</sup>

24. The United States is concerned that the international availability and lack of control of 4-piperidone and 1-boc-4-piperidone are directly contributing to the continued availability of illicitly produced fentanyl, even with the control of these precursor chemicals under the Controlled Substances Act in the United States. While many synthetic routes are possible to manufacture fentanyl, 4-piperidone and 1-boc-4-piperidone are used to make many precursor chemicals, including those that are currently Table I chemicals under the 1988 Convention. Therefore, the United States believes that controlling 4-piperidone and 1-boc-4-piperidone is necessary to prevent the illicit production of fentanyl.

**Law enforcement encounters of 4-piperidone and 1-boc-4-piperidone**

25. Currently, there is little evidence of clandestine fentanyl synthesis in the United States. Law enforcement encounters of fentanyl precursor chemicals in the United States typically occur at ports of entry while in transit to another destination country. The United States appears to be a transit country for fentanyl precursor chemicals, as they are imported to the United States from East Asia with further destinations in Mexico, or states along the south-west border of the United States.

26. 4-Piperidone and 1-boc-4-piperidone have been identified in international transactions. As of March 2023, INCB had reported a total of 10 international transactions of 4-piperidone and 1-boc-4-piperidone. According to the Precursors Incident Communication System, there have been seven incidents involving 4-piperidone and two incidents involving 1-boc-4-piperidone. The Project Ion Incident Communication System contains one additional incident involving 1-boc-4-piperidone. These incidents totalled approximately 2,574 kg and had destinations in North America and Europe. A summary of these incidents involving 4-piperidone and 1-boc-4-piperidone is provided in attachment II (Law enforcement encounters).

**Summation and desired outcome of international control**

27. The United States strongly believes the illicit manufacture of fentanyl is a global problem with far-reaching negative effects on global public health and safety. The fundamental role that 4-piperidone and 1-boc-4-piperidone play in the ever-increasing rise of illicit fentanyl manufacturing and use and in the acceleration of overdose deaths demands immediate and deliberate action on the part of the international community.

28. The international control of these precursor chemicals is a necessary step in stemming the tide of the manufacture and use of illicitly manufactured fentanyl. 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 illicitly manufactured fentanyl. A complex problem such as this requires a comprehensive response, including those taken to prevent the diversion of fentanyl from its legitimate 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

<sup>15</sup> United States, Department of Justice, Drug Enforcement Administration, Diversion Control Division, National Forensic Laboratory Information. Available at [www.nflis.deadiversion.usdoj.gov](http://www.nflis.deadiversion.usdoj.gov) (accessed on 17 April 2023).

opioid use disorders in their path to long-term recovery and actions to address the overall reduction in 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 control of these precursor chemicals will directly support those efforts.

29. The United States fundamentally believes, based upon its own experience, that this action will have a direct and positive impact on this problem on a global scale. 4-Piperidone and 1-boc-4-piperidone are currently regulated within the United States. According to both federal and state law enforcement officials, the number of clandestine laboratories manufacturing fentanyl is extremely low in the United States. It is highly likely that the strict control of named and defined precursor chemicals used in the illicit manufacture of fentanyl within the United States has prevented the widespread growth of domestic clandestine fentanyl laboratories. The United States believes that greater international controls on precursor chemicals offer the international community the best opportunity to prevent the establishment of illicit fentanyl manufacturing laboratories in other countries as well.

30. The availability and use of illicitly manufactured fentanyl, as well as the overdose deaths involving fentanyl, 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 this dangerous drug, as part of a comprehensive global effort to address this complex national security, law enforcement and public health crisis.



## Attachment I

**Chemical information****4-Piperidone**

**Other names:** piperidin-4-one

**Molecular formula:** C<sub>5</sub>H<sub>9</sub>NO

**Molecular weight:** 99.13 g/mol

**CAS number:** 41661-47-6 (base)

709046-15-1 (hydrate)

41979-39-9 (hydrochloride)

320589-77-3 (monohydrate hydrochloride)

40064-34-4 (4,4-piperidinediol hydrochloride)

**Melting point:** for monohydrate hydrochloride – 94–96°C

**Description:** monohydrate hydrochloride – beige crystalline substance

**Illicit use:** precursor in clandestine laboratory manufacture of fentanyl

**Where controlled or regulated:** United States Controlled Substances Act (list I chemical) including its acetals, its amides, its carbamates, its salts and salts of its acetals, its amides and its carbamates, and any combination thereof, whenever the existence of such is possible

**1-Boc-4-piperidone**

**Other names:** *N*-*boc*-4-piperidone; *tert*-butyl 4-oxopiperidine-1-carboxylate

**Molecular formula:** C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>

**Molecular weight:** 199.25 g/mol

**CAS number:** 79099-07-3

**Melting point:** 73–75°C

**Description:** white powder

**Illicit use:** precursor in clandestine laboratory manufacture of fentanyl

**Where controlled or regulated:** United States Controlled Substances Act (list I chemical) as a carbamate of 4-piperidone

## Attachment II

### Law enforcement encounters

#### Domestic seizures<sup>16</sup> from 2020 to 2023

7 December 2020 – United States

United States customs seized 1 kg of 4-piperidone at an airport.

2 May 2021 – United States

United States customs seized 114 kg of 1-boc-4-piperidone at an airport.

4 May 2021 – United States

United States customs seized 112 kg of 1-boc-4-piperidone at an airport.

16 June 2021 – Los Angeles, California, United States

United States customs/police seized 180 kg of 4-piperidone monohydrate hydrochloride at a seaport.

21 September 2022 – California, United States

United States customs seized 28 kg of 1-boc-4-piperidone at a postal facility.

#### Foreign seizures<sup>17</sup> from 2019 to 2023

19 May 2019 – Mexico City

Police seized 13 kg of 4-piperidone at an airport.

24 May 2019 – Grace-Hollogne, Belgium

Customs seized 1 kg of 4-piperidone monohydrate hydrochloride at an airport.

27 January 2021 – Estado de Mexico, Mexico

Customs/police seized 25 kg of 4-piperidone monohydrate hydrochloride at an airport.

12 August 2021 – Vancouver, Canada

Authorities seized 1,500 kg of 4-piperidone monohydrate hydrochloride at a seaport.

23 February 2023 – Vancouver, Burnaby and Surrey, Canada

Authorities seized 600 kg of 4-piperidone monohydrate hydrochloride at a private residence/warehouse.

---

<sup>16</sup> The Precursors Incident Communication System and the Project Ion Incident Communication System were queried on 24 March 2023.

<sup>17</sup> The Precursors Incident Communication System was queried on 24 March 2023.