4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2023-N-0438]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; ADB-BUTINACA; alpha-PiHP; 3-Methylmethcathinone; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distributing restrictions, under international treaties, on certain drug substances. The comments received in response to this notice will be considered in preparing the United States' position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, in March 2023. This notice is issued under the Controlled Substances Act (CSA).

DATES: Submit either electronic or written comments by February 28, 2023.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of February 28, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2023-N-0438 for "International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; ADB-BUTINACA; alpha-PiHP; 3-Methylmethcathinone; Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and,

except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Edward (Greg) Hawkins, Center for Drug Evaluation and Research, Controlled Substance Staff, Food and Drug Administration, 10903

New Hampshire Ave., Bldg. 51, Rm. 5150, Silver Spring, MD 20993-0002, 202-713-8981, Edward.Hawkins@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (1971 Convention). Section 201(d)(2)(B) of the CSA (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the 1971 Convention that the CND proposes to decide whether to add a drug or other substance to one of the schedules of the 1971 Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (Secretary of HHS). The Secretary of HHS must then publish a summary of such information in the *Federal Register* and provide opportunity for interested persons to submit comments. The Secretary of HHS must then evaluate the proposal and furnish a recommendation to the Secretary of State that shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed in the following paragraphs, the Secretary of State has received notification from the Secretary-General of the United Nations (the Secretary-General) regarding three substances to be considered for control under the 1971 Convention. This notification reflects the recommendation from the 45th WHO Expert Committee for Drug Dependence (ECDD), which met in October 2022. In the *Federal Register* of August 3, 2022 (87 FR 47428), FDA announced the WHO ECDD review and invited interested persons to submit information for WHO's consideration.

The full text of the notification from the Secretary-General is provided in section II of this document. Section 201(d)(2)(B) of the CSA requires the Secretary of HHS, after receiving a notification proposing scheduling, to publish a notice in the *Federal Register* to provide the

opportunity for interested persons to submit information and comments on the proposed scheduling action.

The United States is also a party to the 1961 Single Convention on Narcotic Drugs (1961 Convention). The Secretary of State has received a notification from the Secretary-General regarding four substances to be considered for control under this convention. The CSA does not require HHS to publish a summary of such information in the *Federal Register*. Nevertheless, to provide interested and affected persons an opportunity to submit comments regarding the WHO recommendations for drugs under the 1961 Convention, the notification regarding these substances is also included in this *Federal Register* notice. The comments will be shared with other relevant Agencies to assist the Secretary of State in formulating the position of the United States on the control of these substances. The HHS recommendations are not binding on the representative of the United States in discussions and negotiations relating to the proposal regarding control of substances under the 1961 Convention.

II. United Nations Notification

The formal notification from the United Nations that identifies the drug substances and explains the basis for the scheduling recommendations is reproduced as follows (non-relevant text removed):

Reference:
NAR/CL.6/2022
WHO/ECDD45; 1961C-Art.3, 1971C-Art.2
CU 2022/386/DTA/SGB

The Secretariat of the United Nations presents its compliments to the Permanent Mission of the United States of America to the United Nations (Vienna) and has the honour to inform the Mission that, in a letter dated 24 November 2022, the Director-General of the World Health Organization (WHO), pursuant to article 3, paragraphs 1 and 3 of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (1961 Convention), and article 2, paragraphs 1 and 4 of the Convention on Psychotropic Substances of 1971 (1971 Convention), notified the Secretary-General of the following recommendations of the Forty-fifth Meeting of the WHO's Expert Committee on Drug Dependence (ECDD):

Substances recommended to be added to Schedule I of the 1961 Convention:

--2-Methyl-AP-237
IUPAC (International Union of Pure and Applied Chemistry) name: 1-[2-Methyl-4-(3-phenyl-2-

propen-1-yl)-1-piperazinyl]-1-butanone

--Etazene
IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-N,N-diethyl-1H-benzimidazole-1-ethanamine

--Etonitazepyne
IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1Hbenzoimidazole

--Protonitazene
IUPAC name: N,N-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1H-benzimidazole-1-ethanamine

Substance recommended to be added to Schedule II of the 1971 Convention:

--ADB-BUTINACA
IUPAC name: N-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1H-indazole-3-carboxamide

--alpha-PiHP
IUPAC name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one

--3-Methylmethcathinone
IUPAC name: 2-(Methylamino)-1-(3-methylphenyl)propan-1-one

Substances to be kept under surveillance:

In the letter from the Director-General of WHO to the Secretary-General, reference is also made to the recommendation made by the WHO Expert Committee on Drug Dependence (ECDD), at its forty-fifth meeting, to keep the following substances under surveillance:

--Adinazolam
IUPAC name: 8-Chloro-N,N-dimethyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine-1-methanamine

--Bromazolam
IUPAC name: 8-Bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

--Zopiclone
IUPAC name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-Carboxylate

In accordance with the provisions of article 3, paragraph 2, of the 1961 Convention and article 2, paragraph 2, of the 1971 Convention, the notification is hereby transmitted as Annex I to the present note. In connection with the notification, WHO also submitted a summary of the assessments and findings for these recommendations made by ECDD in Annex 1 to the letter to the Secretary-General, which is transmitted herewith in Annex II.

Also, in accordance with the same provisions, the notification from WHO will be brought to the attention of the sixty-sixth session of the Commission on Narcotic Drugs (13-17 March 2023) in a pre-session document that will be made available in the six official languages of the United Nations on the website of the 66th session of the Commission on Narcotic Drugs: https://www.unodc.org/unodc/en/commissions/CND/session/66_Session_2023/66CND_Main.html.

In order to assist the Commission in reaching a decision, it would be appreciated if the Mission could communicate any comments it considers relevant to the possible scheduling of substances recommended by WHO to be placed under international control under the 1961 Convention, namely:

--2-Methyl-AP-237
--Etazene
--Etonitazepyne
--Protonitazene;

as well as any economic, social, legal, administrative, or other factors that it considers relevant to the possible scheduling of substances recommended by WHO to be placed under international control under the 1971 Convention, namely:

--ADB-BUTINACA
--alpha-PiHP
--3-Methylmethcathinone

The Secretariat of the United Nations avails itself of this opportunity to renew to the Permanent Mission of the United States of America to the United Nations (Vienna) the assurances of its highest consideration.

Annex I

Letter addressed to the Secretary-General of the United Nations from the Director-General of the World Health Organization, dated 24 November 2022:

"I have the honour to refer to the Forty-fifth Meeting of the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) that was convened in Geneva, Switzerland from 10 to 13 October 2022.

WHO is mandated by the 1961 and 1971 International Drug Control Conventions to make recommendations to the United Nations Secretary-General on the need for a level of international control of psychoactive substances based on the advice of its independent scientific advisory body, the ECDD. To assess the appropriate control of a psychoactive substance, WHO convenes ECDD annually to review the potential of a substance to cause dependence, abuse and harm to health, as well as any therapeutic applications.

The Forty-fifth WHO ECDD Meeting critically reviewed nine new psychoactive substances: one synthetic cannabinoid receptor agonist (ADB-BUTINACA), four novel synthetic opioids (2-Methyl-AP-237, etazene, etonitazepyne, and protonitazene), two cathinones/stimulants (alpha-PiHP, 3-methylmethcathinone), and two benzodiazepines (adinozolam, bromazolam). These substances had not previously been formally reviewed by WHO and are currently not under international control.

Information was brought to WHO's attention that these substances are clandestinely manufactured, of risk to public health and society, and of no recognized therapeutic use by any party. Therefore, a critical review to consider international scheduling measures was undertaken for each substance so that the Expert Committee could consider whether information about these substances may justify the scheduling of a substance in the 1961 or 1971 Conventions. In addition, the Forty-fifth ECDD carried out a pre-review of zopiclone to consider whether current information justified a critical review.

With reference to Article 3, paragraphs 1 and 3 of the Single Convention on Narcotic Drugs (1961), as amended by the 1972 Protocol, and Article 2, paragraphs 1 and 4 of the

Convention on Psychotropic Substances (1971), WHO is pleased to endorse and submit the following recommendations of the Forty-fifth Meeting of the ECDD:

To be added to Schedule I of the Single Convention on Narcotic Drugs (1961):

--2-Methyl-AP-237
IUPAC (International Union of Pure and Applied Chemistry) name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone

--Etazene
IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-N,N-diethyl-1H-benzimidazole-1-ethanamine

--Etonitazepyne
IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1Hbenzoimidazole

--Protonitazene
IUPAC name: N,N-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1H-benzimidazole-1-ethanamine

To be added to Schedule II of the Convention on Psychotropic Substances (1971):

--ADB-BUTINACA
IUPAC name: N-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1H-indazole-3-carboxamide

--alpha-PiHP
IUPAC name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one

--3-Methylmethcathinone
IUPAC name: 2-(Methylamino)-1-(3-methylphenyl)propan-1-one

To be kept under surveillance:

--Adinazolam
IUPAC name: 8-Chloro-N,N-dimethyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine-1-methanamine

--Bromazolam
IUPAC name: 8-Bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

--Zopiclone
IUPAC name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-Carboxylate

The assessments and findings on which these recommendations are based are set out in detail in the Forty-fifth Meeting report of the WHO Expert Committee on Drug Dependence. A summary of the assessment and recommendations made by the ECDD is contained in Annex 1 to this letter.

I am pleased with the ongoing collaboration between WHO, the United Nations Office on Drugs and Crime, and the International Narcotics Control Board, and in particular, how this collaboration has benefited the work of the WHO Expert Committee on Drug Dependence and more generally, the implementation of the operational recommendations of the United Nations General Assembly Special Session 2016."

Annex II

45th WHO ECDD summary assessments, findings and recommendations, 10–13 October 2022

Substances to be added to Schedule I of the Single Convention on Narcotic Drugs (1961)

2-Methyl-AP-237

Substance identification:

2-Methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) is a methyl derivative of the opioid analgesic AP-237 (or bucinnazine). 2-Methyl-AP-237 has been described as a white crystalline powder, a crystalline solid, and a white solid.

WHO review history:

2-Methyl-AP-237 has been under WHO surveillance but has not been formally reviewed by WHO, and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

2-Methyl-AP-237 is an opioid analgesic with a rapid onset of action and a potency and analgesic effects similar to those of fentanyl, which is listed under Schedule I of the Single Convention on Narcotic Drugs, 1961. In animals, it produces acute toxic effects typical of opioids, including respiratory depression. Limited research has been reported on the effects of 2-methyl-AP-237 in humans, although its respiratory depressant effects have been observed, which can be reversed by the opioid antagonist, naloxone.

Dependence potential:

No controlled studies of the dependence potential of 2-methyl-AP-237 have been reported in animals or humans. As it is a μ-opioid receptor agonist, it would be expected to produce dependence similar to that induced by other opioids, such as morphine and fentanyl. Online self-reports described tolerance and withdrawal.

Actual abuse and/or evidence of likelihood of abuse:

In an animal model predictive of abuse potential, 2-methyl-AP-237 was shown to produce opioid-like effects with a potency between those of morphine and fentanyl. These effects were blocked by the opioid antagonist, naltrexone.

No controlled studies on the abuse potential of 2-methyl-AP-237 in humans have been reported, but, as it is a μ-opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability. Online self-reports support its euphoric and other opioid effects.

Seizures of 2-methyl-AP-237 have been reported in multiple countries in two regions. A number of deaths in which 2-methyl-AP-237 has been found have been reported, often with multiple substances involved. The deaths occurred in a number of countries and regions.

Therapeutic usefulness:

2-Methyl-AP-237 is not known to have any therapeutic use.

Recommendation:

2-Methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) is a synthetic opioid that is liable to abuse and to have ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and is likely to cause substantial harm.

Recommendation: The Committee recommended that 2-methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Etazene

Substance identification:

Etazene (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, is a benzimidazole-derived synthetic opioid. Etazene has been described as a grey crystalline, light-yellow, white, or beige powder. It has also been identified in liquid form and in falsified pharmaceutical opioids.

WHO review history:

Etazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

Etazene binds to the μ-opioid receptor with a potency greater than that of morphine. In studies of analgesia in animals, etazene had full agonist effects, with a potency between those of morphine and fentanyl, which are both controlled under Schedule I of the Single Convention on Narcotic Drugs, 1961. The effects of etazene are reversed by the opioid antagonist, naltrexone.

Dependence potential:

No controlled studies of the dependence potential of etazene in animals or in humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to other opioids, such as morphine and fentanyl. Online self-reports described tolerance with repeated use of etazene.

Actual abuse and/or evidence of likelihood of abuse:

In an animal model predictive of abuse potential, etazene had effects similar to those of morphine. No controlled studies have been conducted of the abuse potential of etazene in humans, but, as it is a potent μ-opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability. Online self-reports support its euphoric and other opioid effects.

Seizures of etazene have been reported in multiple countries in two regions.

A number of deaths have occurred in which the presence of etazene was confirmed analytically and in which it was considered to have contributed to death, although other substances were also identified in these cases.

Therapeutic usefulness:

Etazene is not known to have any therapeutic use.

Recommendation:

Etazene (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, is a synthetic opioid that is liable to abuse and produces ill effects similar to other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and poses a significant risk to public health.

Recommendation: The Committee recommended that etazene (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Etonitazepyne

Substance identification:

Etonitazepyne (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1Hbenzoimidazole), also known as *N*-pyrrolidino etonitazene, is a benzimidazole-derived synthetic opioid. Etonitazepyne is found as a yellow powder and crystalline solid and has been identified in falsified pharmaceutical opioid tablets.

WHO review history:

Etonitazepyne has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

Studies in animals have demonstrated that etonitazepyne is a potent, full agonist at μ-opioid receptors. In animals, it produces effects similar to those of opioids such as morphine, fentanyl, and isotonitazene but with greater potency. There is limited information about the effects of etonitazepyne alone in humans.

Dependence potential:

No controlled studies of the dependence potential of etonitazepyne in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similarly to other opioids, such as morphine and fentanyl. Online self-reports describe tolerance and withdrawal after repeated etonitazepyne use.

Actual abuse and/or evidence of likelihood of abuse:

In an animal model predictive of abuse potential, etonitazepyne was shown to produce effects that indicated greater potency compared to morphine and fentanyl, and these effects were reversed by the opioid antagonist, naltrexone.

Seizures of etonitazepyne have been reported in multiple countries in two regions. It is reported to be administered by various routes, including snorting, sniffing, and oral administration. Etonitazepyne has been identified in falsified medicines, suggesting that its use may sometimes be unintentional.

Etonitazepyne is a relatively new drug on the illicit market, and there is limited information on the prevalence of its use and of its harm, although non-fatal and fatal intoxications have been documented in a number of countries. The number of deaths involving etonitazepyne has increased over a relatively short time but may be underreported because of its recent, rapid appearance.

Therapeutic usefulness:

Etonitazepyne is not known to have any therapeutic use.

Recommendation:

Etonitazepyne (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1Hbenzoimidazole), also known as *N*-pyrrolidino etonitazene, is a synthetic opioid that is liable to abuse and to produce ill effects similar to other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and poses a significant risk to public health.

Recommendation: The Committee recommended that etonitazepyne (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole), also known as *N*-pyrrolidino etonitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Protonitazene

Substance identification:

Protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, is a 5-nitro-2-benzylbenzimidazole synthetic opioid. Protonitazene has been described as a white, yellow, or brown powder and as a crystalline solid.

WHO review history:

Protonitazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

Protonitazene is a chemical analogue of metonitazene and etonitazene, which are controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961. Studies in animals have demonstrated that protonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine and similar potency to fentanyl. Its effects are blocked by the opioid antagonist, naltrexone.

Dependence potential:

No controlled studies of the dependence potential of protonitazene in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to other opioids such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse:

In animals, protonitazene showed potent opioid effects and abuse potential, similar to those of morphine and fentanyl. Its abuse potential has not been studied in humans; however, online self-reports indicate typical opioid effects, including sedation and euphoria.

Protonitazene is relatively new on the illicit drug market, and there is limited information on the prevalence of its use or of its harm. The only available information is that several fatalities have occurred in which the presence of protonitazene was confirmed, usually with other substances. The number of deaths may be underreported because of limitations in testing, including difficulty in differentiating this substance from isotonitazene.

Protonitazene is reported to be administered through various routes, including intranasally and intravenously.

Seizures of protonitazene have been reported in multiple countries in two regions.

Therapeutic usefulness:

Protonitazene is not known to have any therapeutic use.

Recommendation:

Protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, is a synthetic opioid that is liable to abuse and to produce ill effects similar to other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and is likely to cause substantial harm.

Recommendation: The Committee recommended that protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Substances to be added to Schedule II of the Convention on Psychotropic Substances (1971)

ADB-BUTINACA

Substance identification:

ADB-BUTINACA (IUPAC chemical name: *N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) is an indazole-derived synthetic cannabinoid. It is described as a crystalline solid or a beige or yellowish powder and has also been found sprayed onto plant material and paper. It is commonly smoked or vaped, although isolated cases of oral use have also been reported.

WHO review history:

ADB-BUTINACA has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

ADB-BUTINACA is a synthetic cannabinoid that binds to CB1 and CB2 receptors with high affinity and is a potent full agonist at both receptors. Its effects are similar to those of other potent CB1 agonists that are currently controlled under Schedule II of the Convention on Psychotropic Substances of 1971.

No controlled studies of the effects of ADB-BUTINACA have been reported. Online self-reports describe euphoria, appetite stimulation, sedation, and paranoia after its use. These effects are consistent with the known effects of cannabinoid agonists.

Dependence potential:

No controlled studies of the dependence potential of ADB-BUTINACA in animals or humans have been reported. However, its effects at the CB1 receptor suggest that it would be expected to produce dependence similar to other synthetic cannabinoids.

Actual abuse and/or evidence of likelihood of abuse:

In an animal model predictive of abuse potential, ADB-BUTINACA had effects similar to the CB1 receptor agonist *delta*-9-tetrahydrocannabinol. No studies have been conducted to determine the likelihood of abuse of ADB-BUTINACA in humans; however, CB1 receptor agonists have known abuse potential.

A number of countries in various regions have reported use of ADB-BUTINACA and harm related to its use, including multiple deaths and presentations of patients to emergency departments with altered consciousness and loss of consciousness. Other substances were usually also involved in these cases, although a number of deaths involved only ADB-BUTINACA.

Therapeutic usefulness:

ADB-BUTINACA is not known to have any therapeutic use.

Recommendation:

ADB-BUTINACA (*N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) is a potent synthetic cannabinoid receptor agonist with a mechanism of action and effects similar to those of a number of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the likelihood of abuse and potential for dependence. Use of ADB-BUTINACA has been associated with severe adverse effects, including fatal intoxications. ADB-BUTINACA has no known therapeutic use.

Recommendation: The Committee recommended that ADB-BUTINACA (*N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Alpha-PiHP

Substance identification:

Alpha-pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as *alpha*-PiHP, is a synthetic cathinone. It has been described as an off-white solid, a white powder, and a crystalline solid.

WHO review history:

Alpha-PiHP has been under WHO surveillance but has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

Alpha-PiHP is an isomer of *alpha*-PHP, which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Laboratory studies suggest that *alpha*-PiHP can inhibit the uptake of dopamine and norepinephrine more potently than substances with known abuse potential, including methcathinone, cocaine, and methamphetamine. Studies in animals have shown that *alpha*-PiHP is a psychomotor stimulant, with effects comparable to those of cocaine and methamphetamine.

Online self-reports by people who use *alpha*-PiHP describe stimulant effects similar to those of *alpha*-PVP and *alpha*-PHP.

Dependence potential:

No controlled studies of the dependence potential of *alpha*-PiHP in animals or humans have been reported. In view of its actions and effects on the central nervous system, it would be expected to produce dependence similarly to other psychostimulants such as methamphetamine.

Actual abuse and/or evidence of likelihood of abuse:

Studies in animals predictive of abuse liability indicate that *alpha*-PiHP produces effects similar to those of methamphetamine and cocaine. No controlled studies of the abuse potential of *alpha*-PiHP in humans have been reported.

Seizures of *alpha*-PiHP have been described in multiple countries in three regions.

Alpha-PiHP has been identified in a number of serious adverse events and drug-related deaths. As it is usually detected with other substances, including opioids and benzodiazepines, the role of *alpha*-PiHP is unclear in some instances.

Therapeutic usefulness:

Alpha-PiHP is not known to have any therapeutic use.

Recommendation:

Alpha-pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as *alpha*-PiHP, is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants, such as methamphetamine, that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. There is evidence that its abuse is likely to constitute a substantial public health and social problem. It has no known therapeutic use.

Recommendation: The Committee recommended that *alpha*-pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as *alpha*-PiHP, be added to Schedule II of the 1971 Convention on Psychotropic Substances.

3-Methylmethcathinone

Substance identification:

3-Methylmethcathinone (IUPAC chemical name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, is a synthetic cathinone. 3-Methylmethcathinone has been found as a white or off-white powder, a white, yellow, or orange solid, and a crystalline solid. It has been detected in tablet, capsule, and liquid forms.

WHO review history:

3-Methylmethcathinone was critically reviewed by the Committee at its 38th meeting, in 2016, when it decided to request a further critical review once more information became available and to consider it at a subsequent meeting. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use. Information from international agencies suggests that there has been a significant increase in the availability of and harm due to 3-methylmethcathinone in recent years.

Similarity to known substances and effects on the central nervous system:

3-Methylmethcathinone is an isomer of 4-methylmethcathinone (mephedrone), which is a synthetic cathinone listed under Schedule II of the Convention on Psychotropic Substances of 1971.

3-Methylmethcathinone has a typical psychostimulant profile, similar to that of 4-methylmethcathinone, including inhibition of the reuptake of dopamine, norepinephrine, and serotonin, and increased release of dopamine and serotonin.

Clinical features of 3-methylmethcathinone intoxication are consistent with those produced by other stimulants and include tachycardia, hypertension, agitation, aggression, hallucinations, rhabdomyolysis, and kidney failure.

Dependence potential:

No controlled studies of the dependence potential of 3-methylmethcathinone in animals or humans have been reported. Withdrawal symptoms indicative of physical dependence have been documented in people who use 3-methylmethcathinone. In view of its actions and effects on the central nervous system, 3-methylmethcathinone would be expected to produce dependence similar to other psychostimulants, such as methamphetamine.

Actual abuse and/or evidence of likelihood of abuse:

In animal models predictive of rewarding effects, 3-methylmethcathinone produced effects that were similar to those of methamphetamine. 3-Methylmethcathinone also produced behavioural (stimulant) effects similar to methamphetamine. No controlled studies in humans have examined the abuse potential of 3-methylmethcathinone.

3-Methylmethcathinone has been seized in multiple countries in several regions.

Many fatal and non-fatal intoxications involving 3-methylmethcathinone have been reported. Other substances were commonly involved in these cases, although severe intoxication and death have been reported in cases in which 3-methylmethcathinone was the only substance identified.

Therapeutic usefulness:

3-Methylmethcathinone is not known to have any therapeutic use.

Recommendation:

3-Methylmethcathinone (IUPAC chemical name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants such as methamphetamine that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. There is evidence that its abuse is likely to constitute a substantial public health and social problem. It has no known therapeutic use.

Recommendation: The Committee recommended that 3-Methylmethcathinone (IUPAC chemical name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Substances to be kept under surveillance:

Adinazolam

Substance identification:

Adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine) is a triazolobenzodiazepine. Adinazolam appears as a white or yellow powder and is also sold as tablets and capsules, including as falsified pharmaceuticals.

WHO review history:

Adinazolam has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

Adinazolam is a short-acting benzodiazepine with moderate affinity for the benzodiazepine receptor. It is a chemical analogue of alprazolam and triazolam.

Consistent with its benzodiazepine receptor action, adinazolam showed anticonvulsant, anxiolytic and antidepressant properties in animals. In humans, adinazolam (and its metabolite *N*-desmethyladinazolam) produced a dose-dependent decrease in psychomotor performance and increased sedation and amnesia. It also had some subjective effects similar to those of benzodiazepines such as diazepam and lorazepam, which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

Dependence potential:

No studies have been conducted in animals or humans on the dependence potential of adinazolam. In view of its mechanism of action, however, it would be expected to produce typical benzodiazepine dependence.

Actual abuse and/or evidence of likelihood of abuse

In animals, adinazolam shows behavioural effects consistent with those of drugs with abuse liability. In controlled studies in humans, adinazolam produced sedation, and, in one controlled study, adinazolam produced a self-reported “high” feeling, with a greater estimated street value than placebo.

While seizures of adinazolam have been reported in a few countries in two regions, currently there is insufficient evidence that it is being abused to such an extent as to constitute a public health problem.

Adinazolam was identified in a few drug-related deaths in combination with other psychoactive substances, including opioids and other benzodiazepines; however, there was no evidence that adinazolam played a causative role in these deaths.

Therapeutic usefulness:

Adinazolam is not known to have any therapeutic use.

Recommendation:

Adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine) has effects similar to those of substances listed under Schedule IV of the Convention on Psychotropic Substances of 1971. There is, however, insufficient evidence that its use is a public health and social problem to justify its placement under international control.

Recommendation: The Committee recommended that adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine) be kept under surveillance by the WHO Secretariat.

Bromazolam

Substance identification:

Bromazolam (8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) is a triazolobenzodiazepine. Bromazolam has been described as a white or crystalline solid and has been identified in tablets, capsules, powders, solutions, and edible products. Bromazolam has been identified in falsified pharmaceutical benzodiazepine products.

WHO review history:

Bromazolam has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system:

There is currently insufficient information on the pharmacological profile of bromazolam from controlled studies in animals or humans to conclude that it has effects similar to those of benzodiazepines, which are controlled under the 1971 Convention on Psychotropic Substances.

Online self-reports by people who claim to have used bromazolam describe benzodiazepine-like effects, including hypnotic, sedative, muscle relaxant, and euphoric effects. There are, however, no clinical reports or analytical confirmation of bromazolam to confirm these effects.

Dependence potential:

No controlled studies in animals or humans have been reported on the dependence potential of bromazolam. Online self-reports describe withdrawal symptoms after cessation of chronic use.

Actual abuse and/or evidence of likelihood of abuse:

No controlled studies in animals or humans have been reported on the abuse liability of bromazolam. In self-reports online, people have described using the drug for its euphoric and other benzodiazepine-like effects; however, there is no confirmation that that the substance used was bromazolam.

Seizures of bromazolam have been reported in multiple countries in several regions. Bromazolam has been analytically confirmed in a number of deaths, non-fatal intoxications, and instances of driving under the influence of drugs. Because of the presence of other drugs, especially other benzodiazepines; however, the contribution of bromazolam cannot be determined.

Therapeutic usefulness:

Bromazolam is not known to have any therapeutic uses and has never been marketed as a medicinal product.

Recommendation:

While the chemical structure of bromazolam (8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine) is similar to those of other benzodiazepines listed under the Convention on Psychotropic Substances of 1971, its mechanism of action and effects are yet to be confirmed. Although there is increasing evidence of its use, no studies in animals or humans have been reported on the effects or abuse potential of bromazolam. The limited information on its effects provides insufficient evidence to justify placement of bromazolam under international control.

Recommendation: The Committee recommended that bromazolam (8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) be kept under surveillance by the WHO Secretariat.

Zopiclone

Substance identification:

Zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) is a sedative hypnotic drug of the cyclopyrrolone class. Zopiclone has been reported as a white or slightly yellowish powder. Zopiclone is available as pharmaceutical products in tablet form for oral use. Eszopiclone (the S-enantiomer of zopiclone) is marketed as a pharmaceutical product in some countries.

WHO review history:

Zopiclone was pre-reviewed by the Committee at its 29th meeting, when it recommended that surveillance be continued but that a critical review was not required. In view of the abuse liability of the drug and the significant number of reports of adverse drug reactions related to zopiclone abuse sent to the WHO international drug monitoring programme; however, zopiclone was pre-reviewed by the Committee at its 33rd meeting, when it recommended a critical review. Zopiclone was critically reviewed at the 34th meeting, in 2006, when the Committee rated its abuse liability as low and its therapeutic usefulness considerable and recommended continued surveillance by WHO. A pre-review was initiated after a proposal was received from an international agency that suggested a significant increase in the reported number of trafficking cases and seizures involving zopiclone.

Similarity to known substances and effects on the central nervous system:

Zopiclone binds to the benzodiazepine receptor that forms part of the GABAA receptor complex. It may bind to different parts of the receptor or cause different changes in the GABAA receptor complex than benzodiazepines.

In animals, zopiclone has sedative, anxiolytic, anticonvulsant, and muscle relaxant properties similar to those of benzodiazepines. In studies in humans, it was less effective than benzodiazepines for treatment of anxiety.

Dependence potential:

Studies in animals show evidence of zopiclone tolerance and withdrawal, indicating the development of physical dependence. A number of published reports have described physical dependence associated with zopiclone use in humans. Withdrawal symptoms such as increased anxiety and insomnia have been described in people who cease zopiclone use, usually after prolonged use and dose escalation from clinical use. Tolerance and withdrawal have also been reported in clinical trials. Dependence is documented in databases on adverse events associated with pharmaceutical use.

Actual abuse and/or evidence of likelihood of abuse:

Studies in animals suggest that zopiclone may have abuse liability similar to that of benzodiazepines such as midazolam, diazepam, nitrazepam, and alprazolam. The effects indicative of abuse liability were blocked by the benzodiazepine antagonist flumazenil, indicating a mechanism of action involving the benzodiazepine receptor.

No controlled studies in humans have been reported on the abuse potential of zopiclone. Published reports describe effects consistent with benzodiazepine-like abuse potential, its use with alcohol and other drugs and escalation to high-dose use. The extent of harm related to the use of zopiclone is, however, unclear.

Zopiclone is widely used therapeutically in many countries and regions, and it is also listed in databases of adverse events associated with pharmaceutical use. Zopiclone is most likely to be misused by individuals to whom it is prescribed for long periods, who are using other psychoactive drugs or in those with psychiatric comorbidities. While seizures of zopiclone have been reported in multiple countries in several regions, the prevalence of non-medical use of zopiclone by the general population is unknown. Furthermore, there is insufficient evidence that significant public health and social problems related to abuse can be directly attributed to sole use of zopiclone.

Therapeutic usefulness:

Zopiclone is a widely used medicine primarily indicated for the short-term treatment of insomnia, with marketing authorisations in many countries. It is not listed on the WHO Model List of Essential Medicines.

Recommendation:

Zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) is a sedative hypnotic drug of the cyclopyrrolone class. The Committee noted that concern has been expressed in several countries regarding non-prescription use of zopiclone. While there have been reports of adverse effects, overdose, withdrawal symptoms and an increased number of seizures of the substance, there is still insufficient evidence that zopiclone is or is likely to be abused to such an extent as to constitute a public health and social problem.

The Committee also noted that zopiclone is widely used therapeutically in many countries.

Recommendation: The Committee recommended that zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) not proceed to critical review but be kept under surveillance by the WHO Secretariat.

III. Discussion

Although WHO has made specific scheduling recommendations for each of the drug substances, the CND is not obliged to follow the WHO recommendations. Options available to the CND for substances considered for control under the 1971 Convention include the following: (1) accept the WHO recommendations; (2) accept the recommendations to control but control the drug substance in a schedule other than that recommended; or (3) reject the recommendations entirely.

ADB-BUTINACA (chemical name: N-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1H-indazole-3-carboxamide) is a synthetic cannabinoid that is a potent agonist of the cannabinoid (CB) 1 and CB2 receptors. Adverse effects associated with synthetic cannabinoids include euphoria, appetite stimulation, sedation, loss of consciousness, and paranoia. The use of ADB-BUTINACA has been associated with fatalities in the United States in which other drugs were also detected. ADB-BUTINACA is not approved for medical use in the United States. ADB-BUTINACA has been detected in the illicit drug market in the United States since 2020 as evidenced by drug seizures. As a positional isomer of AB-PINACA (N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide), ADB-BUTINACA is controlled under

schedule I of the CSA. As such, additional permanent controls will not be needed if ADB-BUTINACA is placed under schedule II of the Convention on Psychotropic Substances.

Alpha-PiHP (4-methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one) is a synthetic cathinone with chemical and pharmacological properties similar to schedule I and II amphetamines and cathinones such as *alpha*-PHP, *alpha*-PVP, and MDPV. Reports of intoxication indicate that *alpha*-PiHP produces psychoactive effects similar to methamphetamine and cocaine. Adverse events associated with the abuse of synthetic cathinones include, but are not limited to, agitation, hypertension, tachycardia, and death. *Alpha*-PiHP is not approved for medical use in the United States. *Alpha*-PiHP has been identified in a number of drug seizures in the United States and has been detected in mixtures with other drugs including opioids and benzodiazepines. As a positional isomer of *alpha*-PHP (1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one), *alpha*-PiHP is controlled under schedule I of the CSA. As such, additional permanent controls will not be needed if *alpha*-PiHP is placed in Schedule II of the Convention on Psychotropic Substances.

3-Methylmethcathinone (2-(methylamino)-1-(3-methylphenyl)propan-1-one) is a synthetic cathinone with chemical and pharmacological properties similar to schedule I and II amphetamines and cathinones such as amphetamine and 4-methylmethcathinone (mephedrone, 4-MMC). Reports of intoxication of 3-methylmethcathinone indicate that it produces psychoactive effects similar to stimulants such as methamphetamine. These reports also indicate that it produces adverse events which include tachycardia, hypertension, agitation, aggression, hallucinations, rhabdomyolysis, and kidney failure. Several fatalities have been reported in which 3-methylmethcathinone was the only drug detected, however, in some other cases other drugs were detected. 3-Methylmethcathinone is not approved for medical use in the United States. 3-Methylmethcathinone has been identified in a number of drug seizures in the United States and has been detected in mixtures with other drugs including opioids and benzodiazepines. As a positional isomer of 4-methylmethcathinone (2-(methylamino)-1-(4-methylphenyl)propan-1-one; mephedrone), 3-methylmethcathinone is controlled under schedule I of the CSA. As such,

additional permanent controls will not be needed if 3-methylmethcathinone is placed in Schedule II of the Convention on Psychotropic Substances.

FDA, on behalf of the Secretary of HHS, invites interested persons to submit comments on the notifications from the United Nations concerning these drug substances. FDA, in cooperation with the National Institute on Drug Abuse, will consider the comments on behalf of HHS in evaluating the WHO scheduling recommendations. Then, under section 201(d)(2)(B) of the CSA, HHS will recommend to the Secretary of State what position the United States should take when voting on the recommendations for control of substances under the 1971 Convention at the CND meeting in March 2023.

Comments regarding the WHO recommendations for control of 2-methyl-AP-237, etazene, etonitazepyne, and protonitazene under the 1961 Single Convention will also be forwarded to the relevant Agencies for consideration in developing the U.S. position regarding narcotic substances at the CND meeting.

Dated: February 13, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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