DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–N–0105]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; Butonitazene; 3-Chloromethcathinone; Dipentylone; 2-Fluorodeschloroketamine; Bromazolam; 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 2024. This notice is issued under the Controlled Substances Act (CSA).

DATES: Submit either electronic or written comments by February 27, 2024.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before February 27, 2024. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of February 27, 2024. 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–2022–N–0105 for ''International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; Butonitazene; 3-Chloromethcathinone; Dipentylone; 2-Fluorodeschloroketamine; Bromazolam; 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. 5110, Silver Spring, MD 20993–0002, 301–796–0727, *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 four substances to be considered for control under the 1971 Convention. This notification reflects the recommendation from the 46th WHO Expert Committee for Drug Dependence (ECDD), which met in October 2023. In the **Federal Register** of August 24, 2023 (88 FR 52179), 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 one substance 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.18/2023
WHO/ECDD46; 1961C-Art.3, 1971C-Art.2
CU 2023/403/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 Permanent Mission that, in a letter dated 15 November 2023, 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-sixth Meeting of the WHO's Expert Committee on Drug Dependence (ECDD):

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

—Butonitazene
IUPAC (International Union of Pure and Applied Chemistry) name: N,N-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1H-benzimidazole-1-ethanamine

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

—3-chloromethcathinone or 3-CMC
IUPAC name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one
—Dipentylone
IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one
—2-fluorodeschloroketamine
IUPAC name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one

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

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

Substance recommended to proceed to critical review at a future ECDD meeting:

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-sixth meeting, to conduct a critical review of the following substance:

—Carisoprodol
IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl)carbamate

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-sixth meeting, to keep the following substances under surveillance:

—Flubromazepam
IUPAC name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one
—Nitrous oxide
IUPAC name: nitrous oxide

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 NAR/CL.18/2023—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, hereby transmitted in NAR/CL.18/2023—Annex II.

Also, in accordance with the same provisions, the notification from WHO will be brought to the attention of the sixty-seventh session of the Commission on Narcotic Drugs (14–22 March 2024) in a pre-session document that will be made available in the six official languages of the United Nations on the website of the sixty-seventh session of the Commission on Narcotic Drugs: *https://www.unodc.org/unodc/en/commissions/CND/session/67_Session_2024/67CND_Main.html.*

In order to assist the Commission in reaching a decision, it would be appreciated if the Permanent 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:

—Butonitazene

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:

—3-chloromethcathinone or 3-CMC
—Dipentylone
—2-fluorodeschloroketamine
—Bromazolam

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.

12 December 2023

Annex I

Letter Addressed to the Secretary-General of the United Nations From the Director-General of the World Health Organization, Dated 15 November 2023

I have the honour to refer to the Forty-sixth Meeting of the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD), which was convened in Geneva, Switzerland, from 16 to 19 October 2023.

WHO is mandated by the 1961 and 1971 International Drug Control Conventions to make recommendations to the Secretary-General of the United Nations 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-sixth WHO ECDD Meeting critically reviewed six new psychoactive substances: one novel synthetic opioid (butonitazene), two cathinones/stimulants (3-chloromethcathinone or 3-CMC, dipentylone), one dissociative substance (2-fluorodeschloroketamine) and two benzodiazepines (bromazolam, flubromazepam). These substances, with the exception of bromazolam, had previously not

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-sixth ECDD carried out pre-reviews of the medications nitrous oxide and carisoprodol 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-sixth Meeting of ECDD:

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

—Butonitazene
IUPAC (International Union of Pure and Applied Chemistry) name: N,N-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1H-benzimidazole-1-ethanamine

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

—3-chloromethcathinone or 3-CMC
IUPAC name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one
—Dipentylone
IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one
—2-fluorodeschloroketamine
IUPAC name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one

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

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

Substance recommended to proceed to critical review at a future ECDD meeting:

—Carisoprodol
IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl)carbamate

Substances to be kept under surveillance:

—Flubromazepam
IUPAC name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2H–1,4-benzodiazepin-2-one
—Nitrous oxide
IUPAC name: nitrous oxide

The assessments and findings on which these recommendations are based are set out in detail in the forty-sixth meeting report of the WHO Expert Committee on Drug Dependence. A summary of the assessment and recommendations made by the Forty-sixth ECDD is contained in Annex I 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

Summary Assessment and Recommendations of the 46th Expert Committee on Drug Dependence, 16–19 October 2023

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

Butonitazene

Substance Identification

Butonitazene (IUPAC name: N,N-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1H-benzimidazole-1-ethanamine), also known as butoxynitazene, is a benzimidazole-derived synthetic opioid. Butonitazene is found as a crystalline solid and a white or yellow-brown powder.

WHO Review History

Butonitazene has not been reviewed formally by WHO and is not currently under international control. Information was brought to WHO's attention 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

The chemical structure and pharmacological effects of butonitazene are similar to those of opioid drugs such as etonitazene and isotonitazene that are controlled under Schedule I of the United Nations Conventions on Narcotic Drugs of 1961. Butonitazene is an agonist at μ-opioid receptors and has similar analgesic effects as morphine and fentanyl.

Dependence Potential

No studies in experimental animal or humans were found on the dependence potential of butonitazene; however, as it is a μ-opioid receptor agonist, it would be expected to produce dependence.

Actual Abuse and/or Evidence of Likelihood of Abuse

No studies on the abuse potential of butonitazene in humans were found. In an animal model predictive of abuse potential, butonitazene had morphine-like effects, which were blocked by the opioid antagonist naltrexone. As it is a μ-opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability. Butonitazene is reported to be administered by various routes, including smoking, intranasally and by injection. Non-fatal intoxications that involved butonitazene and required hospitalization have been reported. Seizures of butonitazene have been reported in multiple countries in two regions.

Therapeutic Use

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

Rationale and Recommendation

Butonitazene, also known as butoxynitazene, is a synthetic opioid that is liable to abuse and to production of ill effects similar to those of other opioids that are controlled under Schedule I of the Single Convention on Narcotic Drugs, 1961. Its use has been reported in a number of countries. It has no known therapeutic use and is likely to cause substantial harm. The Committee recommended that butonitazene (IUPAC name: N,N-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1H-benzimidazole-1-ethanamine), also known as butoxynitazene, be added to Schedule I of the Single Convention on Narcotic Drugs, 1961.

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

3-Chloromethcathinone (3-CMC)

Substance Identification

3-Chloromethcathinone or 3-CMC (IUPAC name: 1-(3-chlorophenyl)-2-(methylamino)propan-1- one), is a synthetic cathinone. 3-CMC has been described as a grey or white solid and as a white powder. It has been identified in capsule, tablet, and liquid forms.

WHO Review History

3-CMC has not been reviewed formally by WHO and is not currently under international control. Information was brought to WHO's attention 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

3-CMC is a chemical analogue of methcathinone, which is controlled under Schedule I of the United Nations Convention on Psychotropic Substances of 1971. Its structural isomer, 4-CMC, is controlled under Schedule II of the United Nations Convention on Psychotropic Substances of 1971. In common with other cathinone psychostimulants, 3-CMC has been shown to act via dopamine, serotonin and norepinephrine transporters in the central nervous system to increase the concentrations of these neurotransmitters.

Dependence Potential

No controlled experimental studies of the dependence potential of 3-CMC in experimental animals or humans were available; however, clinical admissions associated with dependence to 3-CMC have been reported. Given its action in the central nervous system, 3-CMC would be expected to produce a state of dependence similar to that produced by amphetamine and other psychostimulants.

Actual Abuse and/or Evidence of Likelihood of Abuse

No controlled studies of the abuse potential of 3-CMC in experimental animals or humans were available. In experimental animals, 3-CMC produced locomotor effects consistent with a psychostimulant. Cases of intoxication with 3-CMC alone and with other drugs requiring hospitalization have been reported. The adverse effects included

agitation, restlessness, seizures, high blood pressure, sweating, and chest pain. These adverse effects are similar to those of other psychostimulants, such as amphetamine and various cathinones. Fatal intoxications involving 3-CMC have been documented, including in cases in which 3-CMC was the only substance identified. It is reported to be administered by various routes, including smoking, intranasally and by injection. 3-CMC has been detected in an increasing number of countries in most regions of the world. Seizures of 3-CMC have been reported in multiple countries and regions, with recent increases coinciding with international control of 4-CMC.

Therapeutic Use

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

Rationale and Recommendation

3-Chloromethcathinone or 3-CMC is a synthetic cathinone with effects similar to those of other synthetic cathinones, such as mephedrone and 4-CMC, which are listed as Schedule II substances under the Convention on Psychotropic Substances of 1971. Its mode of action and effects are similar to those of other cathinones. There is evidence of use of 3-CMC in a number of countries and regions, where it has resulted in fatal and non-fatal intoxications. The substance causes substantial harm, constitutes a substantial risk to public health and has no therapeutic use. The Committee recommended that 3-chloromethcathinone or 3-CMC (IUPAC name: 1(3-chlorophenyl)-2-(methylamino)propan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Dipentylone

Substance Identification

Dipentylone or N-methylpentylone (IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one, also known as N,N-dimethylpentylone, dimethylpentylone or bk-DMBDP) is a synthetic cathinone. It is distributed mainly as crystals or tablets.

WHO Review History

Dipentylone has not been reviewed formally by WHO and is not currently under international control. Information was brought to WHO's attention 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

In common with other cathinone psychostimulants, dipentylone has been shown to act via dopamine, serotonin, and norepinephrine transporters in the central nervous system to increase the concentrations of these neurotransmitters. Online self-reports describe insomnia, hallucinations, paranoia and confusion after its use. Adverse effects documented in clinical presentations include agitation and tachycardia. These effects are consistent with a psychostimulant mechanism of action.

Dependence Potential

No controlled experimental studies of the dependence potential of dipentylone in experimental animals or humans were available. In view of its action in the central nervous system, however, dipentylone would be expected to produce a state of dependence similar to that produced by amphetamine and other psychostimulants.

Actual Abuse and/or Evidence of Likelihood of Abuse

Studies in experimental animals demonstrate that dipentylone has an abuse potential similar to that of methamphetamine, which is listed under Schedule II of the Convention on Psychotropic Substances of 1971, and cocaine, which is listed under Schedule I of the Convention on Narcotic Drugs of 1961. Dipentylone has been shown to produce locomotor stimulant effects in animal models. No controlled studies on the abuse potential of dipentylone in humans were identified. Non-fatal intoxication involving dipentylone that required hospitalization has been reported, and fatal intoxications have been reported by a number of countries, in which no other substance was involved in at least one case. Cases of driving under the influence of dipentylone have reported by some countries. Seizures of dipentylone have been reported in a number of countries and regions. Dipentylone appears to be commonly sold as cocaine or MDMA.

Therapeutic Use

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

Rationale and Recommendation

Dipentylone or N-methylpentylone 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. Its mode of action suggests the likelihood of abuse, and it poses a substantial risk to public health. It has no known therapeutic use. The Committee recommended that dipentylone or N-methylpentylone (IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2-Fluorodeschloroketamine

Substance Identification

2-Fluorodeschloroketamine (IUPAC name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one) is an arylcyclohexylamine that is chemically related to the dissociative anaesthetic ketamine. It has been described as a brown oil in its free base form or as a crystalline solid or white powder as a salt. It has been identified in some food products (chocolates).

WHO Review History

2-Fluorodeschloroketamine has not been reviewed formally by WHO and is not currently under international control. Information was brought to WHO's attention 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

The mechanism of action of 2-fluorodeschloroketamine is uncertain, but it has effects similar to those of N-methyl-D-aspartate receptor antagonists such as phencyclidine, which are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Effects documented during clinical admissions due to 2-fluorodeschloroketamine intoxication include dissociation, confusion, agitation, tachycardia and hypertension. Unverified reports from people who use 2-fluorodeschloroketamine describe hallucinogenic and dissociative effects. The clinical and self-reported effects of 2-fluorodeschloroketamine are consistent with the effects of phencyclidine.

Dependence Potential

No controlled studies in experimental animal or humans were found on the dependence potential of 2-fluorodeschloroketamine; however, clinical admissions for dependence on 2-fluorodeschloroketamine have been reported in various countries and regions.

Actual Abuse and/or Evidence of Likelihood of Abuse

Studies in experimental animals indicate that 2-fluorodeschloroketamine has behavioural (locomotor) effects consistent with central nervous system stimulation. Such studies confirm that it has rewarding properties and effects predictive of abuse liability. Cases of intoxication that involved 2-fluorodeschloroketamine and required hospitalization have been reported. The adverse effects included central nervous system effects such as dissociation, confusion, agitation, combativeness, nystagmus, hallucinations and impaired consciousness, loss of consciousness and cardiovascular effects such as tachycardia and hypertension. Fatal intoxications involving 2-fluorodeschloroketamine have been documented, including at least one case in which no other substance was involved. 2-Fluorodeschloroketamine has been analytically confirmed in people driving under the influence of drugs and in clinical admissions due to drug intoxication. It is reported to be administered by various routes including orally, intranasally and by injection. Seizures have been reported in a number of countries in several regions.

Therapeutic Use

2-Fluorodeschloroketamine is not known to have any therapeutic use, is not listed on the WHO Model Lists of Essential Medicines and has never been marketed as a medicinal product.

Rationale and Recommendation

2-Fluorodeschloroketamine has effects similar to those of dissociative substances such as phencyclidine, which are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. The results of studies in experimental animals indicate a high likelihood of abuse. There is evidence

that this substance is used in a number of countries in several regions. 2-Fluorodeschloroketamine causes substantial harm, including impaired driving, emergency department presentations and deaths. It has no known therapeutic use. The Committee recommended that 2-fluorodeschloroketamine (IUPAC name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Substance to be added to Schedule IV of the Convention on Psychotropic Substances (1971):

Bromazolam

Substance Identification

Bromazolam (IUPAC name: 8-bromo-1-methyl-6-phenyl-4H-[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 chewable candy products (''gummies''). Bromazolam has been identified in falsified pharmaceutical benzodiazepine products.

WHO Review History

Bromazolam was critically reviewed at the 45th ECDD meeting. Because of lack of information on its pharmacological effects, it was not recommended for international control but was placed under surveillance. New information on such effects was brought to WHO's attention, in addition to ongoing evidence 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

Bromazolam is a benzodiazepine with relatively high potency and a short-intermediate duration of action. It is structurally related to alprazolam. Like other benzodiazepines, bromazolam binds to γ-aminobutyric acid ($GABA_A$) receptors, and its effects can be reversed by administration of the benzodiazepine receptor antagonist flumazenil. Unconfirmed online reports by people who use bromazolam describe benzodiazepine-like effects, including hypnotic, sedative, muscle relaxant and euphoric effects.

Dependence Potential

No controlled studies in experimental animals or in humans have examined the dependence potential of bromazolam. In view of its pharmacological effects and similarity to other benzodiazepines, however, it would be expected to produce dependence. Online self-reports describe withdrawal symptoms after cessation of chronic use.

Actual Abuse and/or Evidence of Likelihood of Abuse

No studies in humans were found of the abuse liability of bromazolam. In an animal model predictive of abuse liability, bromazolam had effects similar to those of midazolam and diazepam, which are controlled under Schedule IV of the Convention on Psychotropic Substances of 1971. The effects were attenuated by pre-administration of the benzodiazepine receptor antagonist flumazenil, confirming bromazolam's action as a benzodiazepine. Seizures of bromazolam have been reported increasingly in many countries in various regions. Bromazolam has been analytically confirmed as a causal or contributory agent in several deaths and non-fatal intoxications, and its presence has been confirmed in instances of driving under the influence of drugs. These harms have been reported in multiple countries and regions.

Therapeutic Use

Bromazolam is not known to have any therapeutic use, is not listed on the WHO Model Lists of Essential Medicines and has never been marketed as a medicinal product.

Rationale and Recommendation

The mechanism of action and ill effects of bromazolam are similar to those of other benzodiazepines, such as alprazolam and diazepam, that are listed under Schedule IV of the Convention on Psychotropic Substances of 1971. Reports of seizures and detection in fatal and non-fatal intoxications have increased over time. There is sufficient evidence of its abuse to conclude that it constitutes a significant risk to public health and has no known therapeutic use. The Committee recommended that bromazolam (IUPAC name: 8-bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine) be added to Schedule IV of the Convention on Psychotropic Substances of 1971.

Substances to be recommended for critical review:

Carisoprodol

Substance Identification

Carisoprodol (IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-ethylethyl)carbamate) is a centrally-acting skeletal muscle relaxant sold as a single-ingredient preparation and in combination products. Carisoprodol is available as a pharmaceutical product in tablet form, has been detected in falsified pharmaceuticals and is also found as a white powder.

WHO Review History

Carisoprodol was pre-reviewed at the 32nd ECDD meeting in 2000. The Committee did not recommend critical review of carisoprodol at that time, noting that sporadic nonmedical use of carisoprodol was not a new phenomenon and there was no indication of significantly increasing nonmedical use. A new pre-review was initiated in 2023 after information received from an international agency that suggested a significant increase in the reported number of trafficking cases and seizures involving carisoprodol.

Similarity to Known Substances and Effects on the Central Nervous System

Carisoprodol is an analogue of meprobamate and has effects similar to those of other central nervous system depressants such as meprobamate, pentobarbital, diazepam and chlordiazepoxide that are listed under schedules III and IV of the Convention on Psychotropic Substances of 1971. Meprobamate is also a metabolite of carisoprodol. Although its exact mechanism of action is not known, the therapeutic effects of carisoprodol appear to be due to modulation of $GABA_A$ receptors similar to the action of barbiturates. The sedative effects of carisoprodol can be potentiated when it is combined with benzodiazepines, opioids or alcohol.

Dependence Potential

Tolerance and withdrawal have been documented in experimental animals, and the potential for dependence on carisoprodol is considered to be similar to that of barbiturates and benzodiazepines. Tolerance, withdrawal and craving have been documented in humans, and increasing numbers of cases of carisoprodol dependence have been documented in pharmacovigilance reporting systems.

Actual Abuse and/or Evidence of Likelihood of Abuse

In animal models indicative of abuse liability, the effects of carisoprodol were similar to those of pentobarbital, chlordiazepoxide and meprobamate in a dose-dependent manner. In humans, carisoprodol produces central nervous system depressant effects, including drowsiness, sedation, confusion and coma. Public health harm associated with use of carisoprodol has included cases of driving under the influence of the drug. Nonmedical use of carisoprodol is widely documented in multiple countries and regions, including in combination with opioids and/or benzodiazepines. The incidence of poisoning and other public health harm has been reported to have decreased in some countries after increased restrictions on carisoprodol prescription or removal of the drug from the market.

Therapeutic Use

Carisoprodol is a centrally acting muscle relaxant used in some countries in the short term as an adjunct in symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasms. It is not on the 2023 WHO Essential Medicines List or the WHO Essential Medicines List for Children. It has been withdrawn from use in some countries because of concern about increased rates of diversion, nonmedical use, dependence, intoxication and psychomotor impairment.

Rationale and Recommendation

The increasing evidence of misuse and abuse of carisoprodol in a number of countries is a growing cause for concern. Carisoprodol has been shown to produce a state of dependence and central nervous system depression. It has only limited medical use. The Committee recommended that carisoprodol be subject to a future critical review.

Substances to be kept under surveillance:

Flubromazepam

Substance Identification

Flubromazepam (IUPAC name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) is a 1,4-benzodiazepine. Flubromazepam is described as a white powder or a crystalline solid and has been found in infused paper forms.

WHO Review History

Flubromazepam has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention 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

The chemical structure of flubromazepam is similar to that of other benzodiazepines, including phenazepam. Currently, there is insufficient information on the pharmacological profile of flubromazepam from controlled studies in experimental animals or humans to conclude that it has effects that are similar to those of benzodiazepines that are controlled under the Convention on Psychotropic Substances of 1971. Online self-reports by people who claim to have used flubromazepam describe sedative, muscle relaxant and euphoric effects and its use to self-manage benzodiazepine withdrawal. There are, however, no clinical reports to confirm such effects.

Dependence Potential

No controlled study in experimental animals or humans have addressed the dependence potential of flubromazepam.

Actual Abuse and/or Evidence of Likelihood of Abuse

No studies in humans were found of the abuse liability of flubromazepam. People who self-report flubromazepam use describe euphoric effects and other benzodiazepine-like effects that would suggest it has a similar likelihood of abuse, but their use of flubromazepam cannot be confirmed. Results from limited studies in experimental animals suggest abuse liability. Seizures have been reported in multiple countries across a number of regions. Although flubromazepam has been detected in several deaths and cases of driving under the influence of drugs, other drugs were also detected, and the contribution of flubromazepam was unclear.

Therapeutic Use

Flubromazepam is not known to have any therapeutic use, is not listed on the WHO Model Lists of Essential Medicines and has never been marketed as a medicinal product.

Rationale and Recommendation

Flubromazepam is a 1,4-benzodiazepine. Although it is chemically similar to other benzodiazepines listed under Schedule IV of the Convention on Psychotropic Substances of 1971, little information is available on its effects. Few studies in experimental animals and no studies in humans were found on its effects or abuse potential. The limited information on its effects provides insufficient evidence to justify the placement of flubromazepam under international control. The Committee recommended that flubromazepam (IUPAC name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) be kept under surveillance by the WHO ECDD secretariat.

Nitrous Oxide

Substance Identification

Nitrous oxide (IUPAC name: Nitrous oxide, N_2O) is an inhalational anaesthetic marketed under a range of trade names as both a single ingredient gas and in multi-ingredient preparations. It is also manufactured for industrial use, including in food production, as small metal canisters, bulbs and larger cylinders. It is described as a colourless gas.

WHO Review History

Nitrous oxide is not currently under international control and has never been reviewed by the ECDD. Information was brought to WHO's attention by a Member State of increased nonmedical use, such that it presented a risk to public health.

Similarity to Known Substances and Effects on the Central Nervous System

Nitrous oxide appears to have multiple mechanisms of action that are not entirely understood. There is some evidence for effects on opioid, GABAergic, glutamatergic and other neurotransmitter systems. Nitrous oxide produces anaesthesia, analgesia and, in laboratory studies with humans, subjective effects such as perceptual distortion, paranoia, delusions, anhedonia and cognitive disorganization.

Dependence Potential

Acute and chronic tolerance to the effects of nitrous oxide have been documented in experimental animals, with signs of withdrawal when exposure was ended abruptly. Animals that were tolerant to nitrous oxide were partially cross-tolerant to ethanol but not to barbiturates or morphine. Laboratory studies in humans provide evidence of tolerance to some effects of nitrous oxide, but the degree of tolerance varied according to the effect and between individuals. Epidemiological and clinical studies provide evidence of dependence.

Actual Abuse and/or Evidence of Likelihood of Abuse

The evidence from studies in experimental animals on the likelihood of abuse of nitrous oxide is inconsistent. The abuse potential of nitrous oxide has been reported since the 19th century, including its euphoric effects and ability to cause auditory and visual distortions. Nitrous oxide was originally promoted for recreational use as ''laughing gas''; however, laboratory studies with humans have produced inconsistent results on abuse liability. The global prevalence of non-medical use of nitrous oxide is unknown. Reports from several countries indicate that nonmedical use is highest among adolescents and young adults, and evidence from some countries indicates an increase in use in recent years. Nitrous oxide used nonmedically is typically obtained from legal manufacturers, with no evidence of illicit manufacture and minimal evidence of cross-border trading. Nitrous oxide use has been implicated in cases of impaired driving. Deaths directly related to nonmedical use of nitrous oxide appear to be rare and to be due to intended or unintended asphyxia. Long-term exposure can result in neurological and haematological toxicity.

Therapeutic Use

Nitrous oxide is widely used globally for analgesia and sedation during childbirth and in painful short procedures in dentistry and emergency medicine. It is used commonly as a supplementary agent in anaesthesia. Nitrous oxide is listed on the 2023 WHO Model List of Essential Medicines and the Essential Medicines List for Children as an inhalational anaesthetic. Clinical trials of nitrous oxide are being conducted to explore its value as a medication for other indications such as treatment-resistant depression and management of alcohol withdrawal symptoms.

Rationale and Recommendation

Nitrous oxide is a widely used inhalation anaesthetic and is listed on the 2023 WHO Model List of Essential Medicines and Essential Medicines List for Children. While the Committee acknowledged the concerns raised by some countries, it recommended that nitrous oxide not proceed to critical review because of the absence of evidence of illicit manufacture and of common trading across borders, and in recognition of its global therapeutic value. The Committee recommended that nitrous oxide 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.

Butonitazene (chemical name: N,N-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1H-benzimidazole-1-ethanamine) is a benzimidazole synthetic opioid that functions as an agonist of the μ-opioid receptor and has similar psychoactive effects as morphine and fentanyl. Butonitazene is reported to produce euphoria after administration through various routes including smoking, oral, intranasal, and injection. It was first identified in law enforcement seizures in the United States in 2021 and has since (*i.e.,* 2021 to 2023) been identified in 63 different drug seizures. Butonitazene has also been identified in drug toxicology screens and is confirmed to have been responsible for at least one fatality in the United States. There are no commercial or approved medical uses for butonitazene. Butonitazene is controlled in schedule I of the CSA and will not require additional permanent controls if it is placed in Schedule I of the 1961 Single Convention.

3-Chloromethcathinone (3-CMC) (chemical name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one) is a synthetic cathinone that functions to inhibit reuptake of the dopamine, serotonin, and norepinephrine transporters in the central nervous system. Functionally this increases the concentration of these neurotransmitters which leads to psychostimulatory effects. Humans and animals have demonstrated clinical signs of agitation, restlessness, seizures, high blood pressure, and increased locomotor activity. The appearance of 3-CMC on the illicit drug market is similar to other designer drugs trafficked for their psychoactive effects. There are no commercial or approved medical uses for 3-CMC in the United States. Methcathinone was controlled in Schedule I of the CSA on October 15, 1993. As a positional isomer of methcathinone, 3-CMC is controlled in Schedule I of the CSA. As such, additional permanent controls will not be needed if 3-CMC is placed in Schedule II of the Convention on Psychotropic Substances, 1971.

Dipentylone (chemical name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one, also known as N,N-dimethylpentylone, dimethylpentylone or bk-DMBDP) is a synthetic cathinone that produces psychostimulant effects similar to cathinone. Dipentylone functions by increasing the concentration of dopamine, serotonin, and norepinephrine in the central nervous system similar to amphetamines. Anecdotal reports indicate that dipentylone produces clinical effects of insomnia, hallucinations, paranoia, and confusion. As of 2021, dipentylone was identified in 8,368 drug seizures, and was confirmed as the cause of death in at least nine fatalities in 2023. There are no commercial or approved medical uses for dipentylone in the United States. Pentylone was controlled in Schedule I of the CSA on March 4, 2016. As a positional isomer of pentylone, dipentylone is controlled in Schedule I of the CSA. As such, additional permanent controls will not be needed if dipentylone is placed in Schedule II of the Convention on Psychotropic Substances, 1971.

2-Fluorodeschloroketamine (chemical name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one), fluoroketamine, or 2-FDCK) is an arylcyclohexylamine that is related to ketamine and phencyclidine (PCP). 2-FDCK is thought to function as an N-methyl-D-aspartate receptor antagonist and produce effects similar to other dissociative anesthetics (*e.g.,* ketamine). According to anecdotal reports, these effects include dissociation, hallucination, confusion, agitation, stimulation, and tachycardia and hypertension. Studies in animals indicate that 2-FDCK was self-administered (*i.e.,* produced reinforcing effects) and produced a drug cue similar to that of ketamine. As a result, animal data suggests that 2-FDCK has an abuse potential similar to ketamine. 2-FDCK has not been detected in law enforcement seizures, or in toxicology screens in the United States. There are no commercial or approved medical uses for 2-FDCK, and it is not a controlled substance under the CSA. As such, additional permanent controls will be necessary to fulfill U.S. obligations if 2-FDCK is controlled under Schedule II of the Convention on Psychotropic Substances, 1971.

Bromazolam (chemical name: 8-bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine) is a triazolobenzodiazepine that functions as a positive allosteric modulator of γ-aminobutyric acid A ($GABA_A$) channels thereby decreasing neuronal activity. Similar to other benzodiazepines, such as alprazolam, it produces sedative and anxiolytic effects typically taken after oral administration or through injection. Unconfirmed anecdotal reports indicate that it can also produce hypnotic, muscle relaxant, and euphoric effects as well as physical dependence demonstrated through a withdrawal syndrome. Since 2021, bromazolam has been detected in 637 law enforcement seizures and has been implicated in 53 fatalities. There are no commercial or approved medical uses for bromazolam in the United States, and it is not a controlled substance under the CSA. As such, additional permanent controls will be necessary to fulfill U.S. obligations if bromazolam is controlled under Schedule IV of the Convention on Psychotropic Substances, 1971.

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 2024.

Comments regarding the WHO recommendations for control of butonitazene 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 5, 2024.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2024–02573 Filed 2–7–24; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meeting

Pursuant to section 1009 of the Federal Advisory Committee Act, as amended, notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Cancer Institute Special Emphasis Panel; Cancer Technologies for Global Health.

Date: February 13, 2024.

Time: 9:30 a.m. to 6:00 p.m.

Agenda: To review and evaluate grant applications.

Place: National Cancer Institute at Shady Grove, 9609 Medical Center Drive, Room 7W238, Rockville, Maryland 20850 (Virtual Meeting).

Contact Person: Jeffrey E. DeClue, Ph.D., Scientific Review Officer, Research Technology and Contract Review Branch, Division of Extramural Activities, National Cancer Institute, NIH, 9609 Medical Center Drive, Room 7W238, Rockville, Maryland 20850, 240–276–6371, *decluej@mail.nih.gov.*

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)