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Item 5 (a) of the provisional agenda*
Implementation of the international drug control treaties: changes in the scope of control of substances

Changes in the scope of control of substances: proposed scheduling recommendations by the World Health Organization

Note by the Secretariat

Summary

The present document contains recommendations for action to be taken by the Commission on Narcotic Drugs pursuant to the international drug control treaties.

In accordance with article 3 of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, the Commission will have before it for consideration a recommendation by the World Health Organization (WHO) to place *N*-pyrrolidino protonitazene, *N*-pyrrolidino metonitazene, etonitazepipne and *N*-desethyl isotonitazene in Schedule I of that Convention.

In accordance with article 2 of the Convention on Psychotropic Substances of 1971, the Commission will have before it for consideration a recommendation by WHO to place hexahydrocannabinol in Schedule II of that Convention and a recommendation to place carisoprodol in Schedule IV of that Convention.

* E/CN.7/2025/1.

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I. Consideration of the notification from the World Health Organization concerning scheduling under the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol

1. Pursuant to article 3, paragraphs 1 and 3, of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, the Director General of the World Health Organization (WHO), in a letter dated 21 November 2024, notified the Secretary-General of the United Nations that WHO recommended that *N*-pyrrolidino protonitazene, *N*-pyrrolidino metonitazene, etonitazepipne and *N*-desethyl isotonitazene be added to Schedule I of that Convention (see annex for the relevant extract from that notification).

2. In accordance with the provisions of article 3, paragraph 2, of the 1961 Convention as amended, the notification and the information submitted by WHO to the Secretary-General in support of its recommendations were transmitted to all Governments in an annex to a note verbale dated 27 December 2024.

Action to be taken by the Commission on Narcotic Drugs

3. The notification from the Director General of WHO is before the Commission on Narcotic Drugs for its consideration, in accordance with the provisions of article 3, paragraph 3 (iii), of the 1961 Convention as amended, which reads as follows:

> If the World Health Organization finds that the substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II.

4. With regard to the decision-making process, the attention of the Commission is drawn to rule 58 of the rules of procedure of the functional commissions of the Economic and Social Council, which stipulates that decisions are to be made by a majority of the members present and casting an affirmative or negative vote. Members that abstain from voting are considered as not voting.

5. The Commission should therefore decide:

(a) Whether or not it wishes to include *N*-pyrrolidino protonitazene in Schedule I of the 1961 Convention as amended;

(b) Whether or not it wishes to include *N*-pyrrolidino metonitazene in Schedule I of the 1961 Convention as amended;

(c) Whether or not it wishes to include etonitazepipne in Schedule I of the 1961 Convention as amended;

(d) Whether or not it wishes to include *N*-desethyl isotonitazene in Schedule I of the 1961 Convention as amended.

II. Consideration of the notification from the World Health Organization concerning scheduling under the Convention on Psychotropic Substances of 1971

6. Pursuant to article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances of 1971, the Director General of WHO, in a letter dated 21 November 2024, notified the Secretary-General that WHO recommended placing hexahydrocannabinol in Schedule II of that Convention and carisoprodol in Schedule IV of that Convention (see annex for the relevant extract from that notification).

7. In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the notification and the information submitted by WHO in support of its recommendations were transmitted to all Governments in an annex to a note verbale dated 27 December 2024.

Action to be taken by the Commission on Narcotic Drugs

8. The notification from the Director General of WHO is before the Commission on Narcotic Drugs for its consideration, in accordance with the provisions of article 2, paragraph 5, of the 1971 Convention, which reads as follows:

> The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.

9. With regard to the decision-making process, the attention of the Commission is drawn to article 17, paragraph 2, of the 1971 Convention, which stipulates that the decisions of the Commission provided for in articles 2 and 3 are to be taken by a two-thirds majority of the members of the Commission. From a practical point of view, this means that, for a decision to be adopted, an affirmative vote of at least 36 members of the Commission is required.

10. The Commission should therefore decide:

(a) Whether it wishes to place hexahydrocannabinol in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required;

(b) Whether it wishes to place carisoprodol in Schedule IV of the 1971 Convention or, if not, what other action, if any, might be required.

Annex

Extract from the notification from the Director General of the World Health Organization to the Secretary-General dated 21 November 2024

The World Health Organization (WHO) is mandated by the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol and the Convention on Psychotropic Substances of 1971 to make recommendations to the United Nations Secretary-General on the need for and level of international control of psychoactive substances on the basis of the advice of its independent scientific advisory body, the Expert Committee on Drug Dependence. To assess the appropriate control of a psychoactive substance, WHO convenes the Committee annually to review the potential of a substance to cause dependence, abuse and harm to health, as well as to review any therapeutic applications.

At its forty-seventh meeting, the Committee critically reviewed seven new psychoactive substances: one semi-synthetic cannabinoid, four synthetic opioids, one dissociative-type substance and one cathinone/stimulant. The substances had not previously been formally reviewed by WHO and none of them are currently under international control. Information was brought to the attention of WHO that the substances are clandestinely manufactured, pose a risk to public health and society and have no recognized therapeutic use by any party.

Also at its forty-seventh meeting, the Committee carried out a critical review of the medicine carisoprodol, after making a recommendation for pre-review at its forty-sixth meeting.

A critical review to consider international scheduling measures was undertaken for each substance so that the Committee could consider whether information about the substances would justify the scheduling of a substance under the 1961 Convention as amended or the 1971 Convention.

In addition, at its forty-seventh meeting, the Committee received an informal update from the WHO secretariat regarding a critical review of coca leaf planned for 2025.

With reference to article 3, paragraphs 1 and 3, of the 1961 Convention as amended and article 2, paragraphs 1 and 4, of the 1971 Convention, WHO is pleased to endorse and submit the following recommendations of the Expert Committee on Drug Dependence at its forty-seventh meeting:

To be added to Schedule I of the 1961 Convention as amended

***N*-Pyrrolidino protonitazene**
International Union of Pure and Applied Chemistry (IUPAC) name: 2-[(4-propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole
Alternate name: protonitazepyne

***N*-Pyrrolidino metonitazene**
IUPAC name: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole
Alternate name: metonitazepyne

Etonitazepipne
IUPAC name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1*H*-benzoimidazole
Alternate name: *N*-piperidinyl etonitazene

***N*-Desethyl isotonitazene**
IUPAC name: *N*-ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine
Alternate name: norisotonitazene

To be added to Schedule II of the 1971 Convention

Hexahydrocannabinol
IUPAC name: 6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol
Alternate name: HHC

To be added to Schedule IV of the 1971 Convention

Carisoprodol
IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl)carbamate
International Nonproprietary Name: carisoprodol

To be kept under surveillance

***N*-Ethylheptedrone**
IUPAC name: 2-(ethylamino)-1-phenylheptan-1-one
Alternate name: *N*-ethylnorheptedrone

3-Hydroxyphencyclidine
IUPAC name: 3-[1-(1-piperidinyl)cyclohexyl]phenol
Alternate name: 3-OH-PCP

Summary of the assessments and recommendations of the World Health Organization Expert Committee on Drug Dependence at its forty-seventh meeting, 14–18 October 2024

1. Substances to be added to Schedule I of the 1961 Convention as amended

1.1 *N*-Pyrrolidino protonitazene

Substance identification

N-Pyrrolidino protonitazene (IUPAC name: 2-[(4-propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole), also known as protonitazepyne, is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

N-Pyrrolidino protonitazene has been described as a beige powder or a white colourless or crystalline solid. *N*-Pyrrolidino protonitazene has been identified in falsified pharmaceutical opioid tablets.

World Health Organization review history

N-Pyrrolidino protonitazene has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the 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 *N*-pyrrolidino protonitazene closely resemble those of protonitazene, which is controlled under Schedule I of the 1961 Convention as amended.

Studies in animals have demonstrated that *N*-pyrrolidino protonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine and fentanyl. Its effects are blocked by the opioid antagonist naltrexone.

Its adverse effects, which have been documented in clinical presentations, are also consistent with opioid effects, including dizziness, bradycardia, hypotension and respiratory depression.

Dependence potential

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

Actual abuse and/or evidence of likelihood of abuse

In animals, *N*-pyrrolidino protonitazene showed opioid effects and abuse potential, with greater potency than fentanyl. Its abuse potential has not been studied in humans. Online self-reports describe typical opioid effects, including relaxation, euphoria and sedation.

Its presence has been analytically confirmed in many deaths and hospital admissions, including as the only substance detected. *N*-Pyrrolidino protonitazene is reported to be administered by various routes, including smoking, snorting and by injection. *N*-Pyrrolidino protonitazene has been available for sale online by Internet retailers.

Seizures of *N*-pyrrolidino protonitazene have been reported in multiple countries in three regions.

Therapeutic usefulness

N-Pyrrolidino protonitazene is not known to have any therapeutic use.

Recommendation

N-Pyrrolidino protonitazene (IUPAC name: 2-[(4-propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole), also referred to as protonitazepyne, is a synthetic opioid that is liable to abuse and produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Convention as amended. Its use causes substantial harm, including death. It has no known therapeutic use.

> Recommendation: the Committee recommended that *N*-pyrrolidino protonitazene (IUPAC name: 2-[(4-propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole), also referred to as protonitazepyne, be added to Schedule I of the 1961 Convention as amended.

1.2 *N*-Pyrrolidino metonitazene

Substance identification

N-Pyrrolidino metonitazene (IUPAC name: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole), also known as metonitazepyne, is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

N-Pyrrolidino metonitazene has been described as a beige powder.

World Health Organization review history

N-Pyrrolidino metonitazene has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the 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 *N*-pyrrolidino metonitazene closely resemble those of metonitazene, which is controlled under Schedule I of the 1961 Convention as amended.

Studies in animals have demonstrated that *N*-pyrrolidino metonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine. Its potency varies from less than to greater than that of fentanyl, depending on the study model. Its effects are blocked by the opioid antagonist naltrexone.

Dependence potential

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

Actual abuse and/or evidence of likelihood of abuse

In animals, *N*-pyrrolidino metonitazene showed potent opioid effects and abuse potential similar to those of morphine and fentanyl.

Multiple deaths have been reported in which the presence of *N*-pyrrolidino metonitazene was analytically confirmed, including one death in which no other opioids were involved. Other substances were detected in all other cases. *N*-Pyrrolidino metonitazene is reported to be administered by injection.

Seizures of *N*-pyrrolidino metonitazene have been reported in multiple countries in two regions.

Therapeutic usefulness

N-Pyrrolidino metonitazene is not known to have any therapeutic use.

Recommendation

N-Pyrrolidino metonitazene (IUPAC name: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole), also referred to as metonitazepyne, is a synthetic opioid that is liable to abuse and produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Convention as amended. There is evidence that its use causes substantial harm, including death. It has no known therapeutic use.

> Recommendation: the Committee recommended that *N*-pyrrolidino metonitazene (IUPAC name: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole), also referred to as metonitazepyne, be added to Schedule I of the 1961 Convention as amended.

1.3 Etonitazepipne

Substance identification

Etonitazepipne (IUPAC name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1*H*-benzoimidazole), also known as *N*-piperidinyl etonitazene, is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

Etonitazepipne has been described as a crystalline solid or a white-yellowish or yellow powder. Etonitazepipne has been identified in falsified pharmaceutical opioid tablets.

World Health Organization review history

Etonitazepipne has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the 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 etonitazepipne closely resemble those of etonitazepyne, which is controlled under Schedule I of the 1961 Convention as amended.

Studies in animals have demonstrated that etonitazepipne is a full agonist at μ-opioid receptors, with greater potency than morphine. Its potency varies from less than to similar to that of fentanyl, depending on the study model. Its effects are blocked by the opioid antagonist naltrexone. Studies in humans have demonstrated that its adverse effects include respiratory depression and reduced consciousness, which were reversed by the opioid antagonist naloxone.

Dependence potential

No controlled studies of the dependence potential of etonitazepipne 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 that produced by other opioids, such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, etonitazepipne showed potent opioid effects and abuse potential similar to those of morphine and fentanyl. Those effects were blocked by the opioid antagonist naltrexone.

Non-fatal intoxications requiring hospitalization have been reported. Multiple deaths in which the use of etonitazepipne was analytically confirmed have been reported in at least two regions, including some in which etonitazepipne was considered the primary cause of death or no other substances were involved. Online self-reports indicate typical opioid effects, including relaxation, euphoria and sedation.

Seizures of etonitazepipne have been reported in multiple countries and regions.

Therapeutic usefulness

Etonitazepipne is not known to have any therapeutic use.

Recommendation

Etonitazepipne (IUPAC name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1*H*-benzoimidazole), also referred to as *N*-piperidinyl etonitazene, is a synthetic opioid that is liable to abuse. It produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Convention as amended. There is evidence that its use causes substantial harm, including death. It has no known therapeutic use.

> Recommendation: the Committee recommended that etonitazepipne (IUPAC name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1*H*-benzoimidazole), also referred to as *N*-piperidinyl etonitazene, be added to Schedule I of the 1961 Convention as amended.

1.4 *N*-Desethyl isotonitazene

Substance identification

N-Desethyl isotonitazene (IUPAC name: *N*-ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine), also known as norisotonitazene, is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

N-Desethyl isotonitazene hydrochloride has been described as a crystalline solid. *N*-Desethyl isotonitazene has been identified in falsified pharmaceuticals, in the form of round blue tablets.

World Health Organization review history

N-Desethyl isotonitazene has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the 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

N-Desethyl isotonitazene is a major metabolite of, and has a chemical structure and effects similar to those of, isotonitazene, which is controlled under Schedule I of the 1961 Convention as amended.

Studies in animals have shown that *N*-desethyl isotonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine. Its potency varies from similar to, to greater than, that of fentanyl, depending on the study model.

Its effects are blocked by the opioid antagonists naltrexone and naloxone.

Its adverse effects, including analgesia, euphoria, miosis, muscle rigidity, unconsciousness, sedation, respiratory depression, coma and hypercapnia, are consistent with opioid toxicity.

Dependence potential

No controlled studies of the dependence potential of *N*-desethyl isotonitazene 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 that produced by other opioids, such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, *N*-desethyl isotonitazene had potent opioid effects and abuse potential. Its potency was greater than that of morphine, and varied from similar to, to greater than, that of fentanyl, depending on the study model. These effects were blocked by the opioid antagonist naltrexone.

Multiple deaths and hospital admissions have been reported in at least two regions, including deaths to which *N*-desethyl isotonitazene was considered to have contributed.

Seizures of *N*-desethyl isotonitazene have been reported in multiple countries in three regions.

Therapeutic usefulness

N-Desethyl isotonitazene is not known to have any therapeutic use.

Recommendation

N-Desethyl isotonitazene (IUPAC name: *N*-ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine), also referred to as norisotonitazene, is a synthetic opioid that is liable to abuse and produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Convention as amended.

There is evidence that its use causes substantial harm, including death. It has no known therapeutic use.

> Recommendation: the Committee recommended that *N*-desethyl isotonitazene (IUPAC name: *N*-ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine), also referred to as norisotonitazene, be added to Schedule I of the 1961 Convention as amended.

2. Substances to be added to Schedule II of the 1971 Convention

Hexahydrocannabinol

Substance identification

Hexahydrocannabinol (IUPAC name: 6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol), also known as HHC, has three stereogenic centres, indicating that eight stereoisomers are possible. As a semi-synthetic cannabinoid, however, it is usually found as a mixture of (6a*R*,9*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (9*S* epimer) and (6a*R*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (9*R* epimer).

Hexahydrocannabinol has been described as a colourless viscous oil or resin that changes to dark orange after exposure to oxygen. Products containing hexahydrocannabinol include low-tetrahydrocannabinol (THC) cannabis flowers and resins infused or sprayed with the substance, e-liquids and cartridges for electronic cigarettes, edible products such as gummies and marshmallows, tinctures resembling dietary supplements and distillate oils. The routes of administration include inhalation, oral and sublingual.

World Health Organization review history

Hexahydrocannabinol has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the 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 (9*R*)-hexahydrocannabinol epimer has CB1 and CB2 receptor binding affinity similar to that of *delta*-9-THC. Hexahydrocannabinol acts as a partial agonist at the CB1 receptor, as does *delta*-9-THC, and produces psychoactive effects, including adverse effects, similar to those produced by *delta*-9-THC. In animals, it has been shown to produce behavioural effects consistent with *delta*-9-THC. In humans, sleepiness, euphoria, anxiety, agitation, psychosis, tremors and disorientation have been reported, in addition to respiratory, cardiovascular and gastrointestinal effects.

Hexahydrocannabinol is found in trace amounts as a phytocannabinoid in cannabis plants but is usually synthesized from cannabidiol.

Dependence potential

No studies of the dependence potential of hexahydrocannabinol in animals or humans have been reported. Its effects at CB1 receptors suggest that it would produce dependence similar to that produced by other cannabinoid partial agonists, such as *delta*-9-THC. Withdrawal effects in humans have been reported, and multiple countries have reported that people who use hexahydrocannabinol have presented for treatment of drug dependence.

Actual abuse and/or evidence of likelihood of abuse

No studies have been reported in animals or humans on the likelihood of abuse of hexahydrocannabinol; however, CB1 receptor agonists have known abuse potential.

Adverse effects include people presenting, at emergency departments, with non-fatal intoxication and exhibiting symptoms such as dizziness, confusion, unconsciousness, psychosis (hallucinations, delusions and paranoia), anxiety, panic attacks, depression, hypertension, nausea and vomiting, which are similar to the symptoms seen in cases involving *delta*-9-THC.

The presence of hexahydrocannabinol has been analytically confirmed in people driving under the influence of drugs and in clinical admissions for drug intoxication in adults and children in multiple countries, including cases in which

hexahydrocannabinol was confirmed to be the only substance involved. Seizures of hexahydrocannabinol have been reported in many countries in a number of regions.

Therapeutic usefulness

Hexahydrocannabinol is not known to have any therapeutic use.

Recommendation

Hexahydrocannabinol (IUPAC name: 6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol), also known as HHC, is a semi-synthetic cannabinoid receptor agonist with a mechanism of action and effects similar to those of *delta*-9-THC, which is controlled under Schedule II of the 1971 Convention. There is sufficient evidence that hexahydrocannabinol is used in such a way as to constitute a public health and social problem, thus warranting its placement under international control.

> Recommendation: the Committee recommended that hexahydrocannabinol (IUPAC name: 6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol) be added to Schedule II of the 1971 Convention.

3. Substances to be added to Schedule IV of the 1971 Convention

Carisoprodol

Substance identification

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

World Health Organization review history

Carisoprodol was pre-reviewed by the Committee at its thirty-second meeting, in 2000. At that meeting, the Committee did not recommend a critical review of carisoprodol, noting that the sporadic non-medical use of the substance was not a new phenomenon and that there was no indication that its non-medical use was significantly increasing. A new pre-review was initiated in 2023 after an international agency provided information that suggested a significant increase in the reported number of trafficking cases and seizures involving carisoprodol. At its forty-sixth meeting, on the basis of increasing evidence of its non-medical use and harm to public health, the Committee recommended that carisoprodol be subject to a critical review.

Similarity to known substances and effects on the central nervous system

Carisoprodol is metabolized to meprobamate and has effects similar to those of other central nervous system depressants, such as meprobamate, phenobarbital, diazepam and chlordiazepoxide, which are listed under schedule IV of the 1971 Convention. Meprobamate is also a metabolite of carisoprodol. Although its exact mechanism of action is not known, its therapeutic effects appear to be due to modulation of *gamma*-aminobutyric acid ($GABA_A$) receptors, similar to the mechanism of 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 symptoms, of carisoprodol have been documented in experimental animals, and the potential for dependence on carisoprodol is considered to be similar to that of barbiturates and benzodiazepines. In humans, in the context of its prolonged use, tolerance, withdrawal symptoms and craving have been

documented. An increasing number of cases of carisoprodol dependence have been recorded in pharmacovigilance reporting systems and clinical settings.

Actual abuse and/or evidence of likelihood of abuse

In animal models of abuse liability, the effects of carisoprodol were similar to those of pentobarbital, chlordiazepoxide and meprobamate and were dose-dependent. In humans, in the context of its non-medical use at high doses, carisoprodol produces central nervous system depressant effects, including drowsiness, sedation, confusion and coma.

Public health harms, including cases of driving under the influence of the drug and non-fatal and fatal intoxications, due to carisoprodol alone or in combination with other substances, have been observed.

The non-medical use of carisoprodol is widely documented in multiple countries and regions, including in combination with opioids and/or benzodiazepines. Increased restrictions on the prescription of carisoprodol and the removal of the drug from the market in several countries have led to decreased incidences of poisoning and of other harms to public health. Seizures of carisoprodol have been reported in many countries in several regions.

Therapeutic use

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

Recommendation

There is increasing evidence that the non-medical use of carisoprodol in a number of countries constitutes a significant risk to public health. Carisoprodol is a medicine that has been shown to produce a state of dependence, central nervous system depression and ill effects similar to those of other substances that are listed under Schedule IV of the 1971 Convention.

> Recommendation: the Committee recommended that carisoprodol (IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl)carbamate) be added to Schedule IV of the 1971 Convention.

4. Substances to be kept under surveillance

4.1 *N*-Ethylheptedrone

Substance identification

N-Ethylheptedrone (IUPAC name: 2-(ethylamino)-1-phenylheptan-1-one), also known as *N*-ethylnorheptedrone, ethylheptedrone or HEP, is a synthetic cathinone. *N*-Ethylheptedrone hydrochloride has been described as a crystalline solid.

World Health Organization review history

N-Ethylheptedrone has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the 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

N-Ethylheptedrone is a synthetic cathinone with a chemical structure and pharmacological properties similar to those of other synthetic cathinones (e.g. *N*-ethylhexedrone and pentedrone) that are controlled under Schedule II of the 1971 Convention.

In common with other cathinone psychostimulants, *N*-ethylheptedrone has been shown to act via dopamine, serotonin and norepinephrine transporters in the central nervous system to increase the concentrations of those neurotransmitters.

Adverse effects documented in a limited number of clinical presentations include agitation and tachycardia.

Dependence potential

No controlled studies of the dependence potential of *N*-ethylheptedrone in animals or humans have been reported.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals demonstrate that *N*-ethylheptedrone has an abuse potential similar to that of methamphetamine and cocaine. No controlled studies of the abuse potential of *N*-ethylheptedrone in humans have been reported.

A single death was reported to have involved *N*-ethylheptedrone and other substances. Several clinical admissions were reported in two countries.

Seizures of *N*-ethylheptedrone have been reported in two regions.

Therapeutic usefulness

N-Ethylheptedrone is not known to have any therapeutic use.

Recommendation

N-Ethylheptedrone (IUPAC name: 2-(ethylamino)-1-phenylheptan-1-one) is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants. Insufficient evidence was available, however, to establish that its use constitutes a public health and social problem warranting its placement under international control.

> Recommendation: the Committee recommended that *N*-ethylheptedrone (IUPAC name: 2-(ethylamino)-1-phenylheptan-1-one), also known as *N*-ethylnorheptedrone, be kept under surveillance by the WHO secretariat.

4.2 3-Hydroxyphencyclidine

Substance identification

3-Hydroxyphencyclidine (IUPAC name: 3-[1-(1-piperidinyl)cyclohexyl]phenol), also known as 3-OH-PCP, is an analogue of the dissociative anaesthetic phencyclidine (PCP). It has been described as a crystalline solid or a white crystalline powder. It has also been found in food products such as chocolates.

World Health Organization review history

3-Hydroxyphencyclidine has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the 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-Hydroxyphencyclidine is an *N*-methyl-D-aspartate receptor antagonist with a mechanism of action and effects similar to those of phencyclidine, which is controlled

under Schedule II of the 1971 Convention. Its effects include hallucinations and dissociation.

Dependence potential

No controlled studies in animals or humans of the dependence potential of 3-hydroxyphencyclidine were found.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals suggest that 3-hydroxyphencyclidine has abuse potential similar to that of phencyclidine. No studies of the abuse liability of 3-hydroxyphencyclidine in humans have been reported.

It is reported to be administered by various routes, including intranasal and oral. A limited number of cases of fatal and non-fatal intoxication that involved 3-hydroxyphencyclidine in combination with other psychoactive substances have been reported. In most cases, the use of 3-hydroxyphencyclidine was not analytically confirmed, and there was limited evidence that it had played a causative role.

Limited seizures have been reported in several countries.

Therapeutic usefulness

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

Recommendation

3-Hydroxyphencyclidine (IUPAC name: 3-[1-(1-piperidinyl)cyclohexyl]phenol), also known as 3-OH-PCP, is an analogue of, and has effects similar to those of, phencyclidine, which is controlled under Schedule II of the 1971 Convention. Its mode of action suggests the likelihood of abuse, but there is insufficient evidence that its use constitutes a public health or social problem warranting its placement under international control.

> Recommendation: the Committee recommended that 3-hydroxyphencyclidine (IUPAC name: 3-[1-(1-piperidinyl)cyclohexyl]phenol), also known as 3-OH-PCP, be kept under surveillance by the WHO secretariat.