United Nations E/CN.7/2024/12

Economic and Social Council

Distr.: General
4 January 2024

Original: English

Commission on Narcotic Drugs
Sixty-seventh session
Vienna, 14–22 March 2024
Item 5 (a) of the provisional agenda*
Implementation of the international drug control treaties: changes in the scope of control of substances

Changes in the scope of control of substances: 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 butonitazene 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 3-chloromethcathinone (3-CMC), dipentylone and 2-fluorodeschloroketamine in Schedule II of that Convention and a recommendation to place bromazolam in Schedule IV of that Convention.

* E/CN.7/2024/1.

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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 15 November 2023, notified the Secretary-General of the United Nations that WHO recommended that butonitazene 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 12 December 2023.

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 which abstain from voting are considered as not voting.

5. The Commission should therefore decide whether or not it wishes to include butonitazene 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 15 November 2023, notified the Secretary-General that WHO recommended placing 3-chloromethcathinone (3-CMC), dipentylone and 2-fluorodeschloroketamine in Schedule II of that Convention and bromazolam 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 12 December 2023.

Action to be taken by the Commission on Narcotic Drugs

8. The notification by 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 3-chloromethcathinone (3-CMC) in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required;

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

(c) Whether it wishes to place 2-fluorodeschloroketamine in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required;

(d) Whether it wishes to place bromazolam 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 15 November 2023

At its forty-sixth meeting, the World Health Organization (WHO) Expert Committee on Drug Dependence critically reviewed six new psychoactive substances: one novel synthetic opioid (butonitazene), two cathinones/stimulants (3-chloromethcathinone, or 3-CMC, and dipentylone), one dissociative substance (2-fluorodeschloroketamine) and two benzodiazepines (bromazolam and flubromazepam). The substances, with the exception of bromazolam, had not previously been formally reviewed by WHO and are currently not 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. Therefore, a critical review to consider international scheduling measures was undertaken for each substance so that the Expert Committee could consider whether information about the substances would justify the scheduling of a substance under the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol or the Convention on Psychotropic Substances of 1971.

In addition, the Expert Committee carried out pre-reviews of the medications nitrous oxide and carisoprodol at its forty-sixth meeting to consider whether current information justified a critical review.

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-sixth meeting:

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

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

To be added to Schedule II of the 1971 Convention

3-Chloromethcathinone (3-CMC)
International Union of Pure and Applied Chemistry name:
1-(3-chlorophenyl)-2-(methylamino)propan-1-one

Dipentylone
International Union of Pure and Applied Chemistry name:
1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one

2-Fluorodeschloroketamine
International Union of Pure and Applied Chemistry name:
2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one

To be added to Schedule IV of the 1971 Convention

Bromazolam
International Union of Pure and Applied Chemistry name:
8-bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine

To proceed to critical review at a future meeting of the Expert Committee on Drug Dependence

Carisoprodol
International Union of Pure and Applied Chemistry name:
2-[(carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl)carbamate

To be kept under surveillance

Flubromazepam
International Union of Pure and Applied Chemistry name:
7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one

Nitrous oxide
International Union of Pure and Applied Chemistry name:
nitrous oxide

Summary of the assessments, rationale and recommendations of the World Health Organization Expert Committee on Drug Dependence at its forty-sixth meeting, 16–19 October 2023

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

1.1 Butonitazene

Substance identification

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

World Health Organization review history

Butonitazene has not been reviewed formally 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 butonitazene are similar to those of opioid drugs, such as etonitazene and isotonitazene, that are controlled under Schedule I of the 1961 Convention as amended. Butonitazene is an agonist at μ-opioid receptors and has analgesic effects similar to those of morphine and fentanyl.

Dependence potential

No studies in experimental animals or in 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 1961 Convention as amended. 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 (International Union of Pure and Applied Chemistry name: *N*,*N*-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine), also known as butoxynitazene, be added to Schedule I of the 1961 Convention as amended.

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

2.1 3-Chloromethcathinone (3-CMC)

Substance identification

3-Chloromethcathinone, or 3-CMC (International Union of Pure and Applied Chemistry 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.

World Health Organization review history

3-CMC has not been reviewed formally 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-CMC is a chemical analogue of methcathinone, which is controlled under Schedule I of the 1971 Convention. Its structural isomer, 4-CMC, is controlled under Schedule II of the 1971 Convention.

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 those neurotransmitters.

Dependence potential

No controlled experimental studies of the dependence potential of 3-CMC in experimental animals or in humans were available; however, clinical admissions associated with dependence on 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 in humans were available. In experimental animals, 3-CMC produced locomotor effects consistent with those of a psychostimulant.

Cases of intoxication involving 3-CMC alone and involving 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 the 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 1971 Convention. 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 (International Union of Pure and Applied Chemistry name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one) be added to Schedule II of the 1971 Convention.

2.2 Dipentylone

Substance identification

Dipentylone, or *N*-methylpentylone (International Union of Pure and Applied Chemistry 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.

World Health Organization review history

Dipentylone has not been reviewed formally 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

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 those 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 in 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 1971 Convention, and cocaine, which is listed under Schedule I of the 1961 Convention as amended. 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 at least one of those reports, no other substance was involved. Cases of driving under the influence of dipentylone have been 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 1971 Convention. 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 (International Union of Pure and Applied Chemistry name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one) be added to Schedule II of the 1971 Convention.

2.3 2-Fluorodeschloroketamine

Substance identification

2-Fluorodeschloroketamine (International Union of Pure and Applied Chemistry 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 freebase form or as a crystalline solid or white powder as a salt. It has been identified in some food products (chocolates).

World Health Organization review history

2-Fluorodeschloroketamine has not been reviewed formally 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 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 1971 Convention. 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 animals or in 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, impaired consciousness and 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 1971 Convention. The results of studies in experimental animals indicate a high likelihood of abuse. There is evidence that the 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 (International Union of Pure and Applied Chemistry name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one) be added to Schedule II of the 1971 Convention.

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

3.1 Bromazolam

Bromazolam (International Union of Pure and Applied Chemistry name: 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 chewable candy products (“gummies”).

Bromazolam has been identified in falsified pharmaceutical benzodiazepine products.

World Health Organization review history

Bromazolam was critically reviewed by the Expert Committee at its forty-fifth 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 the attention of WHO, in addition to ongoing evidence 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

Bromazolam is a benzodiazepine with relatively high potency and a short to intermediate duration of action. It is structurally related to alprazolam. Like other benzodiazepines, bromazolam binds to g-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 1971 Convention. 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 1971 Convention. 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 (International Union of Pure and Applied Chemistry name: 8-bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) be added to Schedule IV of the 1971 Convention.

4. Substances recommended for critical review

4.1 Carisoprodol

Substance identification

Carisoprodol (International Union of Pure and Applied Chemistry 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 Expert Committee at its thirty-second meeting, in 2000. The Committee did not recommend critical review of carisoprodol at that time, noting that sporadic non-medical use of carisoprodol was not a new phenomenon and that there was no indication of significantly increasing non-medical

use. A new pre-review was initiated in 2023 after information was 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 1971 Convention. 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.

Non-medical 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 Model List of Essential Medicines or the 2023 WHO Model List of Essential Medicines for Children. It has been withdrawn from use in some countries because of concern about increased rates of diversion, non-medical 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.

5. Substances to be kept under surveillance

5.1 Flubromazepam

Substance identification

Flubromazepam (International Union of Pure and Applied Chemistry name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-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.

World Health Organization review history

Flubromazepam has not been formally 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 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 in humans to conclude that it has effects that are similar to those of benzodiazepines that are controlled under the 1971 Convention.

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 in humans has 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 1971 Convention, 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 (International Union of Pure and Applied Chemistry name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) be kept under surveillance by the WHO Secretariat.

5.2 Nitrous oxide

Substance identification

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

World Health Organization review history

Nitrous oxide is not currently under international control and has never been reviewed by the Expert Committee. Information was brought to the attention of WHO by a Member State of increased non-medical 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 of effects on opioid, GABAergic, glutamatergic and other neurotransmitter systems. Nitrous oxide produces anaesthesia, analgesia and, in laboratory studies in 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 nineteenth 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 in humans have produced inconsistent results with regard to abuse liability.

The global prevalence of non-medical use of nitrous oxide is unknown. Reports from several countries indicate that non-medical use is highest among adolescents and young adults, and evidence from some countries indicates an increase in use in recent years. Nitrous oxide used non-medically 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 non-medical 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 commonly used as a supplementary agent in anaesthesia. Nitrous oxide is listed on the 2023 WHO Model List of Essential Medicines and the 2023 WHO Model List of Essential Medicines 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 inhalational anaesthetic and is listed on the 2023 WHO Model List of Essential Medicines and the 2023 WHO Model List of Essential Medicines 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.