Annex 1. 46th WHO ECDD summary assessments, rationale and recommendations, 16–19 October 2023

Substances 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-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.

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-1*H*-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 Substances (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 animls 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 hospitalizatio 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.

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

Bromazolam

Bromazolam (IUPAC 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.

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-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) be added to Schedule IV of the Convention on Psychotropic Substances of 1971.

Substances recommended for critical review:

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.

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-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.

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-2*H*-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.