Annex 1. 47th WHO ECDD summary assessments and recommendations, 14–18 October 2024

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

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.

WHO 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 Single Convention on Narcotic Drugs of 1961.

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, 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)-1H-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 Single Convention on Narcotic Drugs. 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)-1H-benzoimidazole), also referred to as protonitazepyne, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

N-Pyrrolidino metonitazene

Substance identification

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

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

WHO 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 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 *N*-pyrrolidino metonitazene closely resemble those of metonitazene, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

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 way 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 *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)-1H-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 Single Convention on Narcotic Drugs. 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)-1H-benzoimidazole, also referred to as metonitazepyne, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Etonitazepipne

Substance identification

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

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

WHO 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 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 etonitazepipne closely resemble those of etonitazepyne, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

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. In humans, adverse effects include respiratory depression and reduced consciousness, which were reversed by 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. These effects were blocked by the opioid antagonist naltrexone.

Non-fatal intoxications requiring hospitalization have been reported. Multiple deaths in which etonitazepipne use 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)-1H-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 Single Convention on Narcotic Drugs. 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)-1H-benzoimidazole), also referred to as *N*-piperidinyl etonitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

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.

WHO 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 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

N-Desethyl isotonitazene is a major metabolite of and has a similar chemical structure and effects to isotonitazene, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

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 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 or 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-1H-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 Single Convention on Narcotic Drugs.

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-1H-benzimidazole-1-ethanamine), also referred to as norisotonitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

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

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 (6aR,9S,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol (9S epimer) and (6aR,9R,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol (9R epimer).

Hexahydrocannabinol has been described as a colourless viscous oil or resin that changes to dark orange after exposure to oxygen. Hexahydrocannabinol-containing products 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.

WHO review history

Hexahydrocannabinol has not previously been 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 (9R)-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 were 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 have been reported in humans, 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 including emergency departments presentations for non-fatal intoxications, with symptoms such as dizziness, confusion, unconsciousness, psychosis (hallucinations, delusions and paranoia), anxiety, panic attack, depression, hypertension, nausea and vomiting, similar to those seen with delta-9-THC.

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-tetrahydrocannabinol, which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. There is sufficient evidence that hexahydrocannabinol is used in such a way as to constitute a public health and social problem, warranting 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 Convention on Psychotropic Substances of 1971.

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

Carisoprodol

Substance identification

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

WHO review history

Carisoprodol was pre-reviewed at the 32nd ECDD meeting in 2000. At that time, the Committee did not recommend critical review, 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 an international agency provided information that suggested a significant increase in the reported number of trafficking cases and seizures involving carisoprodol. At the 46th ECDD meeting, increasing evidence of nonmedical use and public health harm led the Committee to recommend 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 Convention on Psychotropic Substances of 1971. 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 $GABA_A$ 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 potential dependence on carisoprodol is considered to be similar to that of barbiturates and benzodiazepines. In humans in the context of prolonged use, tolerance, withdrawal symptoms and craving have been documented. Increasing numbers 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 nonmedical use at high doses, carisoprodol produces central nervous system depressant effects, including drowsiness, sedation, confusion and coma.

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

Nonmedical use of carisoprodol is widely documented in multiple countries and regions, including in combination with opioids and/or benzodiazepines. Increased restrictions on carisoprodol prescription or removal of the drug from the market in several countries have led to decreased incidences of poisoning and other types of public health harm. 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 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 therapeutic use in some countries because of concern about increased rates of diversion, nonmedical use, dependence, intoxication and psychomotor impairment.

Recommendation

There is increasing evidence that nonmedical 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 Convention on Psychotropic Substances of 1971.

> Recommendation: The Committee recommended that carisoprodol be added to Schedule IV of the Convention on Psychotropic Substances of 1971.

Substances to be kept under surveillance

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.

WHO 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 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

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

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 these 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 on 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, that its use constitutes a public health and social problem to warrant 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.

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 and white crystalline powder. It has also been found in food products (chocolates).

WHO review history

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

Similarity to known substances and effects on the central nervous system

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 Convention on Psychotropic Substances of 1971. Its effects include hallucinations and dissociation.

Dependence potential

No controlled studies in animals or humans on 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 nonfatal intoxication that involved 3-hydroxyphencyclidine in combination with other psychoactive substances have been reported. In most cases, 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 on Psychotropic Substances. Its mode of action suggests the likelihood of abuse, but there is insufficient evidence that its use constitutes a public health or social problem to warrant 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.