Summary assessment and recommendations of the 43rd ECDD, 12-16 October 2020

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

➢ Isotonitazene

Substance identification

Isotonitazene (Chemical name: N,N-diethyl-2-(2-(4- isopropoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine) belongs to the 2-benzylbenzimidazole group of compounds, which includes the closely related opioids etonitazene, metonitazene, and clonitazene. It is found in yellow, brown, or off-white powder forms.

WHO review history

Isotonitazene has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Isotonitazene is a chemical analogue of etonitazene and clonitazene, both of which are Schedule I compounds under the Single Convention on Narcotic Drugs, 1961. Isotonitazene is a potent opioid analgesic with a rapid onset of action. Preclinical studies have demonstrated that isotonitazene is more potent than fentanyl and hydromorphone, and substantially more potent than morphine. There is limited research on the effects of this compound on the central nervous system, but given its demonstrated potency at the μ-opioid receptor, it would be expected to produce analgesia, respiratory depression and sedation.

Dependence potential

No controlled animal or human studies have assessed the dependence potential of isotonitazene. As a potent μ-opioid agonist, it would be expected to produce dependence. An unverified online report described dependent use and withdrawal symptoms, including flu-like symptoms and anxiety.

Actual abuse and/or evidence of likelihood of abuse

There are no controlled studies of the abuse potential of isotonitazene, but as a potent μ-opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability.

Due to its relatively recent appearance on the illicit drug market, there is limited information on the prevalence of use of isotonitazene or its associated harms. Seizures have been reported in multiple countries and regions. It is noted to be used via a range of routes including sublingually, vaping and intravenously.

The number of deaths involving isotonitazene has increased in a short time span. Deaths commonly occur in combination with other opioids or benzodiazepines. Isotonitazene deaths share common features with heroin deaths, including evidence of injection, and signs consistent with opioid overdose such as pulmonary and/or cerebral oedema. Deaths are likely to be underreported due to its recent and rapid appearance.

Therapeutic usefulness

Isotonitazene is not known to have any therapeutic use.

Recommendation

Isotonitazene (Chemical name: N,N-diethyl-2-(2-(4- isopropoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine) has a mechanism of action such that it is liable to similar abuse and productive of similar ill effects as other opioids which are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects including deaths. It has no known therapeutic use and is likely to cause substantial harm.

- The Committee recommended that isotonitazene (Chemical name: N,N-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

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

- CUMYL-PEGACLONE

Substance identification

CUMYL-PEGACLONE (Chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)- 2,5-dihydro-1H-pyrido[4,3-b]indol-1-one) is a synthetic cannabinoid. It has been found in seized material formulated for smoking and vaping.

WHO review history

CUMYL-PEGACLONE has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

CUMYL-PEGACLONE is a synthetic cannabinoid with a mechanism of action similar to that of other synthetic cannabinoids. It is a potent full agonist at CB_1 receptors.

There are no controlled studies of its effects, but there are online user reports describing euphoria, dissociation, red eyes, dry mouth and appetite stimulation. These effects are consistent with known cannabinoid agonist effects.

Dependence potential

There are no controlled animal or human studies that address the dependence potential of CUMYL-PEGACLONE. However, CUMYL-PEGACLONE has been shown to be a full and potent agonist at the CB_1 receptor and therefore would be expected to produce dependence consistent with other CB_1 receptor agonists.

Actual abuse and/or evidence of likelihood of abuse

There are no controlled animal or human studies that address the abuse potential of CUMYL-PEGACLONE.

A number of countries across several regions have reported that CUMYL-PEGACLONE is being used for its psychoactive properties.

There are reports of adverse effects such as seizures and of fatalities involving CUMYL-PEGACLONE. While other drugs were present, CUMYL-PEGACLONE was deemed to be a causal or contributory factor in a number of these deaths.

Therapeutic usefulness

CUMYL-PEGACLONE is not known to have any therapeutic use.

Recommendation

CUMYL-PEGACLONE (Chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)- 2,5-dihydro-1H-pyrido[4,3-b]indol-1-one), is a synthetic cannabinoid receptor agonist with a mode of action that suggests a likelihood of dependence and abuse, and similar ill-effects to other synthetic cannabinoids. Its use has been associated with severe adverse effects and fatalities. The effects of CUMYL-PEGACLONE are similar to those of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. CUMYL-PEGACLONE has no therapeutic use, and its use constitutes a substantial risk to public health.

Recommendation: The committee recommended that CUMYL-PEGACLONE (Chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)- 2,5-dihydro-1H-pyrido[4,3-b]indol-1-one), be added to Schedule II of the Convention on Psychotropic Substances of 1971.

➢ MDMB-4en-PINACA

Substance identification

MDMB-4en-PINACA (Chemical name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate) is a synthetic cannabinoid. It has been identified in seized material formulated for smoking, and found as white to yellow/brown powder.

WHO review history

MDMB-4en-PINACA has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

MDMB-4en-PINACA is a synthetic cannabinoid that binds to CB_1 cannabinoid receptors as a full and potent agonist. It is structurally similar to 5F-MDMB-PINACA (5F-ADB) which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971.

A report from an unpublished animal study indicates that MDMB-4en-PINACA can produce the characteristic effects of CB_1 cannabinoid agonists such as hypothermia and lethargy.

Reports from online user forums describe cannabis-like euphoria at moderate levels of intake, with dissociation described at higher doses. Both sedation and stimulation have been reported, in addition to memory loss, confusion and agitation.

Dependence potential

No animal or human studies were identified that described the dependence potential of MDMB-4en-PINACA. As a full CB_1 agonist, it would be expected to produce dependence similar to other CB_1 receptor agonists.

Actual abuse and/or evidence of likelihood of abuse

No animal or human studies have been conducted to provide an indication of the likelihood of abuse of MDMB-4en-PINACA, though CB_1 receptor agonists have known abuse potential.

A number of countries across different regions have reported MDMB-4en-PINACA use.

Its use has been associated with cases of impaired driving and death.

Therapeutic usefulness

MDMB-4en-PINACA is not known to have any therapeutic use.

Recommendation

MDMB-4en-PINACA (Chemical name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate) is a potent synthetic cannabinoid receptor agonist with a similar mechanism of action, and similar effects to a number of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Use of MDMB-4en-PINACA has been associated with severe adverse effects, including fatal intoxications, and cases of impaired driving. MDMB-4en-PINACA has no therapeutic use.

- The Committee recommended that MDMB-4en-PINACA (Chemical name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

➢ 3-methoxyphencyclidine (3-MeO-PCP)

Substance identification

3-methoxyphencyclidine (3-MeO-PCP), (Chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) is an arylcyclohexylamine and 3-methoxy derivative of phencyclidine (PCP) which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. It appears as powder and tablets.

WHO review history

3-methoxyphencyclidine has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

3-methoxyphencyclidine is an N-methyl-D-aspartate (NMDA) receptor antagonist with a similar mechanism of action and effects to phencyclidine. These effects include an altered mental state characterized by confusion, disorientation and out of body experiences as well as hallucinations and other psychotic symptoms.

Dependence potential

No human or animal studies have examined the dependence potential of 3-methoxyphencyclidine.

Actual abuse and/or evidence of likelihood of abuse

As an NMDA receptor antagonist, 3-methoxyphencyclidine would be expected to produce similar effects, and have abuse potential similar to that of phencyclidine.

Adverse effects include cardiovascular effects (such as hypertension and tachycardia) and cognitive effects including psychosis, confusion and agitation. There may be a greater risk of psychosis in those with a history of, or vulnerability to psychotic illness. Cases of severe and fatal intoxication are reported from several countries and regions.

Seizures have been reported in a number of countries from several different regions.

Therapeutic usefulness

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

Recommendation

3-methoxyphencyclidine (Chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) is an analogue of, and has similar effects to phencyclidine (PCP), which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances. Its mode of action suggests a likelihood of abuse. There is evidence of use of this substance in a number of countries across different regions. 3-methoxyphencyclidine causes substantial harm, including severe adverse events such as hallucinations, other psychotic symptoms, and fatal intoxications. It has no therapeutic use.

- The Committee recommended that 3-methoxyphencyclidine (Chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

➢ Diphenidine

Substance identification

Diphenidine (Chemical name: 1-(1,2-diphenylethyl)piperidine) is a dissociative and hallucinogenic substance of the 1,2-diarylethylamine class. It appears as powder and tablets.

WHO review history

Diphenidine has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Diphenidine is known to produce hallucinogenic and dissociative effects through its action as an N-methyl-D-aspartate (NMDA) receptor antagonist. This mechanism of action as well as its

effects are similar to those of phencyclidine (PCP) which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

Dependence potential

No animal or human studies have determined the dependence potential for diphenidine.

Actual abuse and/or evidence of likelihood of abuse

As an NMDA receptor antagonist, diphenidine would be expected to have abuse potential similar to that of phencyclidine. In addition, diphenidine causes dopamine release, in a manner similar to, but to a lesser degree, than cocaine. This effect may also contribute to its abuse potential.

Cases of intoxication requiring hospitalization are reported. Adverse effects include cardiovascular effects (such as tachycardia and hypertension) and central nervous system effects including hallucinations, depersonalization, delusions, paranoia, dissociation, confusion, nystagmus and muscle rigidity. These effects have resulted in cases of acute intoxication leading to emergency department admissions. A small number of fatal intoxications involving diphenidine have been documented. All deaths involved multiple drug toxicity, though cardiovascular and hallucinogenic symptoms described in the cases are consistent with the effects of diphenidine.

Seizures have been reported in a number of countries from several different regions.

Therapeutic usefulness

Diphenidine is not known to have any therapeutic use.

Recommendation

The available evidence indicates that diphenidine (Chemical name: 1-(1,2-diphenylethyl)piperidine) has a mechanism of action and effects that are similar to those of phencyclidine (PCP), which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances. Its mode of action suggests a likelihood of abuse. There is evidence of significant harm due to diphenidine, including psychosis and cardiovascular effects, which represents a substantial risk to public health. Diphenidine has no therapeutic use.

The Committee recommended that diphenidine (Chemical name: 1-(1,2-diphenylethyl)piperidine) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

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

➢ Clonazolam

Substance identification

Clonazolam (Chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4H-benzo[f][1,2,4]triazolo[4,3- a][1,4]diazepine) is 1-4 triazolobenzodiazepine similar to clonazepam, triazolam and alprazolam. It is sold in powder, blotter, liquid and tablet form.

WHO review history

Clonazolam has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Clonazolam enhances the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) through binding at the benzodiazepine site of the GABA-A receptor. This mechanism of action, as well as its effects (sedation, muscle relaxation, slurred speech and loss of motor control, amnesia) are similar to those of the benzodiazepines (such as diazepam, triazolam and alprazolam) which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

In cases of clonazolam poisoning, the effects have been reversed with the benzodiazepine antagonist flumazenil, confirming that its action is mediated via the benzodiazepine receptor in the GABA-A receptor complex.

Dependence potential

No controlled animal or human studies have examined the dependence potential of clonazolam, though based on its pharmacological effects, and similarity to other benzodiazepines, it would be expected to have potential to produce dependence.

The development of tolerance to the effects of clonazolam following repeated use and the onset of withdrawal symptoms after cessation of use have been reported on online forums.

Actual abuse and/or evidence of likelihood of abuse

No human or animal studies have examined abuse liability. Online forums describe its recreational use and consistently report its strong anxiolytic effects.

A number of published reports describe the management of cases of intoxication involving clonazolam in emergency departments or intensive care. Clonazolam use has been analytically confirmed in cases of impaired driving, in combination with other substances. Clonazolam has the potential to increase the effects of other drugs, including opioids, and on its own can cause severe central nervous system depression, including somnolence, confusion, sedation and unconsciousness.

There are reports of its identification in multiple countries representing all regions, indicating that its use may be increasing. Clonazolam is increasingly sold as falsified pharmaceutical benzodiazepines.

Therapeutic usefulness

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

Recommendation

Clonazolam (Chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4H-benzo[f][1,2,4]triazolo[4,3- a][1,4]diazepine) is a 1-4 triazolobenzodiazepine that has actions and effects very similar to those of benzodiazepines listed under Schedule IV in the Convention on Psychotropic Substances of 1971. Like other benzodiazepines, clonazolam can produce a state of dependence and central nervous system depression. There have been a number of reports of abuse, impaired driving and non-fatal intoxications. There is sufficient evidence of its abuse so as to constitute a public health problem, and it has no known therapeutic use.

- The Committee recommend that clonazolam (Chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4H-benzo[f][1,2,4]triazolo[4,3- a][1,4]diazepine) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

➢ Diclazepam

Substance identification

Diclazepam (Chemical name: 7-chloro-5-(2-chlorophenyl)-1- methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin2-one) is a 2-chloro derivative of the benzodiazepine diazepam. It appears as a white powder, and is commonly sold as tablets, pellets and liquid.

WHO review history

Diclazepam has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Diclazepam is an agonist at the benzodiazepine site of the GABA-A receptor, acting to increase the effect of the inhibitory neurotransmitter gamma amino butyric acid (GABA). Diclazepam has similar effects to the benzodiazepine diazepam, which is currently controlled under the Convention on Psychotropic Substances of 1971. It is metabolized to the benzodiazepines delorazepam, lorazepam and lormetazepam. These metabolites are active and are also pharmaceuticals that are included in Schedule IV of the Convention on Psychotropic Substances of 1971.

Diclazepam has been demonstrated to cause sedation and muscle relaxation in animals. Central nervous systems depressant effects are also described in humans.

Dependence potential

No controlled animal or human studies have examined the dependence potential of diclazepam.

Online user reports describe cross-tolerance with other benzodiazepines and use to self-manage benzodiazepine withdrawal. This evidence, along with its mechanism of action, suggests that diclazepam has the capacity to produce dependence similar to other benzodiazepines.

Actual abuse and/or evidence of likelihood of abuse

No controlled animal or human studies have examined the abuse liability of diclazepam. However, based on its mechanism of action and effects, it would be expected to have abuse liability similar to other benzodiazepines.

Diclazepam has the potential to increase unintentional opioid overdoses. Its long half-life may increase the risk of accumulation and interactions when combined with other drugs. Fatal intoxications with diclazepam have been reported.

Seizures of diclazepam have been reported from multiple countries across different regions. Diclazepam is increasingly sold as falsified benzodiazepines, commonly as diazepam.

Diclazepam has been implicated in cases of impaired driving, including cases where diclazepam was identified as the main contributor to impairment. It also has been involved in cases of drug-facilitated sexual assault.

Therapeutic usefulness

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

Recommendation

Diclazepam (Chemical name: 7-chloro-5-(2-chlorophenyl)-1- methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin2-one) is a 2-chloro analogue of the benzodiazepine diazepam that has actions and effects very similar to those of benzodiazepines listed under Schedule IV of the Convention on Psychotropic Substances of 1971. It can produce a state of dependence and central nervous system depression, like other benzodiazepines. There have been reports of abuse, impaired driving and fatal and nonfatal intoxications. There is sufficient evidence of its abuse so as to constitute a significant risk to public health, and it has no known therapeutic use.

- Recommendation: The Committee recommended that diclazepam (Chemical name: 7-chloro-5-(2-chlorophenyl)-1- methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin2-one) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

➢ Flubromazolam

Substance identification

Flubromazolam (Chemical name: 8-bromo-6-(2-fluorophenyl)-1- methyl-4H-benzo[f][1,2,4]triazolo[4,3- a][1,4]diazepine) is a 1-4 triazolobenzodiazepine. Flubromazolam is a white powder, often sold as a liquid or as tablets.

WHO Review History

Flubromazolam has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Flubromazolam is a highly potent benzodiazepine with long lasting depressant effects on the central nervous system. Flubromazolam enhances the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) through binding at the benzodiazepine site of the GABA-A receptor. This mechanism of action, as well as its effects, are similar to those of the benzodiazepines triazolam and alprazolam which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

A single pharmacokinetic study showed that a 0.5 mg flubromazolam dose induced strong sedative effects that lasted more than 10 hours, and caused partial amnesia for more than 24 hours. The effects of flubromazolam have been effectively reversed by the benzodiazepine antagonist flumazenil.

Reports from online user forums describe benzodiazepine-like effects including anxiolytic, euphoric and sedative effects.

Dependence potential

No controlled animal or human studies describe the dependence potential of flubromazolam, although multiple reports from online sources describe severe withdrawal symptoms, such as muscle aches, sleeping disorders, severe anxiety and panic attacks, dissociative symptoms, perceptual distortions, cramping, chills, vomiting and risk of seizures. There are also descriptions of loss of control over use, and rapid onset of tolerance. The latter suggests that taking increased doses and developing physical dependence is likely.

Actual abuse and/or evidence of likelihood of abuse

No controlled animal or human studies have assessed the abuse potential of flubromazolam.

Impaired driving with flubromazolam as the sole intoxicant is reported. Non-fatal intoxications requiring hospital admission, and fatal intoxications due to flubromazolam use are documented. In these cases, central nervous system depression and severe sedation were clinical features of presentation. Flubromazolam has the potential to increase unintentional opioid overdoses. Its long half-life may increase the risk of accumulation and interactions when combined with other drugs.

Nonmedical use and seizures of flubromazolam have been documented in multiple countries across different regions. It is increasingly sold as falsified pharmaceutical benzodiazepines.

Therapeutic usefulness

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

Recommendation

Flubromazolam (Chemical name: 8-bromo-6-(2-fluorophenyl)-1- methyl-4H-benzo[f][1,2,4]triazolo[4,3- a][1,4]diazepine) is a 1-4 triazolobenzodiazepine that has actions and effects very similar to those of benzodiazepines listed under Schedule IV in the Convention on Psychotropic Substances of 1971. It can produce a state of dependence and central nervous system depression, like other benzodiazepines. There have been increasing reports of abuse, impaired driving and fatal and non-fatal intoxications. There is sufficient evidence of its abuse to constitute a significant risk to public health, and it has no known therapeutic use.

The Committee recommended that flubromazolam (Chemical name: 8-bromo-6-(2-fluorophenyl)-1- methyl-4H-benzo[f][1,2,4]triazolo[4,3- a][1,4]diazepine) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

To be kept under surveillance:

➢ 2-Methoxydiphenidine (2-MeO-Diphenidine)

Substance identification

2-methoxydiphenidine (Chemical name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine) is also known as 2-MeO-Diphenidine, 2-MXP, and methoxphenidine. It is a dissociative and hallucinogenic substance of the 1,2-diarylethylamine class. It appears as powder and tablets.

WHO review history

2-methoxydiphenidine has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Similar to phencyclidine (PCP), 2-methoxydiphenidine is an N-methyl-D-aspartate (NMDA) receptor antagonist, and produces phencyclidine-like effects. Phencyclidine is controlled under Schedule II of the Convention on Psychotropic Substances of 1971.

Dependence potential

No animal or human studies have examined dependence potential.

Actual abuse and/or evidence of likelihood of abuse

As an NMDA receptor antagonist, 2-methoxydiphenidine would be expected to produce similar effects, and have abuse potential similar to that of phencyclidine.

A small number of case reports, often involving multiple substances, describe adverse effects including acute behavioral effects such as agitation, sedation, depersonalization, hallucinations, delusions, and paranoia and physical effects such as tachycardia, syncope and hyperthermia. Online forums provide reports from individuals describing its use and effects such as euphoria.

While there are reports of 2-methoxydiphenidine use and harms from a number of countries, these have been less frequent over the past two years and it is possible that there is no longer significant use of this substance.

Therapeutic usefulness

2-methoxydiphenidine is not known to have any therapeutic use.

Recommendation

2-methoxydiphenidine (Chemical name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine) has a similar mechanism of action to phencyclidine (PCP). The magnitude of its use has been declining in recent years. There is insufficient evidence of a public health and social problem at this time so as to warrant placing 2-methoxydiphenidine under international control.

- Recommendation: The Committee recommended that 2-methoxydiphenidine (Chemical name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine) be kept under surveillance by the WHO Secretariat.

➢ 5-methoxy-N,N-diallyltryptamine (5-MeO-DALT)

Substance identification

5-methoxy-N,N-diallyltryptamine (Abbreviation: 5-MeO-DALT) (Chemical Name: *N*-allyl-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)prop-2-en-1-amine) is a synthetic hallucinogen. 5-MeO-DALT is a solid, crystalline powder. The color has been described as white, off-white, grey, or light brown/tan. It has also been found as yellow, purple, or green tablets.

WHO review history

5-MeO-DALT has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention suggesting that this substance is clandestinely manufactured, poses a risk to public health, and is of no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

5-MeO-DALT has a chemical structure similar to the hallucinogen 3-[2-(dimethylamino)ethyl]indole (DMT) listed under Schedule I of the Convention on Psychotropic Substances of 1971. 5-MeO-DALT binds to different receptors with no clear mechanism of action, including serotoninergic, adrenergic, histamine, kappa opioid receptors and sigma receptors, as well as the dopamine and serotonin transporters.

Based on its pharmacological profile from animal laboratory studies, the effects of 5-MeO-DALT are consistent with those of hallucinogens such as DOM and LSD. However, some effects of 5-MeO-DALT differ from other hallucinogens.

Dependence potential

No controlled experimental studies have determined the likely dependence potential of 5-MeO-DALT, though there are unvalidated reports on online forums that describe tolerance developing when 5-MeO-DALT was used daily. Based on its similarity to DOM, 5-MeO-DALT would be expected to have little potential to produce dependence.

Actual abuse and/or evidence of likelihood of abuse

Preclinical studies suggest that 5-MeO-DALT has abuse potential as it shares discriminative stimulus effects with DOM. No human studies have been conducted to determine the abuse liability of 5-MeO-DALT.

5-MeO-DALT is sold online, and sale and seizures have been identified in multiple countries from several regions. There have been a small number of reports of adverse effects including agitation and aggression related to possible use of 5-MeO-DALT. However, the presence of this substance was not biologically confirmed in the majority of these cases.

Therapeutic usefulness

5-MeO-DALT is not known to have any therapeutic use.

Recommendation

5-methoxy-N,N-diallyltryptamine or 5-MeO-DALT (Chemical Name: *N*-allyl-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)prop-2-en-1-amine)) is a synthetic hallucinogen with some effects similar to those of other hallucinogens such as DOM, which are controlled in Schedule I of the 1971 Convention on Psychotropic Substances. Its mode of action is unclear and there is very limited information on its effects in humans. While its use may constitute a risk to public health, the current evidence is insufficient to recommend international control.

- Recommendation: The Committee recommended that 5-methoxy-N,N-diallyltryptamine or 5-MeO-DALT, Chemical Name: *N*-allyl-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)prop-2-en-1-amine)) be kept under surveillance by the WHO Secretariat.

➢ 3-fluorophenmetrazine

Substance identification

3-fluorophenmetrazine (Chemical name: 2-(3-fluorophenyl)-3-methylmorpholine) is also known as 3F-phenmetrazine, 3-FPM, 3-FPH, and PAL-593. 3-fluorophenmetrazine is a white, solid, crystalline powder, and has been found in tablets.

WHO review history

3-fluorophenmetrazine has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and is of no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

3-fluorophenmetrazine is a derivative of phenmetrazine, an amphetamine-type substance listed under Schedule II of the Convention on Psychotropic Substances of 1971, with known abuse potential. 3-fluorophenmetrazine is a potent releaser of dopamine and norepinephrine.

In humans, its effects are similar to those of amphetamine and include euphoria, stimulation, increased energy, talkativeness and insomnia. Adverse effects include tachycardia, agitation, delirium and seizures.

Dependence potential

No controlled studies have examined the potential of 3-fluorophenmetrazine to produce dependence in humans or animals. Unverified online reports describe 3-fluorophenmetrazine as habit forming and causing psychological dependence. Based on its similarity to other amphetamine-type substances it would be expected to have the potential to produce dependence.

Actual abuse and/or evidence of likelihood of abuse

Given the structural similarity between 3-fluorophenmetrazine and phenmetrazine (a stimulant with a known abuse liability) and its ability to produce similar biological effects to amphetamine-like substances (i.e. through release of dopamine and norepinephrine), it is expected that 3-fluorophenmetrazine has similar abuse potential as these substances. However, there is no evidence confirming this.

Case reports describe adverse effects including tachycardia, reduced level of consciousness, agitation, anxiety and delirium, and less commonly kidney damage, hypertension and fatal intoxication. However, the role of 3-fluorophenmetrazine in the limited number of serious non-fatal intoxications and fatal intoxications was inconclusive.

Samples purchased online, sold either as 3-fluorophenmetrazine or other substances, have been positively identified as containing 3-fluorophenmetrazine. Seizures are described from six countries across several regions.

Therapeutic usefulness

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

Recommendation

3-fluorophenmetrazine (Chemical name: 2-(3-fluorophenyl)-3-methylmorpholine) has a mode of action and effects that are similar to those of phenmetrazine, an amphetamine-type substance listed under Schedule II of the Convention on Psychotropic Substances of 1971.

While this suggests that it has the potential for dependence and the likelihood of abuse, there is little supportive evidence. In addition, there is a lack of evidence as to the extent of public health and social problems related to the use of 3-fluorophenmetrazine and some uncertainty about the degree of toxicity that it produces.

- The Committee recommended that 3-fluorophenmetrazine (Chemical name: 2-(3-fluorophenyl)-3-methylmorpholine) be kept under surveillance by the WHO Secretariat.