1. Fentanyl Analogues

1.1 Para-fluoro-butyrylfentanyl

Substance identification

Para-fluoro-butyrylfentanyl (N-(4-fluorophenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide) is a synthetic analogue of the opioid analgesic fentanyl. Samples obtained from seizures and from other collections suggest that para-fluoro-butyrylfentanyl appears in powder, tablet, nasal spray and vaping form.

WHO review history

Para-fluoro-butyrylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO Expert Committee on Drug Dependence (ECDD). A direct critical review was proposed based on information brought to WHO’s attention that para-fluoro-butyrylfentanyl poses serious risk to public health and has no recognised therapeutic use.

Similarity to known substances and effects on the central nervous system

Para-fluoro-butyrylfentanyl binds to μ-opioid receptors with high selectivity over κ- and δ-opioid receptors and has been shown to act as a partial agonist at the μ-opioid receptor. In animals, it produces typical opioid effects including analgesia, with a potency between that of morphine and fentanyl. In cases of non-fatal intoxication in humans, para-fluoro-butyrylfentanyl has produced signs and symptoms such as disorientation, slurred speech, unsteady gait, hypotension and pupil constriction that are consistent with an opioid mechanism of action.

Para-fluoro-butyrylfentanyl can be readily converted to its isomer p-fluoro-isobutyrylfentanyl (N-(4-fluorophenyl)-2-methyl-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide), which is an opioid listed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

Dependence potential

There are no studies of the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, para-fluoro-butyrylfentanyl would be expected to produce dependence similar to other opioid drugs.

Actual abuse and/ or evidence of likelihood of abuse

There are no controlled studies of the abuse potential of para-fluoro-butyrylfentanyl and there is very little information on the extent of abuse. The substance has been detected in biological samples.
obtained from cases of fatal and non-fatal intoxication. Fatalities have been reported in some countries where the compound has been identified in biological fluids in combination with other drugs, including cases where death has been attributed to the effects of para-fluoro-butrylfentanyl.

**Therapeutic usefulness**

Para-fluoro-butrylfentanyl is not known to have any therapeutic uses.

**Recommendation**

Para-fluoro-butrylfentanyl is an opioid receptor agonist that has significant potential for dependence and likelihood of abuse. The limited available evidence indicates that it has typical opioid adverse effects that include the potential for death due to respiratory depression. Para-fluoro-butrylfentanyl has caused substantial harm and has no therapeutic usefulness. As it is liable to similar abuse and produces similar ill-effects as many other opioids placed in Schedule I of the 1961 Single Convention on Narcotic Drugs:

- **Recommendation 1.1**: The Committee recommended that Para-fluoro-butryl fentanyl (N-(4-fluorophenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

**1.2 Para-methoxy-butyryl fentanyl**

**Substance identification**

Para-methoxy-butrylfentanyl (N-(4-methoxyphenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide) is a synthetic analogue of the opioid analgesic fentanyl. Samples obtained from seizures and from other collections suggest that para-methoxy-butrylfentanyl occurs in powder, tablet, and nasal spray forms.

**WHO review history**

Para-methoxy-butrylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO’s attention that para-methoxy-butrylfentanyl poses serious risk to public health and has no recognised therapeutic use.

**Similarity to known substances and effects on the central nervous system**

Para-methoxy-butrylfentanyl binds to µ-opioid receptors with high selectivity over κ- and δ-opioid receptors and has been shown to act as a partial agonist at the µ-opioid receptor. In animals, it produces typical opioid effects, including analgesia, and in some tests it has a potency higher than

morphine and close to that of fentanyl.

Reported clinical features of intoxication in which para-methoxy-butyrylfentanyl is involved included the typical opioid effects of reduced level of consciousness, respiratory depression and pupil constriction. In some cases, treatment with the opioid antagonist naloxone was shown to reverse the drug-induced respiratory depression. While this is consistent with an opioid mechanism of action, it should be noted that in all such cases at least one other opioid was present.

**Dependence potential**

There are no studies of the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, Para-methoxy-butyrylfentanyl would be expected to produce dependence similar to other opioid drugs.

**Abuse potential or evidence of likelihood of abuse**

There are no controlled studies of the abuse potential of Para-methoxy-butyrylfentanyl and very little information on the extent of abuse. Para-methoxy-butyrylfentanyl has been detected in biological samples obtained from a limited number of acute intoxication cases. Reported clinical features are consistent with opioid effects and including respiratory depression. However, in all of the documented cases of severe adverse events associated with use of para-methoxy-butyrylfentanyl, other fentanyl derivatives were detected and hence the role of para-methoxy-butyrylfentanyl is not clear.

**Therapeutic applications / usefulness**

Para-methoxy-butyrylfentanyl is not known to have any therapeutic uses.

**Recommendation**

The limited available information indicates that para-methoxy-butyrylfentanyl is an opioid drug, and an analogue of the opioid analgesic fentanyl. There is evidence of its use in a limited number of countries with few reports of intoxication and no reports of deaths. In the intoxication cases, the role of para-methoxy-butyrylfentanyl was not clear due to the presence of other opioids. It has no therapeutic usefulness. At this time, there is little evidence of the impact of para-methoxy-butyrylfentanyl in causing substantial harm that would warrant its placement under international control.

- **Recommendation 1.2:** The Committee recommended that para-methoxy-butyrylfentanyl (N-(4-methoxyphenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide) be kept under surveillance by the WHO Secretariat.
1.3 Ortho-fluorofentanyl

Substance identification

Ortho-fluorofentanyl (N-(2-fluorophenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide) is a synthetic analogue of the opioid analgesic fentanyl. It has two positional isomers (para-fluorofentanyl and meta-fluorofentanyl).

WHO review history

Ortho-fluorofentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A direct critical review was proposed based on information brought to WHO’s attention that ortho-fluorofentanyl poses a serious risk to public health and has no recognised therapeutic use.

Similarity to known substances and effects on the central nervous system

Receptor binding data show that ortho-fluorofentanyl binds to μ-opioid receptors with high selectivity over κ- and δ-opioid receptors. There were no preclinical or clinical studies available in the scientific literature. However, the clinical features present in non-fatal intoxication cases include characteristic opioid effects such as loss of consciousness, pupil constriction and respiratory depression. The effects of ortho-fluorofentanyl are responsive to the administration of the opioid antagonist naloxone, further confirming its opioid agonist mechanism of action.

Dependence potential

There are no studies of the dependence potential of ortho-fluorofentanyl in humans or laboratory animals. However, based on its mechanism of action, it would be expected to produce dependence similar to other opioid drugs.

Actual abuse and or evidence of likelihood of abuse

There are no available preclinical or clinical studies to assess the abuse liability of ortho-fluorofentanyl. There is evidence of use from several countries, including seizures in Europe and the United States. A number of confirmed fatalities associated with the compound have been reported. Ortho-fluorofentanyl is being sold as heroin or an adulterant in heroin. A number of fatalities have been associated with this substance (1 in Europe and 16 in the United States since 2016). As a consequence of ortho-fluorofentanyl cross-reacting with standard fentanyl immunoassays, it is possible that deaths due to ortho-fluorofentanyl have been attributed to fentanyl and hence the number of recorded ortho-fluorofentanyl deaths may be an underestimate. Several countries in different parts of the world have controlled ortho-fluorofentanyl.

Therapeutic usefulness

Ortho-fluorofentanyl is not known to have any therapeutic uses.

Recommendation

Ortho-fluorofentanyl is an opioid receptor agonist that has potential for dependence and likelihood of abuse. The limited available evidence indicates that it has typical opioid adverse effects that include the potential for death due to respiratory depression. Ortho-fluorofentanyl has caused substantial harm and has no therapeutic usefulness. As it is liable to similar abuse and produces similar ill-effects as many other opioids placed in Schedule I of the 1961 Single Convention on Narcotic Drugs:

- **Recommendation 1.3:** The Committee recommended that ortho-fluorofentanyl (N-(2-fluorophenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

1.4 Methoxyacetylfentanyl

Substance identification

Methoxyacetylfentanyl (2-methoxy-N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] acetamide) is a synthetic analogue of the opioid fentanyl. Samples obtained from seizures and from other collections suggest that methoxyacetylfentanyl has appeared in powders, liquids, and tablets.

WHO review history

Methoxyacetylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO’s attention that methoxyacetylfentanyl poses serious risk to public health and has no recognised therapeutic use.

Similarity to known substances and effects on the central nervous system

Methoxyacetylfentanyl binds to μ-opioid receptors with high selectivity over κ- and δ-opioid receptors and has been shown to act as an agonist at the μ-opioid receptor. In animals, it produces analgesia with a potency higher than morphine and close to that of fentanyl. The analgesia was blocked by the opioid antagonist naltrexone, confirming its opioid mechanism of action.

In people using methoxyacetylfentanyl the most serious acute health risk is respiratory depression, which in overdose can lead to respiratory arrest and death. This is consistent with its opioid mechanism of action.

Dependence potential

There are no studies of the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, methoxyacetylfentanyl would be expected to produce dependence similar to other opioid drugs.

Actual abuse and/or evidence of likelihood of abuse

In the animal drug discrimination model of subjective drug effects, methoxyacetylfentanyl produced effects similar to those of morphine. It also decreased activity levels and both the discriminative and rate-decreasing effects were blocked by the opioid antagonist naltrexone. Based on its receptor action and these effects in animal models, it would be expected that methoxyacetylfentanyl would be subject to abuse in a manner comparable to other opioids.

There is evidence that methoxyacetylfentanyl has been used by injection and by nasal insufflation of powder. A large number of seizures of this substance have been reported in Europe and the United States. A number of deaths have been reported in Europe and the United States in which methoxyacetylfentanyl was detected in post-mortem samples. While other drugs were present in most of these cases, methoxyacetylfentanyl was deemed the cause of death or a major contributor to death in a significant proportion of these. Several countries have controlled methoxyacetylfentanyl in their national legislation.

Therapeutic usefulness

Methoxyacetylfentanyl is not known to have any therapeutic uses. The committee considered that methoxyacetylfentanyl is a substance with high abuse liability and dependence potential. It is an opioid agonist that is more potent than morphine and its use has contributed to a large number of deaths in different regions. It has no therapeutic usefulness and it poses a significant risk to public health. The Committee considered that the evidence of its abuse warrants placement under international control.

- **Recommendation 1.4:** The Committee recommended that methoxyacetylfentanyl (2-methoxy-N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] acetamide) be added to Schedule I of the Single Convention on Narcotic Drugs of 1961.

1.5 Cyclopropylfentanyl

Substance Identification

Cyclopropylfentanyl ((N-phenyl-N-1-(2-phenylethyl)-4-piperidyl) cyclopropanecarboxamide) is a synthetic analogue of the opioid fentanyl. Samples obtained from seizures and from other collections suggest that cyclopropylfentanyl has appeared in powders, liquids, and tablets.

WHO review history

Cyclopropylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO’s attention that cyclopropylfentanyl poses a serious risk to public health and has no recognised therapeutic use.

Similarity to known substances and effects on the central nervous system

Cyclopropylfentanyl binds selectively to the µ opioid receptors compared to δ and κ opioid receptors. There is no further information on the actions and effects of cyclopropylfentanyl from controlled studies. Based on its role in numerous deaths, as described below, it is reasonable to consider that cyclopropylfentanyl acts as a µ opioid receptor agonist similar to morphine and fentanyl.

Dependence potential

There are no preclinical or clinical studies published in the scientific literature concerning dependence on cyclopropylfentanyl. However, based on its mechanism of action, cyclopropylfentanyl would be expected to produce dependence similar to other opioid drugs.

Actual abuse and/ or evidence of likelihood of abuse

A large number of seizures of cyclopropylfentanyl have been reported from countries in different regions. In some countries, this substance has been among the most common fentanyl analogues detected in post-mortem samples. In almost all of these deaths, cyclopropylfentanyl was determined to either have caused or contributed to death, even in presence of other substances.

Therapeutic Usefulness

Cyclopropylfentanyl is not known to have any therapeutic uses.

Recommendation

The available evidence indicates that cyclopropylfentanyl has opioid actions and effects. It has been extensively trafficked and has been used by several different routes of administration. Its use has been associated with a large number of documented deaths, and for most of these it has been the principal cause of death. Cyclopropylfentanyl has no known therapeutic use and has been associated with substantial harm.

- **Recommendation 1.5:** The Committee recommended that cyclopropylfentanyl (N-Phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2. Synthetic cannabinoids

2.1 ADB-FUBINACA

**Substance identification**

ADB-FUBINACA (N-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide) is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

**WHO Review History**

ADB-FUBINACA has not been previously pre-reviewed or critically reviewed by the WHO Expert Committee on Drug Dependence (ECDD). A critical review was proposed based on information brought to WHO’s attention that ADB-FUBINACA poses serious risk to public health and has no recognised therapeutic use.

**Similarity to known substances / Effects on the central nervous system**

ADB-FUBINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB₁ and CB₂ cannabinoid receptors with full agonist activity as demonstrated by *in vitro* studies. The efficacy and potency of ADB-FUBINACA is substantially greater when compared to Δ⁹-THC. Reported clinical features of intoxication include confusion, agitation, somnolence, hypertension and tachycardia, similar to other synthetic cannabinoid receptor agonists.

**Dependence potential**

No controlled experimental studies examining the dependence potential of ADB-FUBINACA in humans or animals were available. However, based on its central nervous system action as a full CB₁ agonist, ADB-FUBINACA would be expected to produce dependence in a manner similar to or more pronounced than cannabis.
Actual abuse and/ or evidence of likelihood of abuse

ADB–FUBINACA is sold and used as a substitute for cannabis. It is invariably smoked or vaped (i.e. using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained within such products. Evidence from case reports in which ADB–FUBINACA has been detected in biological samples has demonstrated that use of this substance has contributed to severe adverse reactions in humans including death. However, it was also noted that other substances, including other synthetic cannabinoids, were also present in the urine or blood following non-fatal and fatal intoxications and/or in the product used. Evidence of use has been reported in Europe, the United States and Asia. In recognition of its abuse and associated harm, ADB–FUBINACA has been placed under national control in a number of countries in several different regions.

Therapeutic applications / usefulness

There are currently no approved medical or veterinary uses of ADB–FUBINACA.

Recommendation

ADB–FUBINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the potential for dependence and likelihood of abuse. Its use has been associated with a range of severe adverse effects including death. These effects are similar to those produced by other synthetic cannabinoids which have a mechanism of action the same as that of ADB–FUBINACA and which are placed in Schedule II of the Convention on Psychotropic Substances of 1971. ADB–FUBINACA has no therapeutic usefulness.

**Recommendation 2.1:** The Committee recommended that ADB–FUBINACA (N-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.2 FUB-AMB

Substance identification

FUB-AMB (chemical name: methyl (2S)-2-[(1-[(4-fluorophenyl)methyl]-1H-indazole-3-carbonyl]amino)-3-methylbutanoate) is a synthetic cannabinoid that is also referred to as MMB-FUBINACA and AMB-FUBINACA. FUB-AMB is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded

products with a variety of different names.

**WHO Review History**

FUB-AMB has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO’s attention that FUB-AMB poses serious risk to public health and has no recognised therapeutic use.

**Similarity to known substances / Effects on the central nervous system**

FUB-AMB is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB₁ and CB₂ cannabinoid receptors with full agonist activity as demonstrated by *in vitro* studies. The efficacy and potency of FUB-AMB is substantially greater than Δ⁹-THC and it shares effects with other synthetic cannabinoids including severe central nervous system depression, resulting in slowed behaviour and speech.

**Dependence Potential**

No controlled experimental studies examining the dependence potential of FUB-AMB in humans or animals were available. However, based on its central nervous system action as a full CB₁ agonist, FUB-AMB would be expected to produce dependence in a manner similar to or more pronounced than cannabis.

**Actual abuse and/ or evidence of likelihood of abuse**

Consistent with its CB₁ cannabinoid receptor agonist activity, FUB-AMB produces complete dose-dependent substitution for the discriminative stimulus effects of Δ⁹-THC in mice by various routes of administration. This suggests that it has abuse potential at least as great as that of Δ⁹-THC.

Evidence of the use of FUB-AMB has been reported in Europe, the United States and New Zealand. It is usually smoked or vaped (i.e. using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained within such products.

FUB-AMB use was confirmed in case reports of a mass intoxication in the United States with the predominant symptom being severe central nervous system depression, resulting in slowed behaviour and speech. It was reported that in New Zealand there were at least 20 deaths related to the use of FUB-AMB. It was noted that the amounts of FUB-AMB in confiscated products were 2 to 25 times greater than those reported in the incidents in the United States.

Therapeutic usefulness

There are currently no approved medical or veterinary uses of FUB-AMB

Recommendation

FUB-AMB is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the potential for dependence and likelihood of abuse. Its use has been associated with a range of severe adverse effects including a number of deaths. Its mechanism of action and manner of use are similar to other synthetic cannabinoids placed in Schedule II of the Convention on Psychotropic Substances of 1971. FUB-AMB has no therapeutic usefulness.

- Recommendation 2.2: The Committee recommended that FUB-AMB (chemical name: methyl (2S)-2-((1-[(4-fluorophenyl)methyl]-1H-indazole-3-carbonyl)amino)-3-methylbutanoate) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.3 ADB-CHMINACA

Substance identification

ADB-CHMINACA (N-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexymethyl)indazole-3-carboxamide) is a synthetic cannabinoid that is also referred to as MAB-CHMINACA. ADB-CHMINACA is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

WHO Review History

ADB-CHMINACA has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO’s attention that ADB-CHMINACA poses a serious risk to public health and has no recognised therapeutic use.

Similarity to known substances / Effects on the central nervous system

ADB-CHMINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB1 and CB2 cannabinoid receptors with full agonist activity as demonstrated by in vitro studies. The efficacy and potency of ADB-CHMINACA is substantially greater than Δ9-THC and it is among the most...
potent synthetic cannabinoids studied to date. It shares a profile of central nervous system mediated effects with other synthetic cannabinoids. ADB-CHMINACA demonstrates decreased locomotor activity in mice in a time and dose dependent fashion with a rapid onset of action and long-lasting effects.

Signs and symptoms of intoxication arising from use of ADB-CHMINACA have included tachycardia, unresponsiveness, agitation, combativeness, seizures, hyperemesis, slurred speech, delirium and sudden death. These are consistent with the effects of other synthetic cannabinoids.

**Dependence Potential**

No controlled experimental studies examining the dependence potential of ADB-CHMINACA in humans or animals were available. However, based on its central nervous system action as a full CB1 agonist, ADB-CHMINACA would be expected to produce dependence in a manner similar to or more pronounced than cannabis.

**Actual Abuse and or evidence of likelihood of abuse**

Consistent with its CB1 cannabinoid receptor agonist activity, ADB-CHMINACA fully substituted for Δ⁹-THC in drug discrimination tests. This suggests that it has abuse potential at least as great as that of Δ⁹-THC.

Evidence of the use of ADB-CHMINACA has been reported in Europe, the United States and Japan, including cases of driving under the influence. It is invariably smoked or vaped (i.e. using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained within such products.

ADB-CHMINACA use was analytically confirmed in case reports of several drug-induced clusters of severe illness and death in the United States. In Europe, 13 deaths with analytically confirmed use of ADB-CHMINACA were reported between 2014 and 2016, and another death occurred in Japan.

**Therapeutic usefulness**

There are currently no approved medical or veterinary uses of ADB-CHMINACA

**Recommendation**

ADB-CHMINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material
sprayed with the substance or inhaling vapour after heating. It has effects that are similar to other synthetic cannabinoid receptor agonists placed in Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the potential for dependence and likelihood of abuse. Its use has resulted in numerous cases of severe intoxication and death. There is evidence that ADB-CHMINACA has been associated with fatal and non-fatal intoxications in a number of countries. The substance causes substantial harm and has no therapeutic usefulness.

- **Recommendation 2.3:** The Committee recommended that ADB-CHMINACA (chemical name: N-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

### 2.4 CUMYL-4CN-BINACA

#### Substance identification

CUMYL-4CN-BINACA (chemical name: 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide) is a synthetic cannabinoid. It is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

#### WHO Review History

CUMYL-4CN-BINACA has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO’s attention that CUMYL-4CN-BINACA poses serious risk to public health and has no recognised therapeutic use.

#### Similarity to known substances / Effects on the central nervous system

CUMYL-4CN-BINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB₁ and CB₂ cannabinoid receptors with full agonist activity as demonstrated by *in vitro* studies. The efficacy and potency of CUMYL-4CN-BINACA is substantially greater than Δ⁹-THC and it shares a profile of central nervous system mediated effects with other synthetic cannabinoids. Data have shown that it produced hypothermia in mice in common with other CB₁ cannabinoid receptor agonists.

#### Dependence potential

No controlled experimental studies examining the dependence potential of CUMYL-4CN-BINACA in humans or animals were available. However, based on its central nervous system action as a full
CB₁ agonist, CUMYL-4CN-BINACA would be expected to produce dependence in a manner similar to or more pronounced than cannabis.

**Actual abuse or Evidence of likelihood of abuse**

Consistent with its CB₁ cannabinoid receptor agonist activity, CUMYL-4CN-BINACA fully substituted for Δ⁹-THC in drug discrimination tests. This suggests that it has abuse potential at least as great as that of Δ⁹-THC.

Evidence of the use of CUMYL-4CN-BINACA has been currently reported only from Europe but this may be due to under-reporting including through lack of detection in other countries. In Europe, CUMYL-4CN-BINACA has been among the most frequently seized synthetic cannabinoids. It is invariably smoked or vaped (i.e. using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained within such products.

A number of non-fatal intoxications involving CUMYL-4CN-BINACA have been reported. CUMYL-4CN-BINACA has been analytically confirmed as being present in 11 fatalities and 5 non-fatal intoxications in Europe. In 2 deaths, CUMYL-4CN-BINACA was the only drug present.

**Therapeutic applications / usefulness**

There are currently no approved medical or veterinary uses of CUMYL-4CN-BINACA.

**Recommendation**

CUMYL-4CN-BINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating and is sold under a variety of brand names. It has effects that are similar to other synthetic cannabinoid receptor agonists placed in Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the potential for dependence and likelihood of abuse. There is evidence that CUMYL-4CN-BINACA has been associated with fatal and non-fatal intoxications in a number of countries. The substance causes substantial harm and has no therapeutic usefulness.

- **Recommendation 2.4:** The Committee recommended that CUMYL-4CN-BINACA (chemical name: 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

3. Cathinone

3.1 N-ethylnorpentylone

Substance identification

N-Ethylnorpentylone (chemical name: 1-(2H-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) is a ring-substituted synthetic cathinone analogue that originally emerged in the 1960s during pharmaceutical drug development efforts. It is also known as ephylone and incorrectly referred to as N-ethylpentylone. In its pure form, N-Ethylnorpentylone exists as a racemic mixture in form of a powder or crystalline solid. However, the substance is usually available as a capsule, powered tablet, pill and powder often sold as “Ecstasy” or MDMA. N-Ethylnorpentylone is also available in its own right and is advertised for sale by Internet retailers.

WHO Review History

N-Ethylnorpentylone has not been previously pre-reviewed or critically reviewed by the WHO Expert Committee on Drug Dependence (ECDD). A critical review was proposed based on information brought to WHO’s attention that N-Ethylnorpentylone poses serious risk to public health and has no recognised therapeutic use.

Similarity to known substances / Effects on the central nervous system

The information currently available suggests that N-Ethylnorpentylone is a psychomotor stimulant. N-Ethylnorpentylone users exhibit psychomotor stimulant effects including agitation, paranoia, tachycardia and sweating which are consistent with other substituted cathinone and central nervous system stimulant drugs. Not all reported adverse effects could be causally linked to N-Ethylnorpentylone alone, but there are indications that the observed effects are consistent with those seen with other psychomotor stimulants, with some instances involving cardiac arrest.

Its molecular mechanism of action is similar to the synthetic cathinones MDPV and α-PVP which are both listed in Schedule II of the Convention on Psychotropic Substances of 1971. In vitro investigations showed that N-Ethylnorpentylone inhibited the reuptake of dopamine, noradrenaline and, to a lesser extent, serotonin, which is consistent with closely related other substituted cathinones with known abuse liability and with cocaine.

There is no specific information available to indicate that N-Ethylnorpentylone may be converted into a substance currently controlled under the UN Conventions.

Dependence potential

No controlled experimental studies examining the dependence potential of N-Ethylnopentylone in humans or animals were available. However, based on its action in the central nervous system, it would be expected that N-Ethylnopentylone would have the capacity to produce a state of dependence similar to that of other stimulants such as the ones listed in Schedule II of the Convention on Psychotropic Drugs of 1971.

Actual abuse and/or evidence of likelihood of abuse

In rodent drug discrimination studies, N-Ethylnopentylone fully substituted for methamphetamine and cocaine, and it was also shown to increase activity levels, suggesting it has potential for abuse similar to other psychomotor stimulants.

N-Ethylnopentylone has been detected in biological fluids collected from a number of cases involving adverse effects including deaths. It is frequently used in combination with other drugs. Users may be unaware of the additional risks of harm associated with the consumption of N-Ethylnopentylone either alone or in combination with other drugs. Users may also be unaware of the exact dose or compound being ingested.

A number of countries in various regions have reported use or detection of this compound in either seized materials or biological samples of individuals, including in cases of driving under the influence of drugs. Increased seizures of N-Ethylnopentylone were reported by the United States over the last 2 years. N-Ethylnopentylone has been detected in biological fluids collected from fatal and non-fatal cases of intoxication with a total of 125 toxicological reports associated with N-Ethynorpentylone between 2016 and 2018 having been documented.

The current available data therefore suggest that N-Ethynorpentylone is liable to abuse.

Therapeutic usefulness

N-Ethynorpentylone is not known to have any therapeutic uses.

Recommendation

N-Ethynorpentylone is a synthetic cathinone with effects that are similar to other synthetic cathinones listed as Schedule II substances in the Convention on Psychotropic Substances of 1971. Its mode of action and effects are consistent with those of other central nervous system stimulants such as cocaine, indicating that it has significant potential for dependence and likelihood of abuse. There is evidence of use of N-Ethynorpentylone in a number of countries in various regions and this use has resulted in fatal and non-fatal intoxications. The substance causes substantial harm and has no
therapeutic usefulness. Accordingly:

- **Recommendation 3.1:** The Committee recommended that N-Ethynorpentylone (chemical name: 1-(2H-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) be added to Schedule II of the 1971 Convention on Psychotropic Substances.

### 4. Medicines

#### 4.1 Pregabalin

**Substance identification**

Chemically, pregabalin is (3S)-3-(aminomethyl)-5-methylhexanoic acid

**WHO Review History**

Pregabalin was previewed by the 39th ECDD in November 2017.

**Similarity to known substances / Effects on the central nervous system**

Pregabalin is an inhibitor of alpha-2-delta subunit containing voltage-gated calcium channels (VGCCs). Through this mechanism it decreases the release of neurotransmitters such as glutamate, noradrenaline and substance P. It has been suggested that pregabalin exerts its therapeutic effects by reducing the neuronal activation of hyper-excited neurons while leaving normal activation unaffected. The mechanism(s) by which pregabalin produces euphoric effects or induces physical dependence is unknown.

Despite being a chemical analogue of the neurotransmitter gamma aminobutyric acid (GABA), pregabalin does not influence GABA activity via either GABA receptors or benzodiazepine receptors. However, pregabalin has been found to produce effects that are similar to those produced by controlled substances, such as benzodiazepines, that increase GABA activity.

**Dependence Potential**

Tolerance has been shown to develop to the effects of pregabalin, particularly the euphoric effects. A number of published reports have described physical dependence associated with pregabalin use in humans. The withdrawal symptoms that occur following abrupt discontinuation of pregabalin include insomnia, nausea, headache, anxiety, sweating, and diarrhoea. Current evidence suggests that the incidence and severity of withdrawal symptoms may be dose-related and hence those taking doses
above the normal therapeutic range are most at risk of withdrawal. At therapeutic doses, withdrawal may be minimized by gradual dose tapering.

**Actual abuse and or evidence of likelihood to produce abuse**

While some preclinical research using self-administration and conditioned place preference models has shown reinforcing effects of pregabalin, taken as a whole, the results from such research are contradictory and inconclusive.

In clinical trials, patients have reported euphoria, although tolerance develops rapidly to this effect. Human laboratory research is very limited and only a relatively low dose of pregabalin has been tested in a general population sample; the results indicated low abuse liability. However, a higher dose of pregabalin administered to users of alcohol or sedative/hypnotic drugs was rated similar to diazepam, indicative of abuse liability.

Pregabalin is more likely to be abused by individuals who are using other psychoactive drugs (especially opioids) with significant potential of adverse effects among these subpopulations. The adverse effects of pregabalin include dizziness, blurred vision, impaired coordination, impaired attention, somnolence, confusion and impaired thinking. Other reported harms associated with non-medical use of pregabalin include suicidal ideation and impaired driving. Users of pregabalin in a number of countries have sought treatment for dependence on the drug. Whilst pregabalin has been cited as the main cause of death in over 30 documented overdose fatalities, there are very few cases of fatal intoxications resulting from pregabalin use alone and the vast majority of instances involve other central nervous system depressants such as opioids and benzodiazepines.

There is only limited information regarding the scope and magnitude of the illicit trade in pregabalin, but there is evidence of illicit marketing through online pharmacies.

Pregabalin is under national control in many countries across different regions of the world.

**Therapeutic applications / usefulness**

Pregabalin is used for the treatment of neuropathic pain, including painful diabetic peripheral neuropathy and postherpetic neuralgia, fibromyalgia, anxiety and the adjunctive treatment of partial seizures. The exact indications for which pregabalin has received approval vary across countries. Pregabalin has also been used for conditions such as substance use disorders, alcohol withdrawal syndrome, restless legs syndrome and migraine.

**Recommendation**
The Committee noted that there has been increasing concern in many countries regarding the abuse of pregabalin. A number of cases of dependence have been reported and there are increasing reports of adverse effects. While these problems are concentrated in certain drug using populations, there is presently limited data on the extent of the problems related to pregabalin abuse in the general population. The Committee also noted that pregabalin has approved therapeutic uses for a range of medical conditions, including some for which there are few therapeutic options. Given the limitations in the available information regarding the abuse of pregabalin:

- **Recommendation 4.1:** The Committee recommended that pregabalin (chemical name: (3S)-3-(aminomethyl)-5-methylhexanoic acid) should not be scheduled but be kept under surveillance by the WHO Secretariat.

### 4.2 Tramadol

#### Substance identification

Tramadol (chemical name: (1R*,2R*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol) is a white, bitter, crystalline and odourless powder soluble in water and ethanol. Tramadol is marketed as the hydrochloride salt and is available in a variety of pharmaceutical formulations for oral (tablets, capsules), sublingual (drops), intranasal, rectal (suppositories), intravenous, subcutaneous, and intramuscular administration. It is also available in combination with acetaminophen (paracetamol). Preparations of tramadol are available as immediate- and extended-release formulations.

#### WHO Review History

Tramadol has been considered for critical review by the ECDD five times: in 1992, 2000, 2002, 2006 and 2014. Tramadol was pre-reviewed at the 39th ECDD meeting in November 2017 and it was recommended that tramadol be subject to a critical review at a subsequent ECDD meeting. The Committee requested the WHO Secretariat to collect additional data for the critical review, including information on the extent of problems associated with tramadol misuse in countries. Also, the Committee asked for information on the medical use of tramadol including the extent to which low income countries, and aid and relief agencies, use and possibly rely on tramadol for provision of analgesia. In response to these requests, the WHO Secretariat collected data from Member States and relief agencies on the extent of medical use of tramadol, its misuse and on the level of control implemented in countries.

#### Similarity to known substances / Effects on the central nervous system
Tramadol is a weak opioid analgesic that produces opioid-like effects primarily due to its metabolite, O-desmethyltramadol (M1). The analgesic effect of tramadol is also believed to involve its actions on noradrenergic and serotonergic receptor systems. The adverse effects of tramadol are consistent with its dual opioid and non-opioid mechanisms of action and they include dizziness, nausea, constipation and headache. In overdose, symptoms such as lethargy, nausea, agitation, hostility, aggression, tachycardia, hypertension and other cardiac complications, renal complications, seizures, respiratory depression and coma have been reported. Serotonin syndrome (a group of symptoms associated with high concentrations of the neurotransmitter serotonin that include elevated body temperature, agitation, confusion, enhanced reflexes, and tremor and might result in seizures and respiratory arrest) is a potential complication of the use of tramadol in combination with other serotonergic drugs. Tramadol has been detected in a number of deaths. It is often present along with other drugs, including opioids, benzodiazepines and antidepressants, but fatalities have also been reported due to tramadol alone.

**Dependence potential**

Evidence suggests that the development of physical dependence to tramadol is dose-related, and administration of supra-therapeutic doses leads to a similar dependence profile to morphine and other opioids such as oxycodone and methadone. There are reports of considerable number of people with tramadol dependence seeking help. Withdrawal symptoms include those typical of opioids such as pain, sweating, diarrhoea and insomnia as well as symptoms not normally seen with opioids and related to noradrenergic and serotonergic activity, such as hallucinations, paranoia, confusion and sensory abnormalities. Low dose tramadol use over extended periods is associated with a lower risk of dependence.

**Actual abuse and/or evidence of likelihood of abuse**

Consistent with its opioid mechanism of action, human brain imaging has shown that tramadol activates brain reward pathways associated with abuse. While reports from people administered tramadol in controlled settings have shown that it is identified as opioid-like and tramadol has reinforcing effects in experienced opioid users, these effects may be weaker than those produced by opioids such as morphine and may be partially offset by unpleasant effects of tramadol such as sweating, tremor, agitation, anxiety and insomnia.

Abuse, dependence and overdose from tramadol have emerged as serious public health concerns in countries across several regions. Epidemiological studies in the past have reported a lower tendency for tramadol misuse when compared to other opioids, but more recent information indicates a growing
number of people abusing tramadol, particularly in a number of Middle Eastern and African countries. The sources of tramadol include diverted medicines as well as falsified medicines containing high doses of tramadol. Seizures of illicitly trafficked tramadol, particularly in African countries, have risen dramatically in recent years.

The oral route of administration has been the predominant mode of tramadol abuse as it results in a greater opioid effect compared to other routes. It is unlikely that tramadol will be injected to any significant extent. Abuse of tramadol is likely to be influenced by genetic factors such that some people will experience a much stronger opioid effect following tramadol administration compared to others. The genotype associated with a stronger opioid effect following tramadol administration occurs at different rates in populations across different parts of the world.

Many countries have placed tramadol under national control.

**Therapeutic applications / usefulness**

Tramadol is used to treat both acute and chronic pain of moderate to severe intensity. The conditions for which tramadol has been used include osteoarthritis, neuropathic pain, chronic low back pain, cancer pain and postoperative pain. It has also been used for treatment of restless leg syndrome and opioid withdrawal management. As is the case with abuse potential, the analgesic efficacy and the nature of adverse effects experienced are strongly influenced by genetic factors. Systematic reviews have reported that the ability of tramadol to control chronic pain such as cancer pain is less than optimal, and its use is associated with a relatively high prevalence of adverse effects.

Tramadol is listed on the national essential medicines lists of many countries across diverse regions, but it is not listed on the WHO Lists of Essential Medicines.

As an opioid analgesic available in generic forms which is not under international control, tramadol is widely used in many countries where access to other opioids for the management of pain is limited. It is also used extensively by international aid organisations in emergency and crisis situations for the same reasons.

**Recommendations**

The Committee was concerned by the increasing evidence for tramadol abuse in a number of countries in diverse regions, in particular the widespread abuse of tramadol in many low to middle income countries. Equally concerning was the clear lack of alternative analgesics for moderate to severe pain for which tramadol is used. The Committee was strongly of the view that the extent of abuse and evidence of public health risks associated with tramadol warranted consideration of

scheduling, but the Committee recommended that tramadol not be scheduled at this time in order that access to this medication not be adversely impacted, especially in countries where tramadol may be the only available opioid analgesic or in crisis situations where there is very limited or no access at all to other opioids.

The Committee also strongly urged the WHO and its partners to address, as a high priority, the grossly inadequate access and availability of opioid pain medication in low income countries. WHO and its partners are also strongly encouraged to update and disseminate WHO pain management guidelines and to support both country-specific capacity building needs and prevention and treatment initiatives in order to address the tramadol crisis in low income countries. The Committee also recommended that WHO and its partners support countries in strengthening their regulatory capacity and mechanisms for preventing the supply and use of falsified and substandard tramadol.

- **Recommendation 4.2:** The Committee recommended that the WHO Secretariat continues to keep tramadol under surveillance, collect information on the extent of problems associated with tramadol misuse in countries and on its medical use, and that it be considered for review at a subsequent meeting.