Annex 1: Summary of the rationale for the recommendations of the 42nd Expert Committee on Drug Dependence

Substances recommended to be added to Schedule I of the Single Convention on Narcotic Drugs (1961), as amended by the 1972 Protocol:

**Crotonylfentanyl**

The chemical name for crotonylfentanyl is (2E)-N-phenyl-N-[1-(2-phenylethyl)]piperidin-4-yl]but-2-enamide.

Crotonylfentanyl binds to mu opioid receptors and acts as an opioid agonist. In animal models, crotonylfentanyl produces antinociception, actions predictive of oxycodone-like subjective effects and both central nervous system stimulation and depression. The opioid antagonist naltrexone blocks the effects of crotonylfentanyl. This pharmacological profile indicates that crotonylfentanyl is an opioid and comparative studies suggest that it has a potency intermediate between oxycodone and fentanyl.

Consistent with the results from animal studies, the effects of crotonylfentanyl were reversed by an opioid antagonist in a clinical admission due to overdose. Due to its opioid mechanism of action, crotonylfentanyl has the potential to be associated with substantial harm.

Crotonylfentanyl has been found in seized material from countries across several regions. It has no veterinary or medical use.

Based on its opioid mechanism of action and similarity to drugs such as oxycodone and fentanyl that are controlled under Schedule I of the Single Convention on Narcotic Drugs, it is recommended that crotonylfentanyl also be controlled under Schedule I of the Single Convention on Narcotic Drugs (1961).

**Valerylfentanyl**

The chemical name for valerylfentanyl is N-phenyl-N-[1-(2-phenylethyl)]piperidin-4-yl]pentanamide.

Valerylfentanyl binds to mu opioid receptors and acts as an opioid agonist. In animal models, valerylfentanyl suppresses opioid withdrawal symptoms, produces antinociception and has actions predictive of oxycodone-like subjective effects. The opioid antagonist naltrexone blocks the effects of valerylfentanyl. This pharmacological profile indicates that valerylfentanyl is an opioid and comparative studies suggest that it has a potency less than that of fentanyl.

Valerylfentanyl has been detected in biological samples from a small number of deaths and cases of driving under the influence of drugs.

Valerylfentanyl has been detected in seizures from countries across several regions. It has no veterinary or medical use.

Based on the evidence of its opioid mechanism of action and similarity to drugs such as fentanyl that are controlled under Schedule I of the Single Convention on Narcotic Drugs, it is recommended that valerylfentanyl also be controlled under Schedule I of the Single Convention on Narcotic Drugs (1961).
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**Substance recommended to be added to Schedule I of the Convention on Psychotropic Substances (1971):**

**DOC**

DOC is also known as 4-chloro-2,5-DMA or 2,5-dimethoxy-4-chloroamphetamine. Its chemical name is 1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine.

DOC is an agonist at the serotonergic 5-HT$_{2A}$ receptor, a mechanism it shares with hallucinogens such as LSD.

In animal models, DOC has actions predictive of hallucinogenic subjective effects (similar to LSD and DOM) and shows evidence of rewarding effects. It can produce both central nervous system stimulation and depression.

Based on clinical admissions due to overdose, the adverse effects associated with use of DOC include agitation, aggression, hallucinations, tachycardia, hyperthermia and seizures.

DOC has been detected in 40 countries. It has no veterinary or medical use.

Based on its similarity in mechanism of action and effects to currently scheduled hallucinogens such as LSD and DOM, and the evidence that it is abused so as to constitute a public health and social problem, it is recommended that DOC be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a serious risk to public health, it is recommended that it be controlled under Schedule I of 1971 Convention on Psychotropic Substances.

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

**AB-FUBINACA**

The chemical name for AB-FUBINACA is N-[1-amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide.

In common with other synthetic cannabinoids, AB-FUBINACA is a full agonist at the cannabinoid CB$_1$ receptor that mediates the psychoactive effects of cannabinoids. In animal studies, it produced central nervous system depression and other typical cannabinoid behavioural effects and had actions predictive of cannabinoid subjective effects.

AB-FUBINACA produces neurological signs in animals that are indicative of toxicity, including seizures, hyperreflexia and aggression. Based on its mechanism of action, it would be expected to produce a range of adverse effects in human users that include tachycardia, nausea, vomiting, confusion and hallucinations. There are a large number of cases of intoxication resulting from AB-
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FUBINACA, often in combination with other drugs, and at least one death has been reported that is attributable to the effects of AB-FUBINACA.

AB-FUBINACA use has been reported in over 30 countries across different regions. It has no veterinary or medical use.

Based on its capacity to produce a state of dependence, its ability to produce central nervous system depression and the evidence that it is abused so as to constitute a public health and social problem, it is recommended that AB-FUBINACA be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a substantial risk to public health, it is recommended that it be controlled under Schedule II of 1971 Convention on Psychotropic Substances.

5F-AMB-PINACA

5F-AMB-PINACA is also known as 5F-AMB and 5F-MMB-PINACA. Its chemical name is methyl 2-[[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino]-3-methylbutanoate.

In common with other synthetic cannabinoids, 5F-AMB-PINACA is a full agonist at the cannabinoid CB₁ receptor that mediates the psychoactive effects of cannabinoids. In animal studies it produced central nervous system depression and had actions predictive of cannabinoid-like subjective effects. 5F-AMB-PINACA produces impairment of memory and seizures in animals.

5F-AMB-PINACA use has been associated with a number of cases of fatal and non-fatal intoxication often in combination with other drugs. In a case of non-fatal intoxication due to 5F-AMB-PINACA alone, the effects included cognitive impairment, slowed movement, slurred speech and poor coordination. Based on its mechanism of action, it would also be expected to produce a range of other effects in human users that include tachycardia, nausea, vomiting, confusion and hallucinations. 5F-AMB-PINACA has been identified as a causal factor in motor vehicle accidents, some of which were fatal.

5F-AMB-PINACA use has been reported in over 30 countries across different regions. It has no veterinary or medical use.

Based on its capacity to produce a state of dependence, its ability to produce central nervous system depression and the evidence that it is abused so as to constitute a public health and social problem, it is recommended that 5F-AMB-PINACA be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a substantial risk to public health, it is recommended that it be controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

5F-MDMB-PICA

5F-MDMB-PICA is also known as 5F-MDMB-2201. Its chemical name is methyl 2-[[1-(5-fluoropentyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate.
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In common with other synthetic cannabinoids, 5F-MDMB-PICA is a full agonist at the cannabinoid CB1 receptor that mediates the psychoactive effects of cannabinoids.

Its use has been associated with a number of fatal and non-fatal intoxications that have been characterised by effects such as decreased mental status, agitated delirium and seizures. While 5F-MDMB-PICA has been present in biological samples mostly in combination with other drugs, in at least some of these cases 5F-MDMB-PICA has been assessed as having a high contribution to the effects produced. It has been used by victims of three apparent mass overdose events, but at least one other synthetic cannabinoid was also detected in biological fluids from the victims.

5F-MDMB-PICA has been detected in 20 countries. It has no veterinary or medical use.

Based on its mechanism of action, 5F-MDMB-PICA has the ability to produce a state of dependence and central nervous system depression. There is evidence that it is abused so as to constitute a public health and social problem. It is therefore recommended that 5F-MDMB-PICA be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a substantial risk to public health, it is recommended that it be controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

4F-MDMB-BINACA

4F-MDMB-BINACA is also known as 4F-MDMB-BUTINACA. Its chemical name is methyl 2-[[1-(4-fluorobutyl)-1H-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate.

In common with other synthetic cannabinoids, 4F-MDMB-BINACA is a full agonist at the CB1 receptor that mediates the psychoactive effects of cannabinoids.

Self-reported effects provided by individuals who had used cannabinoid products that included 4F-MDMB-BINACA as the major constituent, included auditory and visual hallucinations, vomiting, paranoia, euphoria, relaxation, irregular heartbeat, agitation, confusion, insomnia, and chest pain. These effects are consistent with the cannabinoid full agonist mechanism of action of 4F-MDMB-BINACA. Its use has been associated with a number of fatal and non-fatal intoxications and of cases of driving under the influence of drugs. However, other synthetic cannabinoids have been detected in most of these cases.

4F-MDMB-BINACA has been detected in a small number of countries to date, but its use may be increasing. It has no veterinary or medical use.

Based on its mechanism of action, 4F-MDMB-BINACA has the ability to produce a state of dependence and central nervous system depression. There is evidence that it is abused so as to constitute a public health and social problem. It is therefore recommended that 4F-MDMB-BINACA be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a substantial risk to public health, it is recommended that it be controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

4-CMC

4-CMC is also known as 4-chloromethcathinone and clephedrone. Its chemical name is 1-(4-chlorophenyl)-2-(methylamino)propan-1-one.
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In common with other stimulants used non-medically, 4-CMC increases neuronal concentrations of the neurotransmitter dopamine. It also has effects on serotonin and, to a lesser extent, noradrenaline.

In animal models, 4-CMC has effects predictive of abuse potential, including actions predictive of MDMA-like subjective effects and stimulation of brain reward centres. It also produces central nervous system stimulation. Users of the drug report effects similar to other stimulants, particularly MDMA-like effects, including increased energy, mood elevation and increased sociability.

4-CMC use has been associated with adverse effects typical of stimulant drugs, including tachycardia, agitation and impaired movement. Based on these effects and its mechanism of action, major risks associated with use of this drug will include cardiac failure and psychosis. In association with other drugs, 4-CMC has been involved in fatalities due to overdose, suicide and traffic accidents. It has been detected in used syringes, indicating the potential for injection related health problems in association with its use.

4-CMC has been detected in many countries across different regions. It has no veterinary or medical use.

Based on its mechanism of action and effects, 4-CMC has the ability to produce a state of dependence and central nervous system stimulation. There is evidence that it is abused so as to constitute a public health and social problem. It is therefore recommended that 4-CMC be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a substantial risk to public health, it is recommended that it be controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

N-ethylhexedrone

The chemical name for N-ethylhexedrone is 2-(ethylamino)-1-phenylhexan-1-one.

In common with other stimulants used non-medically, N-ethylhexedrone increases neuronal concentrations of the neurotransmitter dopamine. It also has effects on noradrenaline.

In preclinical models, N-ethylhexedrone has actions predictive of methamphetamine-like subjective effects and produces central nervous system stimulation. Users of the drug report effects similar to other stimulants, including increased energy, mood elevation, perceptual changes and increased sociability.

Information on the adverse effects is limited, but the effects reported are consistent with the effects of stimulant drugs and include tachycardia, tremor, seizures and hyperthermia. N-ethylhexedrone has been implicated as the cause of at least one fatality and of cases of impaired driving. It has been detected in used syringes, indicating the potential for injection related health problems in association with its use.

N-ethylhexedrone has been detected in 30 countries across different regions. It has no veterinary or medical use.

Based on its mechanism of action and effects, N-ethylhexedrone has the ability to produce a state of dependence and central nervous system stimulation. There is evidence that it is abused so as to constitute a public health and social problem. It is therefore recommended that N-ethylhexedrone
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be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a substantial risk to public health, it is recommended that it be controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

Alpha-PHP

Alpha-PHP is also known as alpha-pyrrolidinoheptanophenone. Its chemical name is 1-phenyl-2-(pyrrolidine-1-yl)hexan-1-one.

In common with other stimulants used non-medically, alpha-PHP increases neuronal concentrations of the neurotransmitter dopamine. It also has effects on noradrenaline.

In animal models, alpha-PHP has effects predictive of abuse and dependence potential, including actions predictive of methamphetamine-like subjective effects and reinforcing properties. It produces central nervous system stimulation in animals. Users of the drug report effects similar to other stimulants, including increased energy, mood elevation, perceptual changes and appetite suppression.

The adverse effects of the drug include tachycardia, paranoia and hallucinations. It has been identified as the cause of multiple deaths and clinical admissions.

Alpha-PHP has been detected in over 20 countries across different regions. It has no veterinary or medical use.

Based on its mechanism of action and effects, alpha-PHP has the ability to produce a state of dependence and central nervous system stimulation. There is evidence that it is abused so as to constitute a public health and social problem. It is therefore recommended that alpha-PHP be controlled under the 1971 Convention on Psychotropic Substances. As it has no medical use and its use constitutes a substantial risk to public health, it is recommended that it be controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

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

Flualprazolam

The chemical name for flualprazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine.

Flualprazolam is chemically similar to the benzodiazepines alprazolam and triazolam and in animal models it produces the typical benzodiazepine effects of sedation, muscle relaxation and anticonvulsant actions. Users have reported effects such as sedation, disinhibition and memory impairment that are common with benzodiazepines and have described it as similar to alprazolam and clonazepam.
In toxicology reports, flualprazolam has been documented as contributing to forensic and clinical events, including fatal and non-fatal intoxications and cases of driving under the influence. It has no medical use.

There is limited information on the extent of global use of flualprazolam with most reported identifications coming from two countries. There are numerous reports of its use on internet forums.

Based on its capacity to produce a state of dependence and central nervous system depression similar to the controlled benzodiazepine alprazolam, which is controlled under Schedule IV of the 1971 Convention on Psychotropic Substances, as well as evidence that it is likely to be abused so as to constitute a public health and social problem, it is recommended that flualprazolam be controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

**Etizolam**

The chemical name for etizolam is 4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. It has been previously reviewed by the ECDD, most recently at its 39th meeting in 2017.

Etizolam is an agonist at the benzodiazepine site on the GABA<sub>A</sub> receptor, inducing central nervous system depression. It has typical benzodiazepine effects that include sedation and muscle relaxation as well as anxiolytic and anticonvulsant actions. Adverse effects include drowsiness, ataxia, slurred speech, cognitive impairment and loss of consciousness.

Etizolam use has been associated with a large number of deaths, generally along with another drug or drugs. Benzodiazepines such as etizolam pose a significant risk when combined with opioids as they can potentiate the respiratory depressant effects of opioids.

Etizolam has been used in a number of countries and in some of these countries has been associated with reports of fatal and no-fatal intoxication as well as cases of driving under the influence. It has marketing authorization for medical use in three countries.

Based on its capacity to produce a state of dependence and central nervous system depression similar to other controlled benzodiazepines, as well as evidence that it is abused so as to constitute a public health and social problem, it is recommended that etizolam be controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

**Substance recommended for surveillance:**

**APINACA**

The chemical name for APINACA (also known as AKB-48) is N-(adamantan-1-yl)-1-pentyl-1H-indazole-3-carboxamide. It was previously reviewed at the 36th meeting of the WHO Expert Committee on Drug Dependence in 2014, but was not recommended for control at that time.
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In common with other synthetic cannabinoids, APINACA is an agonist at the CB₁ receptor that mediates the psychoactive effects of cannabinoids. In animal studies it produced central nervous system depression and had actions predictive of cannabinoid-like subjective effects.

APINACA produces neurological signs in animals that include seizures, hyperreflexia and aggression. However, there are no studies of the adverse effects of APINACA in human users of the drug and no available information regarding fatal or non-fatal intoxications.

APINACA use has been reported in a number of countries but its use has been declining since 2015 and it is now detected very infrequently if at all.

Owing to the lack of significantly more information since the review conducted by the 36th ECDD in 2014, and considering the current insufficiency of data regarding dependence, abuse and risks to public health (including risks to the individual), the Committee recommended that APINACA be kept under surveillance.

Preparations recommended for critical review:

Preparations of acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine, nicodicodine, norcodeine and pholcodine listed in Schedule III of the 1961 Single Convention on Narcotic Drugs

The Committee considered a pre-review of the following preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs: acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine, nicodicodine, norcodeine and pholcodine, when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations.

These preparations have not been previously reviewed. The ECDD Secretariat commissioned a pre-review of these preparations, on the basis of concerns regarding abuse and harm of preparations of codeine that were conveyed to the Secretariat. As many of the substances listed in the first entry of Schedule III of the 1961 Single Convention are chemically and pharmacologically similar to codeine, the eight preparations were considered together.

These preparations have been marketed and used as antitussive medicines and analgesics for mild to moderate pain. In many countries these preparations are available without medical prescription. The active substances in the preparations are opioids and all substances themselves are controlled under Schedule II of the 1961 Single Convention on Narcotic Drugs. Misuse of and dependence on preparations of codeine and dihydrocodeine have been well described. The pre-review suggested that there may be less evidence regarding the other preparations. The Committee also noted evidence of separation of the opioid drug such as codeine from the other ingredients in these preparations by people misusing these preparations.

Based on the evidence available regarding dependence, abuse and risks to public health, the Committee recommended a critical review of the following preparations included in Schedule III of the 1961 Convention at a future meeting: acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine, nicodicodine, norcodeine and pholcodine when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations.