Annex 1. Summary assessments and recommendations of the 48th WHO ECDD, 20–22 October 2025

Coca leaf

Substance identification

Coca leaf is defined in the 1961 United Nations Single Convention on Narcotic Drugs as the leaf of the coca bush, except when all ecgonine, cocaine and any other ecgonine alkaloid have been removed. "Coca bush" refers to the plant of any species of the genus Erythroxylon. "Coca leaf preparations" refer to mixtures or products containing the coca leaf (in whole or in part). This excludes isolated alkaloids such as cocaine and ecgonine, which are controlled separately under the Convention.

More than 250 Erythroxylum species exist, including four primary cultivated varieties: *E. coca* var. *coca*, *E. coca* var. *ipadu*, *E. novogranatense* var. *novogranatense*, and *E. novogranatense* var. *truxillense*. Coca leaf cultivation is most prevalent at high altitudes in the Andean region and in the Amazon basin but is increasingly being reported in other parts of the Region of the Americas. Coca leaf is cultivated from plants grown from seeds or cuttings. Plants can produce leaves for 20–30 years.

Coca leaves are similar in appearance to those of *Laurus nobilis*, the most common characteristic trait in all species being a darker colour on the upper than on the underside of the leaf and two lines parallel to the midrib of the leaf.

Coca leaf preparations are marketed as branded products. They include teas, nutritional supplements, and essential oil. Coca leaves can be pulverized finely into a greenish powder.

Coca leaf products are traditionally administered by two primary routes: chewing and infusion. Chewing of coca leaves is widespread and culturally accepted in the Andean highlands. The process involves placing a wad of dried leaves in the buccal cavity, either alone or with an alkaline substance such as lime or sodium bicarbonate to enhance extraction of alkaloids into the oral mucosa. Coca leaves are also infused in water and consumed as tea. Coca leaf flour (finely ground coca leaves) can be used to make a strong tea and is sold as a nutritional supplement.

WHO review history

Coca-leaf chewing was discussed at the 3rd (1952) and 4th (1954) meetings of the WHO Expert Committee on Drugs Liable to Produce Addiction, which concluded that it was a form of addiction. Coca leaf was subsequently placed under Schedule I of the 1961 Single Convention on Narcotic Drugs.

At its 28th meeting, in 1992, the ECDD conducted a pre-review of coca leaf and considered that coca leaf was appropriately scheduled under the 1961 Convention, as cocaine is readily extractable from the leaf.

In 2023, WHO received an official request from a Member State for a critical review of coca leaf. In accordance with WHO guidance, a critical review was initiated, for conclusion in 2025.

Similarity to known substances and effects on the central nervous system

Coca leaf contains a mix of alkaloids, flavonoids, terpenes, tannins, and phenols. Cocaine and ecgonine are naturally occurring alkaloids of note in the coca leaf. The total alkaloid content is 0.5–2.4%, depending on the species, growth environment, and stage of leaf development. Cocaine, one alkaloid in the leaf, is produced in significant amounts in cultivated varieties of the *Erythroxylum* species, whereas wild species contain either none or only small quantities of this alkaloid. When present, the cocaine content of cultivated species varies among regions from 0.11% to 1.02% of the weight of dried coca leaf. Absorption of alkaloids from coca leaf depends on the route of administration, the quantity of leaves used, the type of alkali added, and if masticated, the duration of

mastication. The plasma concentrations of cocaine resulting from coca leaf chewing or ingestion may overlap with plasma concentrations of cocaine resulting from cocaine use by inhalation or injection.

It has been demonstrated in animal models that coca leaf alkaloids affect the central nervous system, including decreasing food intake. Some coca leaf extracts increase locomotor activity, while others do not. The stimulant effects of coca leaf in animal models may be due to inhibition of monoamine re-uptake. Local anaesthetic effects have also been observed in animal models.

People who chew coca leaf report mild psychostimulant effects, including euphoria, and have described it as an "energizer". Increased heart rate and blood pressure and vasoconstriction have also been reported. Analgesic effects of high-dose coca leaf preparations have been attributed to a local anaesthetic effect.

Convertibility into controlled substances

Coca leaf contains cocaine, a naturally occurring alkaloid that can be processed to obtain coca paste. Coca paste is filtered and dried to obtain cocaine base, which is further processed to obtain cocaine hydrochloride. By chemical definition, the manufacture of cocaine from coca leaf is an extraction; however, the reference in the WHO Guidance document for the understanding of this term reads as follows:

> A substance is convertible if it is of such a kind as to make it, by the ease of the process and by the yield, practicable and profitable for a clandestine manufacturer to transform the substance in question into controlled drugs.[1]

Obtaining coca paste from coca leaf and purification of different forms of cocaine from coca paste are straightforward and do not require special expertise or equipment. Except for kerosene, the chemicals and reagents used in these processes are listed in the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

Most coca leaf is used for clandestine manufacture of cocaine in at least some countries. It is estimated that 1 ha of coca bush cultivation produces approximately 4.2 tonnes of fresh coca leaves per year; 1 tonne of fresh leaves produces approximately 1.5 kg of coca paste or 1.4 kg of cocaine base; 1 kg of cocaine base results in roughly 0.9 kg of cocaine hydrochloride, which typically contains about 85% pure cocaine. Cocaine production has increased significantly in several countries, in parallel with increased coca bush cultivation. Some countries have reported historically high levels in recent years. Globally, a 34% increase in cocaine production was reported in 2023 over the previous year.

The 1961 Convention lists both coca leaf and cocaine as controlled substances under Schedule 1. Accordingly, as coca leaf is used to manufacture cocaine, one controlled substance (cocaine) is made from another (coca leaf), thereby meeting the Convention's criterion for convertibility.

Dependence potential

No controlled studies in animal models of the dependence potential of coca leaf were identified.

A few studies in humans assessed development of a dependence syndrome with coca leaf. Older ethnographic studies did not describe tolerance, withdrawal symptoms, or compulsive patterns of use; however, a recent epidemiological study of more than 1300 people who chewed coca leaf found that 2.3% of those who reported ever chewing coca leaf met the ICD-10 criterion for dependence. People who met the criterion had a lower quality of life than people who did not. Two countries in different geographical regions reported presentations for drug dependence treatment related to coca

[1] In accordance with paragraph 49 of the Guidance on the WHO Review of Psychoactive Substances for International Control, which refers to Commentary on the 1961 Convention, para. 13 (p. 89).

leaf use. No studies were available that provided robust evidence to determine the prevalence of coca leaf dependence.

Actual abuse and/or evidence of likelihood of abuse

In a model of drug discrimination in animals, high-dose preparations of coca leaf produced effects that closely resembled those of cocaine.

Many countries in various regions have reported nonmedical use of coca leaf and increasing numbers of seizures of coca leaf.

Other health harms

Few high-quality data are available on the acute toxicity associated with coca leaf. No fatal overdoses have been documented after traditional use of coca leaf, although coca leaf may not readily be differentiated from cocaine in biological samples from such cases.

Reported adverse effects of chewing coca leaf appear to be limited. They include oral problems (including risk of oral carcinoma) and cardiovascular, intestinal, hormonal, and neurological issues.

Therapeutic usefulness

The potential therapeutic effects of various Erythroxylum species have been investigated in vitro and in animal models. Recent investigations have been conducted of its antioxidant, antibiotic, anticancer, antihypertensive, antidiabetic, and neuroprotective effects. For example, some Erythroxylum species may have anticancer effects, comparable to those of standard chemotherapy agents in some cases; however, the activity varies with different extracts and cell lines. Similarly, studies in vitro and in vivo show variable but sometimes strong antioxidant and anti-inflammatory effects. In humans, use of *E. coca* by chewing and drinking tea reduced post-meal glucose in people with no underlying metabolic disorder. Overall, studies in animals and humans suggest that coca leaf may have some therapeutic applications, although the evidence is limited.

Traditional use of coca leaf in Andean regions includes chewing and infusion to increase energy and prevent altitude sickness, although evidence of its usefulness for treating altitude sickness is mixed. Its use as a nutritional supplement is limited by its cocaine content. Use of coca leaf for the manufacture of pharmaceutical and industrial products has decreased with time.

In a few countries, preparations of coca leaf are used as traditional herbal medicines. Use of coca leaf is permitted under national legislation in some countries when practised within traditional or cultural contexts.

Recommendation

The Expert Committee, when deciding whether to recommend international control, decides whether a substance: "(1) is liable to similar abuse and productive of similar ill-effects as the substances in Schedule I or Schedule II; or (2) is convertible into a substance already in Schedule I or Schedule II." The reference in the WHO Guidance document for the understanding of this term reads as follows:

> A substance is convertible if it is of such a kind as to make it, by the ease of the process and by the yield, practicable and profitable for a clandestine manufacturer to transform the substance in question into controlled drugs.[1]

In the 1961 Single Convention on Narcotic Drugs, coca leaf is defined as the leaf of the coca bush, except when all ecgonine, cocaine, and any other ecgonine alkaloids have been removed. Coca leaf and cocaine are classified as distinct substances under Schedule I of the 1961 Single Convention. The simplicity of extracting cocaine from coca leaf and its high yield and profitability are well known. Accordingly, conversion of coca leaf into cocaine constitutes production of one substance (cocaine) in Schedule I from another substance in Schedule I (coca leaf), thereby meeting the Convention's

criterion for convertibility. The Committee also reviewed evidence of a marked increase in coca leaf cultivation and in the production of cocaine-related substances, in the context of significant, increasing public health concern about cocaine use. In that context, the Committee considered that reducing or removing existing international controls on coca leaf could pose an especially serious risk to public health.

The evidence presented in the critical review and other information considered by the Committee indicate that traditional coca leaf use by chewing or in tea does not appear to pose a particularly serious public health risk, although the safety of long-term use is not well documented. In addition, it was recognized that coca leaf has an important cultural and therapeutic significance for Indigenous peoples and other communities and that there are exemptions for traditional use of coca leaf in certain national frameworks. Emerging research may support the therapeutic applications of coca leaf; however, the current body of evidence does not provide a robust basis for such use.

Recommendation: The Committee recommended that coca leaf be retained in Schedule I of the 1961 Single Convention on Narcotic Drugs.

MDMB-FUBINACA

Substance identification

MDMB-FUBINACA (IUPAC name: Methyl 2-{[1-(4-fluorobenzyl)indazole-3-carbonyl]amino}-3,3-dimethylbutanoate) is a synthetic cannabinoid with a stereogenic centre (C2), which can exist as two stereoisomers (enantiomers): methyl (2*S*)-2-{[1-(4-fluorobenzyl)indazole-3-carbonyl]amino}-3,3-dimethylbutanoate and methyl (2*R*)-2-{[1-(4-fluorobenzyl)indazole-3-carbonyl]amino}-3,3-dimethylbutanoate.

MDMB-FUBINACA has been described as a powder (usually white) and has been found sprayed onto herbal products. It is often marketed as dried leaves or powder and sold in e-liquids for vaping.

WHO review history

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

Similarity to known substances and effects on the central nervous system

MDMB-FUBINACA is a synthetic cannabinoid that binds to CB1 and CB2 receptors with high affinity and is a potent full agonist at both receptors. Its effects are similar to those of other potent CB1 agonists that are currently controlled under Schedule II of the Convention on Psychotropic Substances of 1971. No controlled studies of the effects of MDMB-FUBINACA have been reported. In animals, it has been shown to produce behavioural effects consistent with delta-9-THC, with the effects lasting many hours. In humans, it produces symptoms typical of high doses of cannabinoids, including agitation or sedation, vomiting, short-term memory loss, salivation, rhinorrhoea, mydriasis, tachycardia and anxiety.

Convertibility into controlled substances

MDMB-FUBINACA can be chemically modified to produce structurally related synthetic cannabinoids such as ADB-FUBINACA. The yields and prevalence of such conversions are, however, uncertain.

Dependence potential

No studies of the dependence potential of MDMB-FUBINACA in animals or humans have been reported. Its effects at CB1 receptors suggest that it would produce dependence similar to that produced by delta-9-THC and other synthetic cannabinoid receptor agonists. Countries in two regions reported presentations for treatment of drug dependence due to the use of MDMB-FUBINACA.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, MDMB-FUBINACA had effects similar to delta-9-THC. No studies have been conducted to determine the likelihood of abuse of MDMB-FUBINACA in humans.

Other health harms

MDMB-FUBINACA use has been associated with mortality and morbidity in several countries, including a large number of non-fatal poisonings. Documented adverse effects include agitation or sedation, vomiting, short-term memory loss, salivation, rhinorrhoea, mydriasis, tachycardia and anxiety, similar to those seen with delta-9-THC and other synthetic cannabinoid receptor agonists. The increased detection of MDMB-FUBINACA has been linked to emergence of a simplified one-step synthesis method, which requires readily available precursor chemicals.

Therapeutic usefulness

MDMB-FUBINACA is not known to have any therapeutic use.

Recommendation

MDMB-FUBINACA is a synthetic cannabinoid receptor agonist administered by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the potential for dependence and the 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 that are placed in Schedule II of the Convention on Psychotropic Substances of 1971. MDMB-FUBINACA has no therapeutic use.

Recommendation: The Committee recommended that MDMB-FUBINACA be added to Schedule II of the Convention on Psychotropic Substances of 1971.

N-Pyrrolidino isotonitazene

Substance identification

N-Pyrrolidino isotonitazene (IUPAC name: 5-nitro-2-[4-(2-propoxy)benzyl]-1-[2-(pyrrolidin-1-yl)ethyl]-1H-benzo[d]imidazole, also known as isotonitazepyne) is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

N-Pyrrolidino isotonitazene has been described as a crystalline solid and has also been detected in falsified pharmaceuticals, appearing as coloured tablets.

WHO review history

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

Similarity to known substances and effects on the central nervous system

The chemical structure and pharmacological effects of *N*-pyrrolidino isotonitazene closely resemble those of *N*-pyrrolidino protonitazene, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

Studies in animals have demonstrated that *N*-pyrrolidino isotonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine and fentanyl. Its effects are blocked by the opioid antagonist, naltrexone.

Convertibility into controlled substances

It is not known whether *N*-pyrrolidino isotonitazene can be converted into a controlled substance.

Dependence potential

No controlled studies of the dependence potential *N*-pyrrolidino isotonitazene in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to that of other opioids, such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, *N*-pyrrolidino isotonitazene had effects suggestive of an abuse potential similar to that of morphine and fentanyl. Its potency was greater than that of morphine and fentanyl. These effects were blocked by the opioid antagonist naltrexone. Euphoria and self-management of opioid withdrawal have been described by people who report its use.

Other health harms

The presence of *N*-pyrrolidino isotonitazene has been reported in many countries in many regions, although the extent of use is unknown. *N*-Pyrrolidino isotonitazene has been analytically confirmed in fatal and non-fatal cases of overdose, including in cases in which it was the only substance detected.

Detection of *N*-pyrrolidino isotonitazene in falsified pharmaceutical drugs in many countries and regions indicates a risk of unintentional use and harm.

Therapeutic usefulness

N-Pyrrolidino isotonitazene is not known to have any therapeutic use.

Recommendation

N-Pyrrolidino isotonitazene, also referred to as isotonitazepyne, is a synthetic opioid that is liable to abuse and produces effects similar to those of other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use causes substantial harm, including death. It has no known therapeutic use.

Recommendation: The Committee recommended that *N*-pyrrolidino isotonitazene, also referred to as isotonitazepyne, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

N-Desethyl etonitazene

Substance identification

N-Desethyl etonitazene (IUPAC name: 2-[(4-ethoxyphenyl)methyl]-*N*-ethyl-5-nitro-1*H*-benzimidazole-1-ethanamine) is a 5-nitro-2-benzylbenzimidazole synthetic opioid. *N*-Desethyl etonitazene has been described as a crystalline solid and as a yellow or beige powder. It has been found in falsified pharmaceutical opioid tablets.

WHO review history

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

Similarity to known substances and effects on the central nervous system

N-Desethyl etonitazene is a metabolite of etonitazene, which is controlled under Schedule I of the 1961 Convention on Narcotic Drugs.

Studies of receptor binding in vitro indicate that *N*-desethyl etonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine and fentanyl.

Convertibility into controlled substances

It is not known whether *N*-desethyl etonitazene can be converted into a controlled substance, although this is theoretically possible.

Dependence potential

No controlled studies of the dependence potential of *N*-desethyl etonitazene in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to that produced by other opioids, such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

The presence of *N*-desethyl etonitazene has been reported in at least 10 countries, although the extent of use is unknown.

Other health harms

At least three deaths have been reported in which *N*-desethyl etonitazene was analytically confirmed, including when no other opioids were involved. *N*-Pyrrolidino etonitazene has also been analytically confirmed in non-fatal overdoses. The detection of *N*-pyrrolidino etonitazene in falsified pharmaceutical drugs indicates a risk of unintentional use and harm.

Therapeutic usefulness

N-Desethyl etonitazene is not known to have any therapeutic use.

Recommendation

N-Desethyl etonitazene is a synthetic opioid that is liable to abuse and produces ill effects similar to those produced by other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. It could theoretically be converted into a controlled substance, although this has not been demonstrated. Its use causes substantial harm, including death. It has no known therapeutic use.

Recommendation: The Committee recommended that *N*-desethyl etonitazene be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.