Critical Review Report:

FUB-AMB

(MMB-FUBINACA, AMB-FUBINACA)

Expert Committee on Drug Dependence

Forty-first Meeting

Geneva, 12-16 November 2018

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

Acknowledgements

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a critical review for the 41st Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge Jenny Wiley for the literature review and drafting and Jurgen Rehm, Astrid Otto, and Jakob Manthey for questionnaire analysis and report drafting.

WHO would like to thank the US Drug Enforcement Agency for providing additional information.

Executive Summary

Substance identification: FUB-AMB (CAS: 1971007-92-7) is a synthetic cannabinoid that was first documented (as a derivative) in international patent WO 2009/106980-A2 issued to Ingrid Buchler and colleagues at Pfizer on September 3, 2009.[1] FUB-AMB is also referred to as MMB-FUBINACA and AMB-FUBINACA.

WHO Review History: The WHO has not previously reviewed FUB-AMB.

Chemistry: FUB-AMB is methyl (2S)-2-[[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino]-3-methylbutanoate. FUB-AMB is in the S-configuration and contains a chiral center at the C-2 carbon of the valinate sidechain; hence, a R-AMB-FUBINACA enantiomer is possible.

Ease of convertibility into controlled substances: FUB-AMB is not readily converted into other controlled substances.

Similarity to known substances / Effects on the central nervous system: FUB-AMB is a synthetic cannabinoid that likely shares a profile of centrally mediated effects with other synthetic cannabinoids, including THC-like intoxication. Examination of the in vivo effects of this compound specifically is limited.

General pharmacology: The most likely route of administration for FUB-AMB is inhalation via smoking the chemical after it has been sprayed on plant material or vaping it after formulation in liquid. Dosage required for pharmacological effects in humans is unknown. Because the most common route of administration for FUB-AMB involves heating an e-liquid containing the chemical or burning plant material that contains the chemical, thermolytic conversion is of concern. A recent study suggests that heating FUB-AMB to temperatures that could occur with smoking (400 ^{o}C) released its methyl-ester substituent to produce several thermal degradants as well as cyanide. The degree to which cyanide would reach toxicological concentrations in users is unknown.

Almost nothing in known about the specific pharmacokinetics of FUB-AMB. Based upon analysis of blood and urine of patients who received medical attention during a cluster of FUB-AMB overdoses in New York City in July 2016, metabolism is rapid and extensive. Hydrolysis results in formation of a de-esterified acid metabolite, 2-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-3-methylbutanoic acid, which was detected in all patients.

FUB-AMB is a potent CB_1 receptor agonist, with reported binding affinity (K_i) of 10.04 nM and 0.786 nM in hCB1 and hCB2 receptors, respectively. It is a full agonist in functional tests of CB_1 and CB_2 receptor activation, as demonstrated by FUB-AMB-induced [35S]GTPγS binding (both receptors), inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) (CB1 receptor), and opening of G protein-gated inwardly rectifying potassium channels (GIRKs) (both receptors expressed in mouse AtT20-FlpIn neuroblastoma cells). FUB-AMB was potent at activating the CB1 receptor G-protein (EC50 = 0.54 nM), inhibiting cAMP (EC50 = 0.63 nM), and

stimulated GIRK (EC50 = 2.0 nM). At CB2 receptors, FUB-AMB was a full agonist with potency that was similar to that of CP55,940, with an EC50 value of 0.13 nM. FUB-AMB potency at CB2 receptors in the GIRK assay was less than CP55,940, with EC50 values of 18 nM for FUB-AMB and 4.2 nM for CP55,940. Consistent with its high binding affinity and full activation at CB1 receptors, FUB-AMB fully substituted for Δ^9-tetrahydrocannabinol (THC) in male C57/Bl6 mice trained to discriminate THC from vehicle, with an ED50 of 0.04 mg/kg.

Toxicology: Preclinical evaluation of the acute or chronic toxicological effects of FUB-AMB has not been conducted.

Adverse reactions in humans: Case studies and reports of mass intoxication suggest that acute administration of FUB-AMB has the potential to produce severe adverse reactions in humans up to, and including, death. The most predominant symptom in a cluster of confirmed FUB-AMB overdose cases in New York City in July 2016 was severe CNS depression, resulting in slowed behavior and speech that was labeled as "zombielike" by the popular press. However, dissimilar to cases of confirmed exposure to several other third generation synthetic cannabinoids (e.g., ADB-CHMINACA), FUB-AMB intake was not associated with tachycardia, seizures, or cardiac or renal toxicity during this outbreak. In contrast, New Zealand reported that at least 20 deaths were related to FUB-AMB intake. Of note, concentrations of FUB-AMB in confiscated products were 2 to 25 times greater than those reported in the New York incident, suggesting that toxicity is dose-dependent.

Dependence potential: The dependence potential of FUB-AMB has not been evaluated in humans or in animals.

Abuse potential: The abuse potential of FUB-AMB has not been evaluated in humans. In male and female mice, FUB-AMB (i.p. injection and via aerosol exposure) produced dose-dependent substitution for Δ^9-tetrahydrocannabinol (THC) in male and female mice trained to discriminate 5.6 mg/kg THC from vehicle. FUB-AMB was less potent at producing THC-like effects in females than in males following both routes of administration. The ED_{50} value for males was 0.04 mg/kg (i.p.).

Therapeutic applications / usefulness: None

Listing on WHO Model List of Essential Medicines: Not listed as an essential medicine.

Marketing authorizations: None

Industrial use: None

Non-medical use: The prevalence of non-medical use of FUB-AMB specifically has not been determined; however, synthetic cannabinoids (as a class) is the largest group of substances monitored by the European Union Early Warning System, and user exposure to specific synthetic

cannabinoids is not often analytically confirmed. Non-medical use has also been reported outside of the European Union, including in the United States, Australia, New Zealand, and Asia.

Nature and magnitude of public health problems: Use of synthetic cannabinoids has become a global issue with potential for serious public health problems. While the magnitude of these challenges is difficult to determine, issues that have been reported with synthetic cannabinoids include impaired driving, acute psychiatric distress, and increased aggressiveness. FUB-AMB, specifically, has been associated with several clusters of mass intoxication, illness and death in the U.S. and in New Zealand. In New Zealand, at least 20 deaths related to FUB-AMB have occurred as well as numerous hospitalizations. In the U.S., the most common symptom in mass intoxication clusters appears to have been severe CNS depression that the popular press has labeled "zombielike."

Licit production, consumption, and international trade: None

Illicit manufacture and traffic: FUB-AMB has been detected in the European Union, in the U.S., and in New Zealand. Underreporting is likely due to lack of routine screening for the compound. Synthesis of the compound occurs predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped.

Current international controls and their impact: FUB-AMB is not been subject to international control under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

Current and past national controls: In November 2017, the U.S. Drug Enforcement Agency issued a statement of temporary placement of FUB-AMB under Schedule 1 control measures. While the EMCDDA has not issued an Early Warning System report or risk assessment on FUB-AMB, the compound is scheduled in Germany (Anlage II) and is banned in Sweden. FUB-AMB is also subject to control regulations in Canada and has been reviewed by the New Zealand Ministry of Health for regulatory consideration.

1. Substance identification

A. International Nonproprietary Name (INN)

N/A

B. Chemical Abstract Service (CAS) Registry Number

1971007-92-7

C. Other Chemical Names

AMB-FUBINACA; MMB-FUBINACA

D. Trade Names

N/A

E. Street Names

FUB-AMB has been detected in samples of products labeled AK-47 24 Carat Gold,[2, 3] Train Wreck2,[2, 3] and Scooby Snax Limited Edition Blueberry Potpourri.[4] Other specific street names for FUB-AMB are not available. However, there are dozens of street names for synthetic cannabinoids (which may contain one or more unidentified synthetic cannabinoids). These names include K2, K2XXX, barely legal, iBlaze, spice, cloud 10, herbal incense, fake weed, kush, and zombie, among others.

F. Physical Appearance

Crystalline solid[5]
White to yellowish powder, slightly sweetish to the taste, with a sweet somewhat pleasant aroma[2]

G. WHO Review History

FUB-AMB has not previously been reviewed by the WHO.

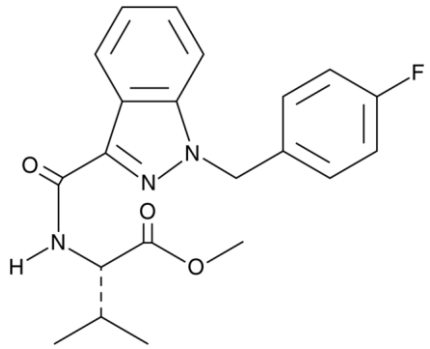
2. Chemistry

A. Chemical Name

IUPAC Name: methyl (2S)-2-[[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino]-3-methylbutanoate
CA Index Name: n/a

B. Chemical Structure

Figure 1: Chemical structure of FUB-AMB



Molecular Formula: $C_{21}H_{22}FN_3O_3$

Molecular Weight: 383.4 g/mol

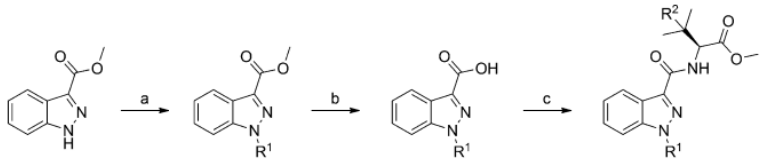
C. Stereoisomers

FUB-AMB is in the S-configuration and contains a chiral center at the C-2 carbon of the valinate sidechain; hence, a R-AMB-FUBINACA enantiomer is possible, but has only been mentioned in the (sparse) literature once.[2]

D. *Methods and Ease of Illicit Manufacturing*

Synthetic methods for FUB-AMB were not described specifically in the patent under which it is covered,[1] but have been described in a recent research paper.[6] Scheme 1 was copied from this publication[6] and delineates steps in the chemical reaction necessary

Scheme 1. Synthesis of indazole cannabinoids (including FUB-AMB)



35

36: $R^1 = (CH_2)_5F$
37: R^1 = 4-F-Bn
38: $R^1 = CH_2Cy$
39: $R^1 = (CH_2)_4CH_3$

40: $R^1 = (CH_2)_5F$
41: R^1 = 4-F-Bn
42: $R^1 = CH_2Cy$
43: $R^1 = (CH_2)_4CH_3$

12: $R^1 = (CH_2)_5F$; $R^2 = H$
13: $R^1 = (CH_2)_5F$; $R^2 = CH_3$
16: R^1 = 4-F-Bn; $R^2 = H$
17: R^1 = 4-F-Bn; $R^2 = CH_3$
20: $R^1 = CH_2Cy$; $R^2 = H$
21: $R^1 = CH_2Cy$; $R^2 = CH_3$
24: $R^1 = (CH_2)_4CH_3$; $R^2 = H$
25: $R^1 = (CH_2)_4CH_3$; $R^2 = CH_3$

[a]Reagents and conditions: (a) *t*-BuOK, BrR^1, THF, 0 °C–rt, 48 h; 65–84%; (b) 1 M aq. NaOH, MeOH, reflux, 24 h, 76–91%; (c) methyl L-valinate or methyl L-*tert*-leucinate, EDC·HCl, HOBt, DIPEA, DMSO, rt, 24 h, 60–77%.

to synthesize FUB-AMB (compound 16).

E. Chemical Properties

Melting point: No data

Boiling point: No data

Solubility:[7] Soluble in CH_2Cl_2 and MeOH. Low solubility in H_2O.

F. Identification and Analysis

UV-Visible spectrum: λmax at 208 and 299 nm[5]
Various methods have been used to identify and/or analyze FUB-AMB. These methods have included Fourier Transform Infrared Spectroscopy with Attenuated Total Reflection sampling (FTIR-ATR),[7] liquid chromatography-quadrupole time-of-flight mass spectrometry (LC–QTOF/MS),[3] gas chromatography-mass spectrometry and infrared analysis (GC-MS-IR),[7] ion chromatography (IC),[7] gas chromatography-mass spectrometer (GC-MS),[4, 7, 8] high performance liquid chromatography with time of flight mass spectrometry (HPLC-TOF),[7] nuclear magnetic resonance spectroscopy (NMR),[7] and surface enhanced Raman scattering (SERS).[9]

3. Ease of Convertibility Into Controlled Substances

Ease of convertibility of FUB-AMB into a controlled, but non-cannabinoid substance, is low.

4. General Pharmacology

A. Routes of administration and dosage

The primary route of administration for FUB-AMB is presumed to be the same as for other synthetic cannabinoids: inhalation via smoking or vaping. Inhalation of smoke from chemical sprayed on herbal material is the most common route of administration for synthetic cannabinoids.[10] Dosage required for pharmacological effects in humans is unknown.

Because the most common route of administration for FUB-AMB involves heating an e-liquid containing the chemical or burning plant material that contains the chemical, thermolytic conversion is of concern. A recent study suggests that heating FUB-AMB to temperatures that could occur with smoking (400 ^{o}C) released its methyl-ester substituent to produce several thermal degradants.[8] Cyanide was also produced. The degree to which cyanide would reach toxicological concentrations in users is unknown.

B. Pharmacokinetics

Little information is available about the pharmacokinetics of FUB-AMB. Analysis of blood and urine of patients who received medical attention during the cluster of overdoses in New York City in July 2016 revealed that none of the samples contained the parent compound.[3] These results are consistent with previous data showing extensive metabolism of synthetic cannabinoids following intake.[10, 11] In the case of FUB-AMB, the process of hydrolysis occurred rapidly, and the de-esterified acid metabolite of FUB-AMB, 2-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-3-methylbutanoic acid, was detected in every patient.[3] Additional information on the specific pharmacokinetics (absorption, distribution, metabolism, or elimination) of FUB-AMB is not available.

C. Pharmacodynamics

In [3H]SR141716A (CB1) and [3H]CP55,940 (CB2) displacement assays, FUB-AMB binds with high affinity at both cannabinoid receptors, each expressed in HEK293 cell membranes.12 Ki values were 10.04 nM and 0.786 nM in hCB1 and hCB2 receptors, respectively. Full activation was also observed at both receptors, as measured by [35S]GTPγS binding (both receptors),12 by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) (CB_1 receptor),[12] and by opening of G protein-gated inwardly rectifying potassium channels (GIRKs) (both receptors expressed in mouse AtT20-FlpIn neuroblastoma cells).[6] At CB_1 receptors, efficacy was substantially greater than that of THC and similar to that seen with the full agonist CP55,940 in all three assays. Consistent with its lower binding affinity compared to CP55,940, FUB-AMB was less potent at activating the CB1 receptor G-protein, with an EC50 value of 0.54 nM (vs. 0.18 nM for CP55,940); however, it was more potent in the cAMP and GIRK assays, with EC50 values of 0.63 nM and 2.0 nM, respectively (vs. 2.1 nM and 42 nM for CP55,940, respectively).6, 12 These results suggest differences between FUB-AMB and CP55,940 in signaling profile. At CB2 receptors, FUB-AMB was a full agonist with potency that was similar to that of CP55,940 in [35S]GTPγS binding, with an EC_{50} value of 0.13 nM (vs. 0.14 nM for CP55,940).[12] FUB-AMB potency at CB_2 receptors in the GIRK assay was less than CP55,940, with EC_{50} values of 18 nM for FUB-AMB and 4.2 nM for CP55,940.

In vivo assessment of FUB-AMB has been similarly sparse. Published data are confined to results from a drug discrimination study in which FUB-AMB was found to fully substitute for Δ^9-tetrahydrocannabinol (THC) in male C57/Bl6 mice, with an ED_{50} of 0.04 mg/kg[12] (further details in Section 8A of the present report).

5. Toxicology

Preclinical evaluation of the acute or chronic toxicological effects of FUB-AMB has not been conducted.

6. Adverse Reactions in Humans

In humans, the acute psychological effects of synthetic cannabinoids (including FUB-AMB) may resemble those reported during acute intoxication with cannabis, ranging from a relaxed and unfocused euphoria to feelings of distress (e.g., confusion, anxiety, and fear). Time perception may be distorted, and in susceptible individuals, hallucinations, paranoia, and more serious psychiatric disorder may occur. Physical effects may include bloodshot eyes (as is characteristic of THC), tachycardia, nausea, vomiting, seizures, and impaired motor performance. Because synthetic cannabinoids are usually more potent (and also may be more efficacious) than phytocannabinoids, their effects occur at lower doses, and overdose may be more common, as suggested by increased reports of deaths and serious adverse reactions with this class of cannabinoids as compared to cannabis.[3, 10, 13-15] Since users usually are unaware of which synthetic cannabinoid is contained in a product, they may administer a chemical with greater potency than the chemical contained in previous products. Further, the chemical may not be evenly distributed throughout the plant material, creating “hot spots” containing higher concentrations of synthetic cannabinoid. For these reasons, dose (in THC equivalents) often exceeds intended dose. Contaminants (e.g., pesticides, heavy metals, rodent feces) may also be present and may contribute to adverse reactions.

Case studies and reports of mass intoxication suggest that acute administration of FUB-AMB has the potential to produce severe adverse reactions in humans up to, and including, death.[2-4] The most predominant symptom in a cluster of confirmed FUB-AMB overdose cases in New York City in July 2016 was severe CNS depression, resulting in slowed behavior and speech that was labeled as "zombielike" by the popular press.[3] However, dissimilar to cases of confirmed exposure to several other third generation synthetic cannabinoids (e.g., ADB-CHMINACA), FUB-AMB intake was not associated with tachycardia, seizures, or cardiac or renal toxicity during this outbreak.[3] In contrast, New Zealand reported that at least 20 deaths were related to FUB-AMB intake.[2] Of note, concentrations of FUB-AMB in confiscated products were 2 to 25 times greater than those reported in the New York incident,[2] suggesting that toxicity is dose-dependent.

Reports on the pharmacological effects of FUB-AMB in humans after chronic use are not available.

7. Dependence Potential

A. Animal Studies

FUB-AMB has not been assessed for dependence potential in animals.

B. Human Studies

FUB-AMB has not been evaluated for its dependence potential in humans.

8. Abuse Potential

A. Animal Studies

FUB-AMB was tested in male C57/Bl6 mice trained to discriminate 5.6 mg/kg THC from vehicle in a standard two-nose poke drug discrimination procedure.[12] At doses from 0.01 to 0.1 mg/kg, FUB-AMB (i.p.) produced dose-dependent increases in responding on the THC-associated lever to a peak of 90% (full) THC-lever responding at the 0.1 mg/kg dose (ED_{50} = 0.04 mg/kg).[12] This dose was not associated with decreases in response rate.

In addition to the single published study on the THC-like discriminative stimulus effects of FUB-AMB, unpublished drug discrimination data from the lab of Dr. Jenny Wiley at RTI International (Research Triangle Park, NC USA) is also available. In the unpublished study, FUB-AMB (i.p.) fully substituted for THC in male and female C57/Bl6 mice (n=13-14) trained to discriminate 5.6 mg/kg THC (i.p.) from vehicle in a two nose poke drug discrimination procedure. (Male mice were different mice than those used in the study described in the preceding paragraph.) Male mice showed full substitution at a 0.1 mg/kg dose that did not decrease response rates. In contrast, female mice did not exhibit full substitution except at the 0.3 mg/kg dose, and this substitution was accompanied by a substantial decrease in response rates. Hence, FUB-AMB appears to be less potent at producing THC-like effects in females than in males. In the second phase of the study, the mice were exposed to vaporized FUB-AMB in a static exposure system. FUB-AMB was aerosolized, released into the chamber for 10-s, and mice were kept in the enclosed chamber for 5 min. Subsequently, they were placed into the operant drug discrimination chambers. Substitution was concentration-dependent, with greater % responding on the THC-associated aperture as

concentrations increased. Maximum responding on the THC-associated aperture occurred at 2.4 mg/ml for both sexes, with 100% responding on the THC-associated aperture for the 3 male mice who continued to respond at this concentration and 77% THC-associated responding in the female mice. Hence, decreased potency in female mice was also observed after aerosol exposure. While inability to calculate dosage and absolute potency is a limitation of the aerosol exposure system, these results demonstrate that FUB-AMB produces THC-like discriminative stimulus effects in male *and* female mice and that it does so following i.p. injection and after aerosol exposure.

FUB-AMB has not been assessed in a self-administration procedure.

B. Human Studies

FUB-AMB has not been evaluated for abuse potential in humans.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

No known medical use or therapeutic applications.

10. Listing on the WHO Model List of Essential Medicines

N/A

11. Marketing Authorizations (as a Medicinal Product)

None

12. Industrial Use

None

13. Non-Medical Use, Abuse and Dependence

The prevalence of non-medical use of FUB-AMB has not been determined specifically, primarily because the chemicals contained in packages of synthetic cannabinoids are not labeled. Hence, users may not even know which synthetic cannabinoids they are using. Prevalence estimates for specific synthetic cannabinoids rely upon analysis of seized materials and bodily fluids of persons who appear in hospital or morgue following administration, both of which undoubtedly underestimate actual use. In a report covering the period from January 2016 to December 2017, synthetic cannabinoids represented the largest group of substances monitored by the European Union (EU) Early Warning System.[10] Non-medical use and abuse of synthetic cannabinoids has also been reported outside of the EU, including in the United States, Australia, New Zealand, and Asia.[16-20]

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Use of synthetic cannabinoids is a global issue with potential for serious public health problems.[10, 20, 21] The magnitude of these challenges is difficult to determine; however, newer compounds

(i.e., "second and third generation" synthetic cannabinoids) may have increased potential for harm.[22] Issues that have been reported include impaired driving,[23, 24] acute psychiatric distress,[25, 26] and polysubstance abuse with several synthetic cannabinoids and/or synthetic cannabinoids and other substances (e.g., alcohol).[27, 28] Increased aggressiveness has also been reported with some of the newer compounds,[29] but a definitive causal link is lacking. This increase could conceivably could be related to recent changes in the population consuming synthetic cannabinoids: i.e., increased use by incarcerated persons and the homeless,[30-32] the former of whom might already be prone to be more aggressive.

FUB-AMB, specifically, has been associated with several clusters of mass intoxication, illness and death in the U.S. and in New Zealand.2, 3 In New Zealand, at least 20 deaths related to FUB-AMB have occurred as well as numerous hospitalizations.2 In the U.S., the most common symptom in mass intoxication clusters appears to have been severe CNS depression that has been labeled "zombielike."3

15. Licit Production, Consumption and International Trade

N/A

16. Illicit Manufacture and Traffic and Related Information

FUB-AMB was first detected in Sweden in 2015.[6] Reported seizures of FUB-AMB have also occurred in the United States and in New Zealand.[2, 3] Similar to other synthetic cannabinoids, underreporting is likely due to lack of routine screening for specific compounds.

Synthesis of FUB-AMB (and many other synthetic cannabinoids) is believed to occur predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped.[10] This hypothesis is supported by the observation that shipments confiscated by law enforcement organizations frequently originate from China. Direct marketing and purchase over the internet also are common.

See Annex 1 for additional information on illicit manufacture and traffic in WHO Member States.

17. Current International Controls and Their Impact

FUB-AMB is not subject to international controls under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

18. Current and Past National Controls

United States: On November 4, 2017, the U.S. Drug Enforcement Agency issued a temporary placement of FUB-AMB under Schedule I control.[33]

European Union: The EMCDD has not issued an Early Warning System report or risk assessment on FUB-AMB; however, the compound is scheduled in Germany (Anlage II) and is banned in Sweden.

Canada: FUB-AMB is classified as a Schedule II controlled substance under Canada's Controlled Drugs and Substances Act passed in 1996.

New Zealand: FUB-AMB has been reviewed by the Ministry of Health in New Zealand for regulatory consideration.[2]

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None.

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