

Synthetic cannabimimetics detected in smoking blends on the Bulgarian territory – toxicological significance

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Synthetic cannabimimetics are some of the most aggressively marketed narcotic drugs. Most often they are added to herbal incenses or are sold in powder as “bath salts”, “research chemicals/not intended for human consumption”, “plant foods”, etc. In our country for the period of 2010-2013 in herbal incenses were identified JWH-018, JWH-073, MAM-2201, UR-144и STS-135. Analysis of the information about their effects after human’s consumption reveals that they are psychoactive substances often with stronger effects than the marijuana itself. The time of their appearance on the market coincides with their worldwide distribution and almost always precedes their inclusion into the List of forbidden substances. Our legislative system attempts to include the new designer drugs under regulation as quickly as possible.

Keywords: cannabimimetics, JWH-018, JWH-073, MAM-2201, UR-144, STS-135

INTRODUCTION

Synthetic cannabinoids and cannabimimetics are amongst the most aggressively marketed narcotic drugs. To this day, more than a hundred substances of this kind have been synthesized. Synthetic cannabinoids are substances structurally similar to Δ^9 -tetrahydrocannabinol (THC) – the active component of marijuana. The chemical structure of cannabimimetics does not bear any resemblance to THC, but produces similar pharmacological/physiological effects on the body. Although the two terms are often used as synonyms, it is important from a judicial point of view to distinguish them; as, according to the legislation of many countries cannabinoids are illegal from the moment of their production, unlike cannabimimetics, the regulation of which comes into effect months, and sometimes years, after they have been synthesized.

Around 2004, herbal smoking blends (‘herbal incense’ or ‘spice’) appeared in Europe as an alternative to cannabis. At first it was thought that their cannabis-like effects were herb-induced; however, it was soon rightly suspected that they also had synthetic substances added to them. Synthetic cannabinoids and cannabimimetics are

commonly added to dried narcotic herbs that, when smoked, produce psychopharmacological effects: *Salvia divinorum*, *Mitragyna speciosa* (Kratom), *Turnera aphrodisiaca* (Damiana), *Leonotis leonurus* (Lion’s ear), *Pedicularis densiflora* (Indian Warrior), *Rosa canina* (Dog Rose, rosehip), *Althaea officinalis* (marshmallow), etc. to produce the so called ‘synthetic marijuana’. Synthetic cannabimimetics are first dissolved in acetone or ethanol, which the herbs are sprayed with and dried, producing various concentrations of these potentially toxic substances [1]. They usually come in small packages, wrapped in foil, with attractive labels.

According to our country’s *National Focal Point for Narcotics and Addiction*, during the last few years there has been a steady trend in the use of synthetic cannabinoids and cannabimimetics.

We present our experience with newly-discovered cannabimimetics in our country – the subject of forensic medicine reports for the period 2010-2013. The subjects for analysis are dried herbal blends, reported to the Center for Expert Forensic Analysis and Trials – Research Institute of Forensic Science and Criminology – Ministry of Interior, Sofia, for the purpose of determining their significance in forensic toxicology.

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METHODS

The following techniques were used for analysis:

1. Visual and microscopic analysis, weighing analysis – conducted on a Sartorius MC 210-S weighing balance, class I accuracy according to The Bulgarian Institute for Standardization (BDS) EN 45501:2001, max – 210 g; min-0.02 g, scale interval (d) 0.0001. The balance has a calibrating certificate from the accredited calibration laboratory Kalibra Bulgaria ltd.

2. Thin-layer chromatography (TLC): TLC plate with adsorbent: silica gel; solvent: chloroform:methanol (9:1); solvent front: 10 cm; developing material: iodine platinate.

3. The following analytical methods were used for measuring the respective proportion of each of the components in the analyzed blends:

a) Gas chromatography: Thermo Finnigan GC Ultra Gas Chromatograph, quartz capillary column EC-5 (30 m × 0.32 mm × 0.25 μm), injector at 270 °C, flame ionization detector at 300 °C, with temperature programming from 160 °C to 290 °C (10 min) with a heating rate of 30°C/min, carrier gas: nitrogen 1.3 ml/min.

b) Gas chromatography: Hewlett Packard 6890 Gas Chromatograph, injector at temperature of 270 °C, quartz capillary column EC™ 20 /15 m × 0.25 mm/ with temperature programming from 100 °C to 290 °C with a heating rate of 15 °C/min, carrier gas: nitrogen 1.5 ml/min. Flame ionization detector with hydrogen 35 ml/min at 300 °C.

4. Gas chromatography was used for identifying the substances in the analyzed samples – mass spectrometry (GC-MS) – Thermo Finnigan Trace GC/MS Gas Chromatograph – column: AT-5MS (30 m × 0.25 mm × 0.25 μm) by Alltech. Temperature programming: 60 °C/4min/ - 15 °C – 290 °C /10min/. Carrier gas: helium at flow rate: 1.0 ml/min. Split injector at split ratio: 1:20 at 270 °C. Interface at 280 °C and ionization chamber at 250 °C. Scan range: 40-460 amu. Ionization mode: electron ionization (EI).

Identification of the obtained mass spectra was done by their comparison with two mass spectral libraries by using computer software.

RESULTS AND DISCUSSION

The active components were isolated from the vegetal matter using methanol. The procedure is easy to perform and gives fixed results, which is most likely due to the substances being added to the vegetal matter, and therefore not having to be isolated from cell components.

As expected, none of the extracts cross-reacted with the cannabinoid panel of our immunological screening laboratory test (Randox Evidence).

By using the above-described analytical methods and by doing comparison with a database and the existing body of literature, we identified the following compounds: JWH-018, JWH-073, MAM-2201, UR-144 and STS-135. As Bulgarian legislation forbids the use of narcotics, regardless of their effects and the level of impact, the precise concentrations were not further discussed.

JWH-018 and JWH-073

In samples analyzed in 2010 and 2011, JWH-018 (see Table 1), and its butyric analog - JWH-073 (see Table 2) were determined. The literature search revealed that these substances were synthesized at the end of the past century [2], with a high affinity for the endocannabinoid receptors CB1 and CB2. In December 2008, two laboratories – THC Pharma (Germany) and AGES PharmMed (Austria), independently determined the presence of JWH-018 in smoking blends [3]. The same results were obtained in other laboratories across Europe and Japan [4, 5]. A direct link was discovered between JWH-018 and the psychotropic effects of smoking blends in which it was present [6].

Before JWH-018 was made illegal in Western Europe at the beginning of 2009, JWH-073 was found in predominantly low concentrations in smoking blends. Blends that possessed it were mostly regarded as impure [7].

However, after the ban, JWH-073 fully replaced JWH-018 (before its ban in 2011).

The effects of JWH-018 and JWH-073 were tested on animals, and it was found that they are similar to those produced by THC – the classic ‘cannabinoid tetrad’ was observed, which includes hypothermia, analgesia, catalepsy, and locomotion suppression [8, 9]. Moreover, the effects of JWH-073 and, to a greater degree those of JWH-018, were much more clearly expressed than the ones produced by THC.

No systemic research has been done on the effects of JWH-018 and JWH-073 on humans. Information about them is mostly found on Internet forums. The most common mode of use of synthetic cannabinoids is smoking, although peroral use is also possible. The contents of JWH-018 and JWH-073 in smoking blends vary between 2.3 mg/g and 35.9 mg/g, and between 5.8 and 22.9 mg/g, respectively [4, 7].

In humans, the effects usually occur either instantaneously, or in 1 to 10 min after smoking. In different individuals, these last 20 min to 4-6 h, and

they resemble those produced by marijuana: high spirits and euphoria; antistressor effect; creative, philosophical, abstract mental activity; increased sense of hearing, smell, taste, vision; altered body sensations; altered perception of time; analgesia; reduced nausea and increased appetite. Adverse effects: increased heart rate (palpitations); eye redness; dry mouth; impaired short term memory; impaired motor coordination; delayed reactions. Although not well documented, excessive use has been found to produce effects not typically observed in marijuana users – agitation and vomiting [10]. There is a reported case of addiction to Spice Gold (a smoking blend containing JWH-018) (after daily consumption of 3 g for several months, followed by the development of withdrawal syndrome, similar to the one produced by hard drugs [11]). There is also a reported case of acute intoxication with seizures and tachycardia, leading to hospitalization [12]. A recently published systematic literature review on psychopathological events resulting from the use of synthetic cannabimimetics summarized the results of 223 trials, leading to its authors coining the term ‘spicephrenia’ [13]. Although there is currently no scientific evidence, these substances have been

found to trigger acute psychosis in susceptible individuals, and/or exacerbate psychotic episodes in individuals with established psychosis.

A literature search revealed that in February 2011, JWH-018 and JWH-073 were included in the list of “Plants and chemicals with high degree of risk for social health because of the harmful effect of their abuse, prohibited for putting in practice in human and veterinary medicine”.

MAM-2201

In samples we analyzed in 2012, we established the presence of a substance called MAM-2201 (see Table 3), which is thought to act as a powerful agonist of the cannabinoid receptors. It was first isolated in laboratories in Germany and Netherlands in June 2011, as a component of synthetic cannabimimetic smoking products [14]. MAM-2201 is a new substance developed by ‘research chemical’ suppliers of grey-market recreational drugs. Structurally, MAM-2201 is a hybrid of two known cannabinoids, JWH-122 and AM-2201, which were used as active components of cannabinoid smoking blends, before being internationally banned. MAM-2201 was banned in New Zealand in July 2012.

Table 1. JWH-018 – general, physical and analytical data

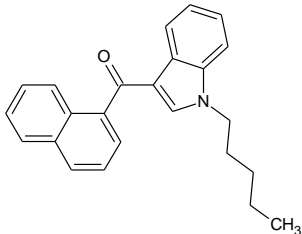
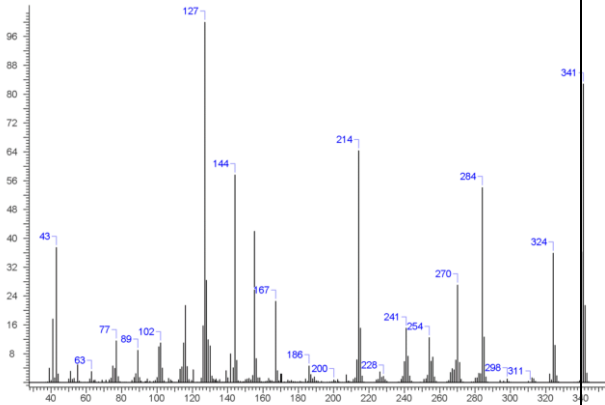
 <p style="text-align: center;">JWH-018</p>	IUPAC name	Naphthalen-1-yl-(1-pentylindol-3-yl)methanone
	Synonyms	AM678, pentyl-3-(1-naphthoyl)indole
Molecular weight	341.189 g/mol	
Chemical formula	C ₂₄ H ₂₃ NO	
Appearance	White to grey powder	
Melting point (°C)	51.9	
GC-MS spectral data	(Principal GC-MS ions) 127.1, 214.2, 270.2, 284.2, 324.3, (341.3 [M ⁺])	

Table 2. JWH-073 – general, physical and analytical data.

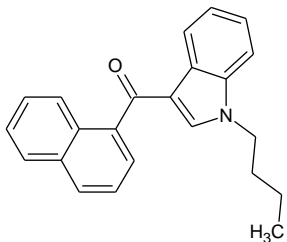
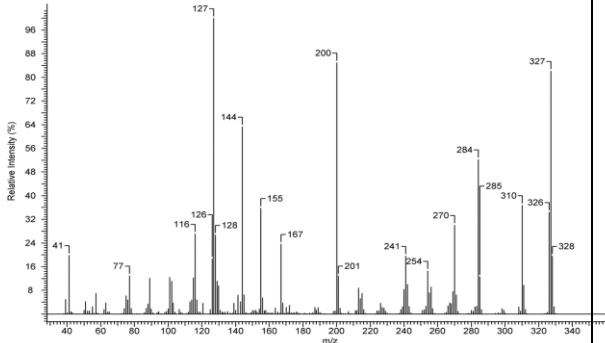
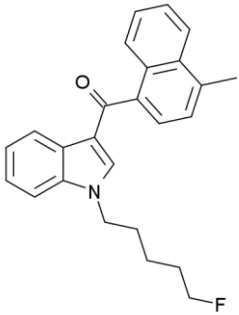
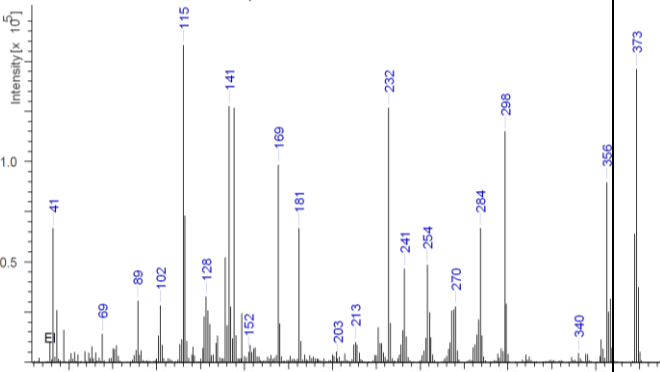
 <p style="text-align: center;">JWH-073</p>	<p>IUPAC name Synonyms Molecular weight Chemical formula Appearance Melting point (°C) GC-MS spectral data</p>	<p>Naphthalen-1-yl-(1-butylindol-3-yl)methanon - 327.16 g/mol C₂₃H₂₁NO White powder 99.8</p> <p style="text-align: center;">(Principal GC-MS ions) 127.1, 144.1, 200.2, 284.2, 310.3, (327.3 [M⁺])</p> 
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Table 3. MAM 2201 – general, physical and analytical data.

 <p style="text-align: center;">MAM 2201</p>	<p>IUPAC name Synonyms Molecular weight Chemical formula Appearance Melting point (°C) GC-MS spectral data</p>	<p>(1-(5-Fluoropentyl)-1H-indol-3-yl)(4-methyl-1-naphthalenyl)-methanone AM 2201 4-methylnaphthyl analog; JWH-122 N-(5-fluoropentyl) analog 373.462 g/mol C₂₅H₂₄FNO White powder 109.4</p> <p style="text-align: center;">(Principal GC-MS ions) 115.2, 141.1, 169.3, 181.1, 232.2, 284.2, 298.1, 356.2, 373.1 [M⁺]</p> 
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Internet forum testimonies of herbal incense smokers claim that MAM-2201 does not cause chest tightness, its taste is not very appealing but its effect is stronger and longer-lasting than that of cannabinoids. The minimal effective dose is 500 µg, and the dose-response curve is very steep. In

some cases, panic attacks and vomiting are observed. There is a lack of clinical data for MAM-2201.

In medical literature, several cases of MAM-2201 intoxication can be found. One of them is that of a 31 year-old man of Japanese origin who, after

smoking 300 mg smoking incense through a bong, falls into a transitory acute psychotic state with agitation, aggression, anxiety and vomiting, with a comorbid sympathomimetic syndrome (arterial hypertension, tachycardia, hyperglycemia) [15]. His condition required immediate hospitalization. One hour after smoking, his blood contained 49 mg/ml MAM-2201. His psychological state recovered 1.5 hours after smoking.

Another case is that of a 59 year-old man, with a fatal outcome [16]. The forensic medical report, done on the 4th day *post mortem*, established the presence of MAM-2201 in the blood and in a number of tissues; its concentration in the adipose tissue being 124 times higher than that in the blood.

There is also a case of an intranasal ingestion of the powdered substance, paired with the local anesthetic benzocaine, by a 20 year-old individual; who was urgently admitted to the emergency room 6 hours later with agitation, xerostomia, chest pain, severe dyspnea, tachycardia, and hypertonia. These effects are thought to be due to the noradrenalin secretion – one of the supposed mechanisms of the cannabinoid receptor agonists [12].

There is a reported case of seizures and death of a 36 year-old man after a simultaneous intake of several synthetic cannabinoids through smoking blends, including MAM-2201 and UR-144, and amphetamines [17].

At the time we identified MAM-2201 in smoking blends (2012), it was not included in the list of “Plants and chemicals with high degree of risk for social health because of the harmful effect of their abuse, prohibited for putting in practice in human and veterinary medicine”. However, its analog AM-2201 was included, which justified the undertaking of legal action.

UR-144

In smoking blends analyzed in 2012-2013, the substance UR-144 or KM-X1 (see Table 4) was also identified. Apart from the compound itself, its main pyrolysis product-artefact was also found in the samples; which is due to the molecular rearrangement caused by the high temperature in the GC injector port.

The chemical structure of UR-144 is very similar to that of JWH-018, the first synthetic cannabinoid. The presence of UR-144 in herbal incense was first reported in Korea in 2012, and it quickly spread throughout Europe and New Zealand [18]. The substance was found in Russia, Croatia, Sweden, Germany, Finland, Norway, Hungary, Japan, and the USA.

UR-144 is a clinical candidate developed by Abbott Laboratories, which acts as a full agonist of the peripheral cannabinoid receptors CB2, but with a much lower affinity for the psychoactive CB1 receptors [19]. The CB2 receptors play a role in the perception of pain, and therefore similar compounds are of medical interest. Despite the relatively low affinity of UR-144 to the CB1 receptors, Internet forum reviews of users of this substance show that it is popularly sought-after for its psychoactive activity.

UR-144 is mainly distributed as a research chemical, in quantities of 0.25 to 100 g. Although it is labeled as ‘unfit for human consumption’, UR-144 is usually smoked like a joint (mixed with tobacco, St. John’s worth, and other herbs). New UR-144-smokers usually start with doses of 0.5-2 mg, and often reach doses of up to 2.5-20 mg (its contents in cigarettes is 0.05%-0.4%). Some users take several doses at a time in order to prolong the effect, which leads to the intake of several tens of mg of the substance in one smoke.

The effect occurs 0.5-2 min after smoking, reaches its peak 3-5 min later, and wears off after 1-2 hours (after 4 hours at high doses). Its users compare its effect to the ones produced by JWH-122, AM-2201, and marijuana. At inhaling, it produces a cocaine-like euphoric and aphrodisiacal effect that comes with an opiate-like tidal feeling, which slowly subsides after 35-40 minutes. During the effect, euphoria, uplifted mood, relaxation, drowsiness, hallucinations, and increased appetite are observed. Most commonly reported adverse effects include anxiety, paranoia, attention deficit, depression and hallucinations, which can last for several days. At high doses, especially during the first few minutes, the hallucinogen effect is very intensive. Overdosing causes tachycardia, nausea, disorientation, dysphoria, blurred vision, inability to communicate, extreme hallucinations, and loss of consciousness. UR-144 tolerance can be developed, compelling the users to increase the doses they take over time. There is one reported case of an epileptic fit after smoking UR-144 [3].

In 2012, UR-144 was the most commonly found synthetic cannabinoid in laboratories in Russia and Poland. It was the most popular synthetic cannabinoid for 2012. In 2013, two UR-144 analogs were released to the market. In many countries, including the UK, Russia and New Zealand, UR-144 was banned in 2012. At the time we discovered this substance in smoking blends, it was not yet banned in Bulgaria. In 2013, it was included in the list of “Plants and chemicals with high degree of risk for social health because of the

harmful effect of their abuse, prohibited for putting in practice in human and veterinary medicine”.

STS-135

STS-135 is a designer synthetic cannabinoid, which acts as a full powerful agonist to the CB1 and CB2 receptors (see Table 5).

This compound has a unique carboxamide bond between the adamantyl side chain and the indole ring, which allows for it to circumvent regulation. STS-135 has a 5-fluoropentyl side chain, which is a commonly found modification in the aminoalkylindole series of designer drugs. It is known that the adamantoyl group is a selective CB1 agonist; the adamantyl carboxamide group is

described in literature and may possess higher affinity for CB2 receptors in the periphery. Similar compounds include AB-001 (1-pentyl-3-(1-adamantoyl) indole), JWH-018 adamantyl carboxamide, AM1248, AKB48, and AKB48-N-(5-fluoropentyl) analogs. The origins of the name of STS-135 are unknown, but it is thought that it is derived from the name of the last US space mission; a metaphor for the psychoactive activity of the substance. There are reported cases of abuse of compounds with the adamantoyl structure, and unpublished reports about the presence of STS-135 in synthetic cannabinoid samples.

Table 4. UR-144 – general, physical and analytical data of the compound (A) and its main pyrolysis product (B)

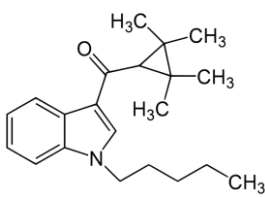
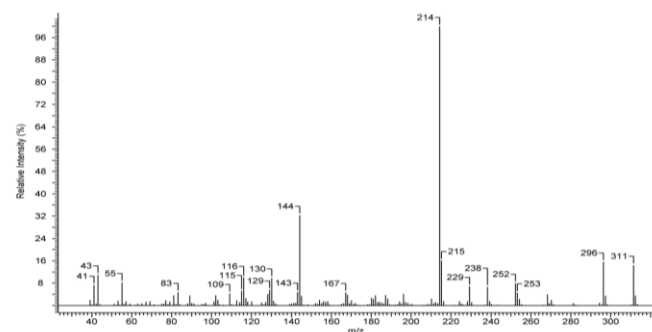
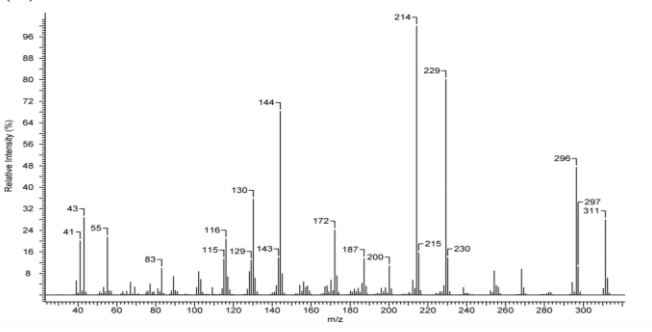
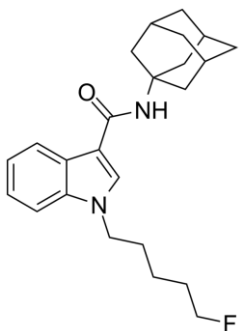
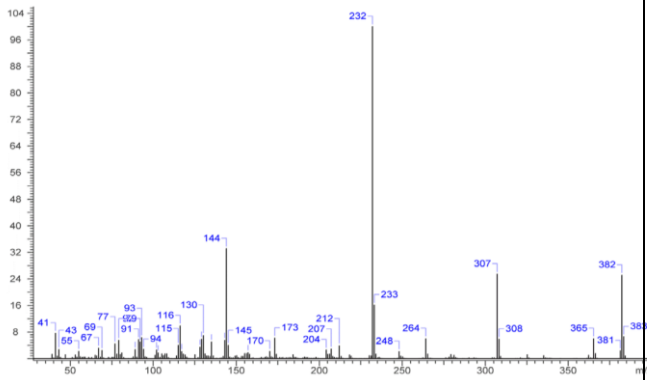
 <p style="text-align: center;">UR-144</p>	<p>IUPAC name</p> <p>Synonyms</p> <p>Molecular weight</p> <p>Chemical formula</p> <p>Appearance</p> <p>Melting point (°C)</p> <p>GC-MS spectral data of UR-144 (A) and its main pyrolysis product (B)</p>	<p>(1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone</p> <p>KM-X1</p> <p>311.461 g/mol</p> <p>C₂₁H₂₉NO</p> <p>White powder</p> <p>68.0</p> <p style="text-align: center;">(Principal GC-MS ions)</p> <p style="text-align: center;">116.2, 130.1, 144.1, 214, 229.1, 296.0, 311.1[M⁺]</p> <p>(A)</p>  <p>(B)</p> 
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Table 5. General, physical and analytical properties of STS-135

 <p>STS-135</p>	IUPAC name	N-adamantyl-1-fluoropentylindole-3-carboxamide
	Synonyms	5F-APICA 5-fluoro-APICA
Molecular weight	382.51 g/mol	
Chemical formula	C ₂₄ H ₃₁ FN ₂ O	
Appearance	White powder	
Melting point (°C)	138.6	
GC-MS spectral data	(Principal GC-MS ions)	116.2, 130.1, 144.1, 173.1, 232.1, 307.0, 365.1, 382.3[M ⁺]
		

There are no official statements on the pharmacological profile of STS-135 as of yet. The only information available is on Internet forums, provided by users of the substance: there are short-term panic attacks of 10-15 minutes. During smoking and evaporating, the substance gives off an unpleasant smell. The effect is pleasant, but less euphoric than that of cannabis. Some report a ‘bipolar effect’ – exaltation, followed by depression. It also causes a certain hallucinogenic effect.

CONCLUSION

The manufacturing, distribution and use of illegal drugs and chemical substances has seen dynamic changes over the last few years, as, together with the wide distribution of explosives, the so-called ‘designer drugs’ or ‘legal highs’ have had an unprecedented success. These are uncontrolled substances whose effects are similar to the controlled ones. Manufactured in semi-legal or illegal laboratories, widely marketed on the Internet, and with misleading labels such as ‘research chemicals/unfit for human consumption’, or as ‘smoking blends’, ‘bath salts’, ‘plant food’, etc., they are either structural analogs of controlled substances, or have different structure but similar effects. Laws for the regulation of these substances are too slow to come into effect, compared to the

speed with which the substances are distributed on the market. Since 2010, designer synthetic cannabinimimetics are categorized by the World Anti-Doping Agency as ‘banned substances prohibited in sport’.

Most of these substances were originally developed by scientists researching the CB1 and CB2 receptors in the human body. Often, the newly-synthesized cannabinoids and cannabinimimetics prove to be more powerful than THC. Therefore it is difficult, and in the case of the cannabinimimetics – downright impossible, to be detected by standard marijuana screening tests. That and the uncontrolled status of synthetic cannabinimimetics at their initial release to the market, is the reason behind the mass consumption of ‘synthetic marijuana’.

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СИНТЕТИЧНИ КАНАБИМИМЕТИЦИ, УСТАНОВЯВАНИ В СМЕСКИ ЗА ПУШЕНЕ НА ТЕРИТОРИЯТА НА БЪЛГАРИЯ– ТОКСИКОЛОГИЧНО ЗНАЧЕНИЕ

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Синтетичните каннабимиметици са едни от най-агресивно налагащите се на пазара наркотични вещества. Най-често те се добавят към растителни смеси за пушене или се продават под формата на прах като „соли за вана“, „химикали за анализ, непредназначени за употреба от хора“, „растителни храни“ и др. В нашата страна за периода от 2010 до 2013 г. в смеси за пушени са идентифицирани JWH-018, JWH-073, MAM-2201, UR-144 и STS-135. Анализът на информацията относно ефектите им след консумирането им от хора показва, че те са психоактивни субстанции, често с по-силни ефекти от самата марихуана. Времето на тяхната поява на пазара съвпада със световното им разпространение и почти винаги предшества включването им в Списъка със забранени вещества. Нашата правна система се стреми да включва колкото се може по-бързо новите дизайнерски дроги в регулация.