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Chemical analysis of substitute drugs of abuse – “legal highs” from Lubuskie province, Poland

Kinga Mruczyk, Krzysztof Durkalec-Michalski, Jan Jeszka,
Joanna Lipińska, Zbigniew Stefański

Department of Human Nutrition Hygiene, Poznań University of Life Sciences, Poland

ABSTRACT

Introduction. Interest in substitute drugs of abuse, commonly called “dopalacze” [literally “after-burns”] that is “legal highs”, in Poland and abuse of such products, which could pose a significant life hazard, led to legislative action taken by the government. The decision by the Chief Sanitary Inspectorate made shops commonly called “smart shops” close down, while confiscated products were subjected to chemical analyses by national research institutes.

Aim. Determination of the chemical composition and possible presence of active substances contained in tested samples of substitute drugs of abuse.

Material and methods. The research material consisted of 171 samples taken for analysis at the end of 2010 from retailers in Lubuskie province. Samples of “legal highs” were tested in a specialized laboratory of the Institute of Rural Medicine, Lublin, by means of liquid chromatography with mass spectrometry (HPLC-MS).

Results. Laboratory analyses of “legal high” samples showed the presence of different psychoactive substances in 136 samples, representing 80% of the tested products. The compounds included psychoactive substances – MDPV (17%), 4-EMC (10%), AM-694 (10%), JWH-203 (7%), TFMPP (6%), as well as narcotics, such as mephedrone (5% samples), *Piper methysticum* (5%), JWH-250 (4%), JWH-200 (5%) and *Salvia divinorum* (2%). Chemical analyses showed that only 35 samples contained no substances that would affect the physiological and psychological condition of the human body.

Conclusions. Analyses of the chemical composition of “legal highs” showed that they contained a large group of different substances or their mixtures exhibiting psychoactive and narcotic activity that may pose a significant health and life hazard.

Key words: legal high, substitute drugs of abuse, active substance, intoxicants.

Introduction

Recently there has been witnessed an increased interest in the use and abuse of the original end use (for collectors’ only) of a new generation of psychoactive substances colloquially referred to as legal highs or uppers, dramatically spanning their markets share. That these products are gaining popularity with young people all the more calls for alert.

As regards their effects, legal highs may be characterised as products containing foreign substances capable of exerting psychoactive and/or narcotic effects on

the human body [1]. They can stimulate the system and enhance the psychophysiological potential of the organism in a non-physiological manner. Although legal highs are not preparations for consumption by humans inter alia, the fact that they are used can be explained by a drive that may eventually bring the user to a state as close as possible to that resembling explicitly delegalised substances [2]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defined legal highs as psychoactive substances, produced illegally and altering the characteristics of a nar-

cotic so that they could be legally distributed, exhibiting narcotic effects upon use.

Production of such compounds involves mixtures of natural origin (*Piper methysticum*, *Salvia divinorum*, caffeine); however, these drugs are mostly based on newly designed and synthesised compounds whose chemical structure is similar to that of known psychoactive substances. Worth noticing is also the fact that the effect on the human body exerted by many components of legal highs has not been fully identified, especially once they have been blended in a single product. Moreover, their technology cannot be seen as controlled production and for that reason the contents of individual compounds in these drugs may vary considerably between different batches of the same product. A significant problem comes up from the fact that some of these substances are not listed on the product label. As a result it is practically impossible to predict any effect of their action. It also greatly hinders possible pharmacotherapy in the case of undesirable symptoms and disorders caused by consumed legal highs [3].

It also needs to be mentioned that until recently substitute drugs of abuse comprised a special group of "legal" narcotics, not covered by specific legal provisions or a ban on sales under the Anti Drug Abuse Enforcement Law or other provisions [4]. It was only amendments to the Anti Drug Abuse Enforcement Law that regulated the legal status of marketing as well as production of substances classified as substitute drugs of abuse. The first amendment of 2009 expanded the list of substances to be monitored by the State authorities to include substances which could have been components of legal highs [5]. A subsequent amendment passed in 2010 added up substances from the group of synthetic cannabinoids as well as a newly specified compound, mephedrone [6]. Furthermore, the same year other alternatives were implemented which provided that substances in legal highs unless subject to separate or appropriate general safety provisions, were to be governed by the provisions of the Anti Drug Abuse Enforcement Law [7]. Concurrently, the Law in force imposed a ban on production and marketing of substitute drugs of abuse, otherwise both being liable to a fine, while the Chief Sanitary Inspector was empowered to supervise enforcement [8].

Aim

As there was no data of scientific worthiness on marketable substitute drugs of abuse available, the objective of the study was shifted to analysis of chemical

composition of and on determination of what substances that might have a potentially negative impact on human health and be ingredients of legal highs, on sale in Lubuskie province in 2010.

Materials and methods

The material for analyses comprised 171 samples of substitute drugs of abuse – legal highs, collected from points of sale in Lubuskie province at the end of 2010. The legality of psychoactive agents identified in the material was interpreted in compliance with the then legislation in force. Chemical analyses of legal high samples were performed by the laboratory of the Institute of Rural Medicine, Lublin, specialising in identification of hazardous substances. The test samples were subjected to ultrasound-assisted methanol extraction. The extracts were analysed in high performance liquid chromatography with mass spectrometry (HPLC-MS). A tandem quadrupole mass spectrometer – a time-of-flight analyser was used. A reversed phase system using a C18 column and the linear gradient of the mobile phase: 0.1% formic acid (A) and 0.1% formic acid in acetonitrile was applied to produce chromatographic separation. Compounds were ionised by means electrospray ionisation (ESI). Cations were collected in an MS scan mode within the range of 100–1000 m/z. The compounds were identified on the basis of a proprietary data base, drawn up specifically for the assays.

Results and discussion

The tested material of 171 substitute drugs of abuse revealed the presence of over 20 psychoactive and narcotic substances, with substances found most commonly in the products and the trade names of preparations containing them as shown in **Table 1**. These substances belonged to the group of cathinones, synthetic cannabinoids, piperazines and tryptamines. Moreover, analyses of legal highs detected the presence of structural analogues of these substances whose chemical structure was similar to that of the narcotic and psychotropic substances listed in appendices to the Anti Drug Abuse Enforcement Law. Apart from the above mentioned compounds, legal highs also contained pharmaceuticals, among which lidocaine was assayed most frequent. Moreover, synthetic derivatives of cocaine and legal substances, such as e.g. caffeine, were detected in the tested material. It has to be pointed out that most samples were of poor quality, while a considerable percentage (13%) contained large quantities of

Table 1. A list of psychoactive substances and intoxicants in the studied substitutes and trade names of “legal highs”, in which these substances have been identified

Type of substances	Name of substances	Number and percent of detected psychoactive substances narcotic drugs	Commercial name of products
Identified the presence of psychoactive substances*	MDPV (methylenedioxy-pyrovalerone)	29 (17%)	<i>Ibiza, Speedway, Fresh and funky, L x2, Saddam x2, Kamikadze, Funky, Strong Men, Kokolino, Up up x3, Lord Koks, Ivory Speed, Diablo MDPV, Coco+, \$, XXX, Matrix, Strong Man 2x, Nitro v2,0 x2, Funky Style, Speedooo x2</i>
	4-MEC and/or 4-EMC (4-Methylethcathinone)	17 (10%)	<i>Mefisto x3, L x2, Przerwa x2, Kokolino, Coco Jumbo x2, Lord Koks, Elektryczny Gisz, Charge+, Speedoo x2, Koko Cherry, Exotic Coco</i>
	AM-694 (1-(5-Fluoropentyl)-3-(2-iodobenzoyl)-indole)	17 (10%)	<i>Mr. Nice, Druits Fantasy, AK-47 x2, Bonzo, Spam x2, Baka x2, Nie ma lipy, Niezły wręć, Spam, Baka, Black widow x2, Hammer, Smart Shiva</i>
	JWH-203 1-pentyl-3-(2-chlorophenylacetyl)indole)	12 (7%)	<i>Kosior, Smile, Mocarz x4, Ale urwał, Mr. Grzmot, Summer Mint, Wyrwidąb, Bobby Sense, Hammer, Smart Shiva</i>
	TFMPP (3-trifluoromethylphenyl-piperazine)	10 (6%)	<i>Super E, ABC, Kokolino, Loved Up x2, Shrooms x3, Lolly Pop, Super E,</i>
	Methylone	7 (4%)	<i>Lick x3, Kamikadze, Limit, Next Explosion, Ex-Extasy</i>
	Butylone	6 (3,5%)	<i>Fresh and Funky, Orange x2, Fresh x2, Ocean Snow</i>
	C11H15N (4-Phenylpiperidine)	8 (5%)	<i>Smiley, Shrek, Ice x2, Crazy Orange, \$, Kolombo, Vanilla Sky</i>
	Caffeine	8 (5%)	<i>Diablo, Blue, Super E, Mitsu, Boom, LZD, Fungeez, Koks</i>
	Naphyrone	6 (3,5%)	<i>Lick x2, ABC, Kiss, Limit, XXX</i>
Identified the presence of narcotic drugs from the List*	Mephedrone	8 (5%)	<i>Vanilla Sky, Kolombo, Smileys, Shrek, Ice x2, Crazy orange, \$</i>
	<i>Piper methysticum</i>	6 (3,5%)	<i>Beg, Smart shiva, Aztek, AK-47, Smart Shiva x2</i>
	JWH-250 (2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone	7 (4%)	<i>Czarny pirat, Aztek, Mr nice, Druits fantasy, Smile x2, Blach widow 2x</i>
	JWH-200 (1-(2-morpholin-4-ylethyl)indol-3-yl)-naphthalen-1-ylmethanone	8 (5%)	<i>Marshmallow, Black widow, Bonzo, Buszek, Mr. Grzmot x 2, Dj Feel, Wild beach</i>
	<i>Salvia divinorum</i>	4 (2%)	<i>Smart shiva x4</i>
	Properdin	3 (1,8%)	<i>Coco Jumbo x2, Koko Cherry</i>

* Act of 10 June 2010 amending the Anti Drug Abuse Enforcement Law (Journal of Laws Dziennik Ustaw of 2010 no. 143 item 962)

chemical contaminants of no psychoactive effects (e.g. tributylamines, dihexylamines, diheptylamines and heptylamines).

Chemical analyses showed that the psychoactive compound identified most frequently in the tested material was methylenedioxypropylvalerone – MDPV (17% samples), a compound exhibiting, among others, stimulant properties. At lower doses it evokes effects comparable to those of methylphenidate, whereas in

higher amounts it is similar to cocaine [9]. Stimulant properties observed following the use of MDPV entail an increase in energy, enhanced concentration, sexual arousal and mild empathogenic effects [9, 10]. Side-effects of this substance include fatigue, insomnia, trismus, fever, hyperhidrosis, cardiac arrhythmia, dilated pupils, headache, loss of appetite, kidney pain, numbness as well as respiratory problems. MDPV overdose causes long-term panic fits and anxiety [10].

Another psychoactive substance whose presence was detected in 8% of the tested samples, was an organic chemical compound, 4-methylonecathionine (4-EMC), a derivative of actinon whose chemical structure is similar to that of mephedrone. 4-EMC has a stimulatory effect on the central nervous system. It is a dopamine and noradrenaline reuptake inhibitor. It causes excitation and euphoria, attention problems, dilated pupils, flushing, hand trembling and tingling sensation. It also leads to elevated blood pressure and arrhythmia. At large doses of 200–500 mg administered e.g. intranasally euphoria is experienced, comparable to that after the use of mephedrone [11].

In this study in the analysed substitute drugs of abuse the synthetic psychoactive substance, AM-694, was identified in 8% samples. A combination of AM-694 with CB1 and CB2 receptors in the brain stimulates the feeling of pleasure and euphoric states [12]. Depending on the dose, this compound enhances the sensation of relaxation. Adverse effects include first of all ocular irritation and hyperaemia, fluctuating arterial blood pressure, dyskinesia, dizziness, vomiting and apathy. In extreme cases anxiety attacks, visual and auditory hallucinations may occur [11].

Analysis of the chemical composition of the tested material in 7% samples showed also the presence of the cannabinoid receptor agonist JWH-203 whose effect on the human body consists among others in inhibiting the neurotransmitter activity. This compound exhibits a strong affinity to CB1 and CB2 receptors [13, 14]. Dose-wise, JWH-203 causes deep relaxation, increased appetite, spatial disorientation, irritations and euphoric states. Adverse effects are connected mainly with ocular hyperaemia, fluctuations of arterial blood pressure, spatial disorientation, dryness of the mucosa and dizziness [13, 14].

A serotonin receptor agonist: 3-trifluoromethylphenylpiperazine (TFMPP), a psychoactive substance exhibiting stimulant properties and frequently combined with benzylpiperazine (BZP), was detected in 6% of the tested samples. It was observed that the effects of this mixture mimic those of 3,4-methylenedioxymetamphetamine (MDMA) [15, 16]. TFMPP together with BZP influence among others serotonin and noradrenalin levels, psychedelic effects and euphoric states, as well as stimulate hyperkinesia, the tingling sensation and the sensation of bliss. A single use effect of BZP mimics the those of amphetamine, while for TFMPP the effects resemble those of ecstasy (i.e. less than 30% MDMA activity) [17, 18, 19].

Chemical analyses of the tested material in 5% of the samples also showed the presence of methylone. Effects of its administration mimic those observed for ecstasy, although certain differences are observed between these substances [20, 21, 22]. According to Alexander Shulgin, who was the first to synthesise methylone, similarly as MDMA this agent exhibits antidepressant properties and influences the general feeling and enhances the sensation of pleasure [20]. Methylone also causes numerous side-effects, e.g. excessive sweating, dilated pupils, nausea, vomiting, abdominal pains, irritation, tachycardia and depression [21, 22].

Chemical analyses of tested substitute drugs of abuse showed that apart from the new substances not legally specified, samples of legal highs also contained substances controlled by the Anti Drug Abuse Enforcement Law in force since 2010, such as mephedrone, *Piper methysticum*, *Salvia divinorum* and synthetic cannabinoids (JWH-250, JWH-200).

In the case of the above mentioned narcotics the presence of mephedrone was detected in 5% of the tested samples. This agent exhibits effects mimicking those of MDMA, amphetamine, as well as cocaine [23]. It causes extreme euphoria, logorrhoea, increased libido and intellectual stimulation [24]. Adverse effects resulting from the administration of mephedrone are connected with palpitation, increased arterial blood pressure, intensive sweating, a cold wave sensation, as well as headaches and dizziness, gnashing teeth and trismus [25].

In 3.5% of the tested samples analyses detected *Piper methysticum*, a plant from the pepper family (*Piperaceae*), grown on islands in the western Pacific. Inhabitants of that regions use infusions from *Piper methysticum* for medicinal, sedative and relaxation purposes [26]. It contains compounds from the group of kavalactones, responsible for psychotropic and spasmolytic effects [27]. They cause a state resembling alcohol intoxication, as well as visual and auditory disorders. Worth noticing here is a study by Stickel et al., which indicated that *Piper methysticum* extracts and preparations may exhibit hepatotoxic effects [28].

Moreover, a chemical analgesic JWH-200, a synthetic cannabinoid receptor agonist, was also detected in the tested material (5% of the samples). JWH-200 shows affinity to the CB1 receptor and its action consists in the inhibition of neurotransmission [29]. Its psychoactive effect is stronger than that of tetrahydrocannabinol (THC) while a sedative action is several times weaker than that shown by THC [30]. Depending on the dose this compound brings about euphoric

states and a sensation of considerable relaxation, and stimulates olfactory and gustatory sensitivity. Adverse effects are connected with irritation and ocular hyperaemia, fluctuating arterial blood pressure, locomotor disorders and dizziness, while in extreme cases they include anxiety attacks, visual and auditory disorders, delusions and chronic mental diseases [11].

The chemical analysis of the tested material also showed (in 4% of the legal highs) the presence of a synthetic cannabinoid JWH-250, being an analgesic. It was synthesised by John Huffman as an analog and metabolite of THC. JWH-250 is a cannabinoid receptor agonist whose effect results from inhibition of neurotransmitters. This compound shows a strong affinity both to the CB1 and CB2 receptors [14]. Its binding with the above mentioned receptors in the brain causes an enhanced sensation of pleasure. The adverse effects of this substance are connected with ocular hyperaemia, fluctuating arterial blood pressure, locomotor disorders, dryness of the mucosa, dizziness and apathy. Anxiety fits, visual and auditory hallucinations, delusions, chronic mental diseases requiring hospitalisation are reported in extreme cases [11].

Analyses showed that 2% of the tested samples contained also one of the most potent natural hallucinogens, Diviner's sage (*Salvia divinorum*). In this plant the hallucinogenic effect is provided by salvinorin A, present in leaves; a compound identified in 1982 by Alfredo Ortega, and, independently, slightly later, by Leander Valdes [31, 32, 33]. Diviner's sage has a short, but strong hallucinogenic effect, accompanied by a lack of control over one's behaviour and serious locomotor impairment [33, 34]. A case of antidepressant effects was also documented [35]. The hallucinogenic effect of the preparation following oral administration is intense and lasts approximately for one to two hours [36, 37]. Individuals using such products declared confusion, as well as perception of sounds from the environment, colours and smells [37]. Side-effects of Diviner's sage have not been sufficiently identified, although users may be susceptible to injuries [38].

The body of scientific literature contains very few studies presenting analyses of chemical composition of commercially available substitute drugs of abuse, colloquially called legal highs. **Table 2** gives results of analyses verifying the presence of psychoactive substances in such products. Tests conducted by the National Institute of Drugs, Warsaw, showed that 15.9% of the examined samples contained narcotics banned by the legal regulations in force and illegally marketed active pharmaceutical agents. All tested samples contained psychoactive substances, mainly structural analogs of controlled substances. Overall approximately 90 substances were identified in analyses of these preparations, including over 57 exhibiting psychoactive properties (these included among others derivatives of cathinone, piperazine, tryptamine, phenylethylamine, synthetic cannabinoids and active pharmaceutical agents) [22]. With reference to the results presented in this paper the analyses performed by the National Institute of Drugs, Warsaw, showed that MDPV (22% vs. 17%) and butylone (11% vs. 3.5%) were found in a slightly higher percentage of examined substitute drugs of abuse, at a lower percentage for TFMPP (4% vs. 6%). High amounts of psychoactive agents in legal highs were also reported in studies conducted by the Research Institute of Sport, Warsaw, in which case the highest percentages of active substances were recorded for caffeine (44%), MDPV (22%), TFMPP (16%), JWH-81 (13%), MBZP (13%), ephedrine (9%), methylone (9%) and butylone (7%) [23]. In turn, results of tests conducted by the Institute of Forensic Research showed that the percentage shares of individual active substances in all tested samples amounted to 19% for caffeine, 14% for JWH-081, 12% for MDPV, 11% for RCS-4, 10% for butylone, 9% for JWH-122, 7% for lidocaine and 6% for TFMPP, respectively [23].

For this reason emphasis has to be made here that – similarly to studies conducted by the Lublin Institute of Rural Medicine, the Warsaw Research Institute of Sport, and the Warsaw Institute of Forensic Research – results

Table 2. Most common active substances in samples of legal highs tested by different research institutes

The active substances	Percent of detected active substances		
	National Medicine Institute	Institute of Sport	Institute of Forensic Research
MDPV	22	22	12
JWH-81	18	13	14
TFMPP	4	16	6
Butylone	11	7	10

of chemical analyses of legal high samples presented in this paper show that commercially available substitute drugs of abuse very often contained psychoactive agents, such as e.g. MDPV, JWH-081 and TFMPP. These data suggest that despite legislative action legal highs may still pose a real social threat and health hazard, as evidenced by an increased interest in this issue on the part of many institutions dealing with narcotic abuse issues, both on the national and European levels.

Conclusions

1. Substitute drugs of abuse, also called legal highs, contain both substances of natural origin obtained from plants and synthetic products.
2. Legal highs contain a group of diverse agents or their mixtures exhibiting narcotic or stimulant effects.
3. Analyses detected structural analogs of substances whose chemical structure is similar to that of narcotics and psychotropic substances listed in appendices to the Anti Drug Abuse Enforcement Law.
4. Analyses of legal high samples show that they are complex products, containing a number of active substances.
5. Required are further studies into the impact of active substances in legal highs on the human body, while educational campaigns need to expose harmfulness and hazards related to abuse of such products.

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Correspondence address:

Krzysztof Jacek Durkalec-Michalski
 Department of Human Nutrition Hygiene
 Poznań University of Life Sciences
 31 Wojska Polskiego Street
 60-624 Poznań, Poland
 phone/fax: +48 61 848 73 32
 email: durkmich@up.poznan.pl